The researchers detected, for the first time, a statistically significant enrichment of larger-scale de novo alterations, called copy number variants (CNVs), in Tourette Disorder.

In the largest DNA sequencing study of Tourette disorder (TD) to date, UC San Francisco researchers and their collaborators have unearthed new data suggesting a potential role for disruptions in cell polarity in the development of this condition.
In their new study, published online September 25, 2018 [1], in *Cell Reports* the researchers focused on "de novo" mutations, or rare mutations that arise anew at conception, rather than being inherited from parents. They observed that these mutations tend to affect genes with a role in cell "polarity," which is the process by which cells differentiate "top" and "bottom." This is particularly important in the brain, where neurons must form with specialized information gathering and transmitting sides to function properly.

Jeremy Willsey, PhD [2]

"You might expect that mutations in these cell polarity genes would affect things like neurons getting to the right place in the brain, or forming the right connections, with the appropriate directionality," said Jeremy Willsey, PhD [3], an expert on psychiatric genetics in the UCSF Weill Institute for Neurosciences [4], a senior author on the paper. "Our group has already started experiments modeling the effect of mutations in these cell polarity genes during early brain development."

Such disruptions to neuronal wiring may eventually explain the uncontrollable chronic vocal and motor tics that mark TD. Although as many as one percent of children worldwide develop TD, the condition has been relatively neglected in studies compared to other child-onset psychiatric disorders, such as autism, intellectual disability, and epilepsy.

Referring to the relatively small number of studies on TD genetics, Matthew State, MD, PhD [5], Oberndorf Family Distinguished Professor and chair of the UCSF Department of Psychiatry [6], said, "Tourette disorder has tended to be marginalized in psychiatric research, but with the promise of these genetic findings and a major recent investment by the National Institute of Mental Health, we can deepen our understanding of TD and potentially use the new insights to develop improved treatments."

**Collaborative research powers new genetic insights**

State and Jay Tischfield, PhD, of Rutgers University, founded the Tourette International Collaborative Genetics (TIC Genetics) consortium in 2009 to collect, study and share genetic data from TD patients and their families across multiple US and international sites. Willsey now serves alongside them, and several of the senior authors of the new paper, on the executive board.
Collaboration was at the heart of the new study, too, with TIC Genetics joining forces with the Tourette Association of America International Consortium for Genetics (TAAICG), and the Tourette Syndrome Genetics Southern and Eastern Europe Initiative (TSGENESEE); the researchers also received samples from the Uppsala Tourette Cohort, based in Sweden.

This pooling of resources allowed researchers to amass genetic data from much larger samples of TD patients, and their unaffected parents, than would otherwise be possible. With this data in hand, the researchers conducted a powerful approach, known in genetics as trio analysis, in order to identify de novo mutations, by determining which mutations were present in patients but not in their parents. These are very rare events, occurring one or two times for every 100 million DNA base pairs sequenced.

De novo mutations arise spontaneously in a sperm or egg cell, or in a zygote soon after fertilization. Unlike inherited mutations, these de novo events are subject to natural selection over only a very short period of time, and mutations that have large effects are thus overrepresented or “enriched” among de novo mutations. De novo mutations have already been strongly linked to autism, epilepsy, and intellectual disability.

Last year, the TIC Genetics group found the same is true for TD [7], based on analysis of 511 trios (1,533 total samples). The new study expands on the 2017 study with 291 more trios (873 new samples), for a total of 802 trios (2,406 samples).

Matthew W. State, MD, PhD [8]

First author Sheng Wang, a graduate student in both the State and Willsey labs, and colleagues set about sequencing the exome – the protein-coding parts of the genome – in DNA samples from each person with TD, plus each of their parents. By focusing on the coding parts of the genomes, the researchers can easily identify mutations that disrupt the corresponding proteins encoded by these sequences.

