Published in final edited form as:
Curr Dir Psychol Sci. 2007 February 1; 16(1): 37–41. doi:10.1111/j.1467-8721.2007.00471.x.

Molecular Genetic Studies of Eating Disorders:

Current Status and Future Directions

Kelly L. Klump and **Kristen M. Culbert**
Michigan State University

Abstract

We review association studies that have examined the genetic basis of eating disorders. Overall, findings suggest that serotonin, brain-derived neurotrophic factor, and estrogen genes may be important for the development of the disorders. These neuronal systems influence behavioral and personality characteristics (e.g., anxiety, food intake) that are disrupted in eating disorders. Future studies would benefit from larger sample sizes and inclusion of behavioral and personality covariates in analyses. Consideration of the mechanisms of genetic effects and interactions between genes and environment is also needed to extend conceptualizations of the genetic basis of these disorders.

Keywords

anorexia nervosa; bulimia nervosa; genetic; gene

Eating disorders have traditionally been viewed as having psychosocial origins. However, twin studies suggest the importance of genetic factors, as over half (58–83%) of the variation in risk for eating disorders may be accounted for by genes. Given this substantial heritability, it is important to identify the specific genes that contribute to the disorders. Genetic information can then be combined with information on environmental and psychosocial risk factors to develop a more comprehensive bio-psychosocial model of eating disorder development.

This article reviews genetic studies that have attempted to identify susceptibility genes for anorexia nervosa and bulimia nervosa and describes promising directions for future research. Because most genetic data for eating disorders come from association studies, this review will focus on association studies and their attempts to identify the genes contributing to eating disorders.

ASSOCIATION STUDIES

Association studies identify genes that contribute to disorders. These designs are conceptually equivalent to case-control studies in which individuals with eating disorders are compared to controls in terms of their allele (alternate form of a gene) and genotype (the combination of alleles) frequencies. A higher frequency of a particular allele or genotype in individuals with eating disorders suggests that that gene may be associated with the disorder.

Address correspondence to Kelly L. Klump, Department of Psychology, Michigan State University, 107B Psychology Building, East Lansing, MI 48824-1116; klump@msu.edu.

Association studies of eating disorders have taken a two-pronged approach to selecting genes for analysis. In a manner similar to association studies of other disorders, eating disorder researchers early on examined genes as they were identified within the genome, without knowing the possible relevance of the gene or the biological system for eating disorders. This atheoretical approach was largely due to the scarcity of identified genes and the lack of knowledge of their functional significance (i.e., their specific biological effect or product).

Although this approach is still used today, it is more common for researchers to choose genes based on biological systems that are relevant for eating disorders. For example, researchers have focused on genes within neurotransmitter (e.g., serotonin), neuropeptide (e.g., neuropeptide Y), and hormone (e.g., estrogen) systems that are known to affect food intake and/or mood states (e.g., anxiety) that are disrupted in eating disorders. Unfortunately, whether and how particular genes within these systems contribute to disrupted food intake and mood remains largely unknown, as the specific functional significance of most genes has not been explicated. An important direction for future research is to further elucidate these functions so that the neurobiological mechanisms by which genes lead to eating disorders can be identified.

Table 1 illustrates these points by depicting all of the genes that have been shown to be associated with eating disorders. Again, the specific functional significance of most of these genes is unknown, although many are within biological systems that influence food intake, metabolism, and/or mood. Nonetheless, only a handful of studies per gene exist, small sample sizes predominate, and nonreplication of results has been the norm. Conclusions about the role of candidate genes in the development of eating disorders therefore await additional research. Promising exceptions include genes involved in the serotonin, brain-derived neurotrophic factor (BDNF), and ovarian hormone systems, as sufficient data exist for an evaluation of these genes.

Serotonin

Serotonin is a neurotransmitter that functions in the brain to control appetite, mood, sleep, memory, and learning. Serotonin genes have been studied more extensively than other genes for eating disorders, likely because of extant data showing serotonergic disturbances in eating disorders that may reflect serotonin's role in food intake and mood. The most promising serotonin genes are the serotonin 2a receptor (5-HT_{2a}) and serotonin transporter (5-HTT) genes. The A allele of the 5-HT_{2a}–1438 gene has been associated with anorexia nervosa in several studies (see Klump & Gobrogge, 2005). The functional significance of this allele versus the G allele is unknown, as some studies show associations with increased 5-HT_{2a} receptor binding while others do not (Norton & Owen, 2005). Future studies should clarify the specific function of the A allele and the extent to which it influences the disruptions in food intake (i.e., decreased food intake) and mood (i.e., increased anxiety) observed in anorexia nervosa.

