The Genetics of Anorexia Nervosa

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twin, linkage, association study

Abstract
Anorexia nervosa is a perplexing illness marked by low body weight and persistent fear of weight gain. Anorexia nervosa has the highest mortality rate of any psychiatric disease. Historically, anorexia nervosa was viewed as a disorder primarily influenced by sociocultural factors; however, over the past decade, this perception has been challenged. Family studies have consistently demonstrated that anorexia nervosa runs in families. Twin studies have underscored the contribution of additive genetic factors to the observed familial aggregation. With these bodies of literature as a starting point, we evaluate critically the current state of research on molecular genetic studies of anorexia nervosa and provide guidance for future research.
THE GENETICS OF ANOREXIA NERVOSA

For decades, anorexia nervosa (AN) was considered a disorder influenced primarily by family and sociocultural factors; however, recent research has focused on the possibility that genetics also play a critical role in vulnerability to this perplexing and often deadly disorder. In this review, we critically appraise the extant literature focusing on family, twin, and molecular genetic studies of AN.

Presentation of Anorexia Nervosa

AN is a serious psychiatric illness marked by an inability to maintain a normal healthy body weight, with patients often dropping well below 85% of expected. Patients who are still growing fail to make expected increases in height, weight, and bone density. Despite increasing emaciation, individuals with AN continue to obsess about body weight and shape, remain dissatisfied with the perceived size and shape of their bodies, and engage in unhealthy behaviors to perpetuate weight loss (e.g., purging, dieting, excessive exercise, and fasting). A subgroup of individuals with AN develop binge eating and purging. Shape and weight become critical markers of self-worth and self-esteem. Although amenorrhea is a diagnostic criterion, it is of questionable relevance as meaningful differences have not been identified between individuals with AN who do and do not menstruate (12, 43). Typical personality features of individuals with AN include perfectionism, obsessionality, anxiety, harm avoidance, and low self-esteem (61).

The most common comorbid psychiatric conditions include major depression (58) and anxiety disorders (11, 21, 28). Anxiety disorders often predate the onset of the eating disorder (11, 28), and depression often persists postrecovery (55). The average prevalence of AN has been reported to be 0.3% (25). The prevalence of subthreshold AN, defined as one criterion short of threshold, is greater—ranging from 0.37%–1.3% (41, 60). Eating disorders are among the ten leading causes of disability among young women (40), the perceived quality of life of sufferers and former sufferers is poor (18), and anorexia nervosa has the highest mortality rate of all psychiatric disorders, with a standardized mortality ratio of over 10 (6, 54).

Etiological Factors

Relatively rare complex disorders such as AN pose a particular challenge for risk factor research because population-based and longitudinal investigations often identify only a small number of cases (41, 51). Moreover, in the presence of etiological heterogeneity, the identification of a small number of cases
reflecting multiple etiological factors renders it particularly challenging to identify risk factors.

Comprehensive reviews on risk factors for eating disorders exist (27). Common risk factors for AN, although not specific to the disorder, are female sex, a history of childhood eating and gastrointestinal problems, prior sexual abuse or other significant adverse experiences, elevated weight and shape concerns, negative self-evaluation, and general psychiatric morbidity (27). Prematurity, smallness for gestational age, and cephalohematoma have been identified as specific risk factors for AN (17). Overall, few longitudinal studies exist in which sufficient numbers of cases have been detected to enable the identification of risk factors for AN. Moreover, it is difficult to differentiate between early symptoms of AN and risk factors (e.g., dieting and high exercise levels). Finally, studies have been unable to explore specificity of risk factors across the eating disorder subtypes, with outcome variables often crossing both diagnostic and threshold boundaries.

Unpacking the Family History Risk Factor

A family history of AN appears to be a risk factor for AN. This observation could be due to genes, environment, or a combination of both. Twin and adoption studies are the main designs by which genetic factors are disentangled from environmental factors in humans. Because there are no adoption studies of AN, we discuss family and twin studies below.

