Mini-Review • DOI: 10.2478/s13380-012-0020-2 • Translational Neuroscience • 3(2) • 2012 • 153-159

Translational Neuroscience

VERSITA

GENETIC ANIMAL MODELS OF TOURETTE SYNDROME: THE LONG AND WINDING ROAD FROM LAB TO CLINIC

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Abstract

Tourette syndrome (TS) is a disabling neuropsychiatric disorder characterised by persistent motor and vocal tics. TS is a highly comorbid state, hence, patients might experience anxiety, obsessions, compulsions, sleep abnormalities, depression, emotional liability, learning problems, and attention deficits in addition to tics. In spite of its complex heterogeneous genetic aetiology, recent studies highlighted a strong link between TS and genetic lesions in the *HDC (L-histidine decarboxylase)* gene, which encodes the enzyme that synthetises histamine, and the *SLITRK1 (SLIT and TRK-like family member 1)* gene, which encodes a transmembrane protein that was found to regulate neurite outgrowth. In addition to validating the contribution of a specific genetic aberration to the development of a particular pathology, animal models are crucial to dissect the function of disease-linked proteins, expose disease pathways through examination of genetic modifiers and discover as well as assess therapeutic strategies. Mice with a knockout of either *Hdc* or *Slitrk1* exhibit anxiety and those lacking *Hdc*, display dopamine agonist-triggered stereotypic movements. However, the mouse knockouts do not spontaneously display tics, which are recognised as the hallmark of TS. In this review, we explore the features of the present genetic animal models of TS and identify reasons for their poor resemblance to the human condition. Importantly, we highlight ways forward aimed at developing a valuable genetic model of TS or a model that has good predictive validity in developing therapeutic drugs for the treatment of tics, hence potentially accelerating the arduous journey from lab to clinic.

Keywords

• Tourette syndrome • Tics • Slitrk1 • L-histidine decarboxylase • Mouse • Knockout • Therapy • Drugs • Obsessive-compulsive disorder

Received 28 March 2012
accepted 12 May 2012

Abbreviations

ADHD - attention-deficit hyperactivity disorder;
CSTC - cortico-striato-thalamo-cortical;
D1CT - D1 receptor cholera toxin;
HDC - L-histidine decarboxylase;
METH - methamphetamine;
miRNA - microRNA;
OCD - obsessive-compulsive disorder;
SLITRK1 - SLIT and TRK-like family member 1;
SMA - spinal muscular atrophy;
SMN - survival of motor neurons;
TS - Tourette syndrome;
TTM - trichotillomania.

INTRODUCTION

Tourette syndrome (TS) is a developmental neuropsychiatric disorder whereby afflicted patients suffer from chronic fluctuating motor and vocal tics. In view of its complex heterogeneous genetic aetiology, for decades, the specific genes involved remained elusive. Breaking the mould, recent studies were successful in identifying genetic lesions in two genes: *L-histidine decarboxylase* (*HDC*), which encodes the rate limiting enzyme in histamine biosynthesis [1], and the *SLIT and TRK-like family member 1* (*SLITRK1*), which encodes a transmembrane protein with strong homology to the axon guidance molecule, SLIT and the neurotrophin receptor, TRK [2]. These two emerging super candidates spurred the development of *Slitrk1*-knockout mice [3] and vigorous reanalysis of extensive data from previously-generated *Hdc*-knockouts [4-6], with the aim of establishing a TS animal model. Both knockout mice are viable and although a shared characteristic is anxiety, which is a trait relevant to the features of TS, the models stop short of spontaneously displaying tics, that are recognised as the hallmark of TS. Mouse models are critical in the study of human disease, primarily because they allow us to validate the contribution of a specific chromosomal or genetic aberration to the disease phenotype. Secondarily, animal models open the door to the use of a variety of tools to dissect the function of disorder-linked proteins, the uncovering of relevant disease pathways through the examination of genetic modifiers, and the discovery as well as the trialing of novel therapeutic strategies. In this review we probe the state of the art with regards to TS genetic models, identify the hurdles and go back to the drawing board to identify new approaches and strategies to hasten the arduous trip from lab to clinic.

