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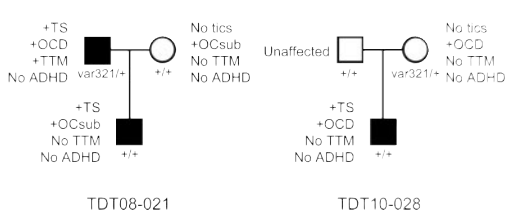
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Tourette syndrome (TS) has a significant genetic component, yet no TS susceptibility genes have been identified definitively. Several studies have determined that first-degree relatives of patients with TS have at least a 5- to 15-fold increased risk of developing the disorder compared with the general population, an increase that represents one of the highest familial recurrence risks among neuropsychiatric diseases that are inherited in a non-Mendelian fashion.¹ Recently, *Slit- and Trk-like 1* (*SLITRK1*) was proposed as a candidate TS susceptibility gene, and a noncoding polymorphism in the 3' untranslated region of this gene (var321) was reported to be associated with TS in a case-control sample.² Additional studies in small samples or population isolates have failed to replicate this association.^{3,4} As part of a 20-year collaborative effort, the Tourette Syndrome Association International Consortium for Genetics (TSAICG) has systematically collected a clinical sample of over 1,000 patients with TS and their family members.⁵ We chose to screen these individuals for *SLITRK1* var321 to determine a more accurate estimate of the prevalence of this variant in the white TS clinic population and to test for any association between var321 and TS.

Methods. A total of 2,300 individuals from 646 independently ascertained nuclear families were recruited from tic disorder specialty clinics from the United States, Canada, Great Britain, and The Netherlands. A total of 1,048 individuals (172 parents and 876 offspring) were diagnosed with either TS (989 subjects) or chronic tics (CT) (59 subjects) (e-Methods on the *Neurology*[®] Web site at www.neurology.org). A total of 440 subjects (158 affected) were of French Canadian descent, while the remainder were primarily of European ancestry. Ninety-four percent of the participants identified themselves as white. The research project was approved by the ethics committees of each participating site. Genomic DNA from all 2,300 individuals was extracted from either peripheral blood or buccal cells and purified using standard techniques. Var321 genotyping was performed by primer extension and detected by mass spectroscopy (e-Methods). The accuracy of this genotyping platform is estimated to be 99.6% (e-Methods). *SLITRK1* var321-positive alleles, as

Figure Genogram of two TS nuclear families segregating *SLITRK1* var321



For each family, shaded boxes indicate a diagnosis of TS. *SLITRK1* var321 genotypes are indicated beneath each individual. + indicates the wild-type G allele; var321 indicates the variant A allele as described previously.² Additional comorbid diagnoses are listed to the left of each family member. TS = Tourette syndrome; OCD = obsessive-compulsive disorder; OCsub = subclinical OCD; TTM = trichotillomania; ADHD = attention-deficit/hyperactivity disorder.

well as wild-type alleles in the offspring of var321 carriers, were confirmed by DNA sequencing.

Results. *SLITRK1* var321 was identified in only two individuals, both of whom were parents of TS probands. One parent had a diagnosis of TS, while the other denied any history of tics. Thus the prevalence of var321 among all TS/CT individuals was 0.1% (1/1,048). Neither of the var321-positive parents transmitted the putative risk allele to their affected offspring (figure).

Because the initial study of *SLITRK1*² reported the presence of gene variants in two parents with TS-related disorders—trichotillomania (TTM) and obsessive-compulsive symptoms—we reviewed the available phenotypic data of both var321/+ parents in further detail (figure). The TS+ parent had both comorbid OCD and hair-pulling compulsions consistent with a diagnosis of TTM. The TS-, var321/+ parent met *DSM-IV-TR* criteria for OCD, but endorsed no hair-pulling compulsions.

Discussion. The current study represents data from the largest existing clinical sample of patients with TS and provides the best estimate to date for the prevalence of *SLITRK1* var321 in the white TS population. Our prevalence estimate of 0.1% is consistent with previous reports that var321 is only rarely present in patients with TS.^{2,4} Furthermore, we failed to observe transmission of *SLITRK1* var321 from an affected parent to a child with TS in the two families segregating this variant. Combined with the data from previous studies, a total of nine TS families have now been reported that segregate var321 with five transmis-

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sions and four nontransmissions.^{2,3} Because this transmission frequency does not deviate from that expected under random Mendelian segregation, these family-based data call into question whether var321 is truly associated with TS.

A recent study of *SLITRK1* var321 in an Ashkenazi Jewish sample noted the presence of this variant in a normal Ashkenazi control, and the authors proposed that the previously reported association between TS and var321 might instead represent subtle population stratification between the case and control groups with respect to Ashkenazi Jewish heritage.³ It is interesting that both of our var321/+ parents were from Jewish families that originated in Eastern Europe. Therefore, our data are consistent with the hypothesis that *SLITRK1* var321 is an Ashkenazi-specific polymorphism rather than a pathogenic mutation.

Finally, *SLITRK1* mutations have been reported in patients with TTM, an OCD spectrum disorder that may be genetically related to TS.⁶ Because both var321-positive parents in our sample had OCD and one had TTM, *SLITRK1* var321 could be associated with TS through the confounding presence of comorbid OCD or TTM in these families. However, both OCD+/var321-positive parents failed to transmit *SLITRK1* var321 to their TS offspring, each of whom also had either OCD or subclinical OCD, arguing against this hypothesis (figure). Similarly, a recent study of 279 OCD probands found no var321 carriers.⁷ Thus *SLITRK1* is not associated with either TS or OCD within this sample.

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APPENDIX

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