From the perspective of a group of individuals with AN, it is critical to view AN as a complex trait. On average, at a group level, AN results from a mixture of genetic and environmental influences. For AN, “nature versus nurture” is a false dichotomy; it is always “nature and nurture.” AN is likely to be complex for a second reason. At the individual level, the pathophysiology of AN is unlikely to be uniform, and any sample of individuals with clinically defined AN is likely to consist of a number of different “types” of illness. Some proportion of individuals may have a highly genetic form of AN, some a highly environmental variant, and, in others, AN may result from interactions between genetic and environmental influences.

Family Studies

The familial nature of AN has been well established. The first-degree relatives of individuals with anorexia nervosa have approximately a tenfold greater lifetime risk of having AN than relatives of unaffected individuals (37, 52, 53). Yet anorexia nervosa does not “breed true” in that there is increased risk for an array of eating disorders in relatives of individuals with anorexia nervosa rather than a disorder-specific pattern of familial aggregation. This reflects the fact that anorexia and bulimia nervosa are indeed not mutually exclusive conditions, with individuals commonly crossing over between anorexic and bulimic presentations (57). Family studies are unable to determine the extent to which the observed familial aggregation is due to genetic or environmental factors.

Twin Studies

Twin studies, which are challenging given the relative rarity of the disorder, have yielded heritability estimates for subthreshold AN in the context of a bivariate twin analysis with major depression \[ r^2 = 58\% \ (95\% \ CI: 0.33–0.84) \] (58), basing analysis on the single question of “Have you ever had AN?” \[ r^2 = 48\% \ (95\% \ CI: 0.27–0.65) \] (35), and broadening the definition of AN syndrome \[ r^2 = 76\% \ (95\% \ CI: 0.35–0.95) \] (34). We recently completed a large twin study on the narrow DSM-IV definition of AN (13) by screening all living, contactable, interviewable, and consenting twins in the Swedish Twin Registry (N = 31,406) born between 1935 and 1958. AN was identified by clinical interview, hospital discharge diagnosis of AN, or cause-of-death certificate. The heritability of
narrowly defined DSM-IV AN was estimated to be $\hat{e}^2 = 0.56$ (95% CI: 0.00–0.87), with the remaining variance attributable to shared environment [$c^2 = 0.05$ (95% CI: 0.00–0.64)] and unique environment [$e^2 = 0.38$ (95% CI: 0.13–0.84)]. Convergence of heritability estimates across populations is encouraging. Evidence of violations of fundamental assumptions of the twin method has not been found (14, 31, 33); however, results are limited to European populations and may not necessarily generalize to world populations.

**Molecular Genetic Studies**

In the past 30 years, human genetic studies have identified more than 1000 genes responsible for human diseases. These successes have largely been for uncommon diseases whose inheritance follows a classical pattern (e.g., Huntington’s disease or cystic fibrosis) or traits for which a more genetically homogeneous subgroup can be isolated for a more common disease (e.g., BRCA1 and familial breast and ovarian cancer or subforms of type 2 diabetes mellitus). The picture for complex traits more generally has been mixed: Despite an enormous effort to identify genes responsible for numerous critically important human diseases (cancer, cardiovascular disease, metabolic diseases, neuropsychiatric disorders, etc.), a surplus of reproducible findings is still lacking.

The pattern of findings for AN resembles that of many disorders—initial intriguing findings diminished by the absence of clear-cut replication and definitive identification of causal DNA sequence variation—with the caveat that far fewer studies exist for AN.

Two main study designs are generally employed to attempt to identify genes responsible for complex traits like AN: linkage and association studies. The purpose of a genomewide linkage study for a complex trait like AN is to identify the genomic regions that might harbor predisposing or protective genes. In essence, linkage is a “discovery science” tool that does not require a priori assumptions about the nature and locations of genes involved in the etiology of AN (15, 49). Linkage analysis for complex traits requires a large sample of pedigrees with multiply affected individuals (1). Anonymous genetic markers across the genome are genotyped and used to identify chromosomal regions that may contain etiological genes. Linkage approaches effectively narrow the search space from the entire genome (3 billion base pairs) to one or several chromosomal regions (perhaps 10–30 million base pairs). Genes known to be in these chromosomal regions become positional candidate genes.