Findings for the 5-HT_{2a} receptor gene in bulimia nervosa are more equivocal. Studies show associations with both A and G alleles. Importantly, the G allele has been associated with increased impulsivity and decreased postsynaptic serotonin activity in bulimic subjects (Bruce et al., 2005). Thus, the association of the G allele with traits (i.e., impulsivity and decreased serotonin levels) that are common in bulimia nervosa but not anorexia nervosa may explain its preferential association with bulimia nervosa. Moreover, differences in impulsivity across bulimia nervosa samples may explain why the G allele is associated with the disorder in some but not all studies. These findings highlight the need to continue utilizing quantitative traits to determine if differential associations between 5-HT_{2a} receptor alleles and eating disorders reflect differences between subjects. Allelic variations may

contribute to the development of eating pathology in only a subgroup of individuals with eating disorders (e.g., those with impulsive traits).

Another serotonin-receptor gene that may prove important for bulimia nervosa is the 5-HTT gene-linked polymorphism region (5-HTTLPR). The short ("s") version of 5-HTTLPR has been associated with both bulimia and higher levels of serotonin in brain synapses (as a result of reduced reuptake into axon terminals). Increased serotonin has been associated with anxiety, exaggerated stress responses, and, to a lesser extent, neuroticism and harm avoidance. All of these characteristics have been linked to the development of eating disorders. An interesting picture is therefore emerging, in which 5-HTTLPR may increase vulnerability to anxiety that then contributes to the development of bulimia nervosa. Notably, one study found the s allele to be associated with impulsivity rather than anxiety in women with bulimia nervosa (Steiger et al., 2005). Thus, a more fine-tuned analysis of this allele is warranted as it may be related to affective instability rather than to single affective states in women with bulimia nervosa.

BDNF

BDNF is a protein that acts within the brain to support the growth, differentiation, and survival of new and existing neurons. BDNF also influences food intake, making it a promising candidate for genetic studies of eating disorders. Increased BDNF causes appetite suppression and weight loss, whereas decreased levels cause weight gain (Hashimoto, Koizumi, Nakazato, Shimizu, & Iyo, 2005).

The Met66 variant of a BDNF gene (i.e., the Val66Met single nucleotide polymorphism) has been associated with anorexia nervosa, particularly restricting-type anorexia nervosa (anorexia nervosa without binge eating or purging). Findings for bulimia nervosa and binge/purge anorexia nervosa are mixed, suggesting that the gene may be specifically linked both to the low weight and sustained dietary restriction characteristic of restricting-type anorexia nervosa. The functional significance of the Met66 variant remains unknown; however, it may be involved in the regulated secretion of the BNDF protein (Hashimoto et al., 2005). Additional research into this candidate gene is warranted given associations between BDNF functioning, anxiety, and increased levels of extracellular serotonin (Hashimoto et al., 2005).

Estrogens

Several lines of evidence highlight the potential importance of estrogen in the genetic underpinnings of eating pathology. Estrogen directly influences food intake and has been linked to eating pathology in women (Edler, Lipson, & Keel, 2007). Moreover, genetic effects on disordered eating are present only after puberty (Klump, McGue,&Iacono, 2003), a developmental stage dominated by ovarian hormone activation in girls.

Variants of the estrogen receptor beta gene have been associated with both anorexia nervosa and bulimia nervosa (see Klump & Gobrogge, 2005, for a review). The functional significance of these variants is unknown, although estrogen receptor beta plays a key role in estrogen's effects on food intake and is associated with depressive and anxiety states (Walf & Frye, 2006).

DISCUSSION

Twin data indicate that genes play an important role in the etiology of eating disorders. Although definitive support for any candidate gene is lacking, association studies offer at least speculative hypotheses about the role of serotonin, BDNF, and estrogen genes. These candidate systems are all involved in affect regulation in general, and anxiety in particular. Anxiety-related traits are prospective risk factors for the development of eating pathology

and have been shown to co-occur with eating disorders in families (Keel, Klump, Miller, McGue, & Iacono, 2005). Thus, the genetic influences on eating pathology may be linked to genes that contribute to anxiety.

