Etiology of Anorexia Nervosa: The Interplay Between Genetics and Environment

Michelle Pillepich

The University of North Carolina at Chapel Hill

Gillings School of Global Public Health

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Introduction

Anorexia nervosa is just one of many eating disorders that exist and can cause significant hardship and damage in patients who suffer from the disorder. Treatment of eating disorders is often lengthy and complex, and part of the difficulty in reaching recovery is the variation in etiology of disease. While no single event or trait is known to cause an eating disorder, current literature suggests that genetics likely play a significant role in the development of anorexia nervosa. Anorexia nervosa (hereon abbreviated as AN) is defined as the “persistent restriction of energy intake relative to requirements leading to significantly low body weight”\(^1\). Another part of the diagnostic criteria as defined by the DSM-5 is an “intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight”\(^2\). A third piece of the diagnostic puzzle includes the patient’s perception of his or her weight. The patient will experience weight in a disturbed way and weight has an increased influence on self-evaluation. A patient could also neglect any recognition of the seriousness of a dangerously low weight\(^2\). Two subtypes of AN are defined: ANR is the restricting subtype in which patients restrict their caloric intake without any binging or purging behavior, and the second subtype is ANBP in which a patient will engage in binge and purge behaviors\(^1\). When looking at both AN types as well as all other eating disorders, the prevalence is 5% in Western countries\(^3,4\). The lifetime prevalence of anorexia nervosa specifically is 1.20% for females and 0.29% for males\(^3,5\). While the prevalence of the disorder in males is less than that in females, there is a higher lifetime risk of developing anorexia nervosa
within a family in which a male has been diagnosed with the disorder. Anorexia nervosa has the highest mortality rate of all psychiatric disorders with a 5% mortality rate per decade and 0.56% per year. Aside from the serious consequence of death, AN is also associated with high rates of both medical complications and psychiatric comorbidities which will be discussed later. First degree relatives of someone with AN have a tenfold greater risk of developing AN during their lifetime than do those with no relatives who have been diagnosed with AN. Relatives of an individual with AN also have a higher risk of developing any eating disorder, including those other than AN. Despite the awareness of these risk factors and the risk of death from the disorder, there has been no well replicated evidence of effective psychological or pharmacologic treatment. This paper will explore the possible genetic causes of AN, how environment plays into one’s genetics to influence development of the disorder, and how these findings can influence the future of the field of eating disorder treatment.

**Study Designs**

Three main types of studies have been conducted thus far to analyze possible genetic underpinnings of the disorder. These types include family studies, twin studies, and genome-wide association studies (abbreviated as GWAS). The methodology of a family study is that it “compares the prevalence of a trait of interest in family members of individuals with the trait of interest to family members of those without the trait of interest”. In the case of AN, the prevalence of this disorder would be studied in families that include a family member who has been diagnosed with AN to the prevalence of AN in families in which no member has been diagnosed with AN. These studies have determined that AN does aggregate in families.
Heritability estimates that have been replicated range from 48-74%, indicating that about half to three quarters of individual variability in AN development is genetic and can be passed down in families.

Twin studies seek to observe the similarities and differences between twins who have the diagnosis of interest. In twin studies, “correlations between monozygotic and dizygotic twins for a trait of interest are compared to determine the extent to which variation in the trait is due to genetic and environmental factors.” It is assumed that monozygotic twins share 100% of their genetic makeup, and dizygotic twins share 50% of their genes. Following this logic, if a trait is twice as strong in monozygotic twins than it is in dizygotic twins, this would prove that genetics are implicated in the development of that trait. Twin studies are limited by the availability of subjects since twins with AN are not as abundant as non-twins with AN in the general population. It is also difficult to do twin studies in males given the low prevalence of AN among males.

GWAS, genome-wide association studies, are a strong option for looking at genetic links. In this study design, individuals that have a certain trait are compared with those who lack the trait of interest. The comparison is done on 300,000 to 1,000,000 genetic markers across the genome. The GWAS studies are considered the best option of a study because of this method. These studies are able to look at millions of genetic loci in many individuals to gather a robust amount of information.
Current Findings

The three types of studies mentioned above have led to various findings and revelations about the etiology and nature of anorexia nervosa. The disorder is polygenic, psychiatric, and metabolic. Polygenic indicates that many genes with small effects contribute to the overall development of the disorder. Table 1 identifies major genes, their functions, and how a change in these genes can contribute to the development of AN. Genetic correlations have also proven that AN is a psychiatric disorder as well as a metabolic one, and it affects both the mind and the body. A separate GWAS study found a significant signal for AN that was also linked to Type I diabetes and other autoimmune conditions, showing that risk for autoimmune issue and AN might be linked.