CLINICAL SPECTRUM OF TS

TS has a male predominance and although the typical onset is around the age of five, it often remains under-diagnosed [7-9]. World-wide prevalence is estimated between 0.3 and 1%

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[10,11]. Tics often peak in severity between age 8 to 12 [12,13] and significantly decline after puberty in 80% of the cases [14]. Tics, which are sudden, repetitive motor and vocal behaviours involving discrete muscle groups, can be simple or complex. Simple motor tics are any sudden, meaningless movements that recur in bouts, such as eye blinking, rapid head jerks and shoulder shrugs. Although any part of the body can be affected, the face, head and shoulders are the most common areas involved. Complex motor tics seem more purposeful but they are still sudden movements, which involve more than one muscle group, such as facial grimaces, touching others, or pivoting movements. Vocal tics typically begin after the onset of motor tics and involve simple sudden utterance of sounds such as throat clearing, sniffing or coughing. More complex forms of vocal tics can be repetitive, purposeless utterance of words, phrases or statements that are out of context and expression of obscenities (coprolalia) [9,15]. The ability to suppress tics for brief intervals and, in most cases, the existence of premonitory sensory urges that are relieved by the execution of a tic, are features that differentiate TS from other movement disorders [15].

TS is a highly comorbid state, hence, in addition to tics, patients might experience anxiety, obsessions, compulsions, sleep abnormalities, depression, emotional liability, learning problems, and attention deficits, which precipitate distress [16-18]. In childhood, the most frequent comorbid disorder with TS is attention-deficit hyperactivity disorder (ADHD), which causes behaviour hyperactivity, impulsiveness and problems with attention focusing [19]. Obsessive-compulsive disorder (OCD) is also very frequent in TS, and usually causes more significant distress and functional impairment than the tics themselves [20]. The symptomatology of OCD is directed at reducing anxiety, is ritualized and changes little over time whereas tics are waxing and waning in course, are usually not dependent on anxiety, and involve fragmented movements. Both tics and obsessive-compulsive behaviours can be suppressed voluntarily and though worsened during periods of emotional excitement and fatigue, they plummet during periods that require focused attention and fine motor or vocal control [9,21,22]. Complex tics are usually difficult to distinguish from compulsions and in this context, TS and OCD are sometimes thought to be a common pathology with OCD being the mental form of TS and TS being the motor form of OCD [23]. Although these two disorders are diagnostically separate, aetiologically there is a common pattern including the involvement of similar brain areas in symptom manifestation [15,20,24]. If tics interfere with the daily life, antipsychotic agents, which reduce the symptoms but do not cure the disorder, are recommended [25,26]. In addition to pharmacological treatment, behavioural therapies and psychosocial interventions can also be effective [27].

TS GENE DISCOVERY: CONTAINED EXCITEMENT?

A significant genetic contribution to TS was identified through twin studies, where concordance rates over 50% were observed in monozygotic twins in contrast to rates below 10% for dizygotic twins [28,29]. Furthermore, TS family studies show a greater rate of TS or chronic tics in first-degree relatives compared to rates in relatives of controls [30-33]. Initially thought to be a monogenic Mendelian disorder, TS is presently recognised as a complex disorder, with multiple genes interacting with various environmental factors to bring about the onset of symptoms. In this regard, several association studies assessing a variety of biologically plausible candidate genes as well as linkage screens were undertaken to underpin TS susceptibility loci [34-37]. Although the results fell short of remarkable considering the lack of independent reproducibility, the recent discovery of two causal genes with a role in TS, albeit minor, has generated considerable excitement in the field.