Association studies contrast cases with AN to appropriate controls without AN. The usual approach has been to select a set of specific candidate genes thought by the investigator to be involved in the pathophysiology of AN. Historically, unlike linkage studies, prior knowledge has been required in order to conduct an association study—to select candidate genes, to genotype a set of genetic markers, and to compare genotype and haplotype frequencies between cases and controls.

Recently, genotyping technologies have progressed to the point where it is possible (although expensive) to genotype hundreds of thousands of genetic markers in all cases and all controls. A large number of genomewide association studies are likely to be published by the end of 2007, and it will be interesting to see if these produce definitive findings. To our knowledge, no such studies are in progress for AN, and the extant literature for AN is limited to a few genomewide linkage studies and a somewhat larger number of candidate gene association studies that have focused on genes in central pathways known to influence feeding, appetite, and mood.

**Linkage Studies of Anorexia Nervosa**

Linkage studies for AN (3, 19, 23) have yielded significant results and underscored the importance of detailed phenotyping. A linkage study of a heterogeneous sample of individuals with broadly defined eating disorders...
yielded no statistically significant findings; however, when the sample was restricted to relative pairs exhibiting the classic restricting AN, it yielded significant evidence for a susceptibility locus on chromosome 1 (23). Additional approaches that enhanced the focus of the linkage analysis by incorporating key behavioral covariates into linkage analyses (19)—drive for thinness and obsessionality—isolated several regions of interest on chromosomes 1, 2, and 13. The chromosome 1 region contained two genes that intersected with pathophysiological theories of the etiology of AN—the serotonin 1D receptor (HTR1D) and the delta opioid receptor (OPRD1)—and a subsequent association study found significant associations with AN (4).

Further work developed a systematic roadmap for utilizing a rich set of phenotypes for genetic analyses and identified variables that were relevant to eating disorders pathology and had published evidence for heritability. Based on these criteria, six traits were analyzed for linkage. Obsessionality, age at menarche, and a composite anxiety measure displayed features of heritable quantitative traits, such as normal distribution and familial correlation, and thus appeared ideal for quantitative linkage analysis. By contrast, some families showed highly concordant and extreme values for three additional variables—lifetime minimum body mass index (lowest body mass index attained during the course of illness), concern over mistakes, and food-related obsessions—whereas others did not. These distributions are consistent with a mixture of populations, and thus the variables were matched with covariate linkage analysis. Linkage analysis found a number of suggestive signals: obsessionality at 6q21, anxiety at 9p21.3, body mass index at 4q13.1, concern over mistakes at 11p11.2 and 17q25.1, and food-related obsessions at 17q25.1 and 15q26.2.

From the perspective of identifying very strong candidate genes for AN, however, the extant studies do not yet narrow the genomic search space in a highly compelling manner. The three linkage reports for AN (3, 19, 23) have 27 findings at a “suggestive” level and two findings at a “significant” type 1 error level. The latter two findings are both on chromosome 1—a 32 million base pair region from 1p36.13–1p34.2 for restricting AN (23) and a 41 million base pair region from 1q25.q–1q41 for a composite phenotype of AN with drive for thinness and obsessionality. These large genomic regions are located on opposite arms of chromosome 1 and contain 546 genes (perhaps 1.4% of all known genes in the human genome). About half of these genes are known to be expressed in brain. A number of genes in these regions overlap with existing theories of the pathophysiology of AN (HTR1D, HTR6) or are relevant to feeding behavior or satiety (the cannabinoid receptor CNR2) along with multiple genes whose products play roles in potentially relevant neuronal processes (e.g., multiple regulator of G-protein signaling family genes).

