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The Genetics of Anorexia Nervosa: Current Findings and Future Perspectives

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Abstract

Anorexia nervosa is a perplexing illness with the highest mortality rate of any psychiatric disease. In this paper, we review the genetic research on anorexia nervosa (AN). Family studies have demonstrated that anorexia nervosa is familial, and twin studies have indicated that additive genetic factors contribute to the familial aggregation. Molecular genetic research, including genomewide linkage and case control association studies, have not been successful in identifying DNA variants that are unequivocally involved in the etiology of AN. We provide a critical appraisal of these studies and discuss methodological issues that may be implicated in conflicting results. Furthermore, we discuss issues relevant to genetic research such as the importance of phenotypic refinement, the use of endophenotypes, and the implications for nosology and genetic analysis. Finally, the future of genetic research for AN is discussed in terms of genomewide association studies (GWAS) and the need for establishing large samples.

Keywords

twin; linkage; molecular genetics; anorexia nervosa

Introduction

Beliefs about the etiology of anorexia nervosa (AN) have undergone remarkable change. For decades, AN was considered to be a culture-bound disorder in which family and sociocultural factors were thought to play a major role, but research suggests that genetic factors are relevant in the vulnerability to this disorder (1). AN is a complex disorder resulting from a combination of genetic and environmental factors. Accordingly, it is important for clinicians and researchers to integrate knowledge of the role of genetics as well as social, psychological, and familial factors into understanding risk for AN.

AN is characterized by low body weight, intense fear of weight gain, body image distortion and amenorrhea. The prevalence of AN among females is approximately 0.9% (2) with subthreshold forms more prevalent (up to 2.4%)(3). Additionally, the mortality rate of AN is approximately 5% per decade (0.56% per year), with a standardized mortality ratio of over 10 (4,5).

In this paper, we present a synthesis of knowledge on the genetic factors associated with the etiology of AN. Family, twin, and molecular genetic studies of AN are reviewed followed by a critical appraisal of the available literature and a brief discussion on future perspectives of genetic investigation in the eating disorders field.

Family History Studies

Family Studies

It has been well documented that eating disorders run in families. First-degree relatives of individuals with AN have approximately a ten-fold greater lifetime risk of having AN than relatives of unaffected individuals (6–8). Research also suggests that there is an increased risk for any eating disorder in relatives of individuals diagnosed with AN indicating that AN and bulimia nervosa do not “breed true,” and pointing to possible shared familial vulnerabilities across eating disorders (9).

Twin Studies

Although informative, family studies do not allow the separation of genetic and environmental influences on familial transmission. However, with twin studies, variance in liability to a trait can be decomposed into independent genetic and environmental influences and provide estimates of their relative magnitude (10). Because monozygotic (MZ) twins are assumed to be fundamentally genetically identical, discordance in MZ twins is likely to result from environmental influences. Conversely, differences between dizygotic (DZ) twins who share roughly 50% of the genome could be due to either genetic or environmental influences. Thus, comparing the concordance of MZ twins compared to DZ twins provides information about the relative contributions of genetic and environmental factors in the etiology of a particular disorder.

Twin studies on eating disorders have demonstrated that a considerable portion of observed familial aggregation is due to additive genetic factors (i.e., heritability) (10). In a large Swedish twin study ($N = 31,406$), Bulik and colleagues (11) reported that heritability of AN was estimated to be $a^2 = 0.56$ (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)]. These findings have been broadly replicated for threshold and subthreshold AN across studies (12–14). Together, they corroborate a genetic diathesis for AN.

Molecular Genetics: Methodologies

Genomewide Linkage and Candidate Gene Association Studies

Two commonly used genetic analytic approaches are genomewide linkage analysis and case control association studies. Large samples of multiplex pedigrees are required for linkage analysis studies. Anonymous genetic markers spread across the genome are genotyped to identify chromosomal regions harboring genes that influence the trait of interest. Candidate genes located under the linkage peaks can be explored using case control association approaches to verify whether they are in fact associated with the phenotype of interest.

