Published in final edited form as:

J Am Acad Child Adolesc Psychiatry. 2015 January ; 54(1): 6–8. doi:10.1016/j.jaac.2014.11.004.

From Bedside to Bench and Back Again: Tourette Syndrome and Translational Clinical Science

Dr. Thomas V. Fernandez, M.D.,

Child Study Center and Department of Psychiatry at Yale University School of Medicine

Dr. Robert A. King, M.D., and

Child Study Center at Yale University School of Medicine

Dr. Christopher Pittenger, M.D., Ph.D.

Department of Psychiatry, Child Study Center, Department of Psychology, and Integrated Neuroscience Research Program at Yale University School of Medicine

Keywords

Tourette syndrome; genetics; animal model; treatment; pharmacology

There is an urgent need for qualitatively new and more effective treatments in psychiatry. Recent advances in genetics are beginning to yield reproducible findings in a variety of psychiatric disorders. This engenders great optimism that using genetic variants to clarify biology will identify unexpected treatment targets (Figure 1). Here we describe a translational story in Tourette syndrome (TS), illustrating the potential for genetics and animal model research to inform our understanding of biology and lead us toward new ways to improve the lives of our patients.

The “R” Family

Mr. R, now in his 40’s, had the onset of blinking tics at age 3. Over the years, he was plagued by neck, mouth, and stomach movements, “dance-step” leg tics, high pitched sounds and “mental coprolalia.” At age 10, he was diagnosed with TS by one of the few clinicians then familiar with the disorder and was treated with haloperidol, 5-7 mg, and subsequently pimozide 6-7 mg. Improvement in tics was accompanied by bothersome akathisia, slurred speech, weight gain, irritability, and impulsive provocativeness.

As an early teen, he was seen at Yale Child Study Center by Dr. Donald Cohen, who was studying clonidine in the hopes that its adrenergic modulating effects might be useful in controlling tics. Clonidine proved effective enough that Mr. R was able to discontinue neuroleptics, with marked relief from what he described as debilitating “zombie-like” effects. (The timing may also have been fortuitous, as this is often the worst period for tics, followed in many cases by spontaneous improvement.)

Over the subsequent 21 years, until his death, Dr. Cohen followed Mr. R. Tics diminished but did not disappear. Despite continued ADHD and low level impulsivity (which he described as “lacking a filter”), Mr. R developed a gainful occupation and became a devoted, loving husband and father of four. He feels his TS has been a “mixed blessing,” giving him a quickness and “an edge” which he cherishes, while being aware of the burdens it confers.

Over the years, each of the children has developed various tics, though none of Mr. R’s severity, as well as other symptoms. They continue to be followed at our TS clinic.

The oldest son, now in college, though bright, had speech and developmental delays when young, a wide scatter on his neurocognitive profile, social awkwardness, and ADHD. He developed motor and vocal tics around age 7. At age 15 he had a hypomanic episode that remitted on a low dose of neuroleptic.

The second son, now in high school, had tics, ADHD, and learning difficulties, though he is academically high-achieving.

Two daughters, one in elementary school and one in junior high, have tics and ADHD, but are more socially fluent than their brothers.

In addition to judicious medication management, mostly using guanfacine and atomoxetine, frequent communication with the school system has been required to address each child’s blend of talents and vulnerabilities. Over the decades, we’ve been privileged to follow this family as they have confronted the joys and worries of parenthood, serious medical crises, and other vicissitudes of life. During that time, they have educated us about the long-term developmental trajectory of tic disorders and its phenotypic heterogeneity, the ability of clinical research to improve quality of life, the complex intermingling of vulnerabilities and resilience, and the importance of long-term clinical commitment.

Just as in Mr. R’s adolescence a new understanding of the impact of adrenergic mechanisms on tic severity led to the then-novel use of alpha-adrenergic agents to treat tics, so it is hoped that a better basic understanding of the genetic pathophysiology of TS will lead to newer, more effective treatments.

Meanwhile, at the bench

Early twin and family studies provide multiple lines of evidence that TS is partially genetic. Initial studies assumed that TS was a rare autosomal dominant disorder resulting from a mutation in a single gene. Despite intensive discovery efforts, no single locus was identified and confirmed based on this hypothesis. Three decades of genetic investigations (including segregation, linkage, and candidate gene association studies, and a recent genome-wide association study) have emphasized that TS is far more common than initially appreciated and that its genetic architecture is complex and heterogeneous, similar to that of other neuropsychiatric disorders.

While most efforts in TS genetics have concentrated on the search for common genetic variants, there has been an increasing recent effort to evaluate the contribution of rare genetic variants. Rare variants of large effect can highlight important biological mechanisms, even if they account for only a small fraction of the overall genetic risk.

In 2010, State and colleagues described a rare two-generation family with an exceptionally high incidence of TS, similar to the R family¹. Linkage analysis identified a rare mutation in the histidine decarboxylase (*HDC*) gene, which encodes the enzyme required for histamine biosynthesis. The TS-associated mutation abrogates this function, and carriers of the mutation are thus deficient in the production of histamine. All known carriers of this mutation have TS – that is, it is of exceptionally high penetrance and can be considered a cause, albeit a rare one. This unexpected finding illustrates the potential of genetics for the identification of new disease-associated biology: histamine was not on anyone's radar as a potential contributor to TS prior to this finding. A subsequent study of copy number variation in TS² and a European family-based association study³ show that while dysregulation of histamine may be a rare cause of TS, it may not be unique to this one family. This encourages optimism that understanding the mechanisms by which histamine abnormalities can lead to TS will shed light on the syndrome more generally.