Focusing on a rare subset of patients with TS that have chromosomal anomalies, Abelson et al. [2] identified the *SLITRK1* gene due to its proximity to a *de novo* chromosome 13 inversion in a child with TS and ADHD but with no family history of either disorder or comorbid psychopathologies. Hypothesising that SLITRK1 expression might be altered by a position effect, the authors genotyped 174 unrelated probands for lesions within the *SLITRK1* gene. A frameshift mutation in the coding region predicted to result in a truncated protein and 2 independent occurrences of a non-coding variant (var321) in the binding site for microRNA (miRNA) hsa-miR-189 were identified in TS probands but not in over 3600 controls. The patient having the frameshift mutation was diagnosed with ADHD in addition to TS and the patient's mother who had the same mutation was affected with trichotillomania (compulsive hair pulling) (TTM) but not TS. The individuals carrying var321 however had OCD-like symptoms in addition to TS and a family history of tics, OCD-like symptoms and/or hair pulling. OCD, ADHD and/or TS might represent alternative manifestations of a single underlying genetic alteration. *SLITRK1* mRNA and miR-189 have an overlapping expression pattern in the developing brain and *in vitro* reporter gene activity is reduced through action of miR-189, with further repression occurring in the presence of the var321. miRNAs are post-transcriptional RNA regulators that bind to complementary sequences on target mRNAs to halt their translation. SLITRK1 was found to regulate neurite outgrowth, a process that is inhibited in the absence of SLITRK1 phosphorylation [38] and the presence of the frameshift mutation [2]. Furthermore, 14-3-3 proteins, which are involved in a multitude of cellular processes, ranging from proliferation and differentiation to membrane excitability, were found to interact with SLITRK1 [38]. Several follow-up studies that screened for the observed *SLITRK1* genetic changes in TS either failed to find them [39-42], or when identified, they did not segregate with the disorder in families [43,44], hence clouding the link between *SLITRK1* and TS. In this context, the original authors rejected claims of confounding population stratification between cases and controls [45], and recent studies by us and other groups have re-highlighted the significance of the initial findings by demonstrating a strong over-transmission of alleles and/or haplotypes of *SLITRK1* to affected individuals [46-48].

The discovery of *HDC* as a TS susceptibility locus shifted a massive knowledge set on histamine biosynthesis and histaminergic

neurotransmission, painstaking gathered in the last two decades, in the direction of TS. Through the analysis of linkage in a two-generation pedigree, in which TS segregated in a rare autosomal dominant manner, Ercan-Sencicek et al. [1] identified a rare functional mutation (W317X) in the *HDC* gene. The W317X nonsense mutation, which is present in a heterozygous form in the affected offspring and affected father but not in the unaffected mother and in more than 3000 controls, is predicted to result in a truncated protein that lacks key parts of the enzyme's active domain. Although the truncating mutation could potentially result in haploinsufficiency (that leads to low histamine levels in the central nervous system), the authors showed convincingly that the retained mutant protein lacked enzymatic activity and had a dominant-negative effect on the function of the wild-type protein. Furthermore, the study established that loss-of-function *HDC* alleles are extremely rare and in this context, the first follow-up study reported no significant association between the *HDC* gene and TS in a cohort of 120 Chinese Han patients [49]. The major active form of the histamine-synthesising HDC enzyme is a homodimer and uses pyridoxal 5'-phosphate as a cofactor. Following conversion from histidine, histamine is stored in synaptic vesicles via the vesicular monoamine transporter-2 (VMAT-2) ready to be released at the synaptic cleft by exocytosis. The effects of histamine in the CNS are achieved through 3 types of guanine nucleotide (G) protein-coupled receptors. H1 and H2 receptors are located postsynaptically and are mostly the mediators of the excitatory actions of histamine. The H3 receptors act as somatodendritic autoreceptors that inhibit firing of neurons or as presynaptic receptors that inhibit the release of histamine and other neurotransmitters from axon terminals [reviewed in 50].

All in all, there is a consensus that the TS gene discovery story has had a promising start. Although mutations in the genes discovered are found in only a small fraction of affected persons, there is presently an impetus to delve into protein function as well as the mechanisms through which loss of function leads to TS. In this regard, the next stop of the journey towards the clinic is definitely animal models.

