COMMENTARY

Genomic Tics in Tourette Syndrome

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It is a striking observation that studies of copy number variation (CNV) in neurodevelopmental phenotypes continue to report an excess of rare variants in case populations. This astonishing result has been observed and replicated in studies of intellectual disability (1), autism (2), schizophrenia (3), and epilepsy (4). In a study published this month in *Biological Psychiatry*, Tourette syndrome (TS) is now added to this growing list (5).

In their newly published study, Fernandez et al. (5) found a 2.45-fold excess of de novo CNV in cases compared with controls. They also found that these CNVs are larger and affect more genes than de novo events present in controls. Although these results are not statistically significant, owing to the small sample size under study, this trend is similar to what has been seen for other neurodevelopmental phenotypes, including autism. Additionally, TS case CNVs are enriched for autism candidate genes, such as contactin-associated protein-like 2 (CNTNAP2), fragile histidine triad protein (FHIT), and astrotactin 2 (ASTN2). This result does reach statistical significance, suggesting that there is a shared pathway between TS and autism. The shared-pathway hypothesis is supported by a prior report of a neuroligin 4 (NLGN4) deletion discovered in an autistic proband. In this pedigree, a brother of the autistic proband who shares the NLGN4 deletion has TS (6). One interpretation of these data is that inherited susceptibility alleles give rise to a core neurobiological insult that could result in any of a range of phenotypes. Current evidence suggests that this range includes both TS and autism, with environmental influences or modifier genes mediating the specific phenotypic manifestation. These intriguing hypotheses will require additional investigation in larger cohorts of TS patients.

The authors chose to explore the qualitative nature of genes affected by rare CNV in their TS cases, using well-known methods to identify biological pathways or processes that might be commonly affected in their TS cases. They find evidence for involvement of the histamine receptor-signaling pathway. This dovetails with prior work of these authors, in which they investigated a Mendelian form of TS. In a pedigree with nine affected individuals, in which TS is segregating in a dominant fashion, linkage analysis, and subsequent sequencing of all genes in the linkage interval identified a rare stop codon mutation in the gene for L-histidine decarboxylase, the rate-limiting enzyme in histamine production (7). The authors showed that this mutation led to a decrease in both enzyme activity and histamine concentration, suggesting that a decrease in histamine transmission may underlie some forms of TS.

In a very recent case report of an adult male with TS and narcolepsy, a pharmacologic intervention was tailored based on the results of the pedigree analysis discussed above. The patient had been treated with various agents, and although some were successful in treating his narcolepsy, they simultaneously increased his tics. The treating clinicians, inspired by the hypothesis of diminished histaminergic activity in TS, chose to treat the narcolepsy with a histamine agonist specific to the H3 receptor (BF2.649 or tiprolisant or pitolisant) to boost histamine signaling (8). The patient’s narcolepsy improved, and his tics did not worsen (although they did not improve); this was sustained over 9 months. Taken together, these exciting results suggest histamine metabolism or signaling as a potential target for treatment of some patients with TS.

Fernandez et al. (5) observed a statistically significant approximately 6-fold excess of deletions at the FHIT locus in TS cases. However, these deletions had highly similar endpoints despite no flanking segmental duplications. One homozygous deletion was also seen. In the face of this evidence, the authors concluded this deletion was not recurrent and was instead likely inherited from a common ancestor shared by the individuals carrying the FHIT deletion alleles. This in turn implied the existence of residual population stratification in their sample, despite efforts to remove such influences with widely accepted methods. The authors took a conservative approach and excluded the FHIT locus.

An alternative explanation may exist. The FHIT gene includes the common fragile site FRA3B. Replication stress has been shown to induce submicroscopic deletions at this locus (9). It is therefore possible that deletions at this locus are in fact recurrent, mediated by replication stress and nonhomologous end joining. This would be consistent with some of the breakpoints not being precisely the same and not to require nearby segmental duplications to mediate recurrence. Although the exclusion of this locus is appropriate until population subdivision can be ruled out, the deletion of the FHIT gene may yet represent one pathway for development of TS and deserves further attention.

The observation of excess de novo CNVs is becoming such a common feature of many neuropsychiatric disorders that one may wonder whether these events are a fundamental feature of these disorders in general or really do point out specific genomic regions in which dosage can impart a substantial predisposing risk. It is therefore reassuring that not all neuropsychiatric disorders exhibit enrichment of de novo CNVs, such as a recent study comparing individuals with intellectual disability (ID), autism, or dyslexia, all performed on the same platform with the same analysis (1). Although excess de novo CNVs in ID and autism replicated many earlier studies, dyslexia showed a burden of de novo events no different from controls. The observations by Fernandez et al. (5) likely provide significant insight into the basis of TS, a disorder long known to have a genetic component but until these recent data resisted revealing the genomic lesions responsible.

Dr. Warren is chair of the scientific advisory board of Seaside Therapeutics, Inc. Dr. Mulle reports no biomedical financial interests or potential conflicts of interest.

References


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