As noted earlier, serotonin, BDNF, and estrogen also strongly influence food intake. All three systems could influence feeding behaviors independently, although they may also interact, with estrogen acting as a regulator. Estrogen influences the expression of genes within the serotonin and BDNF systems by regulating gene transcription (i.e., the process by which a gene's DNA sequence is copied into messenger RNA). Estrogen's mediation of gene transcription is particularly strong for tryptophan hydroxylase (the enzyme influencing the conversion of tryptophan to serotonin; Shively&Bethea, 2004) and 5-HT_{2a} receptors (Norton & Owen, 2005), although it also influences 5-HTT transcription (Shively & Bethea, 2004). Interestingly, the serotonin system and BDNF show differences in function between males and females, and genetic effects on disordered eating are only present after puberty (Klump et al., 2003). Thus, estrogen, which is prominent in females after puberty, is an interesting candidate in the search for mechanisms underlying neurobiological and genetic influences on eating disorders.

The aforementioned hypotheses are tentative, given limitations of past research. Small sample sizes make findings difficult to interpret. Multisite collaborations with aggregated data are needed to ensure adequate power. In addition, studies have generally relied on categorical phenotypes of the *Diagnostic and Statistical Manual of Mental Disorders*. This reliance ignores the substantial heterogeneity in symptom and personality profiles for eating disorders. For example, research has shown that individuals with the same eating disorder diagnosis (e.g., bulimia nervosa) can exhibit very different personality characteristics that have significant implications for disorder course and outcome (Westen & Harnden-Fischer, 2001).

The recognition that this heterogeneity may also have significant implications for understanding the causes of eating disorders has already enhanced genetic research. Association studies have identified relationships between temperament dimensions (e.g., impulsivity) and gene variants (e.g., 5-HTTLPR s allele) that strengthen evidence for association in women with bulimia nervosa. Moreover, studies utilizing narrow categorical definitions of eating disorders (e.g., using restricting-type anorexia nervosa instead of all anorexia nervosa subtypes) have enhanced efforts to identify susceptibility genes. These findings highlight the need for future genetic studies to explore alternative continuous and categorical definitions of eating disorders.

FUTURE DIRECTIONS

In addition to these broad recommendations, there are several novel directions for future research. Genetic research on eating disorders has been hampered by a limited understanding of the biological mechanisms underlying the illnesses. Although general biological mechanisms have been identified (e.g., alterations in serotonin functioning, BDNF), knowledge of specific biological risk factors (as opposed to correlates) is lacking. This knowledge gap is partially due to the nature of eating pathology: Because eating disorders cause physiological changes, it is difficult to examine whether biological alterations are causes or consequences of the disorders. For example, although decreased BDNF levels characterize patients with anorexia nervosa, increased levels are associated with low body weight and decreased food intake in animal studies. Thus, decreased BDNF levels may be a correlate rather than a cause of anorexia nervosa.

Despite the strong need for prospective studies to disentangle biological causes from effects, the low base rate of eating disorders (.5–3% of females) has resulted in lower funding

priorities for this type of research. The currently tight funding climate has exacerbated this problem, as biological data tend to be expensive to collect and analyze, particularly for prospective studies in which multiple biological samples are collected per subject. Nonetheless, until funding priorities and levels change, alternative designs could be used to identify important candidate systems. For example, twin studies can examine whether two phenotypes, such as eating disorder symptoms (e.g., binge eating) and neurobiological functioning (e.g., estrogen), share genetic transmission in twins from the general population. Although such twins may not have clinical eating disorders, knowledge regarding shared genetic factors for disordered eating symptoms and biological alterations could significantly inform genetic models of eating disorders. This approach has provided evidence for shared genetic effects between eating disorders and anxiety-related phenotypes (Keel et al., 2005).

Another approach entails examining endophenotypes. Endophenotypes are heritable neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological traits that are correlates (but not symptoms) of the disorder. Because endophenotypes are purportedly influenced by a fewer number of genes than influence the disorder, identifying the genetic basis of endophenotypes is thought to be more straightforward and could lead to insights regarding the disorder's genetic basis. An ideal strategy for investigating endophenotypes is to examine biological disturbances in unaffected relatives of individuals with the disorder. If unaffected relatives show the biological dysfunction, then the alterations are not consequences of the disorder but are instead familial (and likely genetic) traits. This set of findings would suggest that (a) the genes contributing to the biological alteration directly contribute to the disorder (although the disorder's expression also depends upon other genetic and environmental risk factors); or (b) the genes for the biological dysfunction lie close to the genes for the disorder and, thus, are transmitted together.

