

# Teenager's Odd Chromosome Points To Possible Tourette Syndrome Gene

A bad break that apparently gave a young boy Tourette syndrome may turn out to be a lucky break for researchers studying the neuro-psychiatric disorder.

Tipped off by a suspicious chromosomal rearrangement, a team led by geneticist Matthew State at Yale University Medical School reports on page 317 that it has identified a gene that the researchers believe causes Tourette syndrome when mutated. Although the gene is responsible for at most a small fraction of Tourette cases, it's the best lead yet in tracking down the genetic contributors to the syndrome. "This gives us a key clue to the potential biological pathways that are altered in this disorder," says neurologist Daniel Geschwind, director of the center for autism research at the University of California, Los Angeles (UCLA).

Traditional genetic analyses of people with Tourette and their families have fingered a half-dozen chromosomal regions that appear to be involved in the syndrome, which

attention. Known as *Slit and Trk-like family member 1 (SLITRK1)*, it was related to a group of genes known to be involved in neuronal growth, guidance, and branching.

To test the gene's association with the syndrome, State and his colleagues sequenced *SLITRK1* in 174 people with Tourette. They found one person with a missing nucleotide in the gene that resulted in a truncated protein. State's medical school colleague Nenad Sestan then cultured mouse neurons that expressed either the regular *SLITRK1* gene or the version with the missing nucleotide. The cells with the normal gene grew significantly longer dendrites—the portions of the cell that reach out to receive nerve impulses—than did neurons with the mutated gene. Although the link to Tourette syndrome remains to be determined, the gene appears to have a "functionally important" role in neuronal growth and differentiation, says Sestan.

Among the 174 people with the syndrome, State, Sestan, and their colleagues also found two unrelated individuals who had a change near the coding region of the gene. The change altered a binding site for a short RNA molecule, or microRNA, that regulates expression of the gene. And both the microRNA and *SLITRK1* are expressed in portions of the brain thought to be involved in Tourette syndrome.

State suspects that mutations in or near *SLITRK1* can cause Tourette syndrome when they block or reduce the expression of the gene during development.

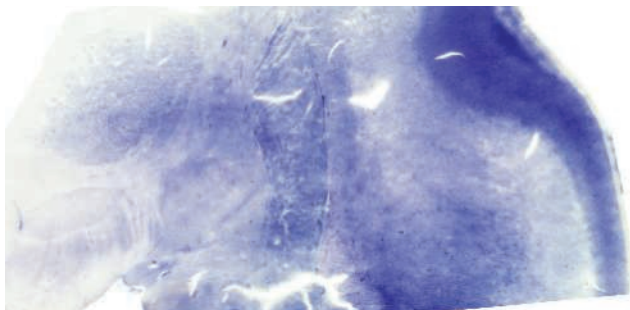
"This finding needs to be replicated," he says. "But we have multiple lines of evidence pointing to the involvement of this gene."

Other researchers warn that the findings, although interesting, remain tentative. "Each piece of the evidence is intriguing but not on its own conclusive," says UCLA geneticist Nelson Freimer. "To what degree can the pieces be combined to make a persuasive case? Opinions will differ on that."

To try to resolve the matter, TSA has given funding to State, Sestan, and their colleague neurobiologist Angeliki Louvi to produce a mouse in which *SLITRK1* has been knocked out and to study how the *SLITRK1* protein functions. "If it holds up, it's a giant leap for Tourette research," says neuropsychiatrist Neal Swerdlow of the University of California, San Diego, School of Medicine.

—STEVE OLSON

Steve Olson is a writer in Bethesda, Maryland.



**Gene find.** The potential Tourette syndrome gene *SLITRK1* is expressed (blue) in this piece of a human fetal brain.

causes as many as 1 in every 100 people to involuntarily move or make sounds (*Science*, 3 September 2004, p. 1390). But difficulties in pinning down susceptibility genes in those regions led State to take a different approach. He has been looking in people with the syndrome for chromosomal breaks and rearrangements that might implicate specific genes.

A little over a year ago, a geneticist associated with a consortium organized by the Tourette Syndrome Association (TSA) told State about a boy who had an inversion in chromosome 13: A portion of his chromosome had an orientation opposite that of normal chromosomes. The boy was the only member of his family with Tourette syndrome and the only one with the inversion.