In case control association studies, cases who display a trait of interest are compared with controls who do not display the trait. Genetic markers or SNPs [single nucleotide polymorphisms or DNA sequence variations that occur when a single nucleotide (A, T, C, or G) in the genome sequence is altered; each individual has many single nucleotide polymorphisms (around 10 million) that together create a unique DNA pattern for that person] from a candidate gene or genes that are hypothesized to be of relevance to the phenotype are examined in all participants, and statistical analyses contrast genotype and haplotype (i.e., combination of alleles located close together on the same chromosome that are often inherited together) frequencies in cases versus controls (15). The case control association approach is suitable when there is considerable prior knowledge of the pathophysiology of a trait which could implicate specific genetic variants. Currently, genome wide association studies (GWAS) allow the assaying of several hundred thousands SNPs, enabling a comprehensive coverage of

common genetic variation across the genome. Unlike case control association studies, GWAS do not represent a candidate gene approach. On the contrary, GWAS do not require a focus on biological candidate genes or *a priori* knowledge of the pathophysiology of the disease (16).

Molecular Genetics: Research Findings in Anorexia Nervosa

Linkage Analysis

Three linkage analyses for AN (17–19) have yielded significant results and underscored the importance of accurate phenotyping in order to reduce both phenotypic and genotypic heterogeneity. A linkage study on AN composed of 192 families with at least two affected relatives resulted in no statistically significant findings; however, when the sample was restricted to relative pairs exhibiting restricting AN, it yielded significant evidence for a susceptibility locus on chromosome 1 (19). Using the same dataset, Devlin and colleagues conducted additional linkage analyses by incorporating drive for thinness and obsessiveness as covariates (18). The inclusion of these covariates revealed several regions of interest on chromosomes 1, 2, and 13. The serotonin 1D receptor (*HTR1D*) and the delta opioid receptor (*OPRD1*) located on chromosome 1 corresponded to the linkage peak identified by Grice et al. (19), and represent genes previously implicated in the pathophysiology of AN (20). Further work focused on six heritable phenotypic traits relevant to eating disorders (17).

Obsessiveness, age at menarche, and a composite anxiety measure displayed normal distribution and familial correlation, and were suitable for quantitative linkage analysis. Conversely, some families showed highly concordant and extreme values for 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 traits were analyzed with covariate linkage analysis, and a number of suggestive linkage signals were observed: obsessiveness 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

Two out of the three linkage reports for AN (18,19) based on the same sample have pointed to two statistically significant findings on chromosome 1, a 32 million base pair region from 1p36.13–1p34.2, for restricting AN (19) and a 41 million base pair region from 1q25.q–1q41 for a composite phenotype of AN with drive for thinness and obsessiveness (18). Among the 546 genes included in these genomic regions, about half are expressed in the brain. Some genes in these regions coincide with existing hypotheses of the pathophysiology of AN (i.e., *HTR1D*, *HTR6*), or are pertinent to eating behavior or satiety (i.e., the cannabinoid receptor *CNR2*), along with various other genes whose proteins are involved in relevant processes at the central nervous system (e.g., multiple regulator of G protein signaling family genes).

Linkage studies should be interpreted judiciously given that the results may either signify areas containing genes of etiological relevance to AN, or may simply reflect false signals. Replication studies with independent samples are essential to determine the reliability of the aforementioned findings.

Case-Control Association Studies

Candidate gene studies in eating disorders have mostly focused on genes encoding proteins implicated in the regulation of feeding and body weight, as well as genes involved in neurotransmitter pathways regulating eating behavior (21). Most of the publications on candidate gene studies are on small samples and consequently statistically underpowered, and not one has been replicated with adequate statistical power. Candidate gene studies not having adequate statistical power are not included in this manuscript due to the lack of robustness. Thus, for this review, a filter was applied – we recalculated power for the case-control association studies by assuming a dominant model with an allele frequency of 0.10, alpha 0.05,

and a relative risk of 2.0. Using these assumptions, a minimum sample size of $N = 178$ cases and $N = 178$ controls is needed for achieving power of 80% and therefore we only selected studies that met this criteria. This filter led to the exclusion of approximately 45 published studies. Case control association studies examining serotonergic genes, dopaminergic genes, genes related to neuropeptides and feeding regulation, and brain-derived neurotrophic factor gene (BDNF) are briefly described in the next section and a summary of positive significant findings are presented in Table 1.