Generally, eating disorder researchers have not used the endophenotype approach. One exception is Steiger and colleagues (Steiger et al., 2006), who found that unaffected female relatives of women with bulimia nervosa exhibited reduced 5-HTT activity that was similar to that of bulimia nervosa patients. These findings attest to the potential role of serotonergic dysfunction in the genetic diathesis of bulimia nervosa and highlight the utility of endophenotypes for identifying genetic risk factors for eating disorders.

A final approach for elucidating biological mechanisms is to combine genetic and neurobiological methods to identify the functional significance of genes. Studies by Steiger and colleagues (e.g., Steiger et al., 2005) exemplify this approach, as they have found associations between genetic variants (e.g., the 5-HTTLPR s allele) and serotonergic functioning in women with bulimia nervosa. A potential problem is noted earlier—namely, that neurobiological alterations may be consequences of the disorder rather than characteristics that were present before the illness onset (i.e., traits). This possibility highlights the need to determine which neurobiological indices are "trait" disturbances that may map onto genetic variations. Careful consideration of the nutritional state of participants, and the sampling of populations at different stages of illness (e.g., recovered subjects), will help with this determination.

In addition to further elucidating biological mechanisms, there is a need to understand how the environment interacts with genetic factors to lead to eating pathology. Moffitt, Caspi, and Rutter (2005) argue that failure to examine these interactions may be the reason for nonreplications in genetic research. If genes only increase risk in individuals exposed to putative environmental risk factors, then genetic studies that include exposed and unexposed individuals will fail to find significant genetic effects. These authors argue that psychiatric

disorders may not be due to several genes of small effect, but may instead be due to fewer genes of large effect that are conditional upon exposure to environmental risk.

An important putative risk factor to investigate for eating disorders is dieting. Dieting is not a sufficient risk factor for eating disorders, as most women diet but only a small proportion develop eating disorders. However, dieting may lead to eating disorders in individuals with genetic risk for eating pathology. Moffitt et al. (2005) argue that examining “exposed samples” (e.g., studying the genotypes of dieting individuals) is a powerful strategy for confirming the role of gene–environment interactions, as well as for identifying candidate genes for the disorder. Given the link between food intake and serotonin, BDNF, and estrogen, future research should examine gene–environment interactions for dieting.

REFERENCES

Bruce KR, Steiger H, Joober R, Ng Yink Kin NMK, Israel M, Young SN. Association of the promoter polymorphism - 1438G/A of the 5-HT2A receptor gene with behavioral impulsiveness and serotonin function in women with bulimia nervosa. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 2005; 37B:40–44.

Edler C, Lipson SF, Keel PK. Ovarian hormones and binge eating in bulimia nervosa. Psychological Medicine. 2007; 37:131–141. [PubMed: 17038206]

Hashimoto K, Koizumi H, Nakazato M, Shimizu E, Iyo M. Role of brain-derived neurotrophic factor in eating disorders: Recent findings and its pathophysiological implications. Progress in Neuro-Psychopharmacology & Biological Psychiatry. 2005; 29:499–504. [PubMed: 15866349]

Keel PK, Klump KL, Miller KB, McGue M, Iacono WG. Shared transmission of eating disorders and anxiety disorders. International Journal of Eating Disorders. 2005; 38:99–105. [PubMed: 16134107]

Klump KL, Gobrogge KL. A review and primer of molecular genetic studies of anorexia nervosa. International Journal of Eating Disorders. 2005; 37:S43–S48. [PubMed: 15852319]

Klump KL, McGue M, Iacono WG. Differential heritability of eating pathology in pre-pubertal versus pubertal twins. International Journal of Eating Disorders. 2003; 33:287–292. [PubMed: 12655625]

Moffitt TE, Caspi A, Rutter M. Strategy for investigating interactions between measured genes and measured environments. Archives of General Psychiatry. 2005; 62:473–481. [PubMed: 15867100]

Norton N, Owen MJ. 5HTR2A Association and expression studies in neuropsychiatric genetics. Annals of Medicine. 2005; 37:121–129. [PubMed: 16026119]

Shively CA, Bethea CL. Cognition, mood disorders, and sex hormones. Institute of Laboratory Animal Resources Journal. 2004; 45:189–199.

