

New Genetic Findings Add To Understanding Of Obsessive-compulsive Disorder ScienceDaily (Jul. 26, 2006) —

Obsessive-compulsive disorder tends to run in families, causing members of several generations to experience severe anxiety and disturbing thoughts that they ease by repeating certain behaviors. In fact, close relatives of people with OCD are up to nine times more likely to develop OCD themselves.

Now, new research is shedding new light on one of the genetic factors that may contribute to that pattern. And while no one gene "causes" OCD, the research is helping scientists confirm the importance of a particular gene that has been suspected to play a major role in OCD's development.

In two papers published simultaneously in the Archives of General Psychiatry, researchers from the University of Michigan, the University of Illinois at Chicago, the University of Chicago and the University of Toronto report finding an association between OCD patients and a glutamate transporter gene called SLC1A1.

The gene encodes a protein called EAAC1 that regulates the flow of a substance called glutamate in and out of brain cells. So, variations in the gene might lead to alterations in that flow, perhaps putting a person at increased risk of developing OCD.

The new findings are especially important not only because of the simultaneous discoveries reported in the papers, but also because of previous studies that show a functional link between glutamate and OCD. Brain imaging and spinal fluid studies have shown differences in the glutamate system between OCD patients and healthy volunteers, including in areas of the brain where the EAAC1 protein is most common.

"Taken together, these findings suggest that SLC1A1 is a strong candidate gene for OCD, which if confirmed could lead to improvements in understanding and treating this condition, and screening those with an elevated risk," says Gregory Hanna, M.D., senior author on one of the papers and an associate professor of psychiatry at the U-M Medical School. "It's possible that altered glutamate activity in some brain regions may contribute to the obsessions and compulsions that are the hallmark of OCD."

Hanna and colleague Edwin Cook, Jr., M.D., of UIC together lead a major study of OCD genetics involving patients and their families who are willing to donate DNA samples and be interviewed by researchers. The study is still seeking OCD patients and their parents to participate in further research on the genetics of OCD.

While the new findings are exciting because they strengthen the evidence for glutamate's role in OCD vulnerability, the researchers caution that more work needs to be done before their discovery has any impact on OCD treatment.

Four years ago, the U-M and UIC team published a genome scan from young OCD patients and their parents that found signs of OCD-related genetic variations on chromosome 9, in the area of SLC1A1.

Since that time, they have been zeroing in on the gene and its nearby stretches of DNA, using analyses of single nucleotide polymorphisms that look at specific differences between individuals within the gene. At the same time, the Toronto group has been focusing on that same area in studies involving adults and children with OCD and their close relatives.

The new U-M, UC and UIC paper is based on genetic samples from 71 OCD patients (children and adults) and their parents. It finds a significant association between early-onset OCD and genetic variations at several sites on the SLC1A1 gene. A strong association at two of those sites was only seen in male early-onset OCD patients, which surprised the researchers but may make sense in light of the fact that early-onset OCD is more common in boys than in girls. As many as half of all OCD patients experience their first symptoms in childhood or adolescence.

The new U-T paper is based on data from 157 OCD patients and 319 of their first-degree relatives. It finds

linkages between OCD and three locations on the SLC1A1 gene.

In a commentary published in the same issue of the journal, two Yale University researchers call the new findings promising, and call for additional research. "These data add to a growing body of work that suggest that SLC1A1 is perhaps a primary candidate gene for OCD," they write.

Hanna notes that the finding of genetic vulnerabilities for OCD are important, but so is the understanding of how environmental factors -- including hormones and infections -- may play a role in the onset of the disorder.

He directs the U-M Child & Adolescent Psychiatry Division's Pediatric Anxiety and Tic Disorders Program, which treats young patients whose OCD may be related to an infection. That disorder, called PANDAS for Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections, causes both OCD and tics in patients.

As their research continues, Hanna and his colleagues hope to eventually conduct clinical trials of glutamate-targeting medications in OCD patients, and to collect more DNA and blood samples from patients and their families. They're also looking at other regions of the genome that might contain gene variations that are more common in people with OCD.

The U-M, UC and UIC study is funded by the National Institutes of Health, the Jean Young and Walden W. Shaw Foundation, the Harris Foundation, the Brain Research Foundation and the Obsessive Compulsive Foundation. The U-T study was funded by the Ontario Mental Health Foundation, the Canadian Institutes of Health, the National Alliance on Research in Schizophrenia and Depression and the Obsessive Compulsive Foundation.

In addition to Hanna, the U-M researchers on the paper are Daniel J. Fischer, MSW, Michelle Van Etten-Lee, Ph.D., and Joseph Himle, Ph.D.

Reference: Dickel et al, and Arnold et al, Archives of General Psychiatry, Vol 63, July 2006. pp 778-785 and pp 769-776. Commentary by Leckman and Kim, pp. 717-719.

Patients and families interested in learning more about OCD treatment and research at U-M may call 734-764-0250.

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