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Flip-Flopped Chromosome Reveals a First Clue to Tourette Syndrome

Researchers have identified the first gene mutation associated with Tourette syndrome - opening a new avenue for understanding the complex disorder that causes muscle and vocal tics.

Until now, causes of Tourette syndrome (TS), which afflicts as many as 1 in 100 people, have eluded researchers because the disease appears to be caused by subtle mutations in many genes.

The researchers published their findings in the October 14, 2005, issue of the journal *Science*. Matthew W. State of the Yale University School of Medicine was senior author of the paper. His research was supported by a Howard Hughes Medical Institute institutional award to Yale that was used to support early research by promising scientists at Yale.

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- **Richard P. Lifton**

Other co-authors at Yale included HHMI investigator Richard P. Lifton, and neurobiologists Nenad Sestan and Angeliki Louvi from the Yale Child Study Center. The Yale scientists collaborated with researchers from the University of California San Diego, Harvard Medical School, University of Missouri-Kansas City, University of Alabama at Birmingham, Johns Hopkins University School of Medicine and Cincinnati Children's Hospital Medical Center.

According to State, early theories suggesting that a single gene mutation causes TS have proven incorrect. "There has been an evolving hypothesis about Tourette syndrome being a much more complex disorder," State said. "I think there is general consensus at this point that there are likely to be multiple genes, likely interacting, and probably different sets of genes in different people, that contribute to TS." The notion of multiple genes is borne

out by the complex phenotype of the syndrome, which is often associated with obsessive-compulsive disorder, attention deficit hyperactivity disorder, or depression, said State.

To search for a TS-related gene, State and his colleagues adapted an approach used by Lifton to search for causative genes involved in cardiovascular, renal, and bone diseases. “We took a page from Rick's playbook in that we looked for unusual patients who have an identifiable genetic anomaly that we could trace to TS,” said State.

The researchers discovered one such instance in a boy who was the only member of his family with TS and who had a gene inversion on chromosome 13. Such inversions occur when a section of chromosome is broken off and flip-flops before reinserting itself back into the chromosome. Using chromosomal anomalies as a roadmap for identifying disease genes has paid off handsomely in leukemia research.

State and his colleagues focused their search near the breakpoints of the inversion. They identified one gene, called *SLITRK1* (for *Slit and Trk-like family member 1*), that is actively expressed in the brain and is associated with the growth and interconnection of neurons.

The researchers did not detect a specific abnormality in the DNA sequence of *SLITRK1* in the boy, so they screened 174 more people with TS, comparing their *SLITRK1* gene to that of individuals without TS. They found one characteristic *SLITRK1* mutation in affected members of one family that was absent in unaffected members. The mutation was not found in another 3,600 chromosomes from people without TS that they analyzed.

In two people with TS, the researchers found another variant sequence within *SLITRK1*, in a region of the gene that was not part of the direct blueprint for the SLITRK1 protein. “This was the strongest piece of genetic evidence in the research paper,” said State. “We found two examples of exactly the same rare sequence change in a regulatory, non-coding region of the gene. And it was in two unrelated individuals with TS.” Furthermore, the researchers did not find the alteration, which they called variant 321, in 4,200 chromosomes from individuals without TS.

Variant 321 was located in a region of the genome predicted to be involved in regulating *SLITRK1* activity by interacting with molecules called microRNAs. In further studies, the researchers found that a specific microRNA that regulates *SLITRK1* binds to the genetic site of variant 321. They also found that *SLITRK1* and the regulatory microRNA are both expressed in regions of the brain believed to be involved in TS. Finally, when they studied the function of *SLITRK1* in cultures of neurons, they found that those with the normal gene showed longer connective branches, called dendrites, than did those with the mutation.

According to Lifton, “Matt's approach of looking for genetic outliers that contribute to the pathogenesis of Tourette's represents a new approach that has great potential to provide an avenue into the pathways that underlie this disease.”

Lifton pointed out that State's approach is somewhat different than his strategy of analyzing rare genetic abnormalities that tend to run in families. These types of genetic studies are complicated in Tourette syndrome, in part because people with TS tend to marry one another, Lifton noted.

“The idea of looking for clues from chromosomal anomalies is a very powerful one that has paid off in this case,” said Lifton. “The findings point for the first time to a pathway that appears to contribute to the pathogenesis of TS and enables further studies not only from a genetic perspective, but also from a pathophysiologic one.”

State emphasized that although the pathway he and his colleagues have identified could prove important in understanding TS, “it still remains to be demonstrated by other labs whether aberrations in this pathway have pathological consequences in TS. Then we'll really pop the cork on the champagne, because this will give us an opportunity to begin to understand one pathway that—while it may be responsible for only a small percentage of TS—gives very concrete clues to disease mechanisms.”