Serotonin and dopamine, two neurotransmitters, are critical pieces of AN development. Serotonin is involved in appetite regulation and behavior. Certain features of AN, which will be later discussed in this paper, have a proven link with serotonin. Perfectionism, obsessionality, and rigidity are serotonin related traits linked with AN. SSRIs, drugs that block the reuptake of serotonin in order to increase the circulating level, are often part of AN treatment. The HTR2A, 5-HTTLPR, and ESSRA genes are all related to serotonin (see Table 1) and, when altered, affect the neurotransmitter in a way that can lead to AN. Dopamine is tied to AN as well because increased dopaminergic activity can lead to food aversion, weight loss, hyperactivity, menstrual dysfunction, distorted body image, and obsessive-compulsive behavior and all of these traits are potential traits of AN. The D2 and D4 dopamine receptor genes have polymorphisms that can genetically contribute to AN development.
Table 1. Relevant genes in the development of anorexia nervosa

<table>
<thead>
<tr>
<th>Gene</th>
<th>Function</th>
<th>Changes in gene that increase risk of AN</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTR2A gene</td>
<td>Encodes for a receptor of serotonin(^8)</td>
<td>A allele of the (-1438G/A) polymorphism is more common in individuals with AN</td>
</tr>
<tr>
<td>5-HTTLPR</td>
<td>Codes for serotonin transporter</td>
<td>Deletion or insertion into this gene creates long and short alleles, short allele is associated with AN</td>
</tr>
<tr>
<td>EBF1</td>
<td>Protein coding gene</td>
<td>Inactivation of the gene causes decreased leptin, consistent with low leptin in AN</td>
</tr>
<tr>
<td>ESRRA</td>
<td>Induce expression of monoamine oxidase A and B</td>
<td>Plays a role in metabolism of monoamine neurotransmitters (ex. serotonin and dopamine)</td>
</tr>
<tr>
<td>HDAC4</td>
<td>Protein coding gene</td>
<td>Mediated by estrogen, could explain why AN is more common in females</td>
</tr>
</tbody>
</table>

**Linkage disequilibrium score regression and cross trait analysis**

There are methods available to test the genetic overlap between disorders, and two of the possible testing methods have been applied to AN\(^5\). One of these methods is cross trait analysis. Cross trait analysis studies genetic variations in a GWAS. This method of study looks at certain variations and determines whether variations that lead to the development of one phenotype are also associated with a second phenotype. The association is determined based on a significant threshold that is pre-determined such as choosing a certain number of the most significant single nucleotide polymorphisms (SNPs)\(^5\).
A second method of overlap identification that has been applied to AN is linkage disequilibrium score regression (LDSC). Linkage disequilibrium is a method that uses the summary statistics from a GWAS and analyzes them in order to make sure that confounding does not increase the number of false positives. The LDSC is a statistical method that is used to determine the genetic correlation between different occurring phenotypes. Since environmental effects are shared when using the LDSC method, it is unlikely to be affected by confounding. An LDSC uses summary statistics from a GWAS for the cases and controls and it is not biased by sample overlap, making it a good method to use for studying correlations.

LDSC has led to findings related to AN. Genetic changes that predispose someone to schizophrenia also increases that individual’s risk for AN. Having genetic variants that predispose someone to a higher than normal BMI decreases the risk of developing AN. In 2017, the largest LDSC was done and it concluded that there is positive genetic correlation with the following traits or conditions and AN: neuroticism, schizophrenia, educational attainment, cross disorder psychiatric risk, and HDL cholesterol.

**Traits that increase risk**

As discussed above, certain conditions are likely to overlap with AN. Additionally, various traits have been identified as traits that can increase an individual’s risk of developing AN. Some of the traits that predispose someone to AN are personality and behavior related. These traits are as follows:

- Perfectionism
- Negative self-evaluation
Obsessive compulsive

Neuroticism

Negative emotionality

Harm avoidance

Low self-directedness

Low cooperativeness

Neuroticism was found in multiple sources to be a risk factor for developing AN.

