

## Psychology

# The genetic metabolic component of anorexia nervosa

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### ABSTRACT

*Anorexia nervosa is a deadly disorder marked by extremely low body weight, a fear of weight gain, and often an inability to appreciate the severity of the condition. Our results suggest that anorexia nervosa ought to be considered as a metabo-psychiatric condition prompted by both psychological and metabolic factors.*



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Anorexia nervosa is the deadliest psychiatric disorder and is notoriously challenging to treat. Currently, no medications are effective in its treatment, in part because we do not have a clear understanding of its biological basis. Despite myriad misconceptions, anorexia nervosa does not discriminate and can occur at any age, in all sexes, genders, racial and ethnic backgrounds, and socioeconomic strata. Like many other psychiatric and somatic illnesses, anorexia nervosa runs in families, and genes play a role. Still, we do not yet know which genes may be responsible and how they act.

We conducted a genome-wide association study by collecting DNA samples from 16,992 individuals with anorexia nervosa and 55,525 controls (people without the illness) from 17 different countries. We then examined millions of markers across their genomes to identify areas that differed between those with anorexia and controls. Those areas point us to the regions in which risk genes for anorexia nervosa may lie. Since we need tens of thousands of individuals, it takes a (global) village to conduct a genome-wide association study. Over a hundred clinicians and researchers contributed DNA samples from their clinical or research practices!

By examining DNA samples from ~70,000 individuals, we successfully identified eight regions in the human genome that may be associated with anorexia nervosa risk. Many of these regions contain more than one gene (in some instances, many genes). We expect that there will likely be hundreds of genes involved with anorexia risk. So, even though this sounds like a large study, we will need many more individuals before we can begin to narrow down specific genes and biological pathways that are implicated in anorexia nervosa. But this study showed us that our methods are working and encourage us to conduct even larger studies to understand the underlying genetic biology of this devastating disorder.

A second important part of the study explored genetic correlations. This exploration helps us understand where the anorexia nervosa “genetic puzzle piece” fits in relation to the much larger “genetic puzzle” of human diseases. First, we found that the genetic basis of anorexia nervosa overlaps with other psychiatric disorders such as obsessive-compulsive disorder, depression, and anxiety. This result explains on a genetic level why we frequently see these illnesses co-occurring with anorexia nervosa. Second, we observed very interesting genetic correlations involving anorexia nervosa and metabolic and anthropometric (or body measurement) traits. For instance, anorexia nervosa may share a genetic basis with lower body weight, lower levels of unfavorable metabolic markers such as fasting blood sugar and bad cholesterol, higher levels of favorable metabolic markers such as good cholesterol, and well as increased levels of physical activity. These findings suggest that there could be a crucial metabolic component to anorexia nervosa in addition to its psychiatric roots. We have much more work to do to understand the biology of the illness.

Still, now we know to look not only at pathways that influence psychiatric factors, but also metabolic ones.

So what does this mean practically for patients and families who are suffering today? It's essential to keep in mind that the goal of a genome-wide association study is to understand the underlying biology. There are features of anorexia nervosa that we simply do not understand. How these individuals lose and maintain such low weights in an environment where weight gain is the norm? Why, even after hospital-based weight restoration, their bodies tend to drop weight rapidly soon after discharge? Why they experience periods of hypermetabolism during the treatment when their bodies just burn through calories? Clinically, identifying this metabolic component may underscore the importance of complete weight restoration and giving the body and metabolism an opportunity to equilibrate and the new higher weight, to prevent relapse. We contend that it is important to attend to both psychiatric and metabolic factors as we strive to improve our ability to treat this illness.

As we progress in this field and increase our sample size, we hope to be able to refine our observations to fully understand the metabolic contribution to this illness. If we are fortunate in our outcomes, biological pathways we identify may point toward targets for which we could develop new medications to assist in the treatment of this disorder. Only 30% of individuals with anorexia nervosa fully recover. We hope that future iterations of this work will help us massively improve that number and ultimately eliminate mortality from anorexia nervosa.