



National Eating Disorders Association

The First Genome Wide Association Study (GWAS) of the Genetics of Anorexia Nervosa

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Although it now well known that anorexia nervosa (AN) and bulimia nervosa (BN) are highly heritable, much work remains to be done on identifying the actual genes. This is a difficult task because behavior is highly complex, and thus it is likely that many genes contribute to AN and BN. Fortunately, we are now entering an era where technology is making it possible to assess the thousands of genes and billions of molecules that make up these genes. Luciana Price had the foresight 20 years ago to recognize that genetics made an important contribution to causing eating disorders. Thus she established and supported the Price Foundation Collaborative Genetic Studies. This collaboration has involved more than 12 different institutes and more than 30 collaborators in the US, Canada, Germany, England, and Italy. It has collected DNA samples on more than 3500 individuals with ED, their families, and comparison subjects. I have been honored to be the Principal Investigator on this study. This month, the PF group, in collaboration with scientists at The Children's Hospital of Philadelphia published the first genome-wide association study in *Molecular Psychiatry* on Nov. 16. Genome-wide association studies (GWAS) search for about a half million single-nucleotide polymorphisms, or SNPs—common gene variants that typically act as pointers to a gene region with a small effect on raising disease risk. The study team also performed a parallel search for copy number variations (CNVs), rarer variants that usually have a stronger impact on disease risk. The sample size was the largest used in an AN gene study—DNA came from 1,003 AN patients, all but 24 of them female, from various sources, having an average age of 27 years. For comparison, there was a control group of 3,733 pediatric subjects (average age of 13), drawn from the Children's Hospital pediatric network.

This study identified both common and rare gene variants active in neuronal signaling and in shaping interconnections among brain cells. The GWAS was done by Hakon Hakonarson, M.D., Ph.D., and his team at the Center for Applied Genomics at The Children's Hospital of Philadelphia. This study confirmed the results of previous studies of anorexia nervosa. That is an opioid gene and a serotonin gene confer risk. The study did not detect other obvious candidate genes, but it did generate a list of other genes that are being analyzed in follow-up studies. One SNP is between the cadherin genes, CHD10 and CHD9, which code for neuronal cell-adhesion molecules—proteins that influence how neurons communicate with each other in the brain and have been associated with autism spectrum disorders. The current anorexia study also investigated CNVs—deletions or duplications of DNA sequences. Previous research by Hakonarson and others has shown that CNVs play a significant role in other neuropsychiatric disorders, such as schizophrenia, bipolar disorder and autism. The current study suggests that CNVs may play a less important role in anorexia than



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they do in schizophrenia and autism. Nonetheless, the study identified several rare CNVs that occurred only in AN cases, including a deletion of DNA on a region of chromosome 13.

"Our study suggests that both common SNPs and rare CNVs contribute to the pathogenesis of anorexia nervosa," said Hakonarson. "The gene variants we discovered are worthy of further analysis in independent cohorts. However, the relatively modest number of anorexia cases explained by these results we found suggests that many other candidate genes remain unknown. Future studies will require much larger sample sizes to detect additional gene variants involved in this complex disorder."

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