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# First GWAS studies of obsessive-compulsive disorder and Tourette syndrome published

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Two papers that will appear in the journal *Molecular Psychiatry*, both receiving advance online release, may help identify gene variants that contribute to the risks of developing obsessive-compulsive disorder (OCD) or Tourette syndrome (TS). Both multi-institutional studies were led by Massachusetts General Hospital (MGH) investigators, and both are the first genome-wide association studies (GWAS) in the largest groups of individuals affected by the conditions.

"Previous studies of these disorders have demonstrated that both TS and OCD are strongly heritable and may have shared genetic risk factors, but identification of specific genes has been a huge challenge," says Jeremiah Scharf, MD, PhD, of the Psychiatric and Neurodevelopmental Genetics Unit (PNGU) in the MGH Departments of Psychiatry and Neurology, a co-lead author of both papers and co-chair of the Tourette Syndrome Association International Consortium for Genetics. "These new studies represent major steps towards understanding the underlying genetic architecture of these disorders."

An anxiety disorder characterized by obsessions and compulsions that disrupt patients' lives, obsessive-compulsive disorder (OCD) is the fourth most common psychiatric illness. Tourette syndrome, a chronic disorder characterized by motor and vocal tics, usually begins in childhood and is often accompanied by conditions like OCD or attention-deficit hyperactivity disorder. Both conditions have a high risk of recurrence in close relatives of affected individuals, but previous studies that compared affected and unaffected individuals were not large enough

to identify specific genes or areas of the genome that contribute to risk.

Since many gene variants probably contribute to risk for both conditions, the research teams undertook GWAS investigations, which analyze hundreds of thousands of gene variants called SNPs (single-nucleotide polymorphisms) in thousands of individuals with and without the condition of interest. The International OCD Foundation Genetic Collaborative, consisting of more than 20 research groups in nine countries, analyzed almost 480,000 SNPs in 1,465 individuals with OCD, more than 5,500 controls and from 400 trio samples consisting of an OCD patient and both parents. The Tourette Syndrome Association International Consortium for Genetics and the TS GWAS Consortium, representing 22 groups across seven countries, analyzed 484,000 SNPs across almost 1,500 cases and more than 5,200 controls.

The OCD study – led by Evelyn Stewart, MD, of the MGH-PNGU, who is now based at the University of British Columbia, and David Pauls, PhD, MGH-PNGU – identified possible associations close to a gene called BTBD3, which is closely related to a gene that may be involved in Tourette Syndrome, and within DLGAP1, a close relative of a gene that produces OCD-like symptoms in mice if it is deleted. The Tourette study was led by Scharf and Pauls and found evidence of a possible association with a gene called COL27A1, which may be expressed in the cerebellum during development, and with variants that help regulate gene expression in the frontal cortex.

None of these or other identified SNPs reached the high threshold of genome-wide significance, which would indicate that the associations represented true risk factors, and the authors stress that additional, larger studies are required. "Although GWAS analysis allows much more comprehensive examination of the entire genome than do studies focused on particular families or candidate genes, these two studies are still underpowered and should be interpreted with caution," says Pauls, a

co-senior author of both papers. "The current results are interesting and provide us with a starting point for analyzing future studies that must be done to replicate and extend these findings."

Scharf adds that the next steps should include testing the SNPs identified by these studies in other groups of patients and controls, analyzing both study groups together to identify genes that contribute to the risk of both disorders, and expanding international collaborations to increase the size and power of patient samples for both OCD and TS. "If future studies confirm that some of these variants do contribute to risk – either directly or by altering the function of other risk genes – that would suggest both novel disease mechanisms and might give us new treatment targets," he says.

Provided by Massachusetts General Hospital

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