Neuroticism is defined as “a broad personality trait dimension representing the degree to which a person experiences the world as distressing, threatening, and unsafe”\(^{11}\). Individuals who are neurotic can range from emotionally stable to emotional chaos, and those who are highly neurotic change emotions very frequently. Neuroticism itself is a genetic trait with heritability estimates ranging from 40-60%, and this indicates that risk of AN is genetic since these traits of neuroticism contribute to risk of AN and can run in families\(^{11}\).

Other factors that contribute to AN are based on socioeconomic description of an individual including his or her education level and age. Young people and those with a high education level, especially a college education, are at a higher risk for AN than those without these characteristics\(^{3,6}\). Other psychiatric disorders can also predispose someone to development of AN. Those who do develop the eating disorder are more likely to have major depressive disorder, generalized anxiety disorder, or features of avoidant personality disorder\(^{3,5}\). Physically, BMI correlates with AN. Those who suffer from AN were found to have a lower BMI than those who do not, even when controlling for current AN. AN patients are likely to have a lower BMI than those who do not have the diagnosis even after weight
restoration and recovery. This low weight contributes to a protective effect of AN against becoming overweight. The mechanism of this protection is unclear in the literature, but it is suspected that low level symptoms of AN continue even after treatment and recovery. A mild level of caloric restriction and increased exercise can contribute to maintenance of a low weight\(^3\). A second hypothesis for the return to a low weight after recovery is a genetically low set point weight that could be common in AN. It is highly likely that a low set point weight is genetic considering the negative correlations between high weight and AN. A study found that there is a negative correlation between AN and high weight related phenotypes. A high BMI and hip circumference, as well as a BMI in the normal and overweight ranges, all negatively correlate with risk for AN\(^6\).

**Bulik study and Clarke study**

Two particular studies led to conclusions on heritability estimates of AN and genetic differences that change perception of weight and shape. A study led by Dr. Cynthia Bulik was conducted using the largest population-based registry of twin births in the world. The Swedish twin registry was the source of subjects for a large twin study on AN. The study was conducted over the course of 4 years and ended in 2004. In this study, a diagnosis of anorexia nervosa was defined as: a hospital discharge record with the diagnosis of AN, a diagnosis based off of the screening of twins for the disorder, or the national cause of death registry with AN listed as a diagnosis. Three different variations of AN were defined. All source AN is a form of the disorder in which full DSM IV criteria were met based on an interview, the registry discharge had a diagnosis of AN, or the death certificate had the AN diagnosis. Narrow DSM IV AN is
defined as a patient meeting full DSM IV diagnostic criteria via interview, and Broad DSM IV AN is defined as a patient meeting full DSM IV diagnostic criteria with the exception of amenorrhea since it has been proven an unreliable diagnostic criterion. In this study, the heritability of narrow and broad AN respectively were found to be 0.56 and 0.31\(^3\). Heritability can range from 0.0 to 1.0, and for most human behavior the estimates are usually between 0.30 and 0.60\(^1\). An estimate close to zero would indicate that all, or almost all, of the variation in a given trait among individuals is due to environmental influences and there is little genetic influence. Some examples of traits with a heritability of zero (those that are not at all tied to genes) are language spoken, religion, and political affiliation\(^\text{13}\). The values from this study indicate that 31-56\% of individual differences observed in AN are due to genetic differences among the individuals\(^3\). What heritability does not tell us is the proportion of a given trait that is determined by genetics; it does not indicate that 31\% of AN symptoms are genetic. Rather, the heritability value speaks to individual variance and how the differences in the trait among the population are tied to genetic differences\(^\text{12}\).

Another study of interest looked at brain function via fMRI tests to observe reactions to images based on the genetic variations of the individuals studied. This study suggests that AN could be related to an alteration in reward and emotional processing\(^1\). During the study, subjects underwent fMRI testing. A functional MRI is a technique that maps brain activity while a subject alternates between a task and a control state. In this case, the task was looking at images of naked female bodies and the fMRI mapped brain activity during the task to look at the response to bodies of different sizes. Participants in the study were instructed to rate on a given scale how they would feel if they had the same body shape as the person portrayed in the
image\(^1\). Before participating in the fMRI test, subjects underwent genetic testing via a saliva sample. The sample was tested for presence of the Val66Met polymorphism. AN patients who did have the polymorphism (those who carried Met rather than a Val homozygote) had a higher frequency of skin conductance response (SCR) when visually processing images of underweight bodies than those without the polymorphism\(^1\). The skin conductance response is a phenomenon that causes skin to become a better conductor of electricity for a moment while an external or internal stimulus is arousing. This is how reactions to the images were measured in study subjects. Since the group of AN patients with the polymorphism had a higher SCR when viewing underweight images, they were more mentally stimulated in a positive way by these underweight bodies, indicating positive reinforcement of this appearance.