Serotonergic genes—Previous research has suggested that the serotonin pathway may play an important role in the pathophysiology of eating disorders, specifically for AN. Serotonin (5-HT) is implicated in the regulation of appetite and eating behavior, and serotonin reuptake inhibitors have been used as a treatment component of AN (22–24). Additionally, individuals who have recovered from AN have persistent 5-HT disturbances (21). These findings suggest that serotonergic dysfunction might be a biological marker for eating disorders. Further, research has shown that the psychopathological features associated with AN such as perfectionism, obsessiveness and rigidity may also be associated with the serotonin pathway (21). Based on these results, genes related to serotonin (serotonin transporter and receptors) have been the focus of many genetic association studies in AN.

Three case-control association studies with adequate statistical power examined the serotonin gene (20,25,26). Two studies focused on the serotonin receptor 1D gene (20,25) with numerous serotonin 1D polymorphisms associated with AN or restricting AN (Table 1). Only one common single SNP (rs674386) was replicated in both studies (20,25). A third study reported negative findings in AN for the rs6311 polymorphism of the serotonin 2A receptor gene (26). However, no assumptions can be made concerning the implication of this genetic variant in the vulnerability to anorexia nervosa given that only one polymorphism has been examined for the serotonin 2A receptor gene in studies with adequate statistical power.

Dopaminergic genes—Research also suggests that impaired dopaminergic function may contribute to symptoms related to AN (21). For example, food aversion, weight loss, hyperactivity, menstrual dysfunction, distorted body image cognitions, and obsessive compulsive behaviors have been found to be related to increased dopaminergic activity (21). Moreover, reduced dopamine metabolites in cerebrospinal fluid occur in malnourished individuals with AN and tend to persist after recovery (27). Thus, dopamine dysfunction might be implicated in reward and affect pathways, decision-making, stereotypic motor activity, and decreased food ingestion in AN (28).

Specifically, dopamine D2 and D4 receptor genes have been examined in individuals with AN using case-control association studies (29,30). Within the D2 receptor gene, rs1800497 and rs6278 polymorphisms were observed for purging-type AN, and the transmission disequilibrium test suggested preferential transmission for the rs6277 and the rs1799732 polymorphisms (29). Single locus analyses showed significant association between rs1800955 within the D4 receptor gene in individuals with AN (30). Further, haplotype analyses showed significant association at a 4-locus haplotype including rs1800955(30).

Research has also investigated the COMT gene which encodes catechol-*O*-methyltransferase, an enzyme responsible for the catabolism of dopamine and norepinephrine (31). However, in a sample of European participants with AN, no association was found between the rs4680 polymorphism located within the COMT gene and AN in a combined transmission disequilibrium test and case-control analysis (32). Despite the fact that replication with larger samples is needed, the D2 and D4 dopamine receptor genes continue to be of interest for AN. Conversely, there is insufficient evidence to endorse the role of rs4680 polymorphism within the COMT gene in AN.

Neuropeptides involved in feeding regulation—Research on the role of the neuropeptides in the regulation of eating behavior and body weight homeostasis has increased considerably in the last decade. Clinical investigations using participants with AN and BN, have focused on selected hypothalamic and gut-related peptide systems for examining effects on eating behavior. Research has demonstrated state-related alterations in a number of peptide measurements, including opioids, neuropeptide Y (NPY), cholecystokinin (CCK), and ghrelin (33). Longitudinal studies are required to address which of these disturbances may play a role in perpetuating eating disorder symptoms. Likewise, studies of recovered individuals may shed light on which changes represent stable biological traits that persist after resolution of the core symptoms—although this design can not resolve whether the traits are of etiologic relevance or represent scars of the illness.