State and his colleagues found three genes close to the breakpoints of the inversion. Two had no plausible connection to Tourette syndrome, but the third immediately drew their

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**Supporting Online Material**  
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# Sequence Variants in *SLITRK1* Are Associated with Tourette's Syndrome

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Tourette's syndrome (TS) is a genetically influenced developmental neuropsychiatric disorder characterized by chronic vocal and motor tics. We studied *Slit and Trk-like 1 (SLITRK1)* as a candidate gene on chromosome 13q31.1 because of its proximity to a de novo chromosomal inversion in a child with TS. Among 174 unrelated probands, we identified a frameshift mutation and two independent occurrences of the identical variant in the binding site for microRNA hsa-miR-189. These variants were absent from 3600 control chromosomes. *SLITRK1* mRNA and hsa-miR-189 showed an overlapping expression pattern in brain regions previously implicated in TS. Wild-type *SLITRK1*, but not the frameshift mutant, enhanced dendritic growth in primary neuronal cultures. Collectively, these findings support the association of rare *SLITRK1* sequence variants with TS.

TS is a potentially debilitating developmental neuropsychiatric disorder, characterized by the combination of persistent vocal and motor tics, that affects as many as 1 in 100 individuals (1, 2). A substantial portion of clinically referred TS patients also suffer from obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), or depression (3). A TS spectrum of disorders that includes chronic vocal or motor tics as well as tic-related OCD and ADHD is widely recognized. Phenomenological and neurobiological evidence also supports the inclusion of some habit disorders, including trichotillomania (TTM), in this phenotypic spectrum (4, 5).

Several decades of investigation have confirmed a substantial genetic contribution to TS (6). Early segregation analyses suggested that the

disorder was inherited as a rare, autosomal dominant trait (7). However, more recent studies have supported poly- or oligogenic inheritance (8). Genome-wide analysis of linkage has implicated intervals on chromosomes 4, 5, 8, 11, and 17 (9–12), but to date no disease-related mutations have been identified. These investigations have been complicated by a phenotype that typically decreases in severity with age, a high population prevalence of transient tics, and symptoms that overlap with common disorders such as ADHD and OCD (13). In addition, marked locus heterogeneity, gene-environment interactions, and the further confounding of assortative mating (14, 15) have all likely hindered gene-mapping efforts.

We focused on a rare subset of TS patients with chromosomal anomalies to circumvent

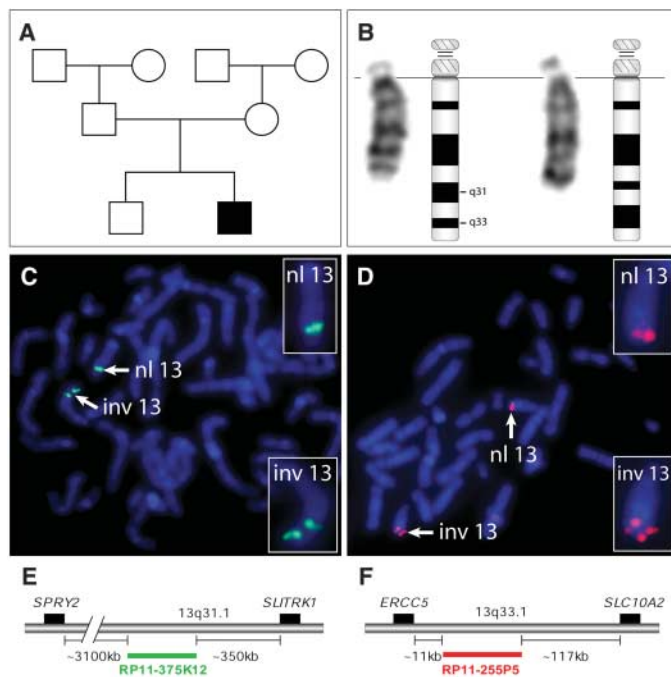
some of these obstacles and identify candidate genes for intensive mutational screening. Such a strategy provides the opportunity to characterize functional sequence variants largely irrespective of their mode of inheritance. We identified a patient presenting with TS and ADHD and carrying a de novo chromosome 13 inversion, inv(13)(q31.1;q33.1) (16). There was no family history of tics, TS, OCD, TTM, or ADHD (Fig. 1). Genotyping with multiple short tandem repeat (STR) markers confirmed paternity (16) (table S1). The co-occurrence of a de novo chromosomal abnormality with the only known case of TS in the pedigree led us to fine map the rearrangement with the use of fluorescence in situ hybridization (FISH). We found that bacterial artificial chromosomes (BACs) RP11-375K12 and RP11-255P5 span the 13q31.1 and 13q33.1 breakpoints, respectively (Fig. 1, C to F, and table S2).

