Genetic variants associated with obsessive-compulsive disorder identified

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Repetitive hand-washing is a common OCD symptom. Credit: Lars Klintwall Malmqvist/public domain

(Medical Xpress)—An international team of researchers has found evidence of four genes that can be linked to obsessive-compulsive disorder (OCD). In their paper published in the journal *Nature Communications*, the group describes their approach to isolating genes linked to OCD and what they found as a result.

OCD is a psychiatric ailment. People who have it tend to compulsively repeat behaviors because their brain tells them something has not been adequately resolved—they experience an urge to resolve an issue such as checking to see if the stove has been turned off, or to ensure their hands have been adequately washed. There is no known cure for the condition, though recent studies have shown that in some cases, the use of drugs that boost serotonin levels can help. Prior research has also shown that it is likely that OCD is an inheritable condition. In this new effort, the researchers sought to bolster that theory by finding the genes likely to cause the disorder.

The research consisted of first obtaining genetic samples from 592 people diagnosed with OCD and 560 people who did not have it to use as a control. The group also included genetic samples from dogs who suffer from a canine form of the disorder.

With the samples in hand, the researchers focused on 600 specific genes possibly linked to OCD, and in some cases, to autism—many people with autism engage in repetitive behavior. After close scrutiny, the group isolated four genes that were different in people with OCD, which had previously been identified as playing a strong role in creating the brain circuitry involved in building links between the thalamus, striatum and cortex regions. This finding was deemed particularly noteworthy because the striatum plays a role in learning and also in conveying messages through the thalamus to the cortex. Researchers believe the cortex is where decisions are made. The researchers suggest the mutated genes could cause higher or lower than normal levels of serotonin, which in

turn could lead to disruption of information as it is interpreted by the brain, leading to false registering of the impact of a behavior.

More information: Hyun Ji Noh et al. Integrating evolutionary and regulatory information with a multispecies approach implicates genes and pathways in obsessive-compulsive disorder, *Nature Communications* (2017). DOI: 10.1038/s41467-017-00831-x

Abstract

Obsessive-compulsive disorder is a severe psychiatric disorder linked to abnormalities in glutamate signaling and the cortico-striatal circuit. We sequenced coding and regulatory elements for 608 genes potentially involved in obsessive-compulsive disorder in human, dog, and mouse. Using a new method that prioritizes likely functional variants, we compared 592 cases to 560 controls and found four strongly associated genes, validated in a larger cohort. NRXN1 and HTR2A are enriched for coding variants altering postsynaptic protein-binding domains. CTTNBP2 (synapse maintenance) and REEP3 (vesicle trafficking) are enriched for regulatory variants, of which at least six (35%) alter transcription factor-DNA binding in neuroblastoma cells. NRXN1 achieves genome-wide significance ($p = 6.37 \times 10{-}11$) when we include 33,370 population-matched controls. Our findings suggest synaptic adhesion as a key component in compulsive behaviors, and show that targeted sequencing plus functional annotation can identify potentially causative variants, even when genomic data are limited.