The researchers then compared the exome sequences between parents and their affected child. This painstaking process identified 309 new de novo sequence mutations, or accidental genetic “typos” that alter a few “letters” of the DNA code.

First and foremost, the new independent sample of 291 trios allowed the authors to
independently confirm the 2017 results. Namely, that de novo mutations deemed to be damaging were present more often in individuals with TD than in unaffected control samples—a suspicious enrichment that suggests these variants directly contribute to the disorder.

It cannot be overstated that in psychiatric genetics it’s critical for replication to happen. It should not be taken for granted, Willsey said, acknowledging that some results that have not been replicated have stymied the field for years.

But in addition to replicating their earlier findings, the researchers arrived at several key new insights. First, de novo variants tend to be enriched in families without any history of TD, suggesting, as expected, that future studies should match the types of genetic analyses conducted with the type of families recruited.

They also observed some evidence for an enrichment of de novo variants in females affected with TD, as compared to males affected with TD. This indicates that females may be more resilient to developing TD. Similar findings have been observed in autism. Understanding the basis of this biological difference in susceptibility holds promise for developing new treatments. Finally, they identified a new, high-confidence risk gene, CELSR3, adding to the first high-confidence gene they identified in 2017, WWC1.

Findings broaden understanding beyond TD’s tics

Both of the proteins these genes encode have known roles in cell polarity. This inspired the team to look at the rest of the genes with de novo mutations in TD patients. Consulting a database of gene function, the others noted that 15 other cell polarity genes had damaging de novo mutations, almost three times as many as would be expected, which suggests that disruption of cell polarity during brain development may be a central biological mechanism in the development of TD.

When looking at all the genes hit by damaging de novo variants in TD, the researchers also found an overlap with genes implicated in obsessive-compulsive disorder (OCD), which suggests the biology of these conditions is intertwined. People with TD often also have OCD, yet when the researchers excluded these cases from their samples, the gene overlap remained. This suggests that the same genes can give rise to TD or OCD, and that pursuing the biology of these genes may offer insights on multiple disorders.

While tics are the defining feature of TD, there are many other symptoms that tend to go along with the disorder, like attention problems, learning difficulties, OCD, depression, and anxiety, State said. If we knew exactly what was going wrong and could target this more specifically, not only could we do a better job of decreasing tics, but we could potentially simultaneously address multiple symptoms that accompany TD, and that in many children are more debilitating than the tics themselves.

The researchers also detected, for the first time, a statistically significant enrichment of larger-scale de novo alterations, called copy number variants (CNVs), in TD. A role for CNVs, which are deletions or duplications of sections of DNA, in TD had been suspected from previous studies, but the enlarged sample in the new study allowed researchers to clearly establish the association for the first time.

The success of the TD collaboration spurred the National Institute of Mental Health to fund a
$10 million dollar grant earlier this year to help the research team pursue their findings. The award will go to seven U.S. and 14 international sites to enroll more than 1,000 parent?child trios (3,000 samples), genetically characterize them, and identify new genes. The researchers expect this will generate new biological insights and potentially opportunities for new and improved treatments.

Authors: First author Sheng Wang is a visiting graduate scholar from China Agricultural University and National Institute of Biological Sciences, in Beijing; co-senior author Jay Tischfield, PhD, is MacMillan Distinguished Professor and chair of the Department of Genetics at Rutgers University; the paper?s co-senior and co-corresponding authors are Willsey, assistant professor of psychiatry and member of UCSF?s Institute for Neurodegenerative Diseases; State, the Oberndorf Family Distinguished Professor and chair of UCSF?s Department of Psychiatry; and Peristera Paschou, PhD, associate professor of biological sciences at Purdue University. A complete list of authors, including members of the TAAICG and TSGENESEE, is available in the online version of the paper.

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Read the research paper

- **Cell Reports:** De novo sequence and copy number variants are strongly associated with Tourette disorder and implicate cell polarity in pathogenesis [1]

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