MOUSE MODELS OF TS: TICKLISH QUESTIONS

What makes a valuable animal model of human disease? Considering, for instance, the paediatric neurological disease spinal muscular atrophy (SMA) [51-53], we note that the underlying neurodegenerative pathology can be fully reproduced in an animal because: firstly, the aetiology, which involves a deficiency of the survival of motor neurons (SMN) protein, is clearly defined [54]; secondly, the disease manifestations in mice are noticeable and quantifiable including decreased lifespan, motor neuron loss, atrophic muscle fibres as well as motor defects [55-58]; and, thirdly, such abnormalities can be relieved by therapies known to be effective in humans such as those that increase SMN levels [59-62]. From a neuroanatomical viewpoint, there is increasing evidence pointing towards the cortico-striato-thalamo-cortical (CSTC) pathways as the site of origin of tics as well as the accompanying neuropsychiatric problems. However, because the precise cellular and molecular mechanisms of the underlying abnormalities in TS are still hazy, animal models of TS have been hard to come by. The recent successes in TS gene discovery were thought to pave the way for genetic models that closely replicate the TS phenotype.

In the era preceding TS gene discovery, the animal model that by far exhibited the greatest behavioural similarities to TS is the D1 receptor cholera toxin (D1CT-7) transgenic mouse [63,64]. This model has cortical-limbic hyperactivity triggered through the expression of a transgene constructed by fusing the promoter region for the human D1 dopamine receptor with the intracellular A1 subunit of the cholera toxin. In addition to OCD-like behaviours that include generalised behavioural perseveration, repetitive leaping and compulsion-like grooming-associated pulling and biting of skin and hair [63], D1CT-7 mice spontaneously display TS-like behaviours such as tics and 'twitch' flurries of the head, limbs and trunk that have a juvenile-onset [64]. Notably, tics were reduced following treatment with clonidine, an α2-adrenergic agonist that is frequently used to treat patients with TS. In this context, knockout of *Slitrk1* or *Hdc* was predicted to result in a mouse model that resembled the D1CT-7 mice, which due to their striking similarity to human tic behaviours were thought to have good predictive validity in developing therapeutic drugs for the treatment of tics.

Slitrk1-knockout mice, which are totally deficient or null for Slitrk1, did not exhibit any external abnormalities though viability was slightly decreased and males had a reduced body weight. In the elevated plus-maze test, which involves placing a mouse in a plus-shaped apparatus with two open and two enclosed arms, elevated from the floor, *Slitrk1*-deficient mice exhibited a reduction in the number of entries into open arms as well as time spent in open arms, with such phenotypes pointing towards an elevated anxiety-like behaviour. An increased immobility time in the tail suspension and forced swimming tests was also noted, with the latter indicating that *Slitrk1*-knockouts exhibit depression-like behaviour. Brains of mutant mice had an elevated level of noradrenaline as well as its metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) and administration of clonidine attenuated the anxiety-like behaviour of the knockout animals [3]. Although anxiety and depression are at times part of the clinical repertoire of TS [65,66], *Slitrk1*-null mice had no compulsive and/or tic-related behaviours, a result that was unexpected given that in addition to TS, *SLITRK1* has also been linked to TTM [2,67], which like TS is believed to belong to the OCD spectrum.

Hdc-knockout mice are not able to produce histamine and, hence, lack histamine-dependent activation through histamine receptors. *Hdc*$^{-/-}$ mice are viable, fertile and healthy but display altered mast cell morphology and low mast cell numbers [68]. Generated well before HDC was linked to TS, these knockout mice have been utilised to investigate the role of histamine in immunity, wound healing, cardiovascular function, parasitic infections, inflammation, gastric acid secretion and allergic disorders [reviewed in 69,70]. To uncover the function of *Hdc* in neurophysiology, several studies subjected *Hdc*-deficient mice to an array of behavioural assays. Mutant animals have

reduced spontaneous locomotor activity in the dark and exhibit a decreased exploratory activity in an illuminated open-field [4,5]. However, repeated administration of methamphetamine (METH) induced marked hyperactivity and behavioural sensitisation in knockout mice compared to their wild-type counterparts [4]. By inhibiting the reuptake and facilitating the release of dopamine, repeated treatment with METH induces behavioural sensitisation in mice, which involves a progressive and long-lasting elevated locomotor activity as well as stereotyped behaviour or behaviour that is both repetitive and excessive in nature. *Hdc*-knockouts had heightened measures of anxiety in the elevated plus-maze test which might explain their hypoactivity [5,6]. Although such an observation is similar to *Slitrk1*-deficient mice [3], *Hdc*-null brains had low levels of noradrenaline [4]. *Hdc*$^{-/-}$ mice display traits that resemble features of TS including anxiety and dopamine agonist-triggered stereotypic movements, however, the murine phenotype certainly never reaches the levels of TS resemblance seen for instance in the D1CT-7 transgenic mouse.