It is not clear whether these linkage findings truly contain one or more genes relevant to AN. To our knowledge, there has not yet been a comprehensive fine-mapping study of these regions. Therefore, at present, these findings constitute tentative knowledge—they may contain genes of etiological relevance to AN, or they may represent false signals. Encouragingly, a replication study with an independent sample is nearing completion (W. Kaye, personal communication). A hard replication would be a valuable next step in advancing the field.

Association Studies of Anorexia Nervosa

The volume of genetic association studies along with their specialized terminology can be dizzying to the reader unfamiliar with genetic research. One feature of this work that deserves particular mention is the tendency of significant initial reports not to replicate in subsequent studies (24). This phenomenon has been dubbed the “Proteus effect” (26) and underscores the methodological
and statistical challenges of finding a needle in a haystack while dealing with issues of multiple comparisons and uncertain prior probabilities. We briefly review the association studies for AN and discuss challenges in interpreting the literature.

**Serotonergic Genes**

The serotonin pathway has been studied intensively in anorexia nervosa. It is involved in a broad range of biological, physiological, and behavioral functions (7, 8, 50). Serotonin is involved in body weight regulation, specifically in eating behavior, and has also been implicated in the development of eating disorders (9, 30, 59).

Many small, statistically underpowered association studies on genes belonging to the serotonin pathway have been performed. We recalculated the power of the studies, assuming a dominant model with an allele frequency of 0.10, alpha 0.05, and a relative risk of 2. To obtain a power of 80% under these assumptions, at least 178 cases and 178 controls are required. Only three association studies have been performed that had adequate statistical power to detect an effect (4, 10, 22); results of these studies are listed in the first section of Table 1. Two studies focused on the serotonin receptor 1D gene (4, 10). Several serotonin 1D polymorphisms were associated with AN or restrictive AN (4, 10). However, only one single nucleotide polymorphism (SNP), rs674386, was replicated in both studies. The third association study tested whether the rs6311 polymorphism of the serotonin 2A receptor gene was associated with AN (22). This analysis yielded no association. A recent investigation examined four SNPs in HTR1D in 276 women with AN and 768 controls and found evidence of association between two polymorphisms within HTR1D and RAN (10).

Overall, the serotonin 1D gene looks promising, and, notably it is located under the linkage peak for restricting AN (23). However, no hard replications in adequately powered samples have yet been published. Since only one polymorphism was examined in the serotonin 2A receptor gene, no conclusions can be drawn about the involvement of this gene in the etiology of anorexia nervosa.

**Dopaminergic Genes**

Increased dopaminergic activity has been hypothesized to be involved in many of the major symptoms related to AN. Repulsion to food, weight loss, hyperactivity, menstrual abnormalities (amenorrhea), distortion of body image, and obsessive-compulsive behavior have all been related to dopamine activity (29).

The results of two association studies in AN with genes from the dopamine pathway are presented in the second section of Table 1. The COMT gene encodes catechol-O-methyltransferase, which catabolizes brain catecholamine neurotransmitters such as dopamine and norepinephrine (2). No association was found between the rs4680 polymorphism located within this gene and AN in a combined transmission disequilibrium test and case-control analysis (20). Several polymorphisms within the dopamine D2 receptor gene were tested for association with AN (5). Association was reported with the purging-type AN for the rs1800497 and rs6278 polymorphisms in a case-control design, and the transmission disequilibrium test yielded preferential transmission for the rs6277 and the rs1799732 polymorphisms.

The dopamine receptor D2 gene remains of interest, although the findings require replication in a large independent sample. For catechol-O-methyltransferase, the existing data do not support a role for the rs4680 polymorphism in AN.

