A novel link between Tourette’s syndrome and histaminergic signalling

AK Mah

Department of Medical Genetics, Centre for Molecular Medicine and Therapeutics, Child and Family Research Institute, 950 West 28th Avenue, Vancouver, BC, Canada V5Z 4H4.
e-mail: amah@cmmt.ubc.ca

1-Histidine decarboxylase and Tourette’s syndrome
Ercan-Sencicek et al. (2010)

Tourette’s syndrome (TS) is a heritable neuropsychiatric disorder that is characterized by the display of repetitive tics. These tics are defined as sudden and recurring stereotyped vocalizations or movements. The incidence of TS includes a large environmental component as considerable phenotypic variability between monozygotic twin TS cases has been observed (1). Although TS is not associated with lower life expectancy or intelligence, the condition can nonetheless be socially debilitating. Fortunately, most cases of TS are rather mild, and hence many cases probably remain undiagnosed.

Recently, significant progress has been made in identifying genetic components of TS, including the discovery of copy number variations (2) and genes (3) associated with the disease. Some of these genetic changes are associated with other neuropsychiatric disorders including schizophrenia, autism, and attention-deficit hyperactivity disorder (2). Thus, the picture of the genetic factors that contribute exclusively to TS remains somewhat blurred.

Because the molecular pathways underlying TS have yet to yield many direct therapeutic targets, the current treatments are non-specific to TS and are limited to alleviating the symptomatic tics. Moreover, many TS treatments are undesirable due to their highly invasive nature. Therapies for TS consist of neurosurgery, deep brain stimulation, behavioural modification, and medication (4). The drugs used to treat TS include anti-psychotics, stimulants, anti-hypertensives, and anti-depressants; many of these evoke strong side effects (4). Therefore, there is a clear need to discover and characterize novel pathways associated with TS to develop alternative treatment strategies.

In the current study, Ercan-Sencicek et al. aimed to identify mutations associated with a familial form of TS. In the affected family, all eight

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children of a non-consanguineous couple were diagnosed with TS, including two that suffered from co-occurring obsessive compulsive disorder like their father; the mother had no history of neurological disease. Thus, the inheritance pattern of TS was consistent with autosomal dominance. Through logarithm of the odds (LOD) analysis, the authors identified an 8.13 Mb interval on chromosome 15, which potentially contained a dominant genetic lesion. Within the genetically defined interval, a point mutation was found in the coding sequence of the \( l \)-histidine decarboxylase (HDC) gene. Importantly, this mutation was shared among all affected family members, but was absent in the mother’s genome. The point mutation results in premature termination of translation (W317X), resulting in a truncated protein product.

HDC homodimers catalyse the conversion of \( l \)-histidine to histamine. In the brain, histamine acts as a neurotransmitter that exerts its effects through four G-protein coupled receptors (GPCRs). Intriguingly, many GPCRs are enriched in the cortex and in the striatum, brain regions that have been linked to TS (5). Ercan-Sencicek et al. showed that the mutant form of HDC inhibits the wild type form’s ability to catalyse the biosynthesis of histamine from \( l \)-histidine \textit{in vitro}; thus, HDC W317X acts as a dominant negative, in agreement with the observed inheritance pattern.

To determine whether the \( HDC \) W317X allele is common among TS patients, Ercan-Sencicek et al. sequenced the \( HDC \) locus in samples from TS patients and the general population. Although they did not find any other incidences of the W317X allele, additional \( HDC \) alleles were identified. Each of these was non-conservative point mutations, with one allele identified in a TS patient and two alleles from undiagnosed control individuals. All three of these mutations were predicted to be detrimental to protein function. As one of these non-synonymous single nucleotide polymorphisms (SNPs) is associated with a bona fide TS patient, it would be interesting to determine whether this newly discovered allele is also implicated in the pathology of TS. The lack of evidence that the W317X allele occurs outside of the initially studied family suggests that either this allele is exceedingly rare in the general population, or alternatively, that it resulted from a spontaneous mutation that occurred in the paternal lineage.

Even though \( HDC \) mutations are not generally associated with TS, histaminergic signalling might frequently be altered in patients suffering from TS. This raises the possibility of applying therapies directed at targeting histaminergic pathways to treat this condition. Drugs that target this signalling pathway exist, with some showing promise as modulators of neurological disease. For example, antagonists are available that block histamine signalling through the H3R histamine receptor. When these agents are applied to mice, sensitivity to stimulants is decreased (6). Thus, the discovery that a key enzyme in histamine synthesis is involved in familial TS may eventually open up new possibilities for TS treatment through modulation of histaminergic signalling in the brain.

References