Three genes map within 500 kilobases (kb) of these two breakpoints (Fig. 1, E and F). Of these, *Slit and Trk-like family member 1 (SLITRK1)*, encoding a single-pass transmembrane protein with two leucine-rich repeat (LRR) motifs in its extracellular domain, was considered the strongest candidate for further study because of its

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**Fig. 1.** Mapping of a de novo chromosome 13 paracentric inversion in a child with TS. (A) Pedigree of Family 1, with a single affected male child with TS and ADHD (16). The parents, grandparents, and younger sibling are not affected with TS, tics, ADHD, TTM, or OCD. Four maternal siblings, not presented on the pedigree, are all unaffected. (B) G-banded metaphase chromosomes 13. The ideogram for the normal (left) and inverted (right) chromosomes are presented. (C and D) FISH mapping of BAC RP11-375K12 (C) and BAC RP11-255P5 (D). The experimental probe is visualized at the expected positions on the normal (nl) chromosomes 13q31.1 and 13q33.1, respectively. Two fluorescence signals are visible on the inverted (inv) chromosomes, indicating that the probes span the breakpoint. Photographs were taken with a 100× objective lens. (E) Diagram of the interval surrounding the spanning BAC RP11-375K12 at 13q31.1. *SLITRK1* (National Center for Biotechnology Information accession code NM\_052910) maps approximately 350 kb telomeric, and *SPRY2* (NM\_005842) maps more than 3 million base pairs centromeric, to the breakpoint. (F) Diagram of the interval surrounding the spanning BAC RP11-255P5 at 13q33.1. The gene *ERCC5* (NM\_000123.2), mutated in xeroderma pigmentosum group G, maps 11 kb from the spanning BAC clone. The gene *SLC10A2* (NM\_000452.1), implicated in primary bile acid malabsorption, maps approximately 100 kb from the spanning BAC clone.

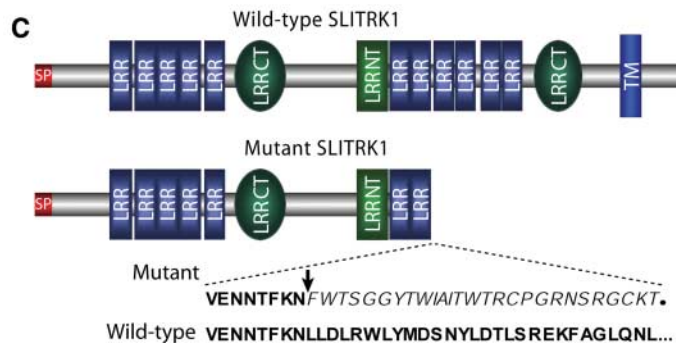
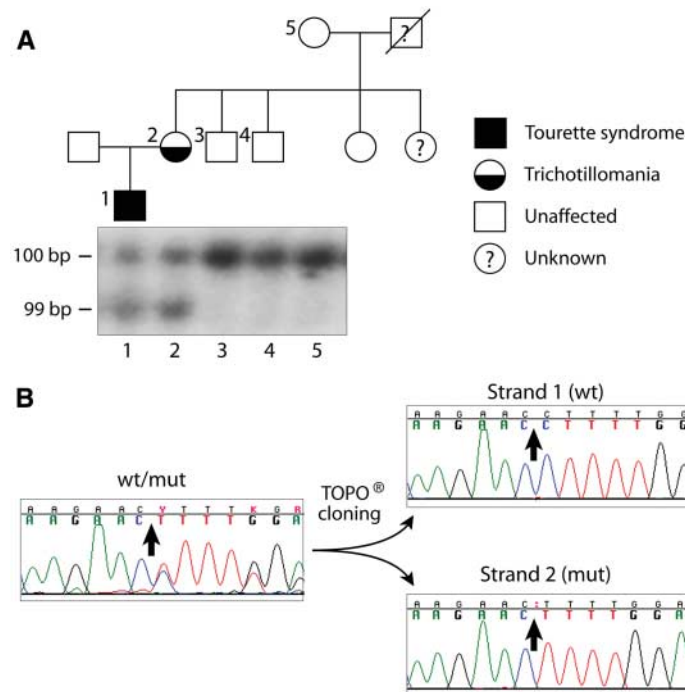


high relative expression in brain regions previously implicated in TS and its suggested role in neurite outgrowth (17, 18). *ERCC5* and *SLC10A2*, mapping immediately centromeric and telomeric, respectively, to the 13q33.1 breakpoint, were not excluded as candidates but were considered less likely alternatives because both have been shown to lead to disorders with no known relationship to TS (19, 20) (Fig. 1F).