Three genes involved in neuropeptide and feeding regulation have been tested using association studies in samples with adequate sample sizes: preproghrelin (34), ghrelin (35), hypocretin receptor (20) and opioid receptor delta-1 (20,25). No association was found for either ghrelin or hypocretin receptor 1 genes and AN. In addition, although a positive finding was reported for bulimia nervosa, no association was observed for six polymorphisms in the preproghrelin gene and AN in a sample of Japanese participants (34). Thus, the available evidence does not support involvement of preproghrelin, ghrelin, and hypocretin receptor 1 in the etiology of AN.

Two studies reported associations between the opioid receptor delta-1 gene, AN, and restricting AN, however different genetic markers were investigated for each study (20,25). Replication using an independent sample is needed to validate the reported association examining the implication of opioid receptor delta-1 for the vulnerability to AN.

Other candidate genes—There are many systems known to modulate feeding and related functions yet to be investigated in eating disorders. Different lines of evidence suggest that brain-derived neurotrophic factor (*BDNF*), which encodes for a neurotrophin and plays a role in synaptic plasticity and neuronal growth and development (36), might affect eating behavior and weight regulation (37,38). Accordingly, animal models have shown that BDNF induces appetite suppression and weight loss (38,39). Hence, changes on this neurotrophic system could be involved in the etiopathology of eating disorders.

The *BDNF* gene and AN has been examined in three studies with mixed results. The association between AN and two polymorphisms located in the gene encoding for BDNF has been examined in two collaborative studies using a European sample (40,41). Results from both studies suggest that the rs6265 polymorphism was associated with AN, particularly restricting AN. Conversely, no association was detected in a study that included Dutch patients with AN, in addition to individuals with schizophrenia and healthy controls (42). Despite conflicting results, the *BDNF* gene shows promise. Independent replication is required.

Genetic variants implicated in the aforementioned findings for AN (e.g., serotonergic and dopaminergic genes, and brain derived neurotrophic factor gene) do not appear to be specifically related to AN vulnerability as many of these same genes have been implicated in the etiology of other psychiatric disorders such as attention deficit hyperactivity disorder, autism, bipolar disorder, and schizophrenia (43–46). One possibility is that genetic variants identified through these approaches may index general vulnerability to psychiatric disorders rather than honing in on genes that specifically influence AN.

Critical Appraisal of the Genetic Literature on AN

Assessing the association between DNA sequence variation and disease has been used extensively to identify regions of the genome and candidate genes that contribute to disease.

Nevertheless, the lack of replication has led to skepticism about the utility of the candidate gene approach in case control association studies for complex disorders. It is important to critically evaluate the design of case control association studies such that methodological errors can be prevented and the potential to identify genetic etiological factors can be maximized. Factors affecting failure to replicate often relate to poor study design and lack of knowledge regarding the underlying genetic contributions to complex disorders. Additional problems inherent with case control association studies of complex diseases include small sample size, failure to consider power on a subgroup analysis within a larger sample, failure to report all SNPs genotyped, failure to correct for multiple testing, failure to consider random error with positive findings, poorly matched control groups, failure to detect linkage disequilibrium with adjacent loci, not publishing negative findings, and overinterpreting results (47).

Genetic studies of AN are still in an early phase of scientific development. Compared to other psychiatric disorders such as schizophrenia and bipolar disorder, few linkage and association studies have been conducted. Of the candidate gene studies that have been completed, most were underpowered (Type 2 error) and/or had multiple testing problems which increases Type 1 error (48). Thus, replication studies must be interpreted cautiously given that they may have been based on studies that were underpowered to detect effects.