**Neuropeptides and Feeding Regulation**

Three genes involved in neuropeptide and feeding regulation (Table 1) have been tested in methodologically adequate association studies: ghrelin (16), hypocretin receptor
Table 1  Candidate gene studies performed by collaborations

<table>
<thead>
<tr>
<th>Gene</th>
<th>Polymorphism</th>
<th>Phenotype</th>
<th>N</th>
<th>p-Value</th>
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<td>Serotonin receptor 2A, HTR2A (13q14)</td>
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<td>NS</td>
<td>(22)</td>
<td>TDT and HHRR, France, Germany, U.K., Italy, and Spain</td>
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<td>Catecholamine</td>
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<td>Catechol-O-methyltransferase COMT (22q11)</td>
<td>Val-158-Met (rs4680)</td>
<td>AN</td>
<td>266</td>
<td>NS</td>
<td>(20)</td>
<td>OR 0.98, TDT NS Austria, Germany, Italy, Slovenia, Spain, and U.K.</td>
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<tr>
<td>Dopamine D2 receptor DRD2 (11q23)</td>
<td>−141→C (rs1799732)</td>
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<td>NS</td>
<td>(5)</td>
<td>Haplo rs6275 0.013, 0.050 (RAN); Haplo rs6277 0.011; TDT 0.014, haplo TDT (2) rs6275 (1), rs6277 (1) 0.0015 U.S., U.K., and Germany</td>
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<td>TDT NS U.S., U.K., and Germany</td>
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<td>Haplo rs6275 0.021 (RAN); TDT ns U.S., U.K., and Germany</td>
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Neuropeptide and feeding regulation

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<tr>
<th>Hypocretin receptor 1 HCRTR1 (1p35)</th>
<th>C114T (rs1056526)</th>
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<td>98</td>
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Opioid receptor delta-1 OPRD1 (1p35)

| T80G (rs1042114)                  | AN Controls       | 196               | 98  | NS       | (4)       | OR 0.98, TDT NS Germany, U.K., and U.S.                             |
| T8214C (rs536706)                 | AN Controls       | 196               | 98  | 0.045    | (4)       | OR 1.46, TDT NS Germany, U.K., and U.S.                             |
| G23340A (rs760589)               | AN Controls       | 196               | 98  | 0.046    | (4)       | OR 0.68, TDT NS Germany, U.K., and U.S.                             |
| A47821G (rs204081)              | AN Controls       | 196               | 98  | 0.01     | (4)       | OR 0.61, TDT 0.06 Germany, U.K., and U.S.                           |
| A51502T (rs204076)              | AN Controls       | 196               | 98  | 0.03     | (4)       | OR 0.70, TDT 0.06 Germany, U.K., and U.S.                           |

Other candidate genes

| Brain-derived neurotrophic factor BDNF (11p13–14) | C-270T | AN unclassified ANr ANbp BN Controls | 98 | 347 308 389 510 | NS | (46) | France, Germany, Italy, Spain, and U.K. |

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### Table 1 (Continued)

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<td></td>
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<td>AN unclassified</td>
<td>98</td>
<td>0.0008 (AN versus C; genotype)</td>
<td>(46)</td>
<td>OR AN 1.37 (Met-allele) OR ANr 1.43 (Met-allele) OR ANbp 1.29 (Met-allele) OR BN 1.59 (Met-allele) France, Germany, Italy, Spain, and U.K.</td>
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<td></td>
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<td>347</td>
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<td>ANr</td>
<td>219</td>
<td>0.019 (ANr versus C; HRR)</td>
<td>(47)</td>
<td>HRR and TDT Austria, France, Germany, Italy, Slovenia, Spain, and U.K.</td>
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<sup>a</sup>p-Values are reported for the allele-wise association of the polymorphism, unless stated otherwise.

Abbreviations: AN, anorexia nervosa; ANbp, anorexia nervosa binge/purging; ANr, anorexia nervosa restrictive; BDNF, brain-derived neurotrophic factor; BN, bulimia nervosa; COMT, catechol-O-methyltransferase; DRD2, dopamine D2 receptor; HCRTR1, hypocretin receptor 1; HRR, haplotype relative risk; OPRD1, opioid receptor delta-1; TDT, transmission disequilibrium test.