With recent advances in high-throughput genome sequencing, we are beginning to see, for the first time, genetic variants of large effect that are reproducibly associated with neuropsychiatric disease. This long-delayed progress represents a watershed moment in our field. The identification of the *HDC* mutation is one example. Nevertheless, the identification of genetic variants contributing to disease is only the first step in the development of a deeper understanding of pathophysiology and the development of new treatment strategies (Figure 1).

The use of animal model systems has been an extraordinarily powerful tool for the elucidation of pathophysiology in many areas of medicine and provides unique power to elaborate the consequences of a disease-associated genetic abnormality. Unfortunately, the complexity of neurodevelopmental disorders has complicated this endeavor; there are few animal models of TS, and their validity is questionable⁴. Only certain mutations are well suited to modeling pathophysiology in an animal. An animal modeler's dream mutation has a clear effect on a protein of known function; ideally, this permits us to perform a biochemical assay to confirm the effect of the mutation, at the molecular level. The ideal mutation also has high penetrance – that is, it does not just marginally increase the risk of disease, but rather increases disease risk so dramatically (that is, has such a large effect size) that it can reasonably be considered a cause.

This is a tall order; most disease-associated mutations subtly modulate risk, and most fall between protein-coding genes, making their effect on cellular processes difficult to decipher. The *HDC* mutation described above,¹ however, has all of the desirable characteristics for pathophysiological analysis in mice.

Mice lacking one or both *Hdc* genes functionally recapitulate the TS-associated mutation and therefore are a candidate pathophysiological model for TS. Recent work has established

that these animals have increased tic-like stereotypic movements and a sensory processing abnormality (a deficiency in prepulse inhibition) that recapitulates what is seen in TS. Furthermore, their tic-like movements are modulated by the dopamine antagonist haloperidol, an established pharmacotherapy for TS. These observations engender confidence that these animals recapitulate key aspects of the brain dysregulation that causes TS and therefore merit close further study⁵.

But can they tell us something new about what is happening in our patients? The power of an animal model is that it permits us to ask mechanistic questions that we cannot ask in humans. Initial investigations in the *Hdc* knockout mouse have focused on the basal ganglia system, and specifically on the modulation of this circuitry by the neurotransmitter dopamine, because these systems have previously been associated with TS and are the target of existing treatments. Targeted analysis revealed disruption of both dopamine and some of its receptors in the basal ganglia in the animals. Closing the loop, the same receptor abnormality – an elevation of D2/D3 receptors in the substantia nigra – was seen using brain imaging in TS patients carrying the *HDC* mutation⁵. This is the first example of a TS animal model teaching us something new that has then been confirmed in patients.

Back to Bedside?

If the identification of a disease-associated genetic abnormality is the first step in this journey, the validation of an animal model such as the *Hdc* knockout mouse is only the second (Figure 1). This endeavor aims towards the development of new ways to alleviate human suffering. Can gene discovery followed by animal model validation lead to new treatments? It may. One of the brain's histamine receptors, H3, is known to modulate brain dopamine and basal ganglia signaling; we hypothesize that it represents a key link between histamine disruption, dopamine dysregulation, and basal ganglia signaling abnormalities in the animal model and in patients. Several pharmaceutical companies have developed compounds targeting this receptor for other purposes. Based on these findings, therefore, a clinical trial of a histamine receptor (H3)-modulating compound is currently underway in individuals with TS (ClinicalTrials.gov ID:NCT01904773). We, and our patients, eagerly await the results.

Acknowledgements

We thank the families and patients who participate in our research. Research reported in this publication was supported by the National Institute of Mental Health of the National Institutes of Health under Award Numbers K08MH099424 (TVF) and R01MH092203 (RAK). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Financial Disclosures: Dr. Fernandez receives research funding from NIMH, the Simons Foundation, Allison Family Foundation, and Shire. Dr. King receives research funding from NIMH and Rutgers University. Dr. Pittenger receives research funding from NIMH, the Allison Family Foundation, the Nancy Taylor Foundation for Chronic Disease, the MGH Research Fund, F. Hoffman La Roche, Ltd., and the State of Connecticut through its support of the Ribicoff Research Facilities at the Connecticut Mental Health Center.

References

1. Ercan-Sencicek A, Stillman A, Ghosh A, et al. L-Histidine Decarboxylase and Tourette's Syndrome. *New England Journal of Medicine*. 2010; 362(20):1901–1908. [PubMed: 20445167]

2. Fernandez TV, Sanders SJ, Yurkiewicz IR, et al. Rare copy number variants in tourette syndrome disrupt genes in histaminergic pathways and overlap with autism. *Biol Psychiatry*. 2012; 71(5):392–402. [PubMed: 22169095]
3. Karagiannidis I, Dehning S, Sandor P, et al. Support of the histaminergic hypothesis in Tourette syndrome: association of the histamine decarboxylase gene in a large sample of families. *J Med Genet*. 2013; 50(11):760–764. [PubMed: 23825391]
4. Pittenger, C. Animal models of Tourette syndrome and obsessive-compulsive disorder. In: LeDoux, M., editor. *Animal Models of Movement Disorders*. Elsevier; New York: 2014.
5. Castellan Baldan L, Williams KA, Gallezot JD, et al. Histidine decarboxylase deficiency causes tourette syndrome: parallel findings in humans and mice. *Neuron*. 2014; 81(1):77–90. [PubMed: 24411733]

Figure 1. Translating genetic discoveries to treatment targets, highlighting Fragile X syndrome and Tourette syndrome
FMRI = human fragile × mental retardation 1 gene, *Fmr1* = fragile × mental retardation 1 mouse ortholog gene, KO = knockout, FMRP = fragile × mental retardation protein, mGluR = metabotropic glutamate receptor, *HDC* = human L-histidine decarboxylase gene, *Hdc* = L-histidine decarboxylase mouse ortholog gene, H3R = histamine receptor, type 3.