Genetic Research and AN Classification: Clarifying Phenotypes, Endophenotypes and Subphenotypes

Possibly contributing to the failure to find and replicate genetic variants for eating disorders are problems with the current diagnostic schema (49). Diagnostic clarification could assist with collecting more homogeneous samples that could theoretically increase the likelihood of identifying relevant genes (48). Some suggest that focusing genetic studies on endophenotypes may be a valuable approach, although the yield to date has not been particularly promising (50). Endophenotypes represent intermediate phenotypes related to a particular disorder that mark the pathway between the genotype and the behavior of interest (31). Examining endophenotypes could theoretically simplify genetic analyses because the number of genes involved in a disorder may be larger than the genes associated with a single endophenotype. Refined definitions of the phenotypes along with the identification of thresholds or disorder subtypes, and endophenotypes that index disease both genetically and phenotypically may improve psychiatric nosology and allow more accurate genetic analyses. In the case of AN, it is possible that some of the core symptoms (e.g., maintenance of low body weight) could be clearly genetically mediated symptoms, whereas others, such as placing undue influence of shape and weight on self-evaluation, could represent more environmentally mediated symptoms. Indeed, those symptoms are not observed in anorexia nervosa across all cultures (51). Notwithstanding the difficulties in correctly identifying endo- and subphenotypes for AN, genetic research looking at these traits may lead to the identification of genetic markers that will ultimately assist in improving diagnostic nosology (49).

Future Directions in Genetics of AN Research: The Era of Genomewide Association Studies

Linkage and case control association studies have dominated the field in terms of genetic methodology; however, genomewide association studies (GWAS) have recently become a powerful method for discovering genetic risk factors that contribute to complex diseases and related quantitative traits. Indeed, by 2007, >100 new genes for complex traits ranging from obesity to age-related macular degeneration had been identified by GWAS, most of which had never been on the list of suspected genes for their respective disorders (52,53). Unlike linkage and case control association methods which focus on several hundred markers or specific

candidate genes, GWAS combines an inclusive and unbiased scan of the genome (>500,000 genetic markers) with the power to identify common alleles with fairly small phenotypic effects (16). The ability to conduct a scan across the entire genome rather than specifying *a priori* candidate genes allows for a “hypothesis free” test (52). As with all genetic analyses it is important to keep in mind methodological issues such as design and power. The sample sizes required for adequate statistical power for GWAS vary according to the design, (e.g., single stage vs. multi-stage designs), effect size (i.e., allele frequency, genetic model, and genotypic relative risk), and the alpha value (i.e., .05/number of SNPs). It remains critical to adjust for multiple-hypothesis testing when conducting GWAS (54). Given the cost of GWAS (currently ~\$500/sample) (16), researchers can find a balance between power to detect modest effects and the cost of genotyping large numbers of markers, by combining data across studies and performing multi-stage analyses (16,53). Although beyond the scope of this paper, the issue of population stratification (i.e., differences in allele frequency between cases and controls due to differences in ancestry, and not genetics of a disease) within the study sample must be dealt with appropriately as it can lead to false-positive results possibly outweighing true associations (16,53). Despite its challenges, GWAS have the potential to identify many genes for common diseases and quantitative traits.

Given the large samples needed to detect genotypic differences for eating disorders, and most complex disorders, collaborative data sharing of samples for the discovery of the genetic link to AN will make GWAS a realistic possibility. With this in mind, networks of collaborative GWAS encompassing distinct study samples and various phenotypes have been formed. The Wellcome Trust Case Control Consortium (WTCCC) (55) represents the pioneering example with research efforts focused on seven complex diseases (bipolar disorder included as the only psychiatric disorder) and common controls. The Genetic Association Information Network (GAIN) is another example (56). GAIN involves six phenotypes, including attention deficit hyperactivity disorder (ADHD), major depressive disorder, schizophrenia, bipolar I disorder, diabetic nephropathy and psoriasis (56). Similar consortia will be essential to ascertain sufficiently large samples for relatively rare disorders such as anorexia nervosa.

Family, twin, linkage and association studies have indicated that eating disorders run in families, largely due to the effect of genes, and that some areas of the genome may be considerably more likely to harbor risk genes. In this rapidly changing field, investigators now have the opportunity to move the field forward by creating research networks that can leverage available technology to search for genes that may be of etiological relevance to anorexia nervosa. The resulting insights could potentially shed light on important features of disease pathophysiology, such as appetite regulation, energy balance and other comorbid disorders (anxiety disorders, mood disorders, substance use and impulse control disorders). Ultimately, these advancements could assist with clinical management including tailored interventions and guide the development of innovative treatments, representing a significant evolution in mental health research.