Steiger H, Gauvin L, Joober R, Israel M, Ng Yin Kin NMK, Bruce KR, Richardson J, Young SN, Hakim J. Intrafamilial correspondences on platelet [^{3}H-] paroxetine-binding indices in bulimic probands and their unaffected first-degree relatives. Neuropsychopharmacology. 2006; 31:1785–1792. [PubMed: 16407896]

Steiger H, Joober R, Israel M, Young SN, Ng Yin Kin NMK, Gauvin L, Bruce KR, Joncas J, Torkaman-Zehi A. The 5HTTLPR polymorphism, psychopathologic symptoms, and platelet [^{3}H-] paroxetine binding in bulimic syndromes. International Journal of Eating Disorders. 2005; 37:57–60. [PubMed: 15690467]

Walf AA, Frye CA. A review of mechanisms of estrogen in the hippocampus and amygdala for anxiety and depression behavior. Neuropsychopharmacology. 2006; 31:1097–1111. [PubMed: 16554740]

Westen D, Harnden-Fischer J. Personality profiles in eating disorders: Rethinking the distinction between axis I and axis II. American Journal of Psychiatry. 2001; 158:547–562. [PubMed: 11282688]

Recommended Reading

Gottesman II, Gould TD. The endophenotype concept in psychiatry: Etymology and strategic intentions. American Journal of Psychiatry. 2003; 160:1–10.

Hashimoto K, Koizumi H, Nakazato M, Shimizu E, Iyo M. 2005 (See References).
Moffitt TE, Caspi A, Rutter M. 2005 (See References).

TABLE 1

Summary of Genes Associated With Eating Disorders

Genes	Anorexia nervosa			Bulimia nervosa		
	No. of studies conducted	No. of studies reporting significant results	Sample size range	No. of studies conducted	No. of studies reporting significant results	Sample size range
Systems involved in food intake and mood						
Serotonin						
5-HT_{2a} (serotonin 2a receptor)	16	7	*n* = 43–316	8	2	*n* = 22–110
5-HT_{2c}(serotonin 2c receptor)	4	2	*n* = 45–118	2	0	*n* = 40–59
5-HTT (serotonin transporter)	7	2	*n* = 55–138	4	3	*n* = 50–125
HTR1D (serotonin 1D receptor)	1	1	*n* = 191	0	–	–
BDNF (brain-derived neurotrophic factor)						
BDNF	6	4	*n* = 26–510	4	1	*n* = 70–403
Estrogens						
ER β (estrogen receptor beta)	2	2	*n* = 50–170	2	1	*n* = 28–76
Systems involved in food intake and/or energy balance						
Neuropeptides						
AgRP (agouti-related protein)	1	1	*n* = 145	0	–	–
UCP (uncoupling protein)						
UCP-2/UCP-3 (uncoupling protein 2/3 gene cluster)	2	1	*n* = 139–170	0	–	–
Systems involved in pleasure and reward						
Dopamine						
DAT1 (dopamine transporter)	0	–	–	1[a]	1	*n* = 90
DRD2 (dopamine D2 receptor)	1	1	*n* = 191 & 253	0	–	–
DRD3 (dopamine D3 receptor)	1	1	*n* = 39	0	–	–
Opioids						
OPRD1 (opioid delta receptor)	1	1	*n* = 191	0	–	–
Catecholamines						
COMT (catechol-O-methyltransferase)	3	2	*n* = 45–66	0	–	–

Genes	Anorexia nervosa			Bulimia nervosa		
	No. of studies conducted	No. of studies reporting significant results	Sample size range	No. of studies conducted	No. of studies reporting significant results	Sample size range
Miscellaneous systems						
Small Conductance Ca+2 activated K+						
KCNN3 (calcium-activated potassium channel)	2	2	n = 40–90	0	–	–
NMDA (*N*-methyl-D-aspartate)						
NR2B (NMDA receptor 2B)	1	1	n = 90	0	–	–

Note. Genes are arranged by the biological system in which they reside. Only genes that show significant associations with eating disorders in at least one study are included in the table. Association study results were considered significant and included in the "No. of Studies Reporting Significant Results" column if the association was significant at $p < .05$. Some studies report results from two samples; the "Sample size range" column for these studies includes both sample sizes separated by an "&".

[a]This study examined a combined sample of women with bulimia nervosa and anorexia nervosa binge-purge subtype.