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The Origins of Tourette Syndrome: Prenatal Risk Factors and the Promise of Birth Cohort Studies

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Tourette syndrome (TS) is a clinically heterogeneous childhood-onset neuropsychiatric disorder that affects neural circuits involved in sensory and motor processing as well as cognitive control. The etiology of TS is complex. Tic disorders cluster in families.

Indeed, tic disorders are among the most heritable neuropsychiatric conditions (1). While large-effect rare variants have been discovered, current evidence indicates that the risk for TS is also mediated by multiple genes harboring small-effect common variants combined with environmental influences. A number of environmental risk factors have been implicated. The strongest evidence to date concerns pre- and perinatal adversities, including maternal smoking and life stressors during pregnancy as well as low birth weight (2).

In this issue of the *Journal*, Browne *et al.* (3) assessed the role of perinatal maternal smoking as a risk factor for TS and other chronic tic disorders (TS/CT) using data from the Danish National Birth Cohort (DNBC) study. This study enrolled approximately 100,000 women early in pregnancy from 1996-2002. The authors found that the offspring of mothers with a history of heavy smoking (≥ 10 cigarettes/day) during pregnancy were at approximately a 66% higher risk of developing TS/CT. In adjusted analyses, heavy prenatal maternal smoking was also associated with a two-fold increased risk of TS/CT with comorbid Attention Deficit Hyperactivity Disorder (ADHD). Remarkably, both light and heavy smoking were associated with over a twofold increased risk of TS/CT with any non-ADHD psychiatric comorbidity. The data concerning the mother's smoking during pregnancy was extracted from three research interviews, conducted on average at the 17th and 32nd weeks of gestation, and six months after birth. Other strengths of the study include the prospective design, and the inclusion of several relevant potential confounders. In their primary analysis, the potential confounding variables included birth year, sex, maternal age, parity, maternal psychiatric disorders, socioeconomic status, as well as the consumption of alcohol, cannabis products, and coffee. The weaknesses of this study are few and mostly relate to the inherent limitations of the data available from the Danish national registries.

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This is a compelling finding with public health significance that needs to be widely disseminated to the TS community and medical professionals. It will also be important to replicate and extend these findings. In this DNBC study, 11.7% (50/427) of the mothers were heavy smokers, but clearly a larger percentage of the mothers were exposed to other risk factors during gestation. For example, in the DNBC study more than 20% of the mothers experienced a high level of psychosocial stress during their pregnancy. Ideally, future studies will be able to model a larger number of additional perinatal risk exposures using prospectively collected population-based birth cohorts from other Nordic countries. The Swedish Medical Birth Registry (SMBR) comes to mind. Although data on some of the potentially relevant variables, including psychosocial stress, will not be available, it should be possible to use the SMBR, in combination with the other Swedish national registries, to model multiple risk factors in the same analysis with data from a much larger birth cohort (1). Ideally these studies would include the child's gestational age, labor presentation, delivery method, birth weight, head circumference, Apgar scores, and breast feeding in addition to heavy maternal smoking. Another perinatal risk factor to explore is the impact of maternal autoimmune disease and other infectious and allergic illnesses that were active during the pregnancy (4). The use of twin and sibling-comparison designs will also be of value as they provide a degree of control for shared familial confounders. These studies should have sufficient power to examine, in addition to TS and TS/CT, other relevant outcomes including comorbid ADHD, Obsessive-compulsive Disorder, Autism Spectrum Disorder, as well as mood and anxiety disorders.

Additional studies are needed to understand the specific molecular mechanisms linking maternal smoking and TS/CT. While the use of animal model systems may provide key insights, it is also clear that the regulatory regions of the human genome are unique to our species and directly impact the complex and dynamic regulation of gene expression in the developing fetal human brain (5). These findings in turn point to the likely importance of epigenetic modifications that alter how our DNA is read and transcribed very early in human brain development. Indeed, heavy maternal smoking may set the stage for TS/CT to emerge in genetically vulnerable individuals before they are even born. Consistent with this hypothesis are the findings of the recently completed epigenome-wide association study (EWAS) of tic disorders (6). Despite the fact that methylation events were assessed in the DNA isolated from peripheral blood, these epigenetic findings and those from forthcoming epigenetic investigations will likely contribute to a deeper understanding of the etiology of tic disorders and will hopefully inform future gene-by-environment interaction studies.

Another area of great promise, in our estimation, is the exploration of the potential role of the immune system in the pathobiology of TS and other neuropsychiatric disorders (7). For example, positron emission tomography neuroimaging studies and postmortem whole transcriptome analyses of postmortem basal ganglia tissue from individuals with TS now provide clear evidence implicating a specific set of CNS immune cells, the microglia, in the pathobiology of TS (8). Microglia are the resident macrophages of the brain, and act as the first and main form of active immune defense in CNS. The microglia also secrete immune-related signaling molecules that alter synaptic transmission and plasticity even in the absence of inflammation. As a result, they play a crucial role in very early brain

development and circuit formation (9). So perhaps activated microglia contribute to the alterations in functional connectivity that have been reported in TS (10)?

It will also be of interest to determine when during CNS development the genes identified in TS genome, epigenome, and transcriptome analyses are normally expressed. These analyses should provide additional clues to when during brain development the crucial events occur that set the stage for tic disorders to emerge. Data from the BrainSpan Atlas of the Developing Human Brain (<http://www.brainspan.org>) can be used to obtain gene expression trajectories across multiple brain regions over the course of human development. Indeed, it is fascinating to see that genes emerging from the first TS EWAS (7) and first postmortem brain RNA sequencing transcriptome study (8) both show peaks of expression in the striatum, a brain region suspected to play a key role in TS pathophysiology, in the early prenatal and perinatal periods, respectively (Figure 1). Considering the present findings by Browne *et al.* (3), we may be seeing the first signs of convergence of environmental exposures, epigenetic changes, and transcriptomic alterations onto a critical developmental time period that is highly relevant for TS and chronic tic disorders. Further studies are required to confirm this, and to determine whether perinatal risk factors also influence the long-term course of TS and contribute to the persistence of severe tics into adulthood as opposed to their usual remission by early adulthood.

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Figure 1. Gene expression trajectories in the striatum

Expression data is from the BrainSpan Consortium, generated using RNA sequencing. Vertical axis is the log₂-transformed array signal intensity which is proportional to transcript expression. Horizontal axis represents periods of human development as previously defined by Kang *et al.* (ref 5). Birth occurs at period 8 (dashed vertical line) and adolescence begins period 12. Data points represent the median expression of gene lists in the striatum at each period of human development. Gene lists are comprised of (A) the top CpG sites with *p*-value <0.0001 in a recent EWAS (ref 6, Table 3) and (B) significantly differentially expressed genes from a recent transcriptome study (ref 8) that cluster within a module enriched for immune activation.