A specific variant of the polymorphism observed in this study, the rs6265 variant of Val66Met, is associated with higher secretions of BDNF (brain derived neurotrophic factor-a neurophin that is necessary for the development and survival of neurons\(^1\)) and altered levels of BDNF are associated with susceptibility to EDs\(^1\). Animal models have also shown that BDNF suppresses appetite and can lead to weight loss\(^4\). These changes can also be implicated in ED development, especially AN. Overall, the study found that there was a higher positive response when processing underweight stimuli in patients vs. controls and the overall heritability estimate of AN from this study was 0.7\(^1\).
Limitations of Current Research

The studies that have been conducted thus far on the genetic causes of anorexia nervosa largely suffer from similar limitations. A common criticism is that the studies have a small sample size. Difficulty increasing sample sizes is problematic because of the low prevalence of the disorder. Twin studies, as discussed earlier, are a popular method used for studying the genetics of AN, but twins with the disorder can be hard to come by. Twin studies have also only been done in females since AN is not as prevalent in males as it is in females\(^5\). Due to small sample sizes, the studies that have been conducted have low statistical power. With low power, there is increased chance of error in the studies. rGE studies (gene-environment correlation studies) have not yet been done on AN, and this would be a beneficial analysis of the disorder. These types of studies look at the outcome of a subject with a genetic predisposition for AN entering an environment that puts them at a higher risk of developing AN such as a weight focused sport\(^1\). This type of study is crucial for advancing understanding of AN’s etiology since it seems to be a combination of genetic and environmental causes. Other limitations of current studies include unclear changes in prevalence. The Bulik study showed an increased prevalence of AN as compared to prior populations, but the increase in prevalence could be due to increases in diagnosis. Many cases likely remain undiagnosed so the prevalence is not truly known. Some studies have come up with mixed results and replication is needed to clarify findings\(^4\). In addition to replication, diagnostic criteria need to be solidified. Genetic associations can be difficult to conclude because of the diagnostic criteria. Clearer criteria would lead to a more homogeneous sample to study\(^5\).
The Role of Environmental Factors

Dr. Bulik has been quoted saying your “genes load the gun, environment pulls the trigger” in reference to development of AN. Genetic causes have been discussed above, and many of these studies also touched on environmental contributors to the disease. The following environmental factors increase one’s risk of developing AN:

- Childhood trauma
- Sexual abuse
- Overprotective family dynamic
- Intrusive family
- Controlling family
- Emotionally unresponsive parents
- Preoccupation with weight within the family
- Athletic competition

It is even suggested that environmental exposures, if strong enough, can cause epigenetic alterations such as hypermethylation that are associated with AN. When anyone with a genetic predisposition to AN is put in an environmental situation such as those listed above, the chance of developing AN becomes higher. That is further evidence that environmental factors do play a strong role in AN development.

What needs to be done

At this point, more research is needed to determine clear causes of AN. New studies need increased sample sizes to increase the statistical power of the studies. In order to
increase sample size, inclusion of heterogeneous cases may be necessary. It will also be helpful in future studies to look at endophenotypes. Endophenotypes are intermediate phenotypes, characteristics that are not easily observed at a surface level but can make someone more susceptible to a particular condition. Studying endophenotypes can be a better way to detect genetic risk because endophenotypes are related to fewer genes than are specific phenotypes. It remains uncertain whether or not information about genetic risk should be communicated with patients who are diagnosed with AN. Advocates for this communication believe that it could reduce stigma surrounding the disorder, but opponents say that it could reduce recovery efforts if patients know that they are at a high risk biologically.

**Prevention**

Given the current findings about genetic causes of anorexia nervosa, prevention of this disorder should be a high priority in the field of nutrition. Since it is impossible to know based on looking at someone whether or not they are at a genetic risk of developing AN, nutrition educators should be communicating with all people as if they are at risk. There is no well documented effective treatment for AN, and that makes prevention even more vital. Environment can, in some cases, be altered to protect against development of AN, and of eating disorders in general, and positive nutrition communication that does not focus on weight, given the fact that preoccupation with weight in a family community can heighten risk, will help to decrease risk even if just by a small percent.
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