The 13q31.1 chromosomal breakpoint mapped well outside the coding region of *SLITRK1*, and direct sequencing of the transcript in the affected individual showed no abnormalities (16). Consequently, we hypothesized that the expression of the gene might be altered by a position effect (21). However, the genomic organization of the transcript in a single coding exon, in conjunction with its low levels of expression in peripheral lymphocytes, precluded our direct quantitative assessment of *SLITRK1* mRNA in the patient versus controls.

We reasoned, however, that if altered *SLITRK1* function contributed to the risk for TS in the patient carrying the inversion, we would expect a subset of TS patients to have mutations in this gene. Accordingly, we screened *SLITRK1* in 174 affected individuals (16). We identified one proband, diagnosed with TS and ADHD, who possessed a single-base deletion in the coding region leading to a frameshift, predicted to result in a truncated protein lacking a substantial portion of the second LRR as well as its transmembrane and intracellular domains (Fig. 2).

Four additional family members were ascertained and genotyped (16). The mutation



**Fig. 2.** Identification of a truncating frameshift mutation in *SLITRK1*. (A) Pedigree of Family 2 showing the proband (individual 1) diagnosed with TS and ADHD. The patient's mother (individual 2) was retrospectively diagnosed with TTM. Individuals 3 to 5 are unaffected. The affected individuals possess a predicted 100–base pair as well as a mutant 99–base pair fragment amplifying with the same polymerase chain reaction primer pair analyzed by denaturing polyacrylamide gel electrophoresis (16). The unaffected individuals in the pedigree carry only the single expected homozygous 100–base pair band. (B) A heterozygous sequence trace from the proband shows the overlap of normal and frameshift sequence beginning at the vertical arrow. Topoisomerase (TOPO®) cloning and subsequent sequencing of the patient's DNA shows the normal sequence on one strand (top) and the mutant sequence, missing a single nucleotide, on the other (bottom). (C) Diagram of the normal and predicted mutant *SLITRK1* protein (<http://smart.embl-heidelberg.de/>). SP, signal peptide; LRRNT, LRR N-terminal domain; LRRCT, LRR C-terminal domain; TM, transmembrane domain. The predicted amino acid sequence of the mutant protein, showing 27 nonsynonymous substitutions followed by a premature stop codon (●), is presented under the truncated protein diagram and is compared with the wild-type sequence.

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was found in the patient's mother, affected with TTM, but not in the two at-risk maternal uncles or in the maternal grandmother, all of whom were unaffected (Fig. 2A). Moreover, the mutation was not present in 3600 control chromosomes (16). Finally, no truncating mutations or apparently deleterious variants were identified upon comprehensive mutation screening of the *SLITRK1* coding region in 253 controls (16) (table S4).