1 (4), and opioid receptor delta-1 (4, 10). No association was found between AN and the ghrelin and hypocretin receptor 1 genes. Despite the use of different polymorphisms, two studies reported associations between the opioid receptor delta-1 gene, AN, and the restrictive subtype of AN. Recently, a third study genotyped six SNPs in OPRD1 and found three SNPs to be associated with both RAN and binge-purge AN (10).

The accumulated data do not support the involvement of ghrelin and hypocretin receptor 1 in the etiology of AN. The involvement of opioid receptor delta-1 should be replicated in an independent sample to confirm the reported association.

**Other Candidate Pathways**

Brain-derived neurotrophic factor (BDNF) plays an important role in the growth and maintenance of several neuronal systems, serves as a neurotransmitter modulator, and participates in use-dependent plasticity mechanisms, such as learning and memory (36, 56). Physiological and animal models have shown that BDNF induces appetite suppression and body weight reduction (32, 39, 42, 48) and support the hypothesis that alterations in this neurotrophic system and their consequences could determine abnormalities in eating behavior predisposing to eating disorders.

Two European collaboration studies have investigated the association between AN and two polymorphisms located in the gene encoding for BDNF (46, 47). As can be seen in the final section of Table 1, the rs6265 polymorphism was associated with AN, especially the restrictive subtype, in both studies. Again, this gene looks promising, although replication is required.

**Critical Evaluation of the Genetic Literature**

Genetic studies of AN clearly are in an early phase. Compared with many other complex traits, relatively few linkage and association
studies have been completed. Most of the association studies were underpowered (type 2 error) and/or suffered from multiple testing (thus increasing type 1 error). Consequently, it is not currently possible to evaluate replication in the literature to determine which findings are true. Researchers need to pay careful attention to published standards, as with association studies in all of biomedicine (38).

What’s the Phenotype? Clarifying Phenotypes, Endophenotypes, and Subphenotypes

Although replicated across primarily European populations, a hidden complication may exist in twin and genetic studies of AN. Substantial differences in genetic and environmental contributions to component symptoms of AN suggest that we may be obscuring our ability to detect loci that contribute to risk by focusing on a contrived and heterogeneous condition. Our search for relevant genes may be more effective if we focus on homogeneous and measurable component behaviors rather than on compound syndromes that comprise our DSM categorical definition of AN. We have suggested that there may be distinct sources of familial resemblance for different symptoms of bulimia nervosa, an eating disorder related to AN. As codified in the DSM-IV, binge eating and self-induced vomiting represent more genetically mediated symptoms of bulimia nervosa (44), whereas psychological features, such as placing undue importance on weight as an indicator of self-worth, represent more environmentally mediated symptoms (45). The same may hold true for AN. Thus, our multipart diagnostic syndromes may represent commonly co-occurring mixtures of genetically and environmentally influenced symptoms that also differ by sex. In order to reduce the potential obscuring effects of focusing on compound syndromes, investigators in the future may choose to focus on heritable and homogeneous subphenotypes for AN.

Future Directions and Research Needs

The needs for the future are clear: The genetics of AN needs more and larger studies. Given the current rush to conduct genomewide association studies (a type of case-control association study with >500,000 genetic markers spaced across the genome), it may be possible for AN researchers to avoid the mistakes of the early adopters of this approach. Adequate sample sizes are especially critical for genomewide studies. The potential payoffs of this line of inquiry are also apparent. The clear-cut identification of the genomic variation that predisposes to AN would likely revolutionize the field by providing researchers and clinicians with a hard finding upon which to base the next generation of research. Moreover, hard findings on AN may be advantageous to the understanding of related psychopathology (e.g., depression, anxiety disorders, and obsessive-compulsive disorder) as well as critical aspects of appetite and weight dysregulation.

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