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Gene links to anorexia found

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Scientists at The Children's Hospital of Philadelphia have identified both common and rare gene variants associated with the eating disorder anorexia nervosa. In the largest genetic study of this psychiatric disorder, the researchers found intriguing clues to genes they are subjecting to further investigation, including genes active in neuronal signaling and in shaping interconnections among brain cells.

Anorexia nervosa (AN) affects an estimated 9 in 1000 women in the United States. Patients have food refusal, weight loss, an irrational fear of weight gain even when emaciated, and distorted self-image of body weight and shape.

Women are affected 10 times more frequently than men, with the disorder nearly always beginning during adolescence. AN has the highest mortality rate of all psychiatric disorders, and successful treatment is challenging.

Twin studies and other family studies have suggested that AN is strongly heritable. "However, despite various genetic studies that identified a handful of candidate genes associated with AN, the genetic architecture underlying susceptibility to AN has been largely unknown," said study leader Hakon Hakonarson, M.D., Ph.D., director of the Center for Applied Genomics at The Children's Hospital of Philadelphia. The research appeared online in Molecular Psychiatry on Nov. 16.

"This is the first genome-wide association study on a large anorexia cohort, as well as the first study of copy number variations in the

disorder," said Hakonarson. Genome-wide association studies (GWAS) search for 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.

"We confirmed results of previous studies of anorexia nervosa: SNPs in the gene OPRD1 and near the gene HTR1D confer risk for the disease," said Hakonarson. "We did not detect other obvious candidate genes, but we did generate a list of other genes that we are analyzing in follow-up studies." One SNP is between the CHD10 and CHD9 genes, a region that Hakonarson associated with autism spectrum disorders in 2009. Called cadherin genes, CHD10 and CHD9 code for neuronal cell-adhesion molecules—proteins that influence how neurons communicate with each other in the brain.

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 they do in schizophrenia and autism. Nonetheless, the researchers 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."

More information: K. Wang et al, "A Genome-wide Association Study on Common SNPs and Rare CNVs in Anorexia Nervosa," *Molecular Psychiatry*, published online Nov. 16, 2010. doi:10.1038/mp.2010.107

Provided by Children's Hospital of Philadelphia