Considering their poor resemblance to the human condition, it is certainly clear that both the *Slitrk1* and *Hdc* mouse knockouts are not good models of TS (Figure 1). How can we overcome the existing hurdles in the development of a genetic model of TS? A key approach should involve a rethink of model design. It is highly probable that patients with *SLITRK1* mutations have an altered SLITRK1 expression and not a total knockout as happens in *Slitrk1*$^{-/-}$ mice. Indeed, *SLITRK1* was originally implicated in TS because it neighboured a chromosomal inversion that was hypothesised to influence SLITRK1 expression pattern and levels [2]. Furthermore, the proximity of *SLITRK5* (13q31.2) and *SLITRK6* (13q31.1) to the *SLITRK1* gene (13q31.1) means that these two SLITRK family members (and, possibly, other nearby genes) could also be influenced by a position effect. The recent finding of OCD-like behaviours manifesting as excessive self-grooming in the *Slitrk5* mouse knockout seems to point in this direction [71]. In contrast to the *Slitrk1*$^{-/-}$ mouse, the genetic lesion in *Hdc*$^{-/-}$ mice is probably quite similar to that described in patients with TS that have *HDC* mutations. Indeed, *Hdc*$^{-/-}$ mice have a targeting vector that entirely replaces exons 6-8 of the murine 12 exon-long *Hdc* gene. Hence, similar to patients with TS who carry the W317X nonsense mutation [1], a truncated Hdc protein lacking the pyridoxal 5′-phosphate (PLP) domain and probably acting in a dominant-negative way could be produced in *Hdc*$^{\Delta 6\text{-}8}$ mice. To our knowledge, Western blotting experiments as well as studies that assess the effect of the truncated Hdc protein on its wild-type counterpart still