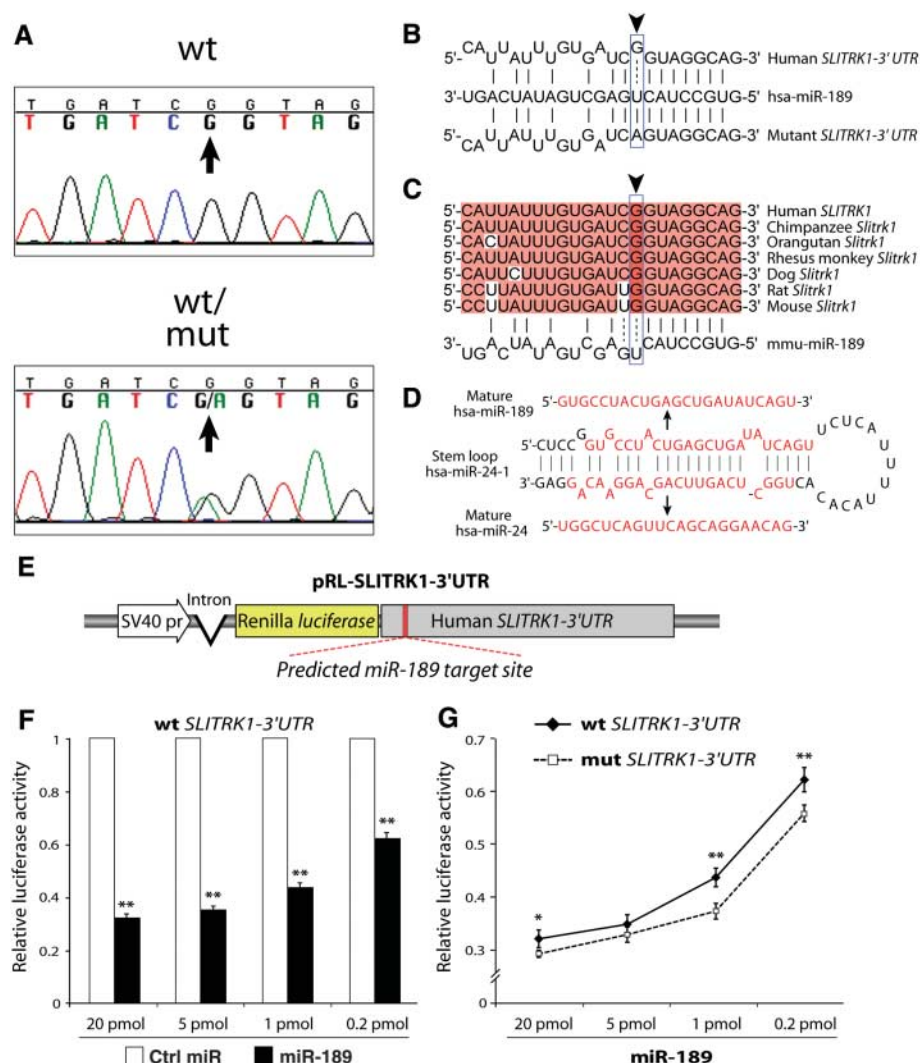
In addition to this frameshift mutation, the identical noncoding sequence variant (var321) was identified in two apparently unrelated individuals with TS and obsessive-compulsive (OC) symptoms. The single-base change maps to the 3' untranslated region (UTR) of the transcript and corresponds to a highly conserved nucleotide within the predicted binding site for the human microRNA (miRNA) hsa-miR-189, one of two mature miRNAs derived from the hsa-miR-24 precursor (22, 23) (Fig. 3, A to D, and table S6). This variant was absent from 4296 control chromosomes, demonstrating a statistically significant association with TS ( $P = 0.0056$ ; Fisher's exact test) and raising the question of whether the two occurrences might represent independent genetic events. To evaluate this, we genotyped STRs and single-nucleotide polymorphisms in close proximity to var321. In each case, the variant was found to reside on a distinct haplotype, with distinguishing polymorphisms 83.5 kb centromeric and 3.8 kb telomeric to the variant (table S7), providing strong evidence that the two occurrences arose independently. With a conservative estimate of the mutation frequency at this base ( $\sim 10^{-7}$ ), the likelihood of identifying an independent recurrence of the variant by chance among 346 chromosomes is remote ( $P = 0.000056$ ) (16).

DNA samples from the families of both probands carrying var321 were sought. Samples were unavailable from family 3, in which both the mother and father were affected; the mother had a history of chronic motor tics and the father suffered chronic vocal and motor tics, OC symptoms, and hair pulling. In family 4, only the proband carried a formal diagnosis; however, her mother, sister, a maternal grandfather, and a paternal uncle all had a history of tics, subclinical OC symptoms, or both (16). DNA was obtained from the immediate family, and its analysis showed that the proband and her mother carried the variant (16).

