Gene discovery may hold key to better therapies for OCD

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In the first analysis of its kind, researchers at Columbia University Vagelos College of Physicians and Surgeons and several other institutions have linked distinct patterns of genetic mutations with

obsessive-compulsive disorder (OCD) in humans.

The work, published online June 28 in *Nature Neuroscience*, confirms the validity of targeting specific genes to develop new OCD treatments and points toward novel avenues for studying this often debilitating condition.

OCD, which affects 1% to 2% of the population, often runs in families and genes are known to play a large role in determining who develops the disease. However, the identity of many OCD genes remains unknown.

"Many neurological diseases are influenced by strongly acting mutations which can cause disease by themselves," says David Goldstein, Ph.D., director of the Institute for Genomic Medicine at Columbia and a senior author on the new paper. "These mutations are individually very rare but important to find because they can provide a starting point for the development of therapeutics that target precise underlying causes of disease."

Although strongly acting mutations have been hypothesized to exist in OCD, statistically reliable evidence has been difficult to obtain.

Most previous studies on the genetics of OCD have used a "candidate gene" approach, in which researchers focus on plausible genes that might be involved in pathogenesis and look for genetic signatures of risk. Although that approach has had some successes, it can lead to challenges in statistical interpretation and can miss unexpected genes. As a result, both funding agencies and the pharmaceutical industry increasingly focus on genome-wide analyses that can securely implicate genes in disease risk.

"The solution to the problem is to study all the genes in the genome at

the same time and ask whether any of them have significant evidence of influencing risk. That had not been done yet at scale in OCD," says Goldstein.

In collaboration with Gerald Nestadt, MBBCh, a psychiatrist at Johns Hopkins University with access to a cohort of OCD patients, Goldstein's team took this genome wide approach, which uses high-throughput sequencing and computational biology techniques to identify relevant genes anywhere in the genome.

The investigators looked at genes that encode protein using whole exome sequencing in more than 1,300 OCD patients and compared them to similarly large control groups. The multi-institution collaboration also included scientists from the University of North Carolina at Chapel Hill, the David Geffen School of Medicine in Los Angeles, Harvard Medical School, and SUNY Downstate Medical Center in Brooklyn.

The analysis showed a strong correlation between OCD and rare mutations, particularly in a gene called SLITRK5 that had been previously linked to OCD in candidate-gene studies.

Goldstein expects that the new data on SLITRK5 will encourage pharmaceutical companies and translational researchers to develop drugs that target this gene.

The study also identified a specific pattern of variation in other genes. "When you look at genes that do not tolerate variation in the human population, those are the genes most likely to cause disease, and with OCD, we see an overall increased burden of damaging mutations in those genes compared to controls," Goldstein says. "That's telling us that there are more OCD genes to be found and where to find them."

For patients suffering from OCD and their doctors, new treatments can't

come too soon. OCD causes uncontrollable, recurring thought patterns and behaviors that interfere with patients' daily lives.

"OCD is a disabling disorder that is twice as common as schizophrenia," says H. Blair Simpson, MD, Ph.D., professor of psychiatry at Columbia University Vagelos College of Physicians and Surgeons and director of the Center for OCD & Related Disorders at New York State Psychiatric Institute, who was not involved with the new study.

Two available treatments, serotonin reuptake inhibiting drugs and cognitive-behavioral therapy, are highly effective, Simpson adds, but only work on about half of patients. "Thus, these genetic findings are very exciting; they indicate that the promise of precision medicine could include OCD, ultimately transforming how we diagnose and treat this disorder."

The paper is titled "Exome sequencing in obsessive-compulsive disorder reveals a burden of rare damaging coding variants."

More information: Mathew Halvorsen et al, Exome sequencing in obsessive–compulsive disorder reveals a burden of rare damaging coding variants, *Nature Neuroscience* (2021). DOI: 10.1038/s41593-021-00876-8 , www.nature.com/articles/s41593-021-00876-8

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