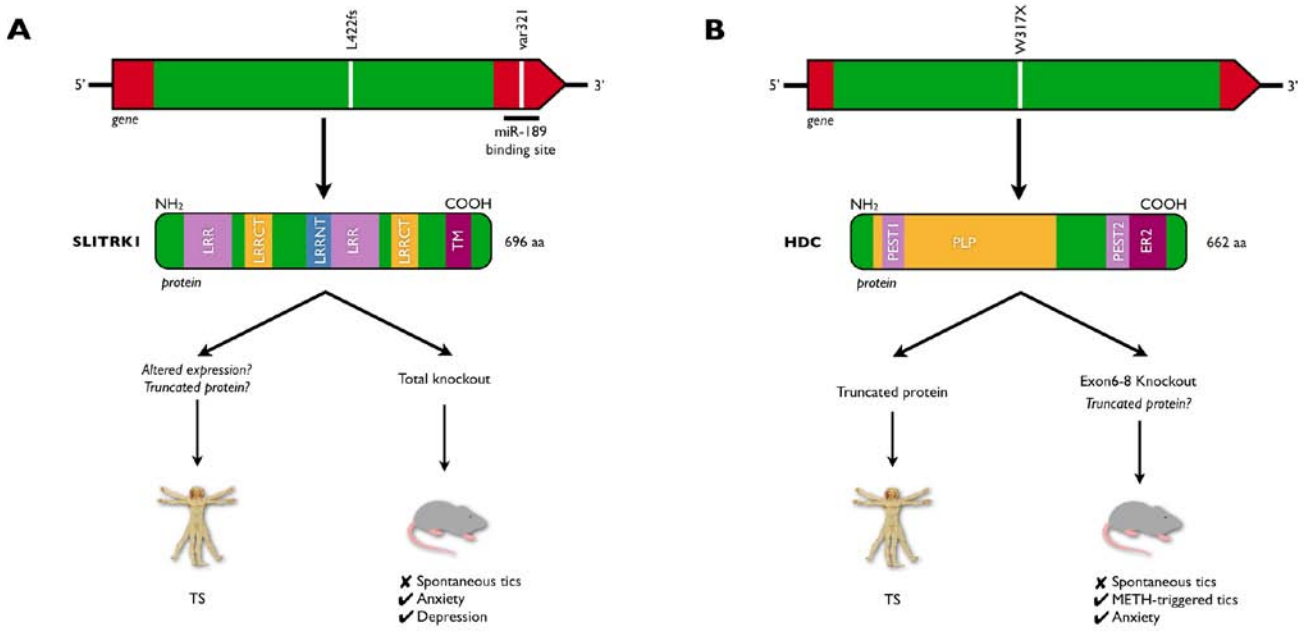

Figure 1. Genetic alterations in *SLITRK1* and *HDC* genes in patients with TS and present genetic mouse models. (A) A schematic of the *SLITRK1* gene (green = translated; red = untranslated regions) with the reported alterations in TS (white strips) and its translated product. *SLITRK1* protein has several conserved protein domains including leucine-rich repeats (LRR), a leucine-rich repeat C-terminal domain (LRRCT), a leucine-rich repeat N-terminal domain (LRRNT) and a transmembrane domain (TM). Patients with TS that have genetic alterations in the *SLITRK1* gene are hypothesised to have either altered expression (var321) or expression of a truncated version (L422fs) of *SLITRK1*. Mice have a total knockout of the *Slitrk1* gene and exhibit anxiety and depression but no spontaneous tics. (B) A schematic of the *HDC* gene (green = translated; red = untranslated regions) with the reported alterations in TS (white strips) and its translated product. *HDC* protein has several conserved protein domains including the pyridoxal 5′-phosphate (PLP) domain at the N-terminal end, two proline, glutamic acid, serine and threonine-rich PEST domains (PEST1 and PEST2) and a C-terminal intracellular targeting domain (ER2). Patients with TS that have genetic alterations (W317X) in the *HDC* gene are thought to express a truncated version of *HDC* lacking a part of the PLP domain, the PEST2 domain and the ER2 domain. In *Hdc*$^{-/-}$ mice, the targeting vector replaces exons 6-8 (and part of exon9) and a truncated protein similar to the one described in patients could be produced. Mice exhibit anxiety and tics that are not spontaneous but dopamine agonist-induced. Alteration of the PLP domain has a negative impact on the binding of pyridoxal 5′-phosphate, an essential coenzyme for *HDC* activity. aa - amino acids.

need to be done to prove these hypotheses. The absence of TS-like behaviours in mice with a genetic lesion which is similar to that described in patients with TS would certainly raise questions about the causative link between HDC and TS.

CONCLUSIONS

If *SLITRK1* and *HDC* are indeed linked to TS, genetic alterations of the respective gene locus most probably account for an extremely small fraction of TS cases. Nonetheless, the discovery of these rare genetic lesions have spurred research efforts aimed at the identification of the pathophysiological mechanisms underlying TS including development of genetic animal models. However, the incomplete phenotypic penetrance in the existing genetic models of TS renders them unsuitable for use in translational medicine. In this regard, establishing a genetic animal model that faithfully mimics the hallmark features of TS remains a major stumbling block in deciphering the molecular basis of this disorder as well as the discovery of novel drugs that alleviate the phenotypic spectrum of affected patients. Ways forward should involve the construction of mice models, which have a genetic aberration that closely mimics the one found in patients and the use of alternative animal models. In this respect, the fruit fly *Drosophila melanogaster* is an excellent choice in view of its role in deciphering the genetic basis of behaviour and the successes in modelling various neurological disorders including neuropsychiatric conditions such as schizophrenia, bipolar disorder and autism [72-75]. The road from lab to clinic is unquestionably long and winding but nevertheless filled with exciting opportunities.

ACKNOWLEDGEMENTS

The authors are both supported by COST Action BM0905 (http://tourette-eu.org/).

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