The var321 replaces a G:U wobble base pair with an A:U Watson-Crick pairing at position 9 in the miRNA binding domain. The extent of conservation of this G:U pairing, in both *SLITRK1* 3'UTR and miR-189 (Fig. 3B and C), as well as evidence that G:U wobble base pairs inhibit miRNA-mediated protein repression to a greater degree than would be expected on the basis of their thermodynamic properties alone (24), suggested that var321 might affect *SLITRK1* expression. To test this hypothesis, we

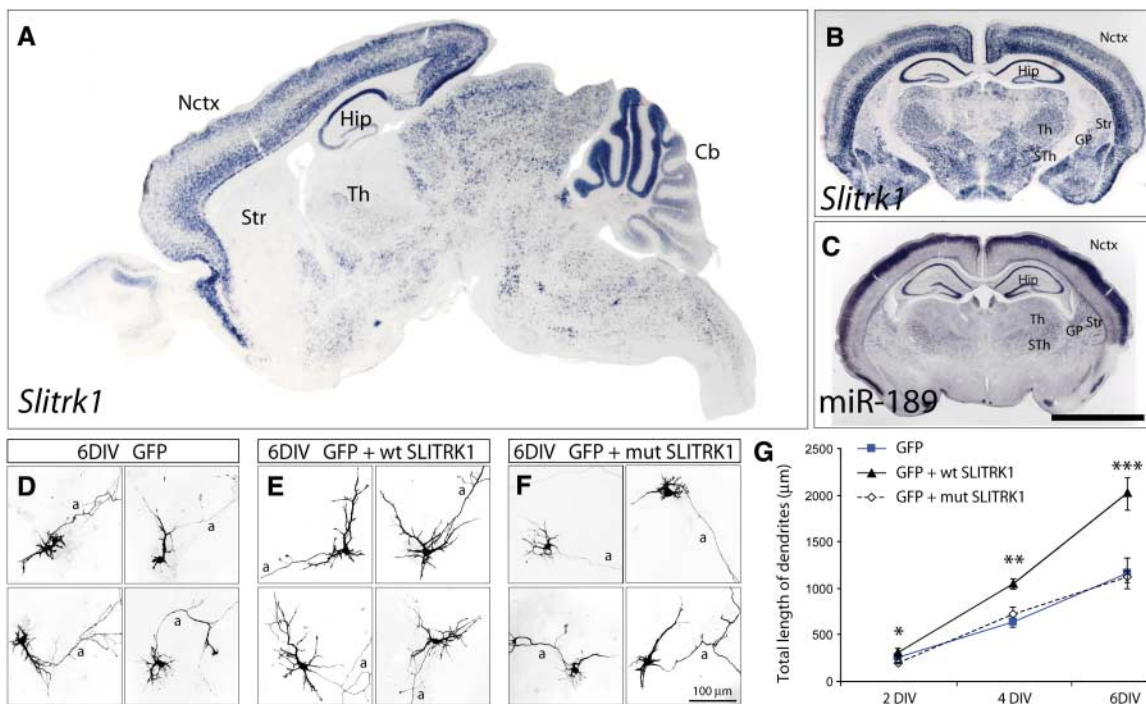
inserted the full-length *SLITRK1* 3'UTR downstream of a luciferase reporter gene and transfected the construct into Neuro2a (N2a) cells. In the presence of miR-189, the expression of luciferase was significantly reduced (Fig. 3, B to D, and table S8), confirming the functional potential of the mRNA-miRNA duplex. We next inserted the 3'UTR containing var321 and found that the sequence variant resulted in a modest but statistically significant and dose-dependent further repression of luciferase expression compared with that of the wild type (Fig. 3G and table S8).

On the basis of the hypothesis that an altered interaction of *SLITRK1* mRNA with miR-189 contributed to TS in the patients carrying var321, we reasoned that *SLITRK1* and miR-189 expression should overlap in the developing brain. In situ hybridization in postnatal mouse demonstrated that *Slitrk1* mRNA is expressed in the neocortex, hippocampus, thalamic and subthalamic nuclei, striatum, globus pallidus, and cerebellum, in agreement with earlier findings (Fig. 4, A and B) (17). We observed mmu-miR-189 expression in the developing neocortex, hippocampus, thalamus, basal ganglia, and cerebellum, overlapping



**Fig. 3.** Characterization and functional analysis of the *SLITRK1* 3'UTR. (A) The sequence of the normal 3'UTR and the substitution of G to A found in two probands. (B) The substitution maps within a predicted miRNA binding site for miR-189. Base pairing is indicated by a solid (Watson-Crick) or a dashed (wobble) vertical line. (C) Conserved bases in the binding domain are shown in red. (D) The precursor molecule hsa-miR-24-1 gives rise to hsa-miR-189 and hsa-miR-24. (E) pRL-*SLITRK1*-3'UTR contains an SV40 promoter, the *Renilla luciferase* gene, and the full-length 3'UTR of human *SLITRK1*. (F) miR-189 and pRL-wt *SLITRK1*-3'UTR, containing the native human sequence, were cotransfected into N2a cells. Relative luciferase activity (y axis) versus a random 23-base pair control miRNA. Each experiment was repeated six times for each of four different quantities of miRNA. \*\*,  $P = 0.002$  (Mann-Whitney U test). Error bars show maximum values. (G) Relative luciferase activity in the presence of miR-189 is shown for the wild-type (wt) *SLITRK1* 3'UTR (solid line) and mutant (mut) *SLITRK1* 3'UTR, containing the substitution of G to A (dashed line). \*,  $P = 0.009$ ; \*\*,  $P = 0.002$  (Mann-Whitney U test). Error bars show maximum and minimum values.