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Table 1

Candidate gene studies in anorexia nervosa: significant associations only

Gene	Reference	Phenotype (N)	Polymorphism*	p ^d value	Note
Serotonin					
Serotonin receptor 1D HTR1D (1p36)	(20)	AN (196) Controls (98)	C1080T (rs17850242)	0.01 0.01 (genotype)	OR 2.63, TDT NS Controls U.S., U.K., and Germany
	(25)	ANr (122) AN binge-purging (104) Controls (678)	T-1123C (rs674386)	0.026 for ANr/Controls	OR 1.44
Catecholamine					
Dopamine D2 receptor DRD2 (11q23)	(29)	ANr (108) AN purging (88) Controls (98)	725 bp 3_ C/T (rs6278)	0.042 (genotype PAN)	Haplo rs6275 0.038 TDT ns U.S., U.K., and Germany
	(30)	ANr (108) AN purging (88) Controls (98)	C10620T (rs1800497)	0.045 (genotype PAN)	Haplo rs6275 0.021 (RAN); TDT ns U.S., U.K., and Germany
Dopamine D4 receptor (11p15.5)	(30)	AN (202 trios, including 111 ANr and 67 AN binge-purging) Controls (418 families, 542 daughters)	C(521)T (rs1800955)	0.009 for TDT	LRS Haplo C-521T & C-616G & A-809G & 120 bp tandem repeat p=0.0001; C-521T & A-809G & exon III & 120 bp tandem repeat p=0.007.
Neuropeptide and feeding regulation					
Opioid receptor delta-1 OPRD1 (1p35)	(20)	AN (196) Controls (98)	T8214C (rs536706)	0.045	OR 1.46, TDT NS Germany, U.K., and U.S.
		AN (196) Controls (98)	G23340A (rs760589)	0.046	OR 0.68, TDT NS Germany, U.K., and U.S.
		AN (196) Controls (98)	A47821G (rs204081)	0.01 0.03 (genotype)	OR 0.61, TDT 0.06 Germany, U.K., and U.S.
Preproghrelin gene (3p26-25)	(34)	AN r (131) AN binge-purging (97) BN purging type (108) Controls (300)	Leu72Met (408 C>A) (rs696217)	0.0002 (geno) 0.0410 (allele) for BN purging type/controls	

Gene	Reference	Phenotype (N)	Polymorphism*	p ^a value	Note
		ANr (131) AN binge-purging (97) BN purging type (108) Controls (300)	Leu72Met (3056 T>C) (rs2073356)	0.006 (geno) 0.0035 (allele) for BN purging type/controls	Leu72Met (408 C>A) and 3056 T>C Haplo in BN patients 0.0059, OR =1.71).
Other candidate genes					
Brain-derived neurotrophic factor BDNF (11p13-14)	(40)	AN unclassified (98) ANr (347) AN binge purging (308) BN (389) Controls (510)	Val-66-Met (rs6265)	0.0008 (AN versus C; genotype) 0.003 (ANr versus C; genotype) 0.012 (AN binge purging versus C; genotype) <0.001 (BN versus C; genotype)	OR AN 1.37 (Met-allele) OR ANr 1.43 (Met-allele) OR AN binge purging 1.29 (Met-allele) OR BN 1.59 (Met-allele) France, Germany, Italy, Spain, and U.K.
	(41)	ANr (219) AN binge purging (140)	Val-66-Met (rs6265)	0.019 (ANr versus C; HRR)	HRR and TDT Austria, France, Germany, Italy, Slovenia, Spain, UK

p^a-Values are reported for the allele-wise association of the polymorphism, unless stated otherwise.

Abbreviations: AN, anorexia nervosa; ANr, restricting anorexia nervosa; 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, OR, odds ratio; NS, non significant; TDT, transmission disequilibrium test; HRR, haplotype relative risk; LRS, likelihood ratio statistic

* SNP number and id as given either by HCVBASE at <http://hgvsbase.cgb.ki.se/> or dbSNP at <http://www.ncbi.nlm.nih.gov/SNP>