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What makes you tic?: A new lead in Tourette syndrome genetics

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Tourette syndrome (GTS) is a developmental neuropsychiatric disorder characterized by motor and vocal tics that can range in severity from mild to disabling. Despite accumulated evidence for a substantial genetic contribution to disease risk, gene discovery in GTS has been challenging. Decades of candidate gene association studies initially reporting positive findings have failed to replicate in larger patient cohorts, and genome-wide association studies have yet to generate statistically-significant signals. As in other complex neurodevelopmental disorders, specific risk genes have been more difficult to identify than initially anticipated, particularly given early data interpreted to suggest that GTS was a single-gene autosomal dominant disorder. Rather, it seems most likely that risk for GTS is mediated by a conspiracy of multiple genes harboring small effect common variants and large effect rare variants, combined with environmental and epigenetic influences (1).

Reflecting back on nearly a decade of studies of genomic copy number variants (CNVs) in neurodevelopmental disorders, several trends are immediately clear. First, a few select disorders, most notably autism and schizophrenia, predominate the literature reports, while the number of studies in other phenotypes such as GTS and obsessive-compulsive disorder are relatively few. Second, the likelihood of discovering and confirming CNVs associated with such disorders is a direct function of the number of samples studied, typically requiring cohorts in the hundreds or thousands (2). Third, many CNV studies have focused only on rare (<1% population frequency) and/or large CNVs, as these characteristics tend to yield associations with the largest effect sizes. It is in this setting that the newly published study by Bertelsen et al. (3) in the current issue of *Biological Psychiatry* represents a significant contribution to the CNV literature.

In this report, the authors use as a starting point an early study of CNVs by Sundaram et al. (4), which found four genes (*NRXN1*, *CTNNA3*, *FSCB*, *AADAC*) recurrently overlapped by CNVs in 111 GTS patients. In a discovery cohort of 243 Danish patients with GTS and 1887 ancestry-matched control subjects, the present study examined these four candidate genes

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and found eight patients with a 36 kb deletion CNV spanning *AADAC* and a single deletion in *CTNNA3*. While the overall frequency differential between GTS and controls did not achieve statistical significance in the discovery group for any of these four genes, the authors proceeded to investigate CNVs in *AADAC* in a larger cohort, as deletions in this gene displayed the most favorable allelic frequencies consistent with a GTS risk locus (1.65% in GTS vs. 1.17% in controls, $p=0.38$). In total, an impressively-sized cohort of 1181 GTS patients from six European countries and 118,730 nationally matched control subjects were queried for deletions in *AADAC*. Deletions were detected in 3.6% of GTS and 2.0% of control individuals (allele frequencies of 1.82% and 0.99%, respectively), yielding a significant association for this CNV with GTS ($p=4.4 \times 10^{-4}$; OR = 1.9; 95% CI = 1.33–2.71). Furthermore, expression analyses and in situ hybridization studies performed by the authors show expression of *AADAC* throughout the brain, including regions previously implicated in GTS pathology, and particularly elevated expression in the Purkinje cell layer of the human cerebellum.

This finding by Bertelsen et al. (3) is the first claim of an association between a particular CNV and GTS. While a previous CNV study in GTS reported nominal significance for a 6-fold excess of deletions in the fragile histidine triad gene (*FHIT*), careful investigation of this locus concluded that this association was most likely the result of residual population stratification within the sample and inheritance of the *FHIT* deletion from a shared common ancestor (5). One may wonder if a similar scenario could account for the excess of *AADAC* deletions seen in GTS in the current study, especially given the seemingly identical breakpoints for these CNVs across all carriers. Given the targeted nature of assays used to detect CNVs in this study, an analysis to rule out this possibility of within-sample stratification was not feasible. However, as the authors note, this possibility was made less likely by their deliberate efforts to ensure uniform ancestry within each population.

Another potential confounding variable addressed in detail by the authors is the different CNV detection methods employed in each of the populations; these included chromosomal microarray, quantitative polymerase chain reaction (qPCR), or genome-wide genotyping using microarrays of varying probe sets. As the authors note, each of these detection platforms have varying resolution at different loci throughout the genome, including across the *AADAC* deletion region, which could potentially result in a differential ability to detect CNVs in this region between cases and controls. However, a visualization of probe coverage across *AADAC*, minimum probe thresholds set to call deletions, and a comparison of *AADAC* deletion detection rates among the various platforms suggests that the significant association of the *AADAC* deletion with GTS does not appear to be due to different detection methods. An ideal test of association would be a comparison of CNV rates between cases and controls using identical detection platforms. But as existing data from various independent research groups and consortia are re-examined and analyzed together (a commendable advancement on its own and one that is vital for detection of risk variants with effect sizes seen in complex disorders), attention to batch effects attributable to differences in detection platforms and other variables is crucial, as it can be the source of type I or type II error.

The *AADAC* deletion highlighted in the present study appears to be a “common” variant, reported to have an overall population frequency of ~1% in the Database of Genomic Variants (DGV Gold Standard Variants track, <http://dgv.tcag.ca/>, accessed December 15, 2015). This is in contrast to reports of rare variant association which have garnered more attention recently (1). The present finding provides rationale to re-examine prior CNV data sets in GTS which have focused on rare and large CNVs. Little is currently known about the function of *AADAC* in the brain and central nervous system. Interestingly, an examination of publicly-available data on gene expression throughout the human brain across development (<http://www.brainspan.org>), shows that *AADAC* expression appears to peak in the striatum between birth and adolescence (Figure 1), consistent with the typical clinical time course of tic onset in a brain region long suspected as mediating risk for GTS. If confirmed, this finding of excess deletions spanning *AADAC* will be an important inroad into better understanding GTS biology, a prerequisite for developing new strategies for diagnosis, treatment, and prevention.

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Figure 1. Brain expression trajectories of AADAC

Expression data is from the Brainspan Consortium (<http://brainspan.org>), generated using the Affymetrix GeneChip Human Exon 1.0 ST Array platform. Vertical axis is the log₂-transformed array signal intensity which is proportional to transcript expression. Horizontal axis represents periods of human development and adulthood as previously defined by Kang et al (2011). Birth begins period 8 and adolescence begins period 12. Brain regions are by color: neocortex (NCX), hippocampus (HIP), amygdala (AMY), striatum (STR), mediodorsal nucleus of the thalamus (MD), cerebellar cortex (CBC). Data points represents the median expression of AADAC in each specific brain region at each period of human development.