**Fig. 4.** Overlapping expression of *Slitrk1* mRNA and miR-189. (A and B) *Slitrk1* mRNA is detected in the neocortex (Nctx), hippocampus (Hip), striatum (Str), globus pallidus (GP), thalamus (Th), subthalamus (STh), and cerebellum (Cb) of postnatal day 14 (P14) mouse. (C) miR-189 expression is detected in neocortex, hippocampus, and cerebellum at P14. At P9, miR-189 expression is also detected in the striatum, thalamus, and subthalamus (fig. S1). Scale bar, 2 mm. (D to G) SLITRK1 overexpression enhances dendritic growth in cortical neurons. Images of cell bodies and dendrites, as well as proximal axonal segments (a), of representative GFP-immunopositive cortical neurons cultured for 6 DIV [(D) to (F)]. Primary cultures were prepared from embryonic day 15.5 (E15.5) embryos that were electroporated in utero at E14.5 with control GFP plasmid (GFP), GFP and wild-type human *SLITRK1* (GFP + wt *SLITRK1*), or GFP and human *SLITRK1* carrying the frameshift mutation (GFP + mut *SLITRK1*). (G) The total length of dendrites of GFP-immunopositive neurons was measured with the NeuroLucida system (16) at 2, 4, and 6 DIV. \*,  $P = 0.002$ ; \*\*,  $P = 0.001$ ; \*\*\*,  $P = 0.0007$  (Student's *t* test for wild-type *SLITRK1* versus mutant *SLITRK1*). Error bars show mean  $\pm$  SEM.



substantially with *SLITRK1* (Fig. 4C and fig. S1). In fetal human brain at 20 weeks of gestation, we detected *SLITRK1* mRNA in multiple regions, including the developing neocortical plate, subplate zone, striatum, globus pallidus, thalamus, and subthalamus (fig. S2). hsa-miR-189 was highly expressed in the cortical plate and intermediate zone (fig. S2), but not in the basal ganglia or thalamus. Overall, our results demonstrate a developmentally regulated and overlapping pattern of expression of *SLITRK1* mRNA and miR-189 in the neuro-anatomical circuits most commonly implicated in TS, OCD, and habit formation (25).

Among the six known members of the *SLIT* and *TRK*-like gene family, *SLITRK1* is unique in that it lacks tyrosine phosphorylation sites in its short intracellular domain. In this respect, it resembles the *SLIT* proteins, multifunctional secreted molecules with roles in axon repulsion (26) as well as dendritic patterning in the cerebral cortex (27). Given the high levels of cortical expression of *SLITRK1*, we investigated its effects on dendritic growth and morphology. Cortical pyramidal neurons were placed in culture after in utero electroporation of mouse embryos with wild-type human *SLITRK1* or the frameshift mutant, along with green fluorescent protein (GFP) (Fig. 4, D to F). At 2 days in vitro (DIV), dendrites expressing wild-type *SLITRK1* were significantly longer than those expressing the frameshift ( $P = 0.002$ ; Student's *t* test). By 4 and 6 DIV, dendrites expressing wild-type *SLITRK1* were significantly longer

than either comparison group, control or frameshift (Fig. 4G and table S9). These findings resemble, in part, the phenotype elicited by the exposure of cortical neurons to *SLIT1* (27) and suggest both that *SLITRK1* may promote dendritic growth and that the frameshift mutation likely results in a loss of function.

For many complex disorders, the discovery of rare mutations in small subsets of patients has had a major impact in the identification of fundamental pathways that underlie disease pathogenesis. Further study of this new candidate gene, *SLITRK1*, may serve a similar role in the effort to better understand TS at the molecular and cellular level.

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**Supporting Online Material**

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 References

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