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Consanguineous Iranian Kindreds with Severe Tourette Syndrome

Maria G. Motlagh, MD^{1,2,*}, Arshia Seddigh, MD^{2,3}, Behnoosh Dashti, MD, MPH², James F. Leckman, MD¹, and Javad Alaghband-Rad, MD^{2,4}

¹Child Study Center Yale University School of Medicine, New Haven, Connecticut, USA

²Department of Psychiatry, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran

³Department of Psychological Medicine, Institute of Psychiatry at the Maudsley, London, United Kingdom

⁴Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada

Abstract

The search for vulnerability genes for Tourette syndrome has been ongoing for nearly three decades. The contribution of recessive loci with reduced penetrance is one possibility that has been difficult to explore. Homo-zygosity mapping has been successfully used to detect recessive loci within populations with high rates of consanguinity. Using this technique, even quite small inbred families can be informative due to autozygosity in which the two alleles at an autosomal locus are identical by descent (i.e., copies of a single ancestral gene). To explore the utility of this approach, we identified 12 consanguineous Iranian families. Remarkably, these families were seen with an unusual natural history characterized by the early onset of vocal tics and coprolalia and frequent comorbidity with obsessive-compulsive disorder. Genotyping the affected and unaffected members of these pedigrees has the potential to identify rare recessive contributions to this disorder.

Keywords

Tourette syndrome; homozygosity mapping; recessive inheritance; coprolalia; self-injurious behavior

Tourette syndrome (TS) is a chronic neuropsychiatric disorder with onset in early childhood and characterized by motor and phonic tics. Tics are repetitive muscle contractions that produce stereotyped movements (motor tics) or sounds (phonic tics). Tics are often preceded by subtle, seemingly irresistible sensory urges that are momentarily relieved with the performance of the tic. Cooccurring disorders of attention and impulse control are common, including attention-deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD).¹

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*Correspondence to: Dr. Maria Motlagh, Child Study Center, Yale University School of Medicine, I-265 SHM, 230 South Frontage Road, New Haven, Connecticut 06520-7920. mariamotlagh@yahoo.com.

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The familial aggregation of TS, the results of twin studies, and the description of several large pedigrees with several affected members indicate that TS has a genetic basis.² Some segregation analyses in TS families found evidence for autosomal dominant inheritance, but other studies concluded for a more complex inheritance.² Recessive inheritance has received less attention although nonparametric linkage studies have suggested both dominant and recessive allelic contributions.³

Autozygosity is a term used to mean homozygosity for markers identical by descent, inherited from a recent common ancestor. Individuals with rare recessive diseases in consanguineous families have an increased likelihood to be autozygous for markers linked to the disease locus. The rarer the allele is in the population, the greater the likelihood that homozygosity represents autozygosity. It is also clear that in cultures where parental inbreeding has been long standing, the background level of homozygosity is increased by as much as 5% over and above that predicted by simple models of consanguinity.⁴⁻⁷ Homozygosity mapping has been successful in identifying rare recessive loci.⁸

In this study, we report the clinical characteristics of 12 Iranian consanguineous families. Based on an extensive clinical neurological and psychopathological assessment of all available family members, it appears that many of the probands have a distinctive and severe clinical phenotype characterized, in part, by the early onset of vocal tics and coprolalia.

SUBJECTS AND METHODS

The subjects were consecutive admissions to three tertiary referral centers in Tehran, Iran (namely Roozbeh, Iran, and Emam Hossein Hospitals). Families whose parents were biological relatives of one another were identified. All subjects met both the Tourette Syndrome Classification Study Group (TSCSG) criteria for TS⁹ and the DSM-IV-TR criteria for Tourette disorder¹⁰ as diagnosed by expert child and adolescent psychiatrists. Written informed consent was obtained for all participants after each of the procedures were fully explained. Children were also asked to assent to participate in the study in the presence of their parents after the purpose of the study and the nature of the interviews, and the blood collection procedures were described in age-appropriate language.

Patients, their parents, and all their available relatives completed clinical structured interviews by expert clinicians (MGM and JA-R). If the relative was not available, information provided by the first-degree family members was used to establish the best-estimate diagnoses. Index patients were also rated on a standard battery of instruments including the Yale Global Tic Severity Scale (YGTSS) and the Yale-Brown Obsessive Compulsive Scale (Y-BOCS).¹¹⁻¹³

An expert clinician also completed a semistructured questionnaire that included information on the onset and course of tics, obsessive-compulsive symptoms, attention deficit-hyperactivity disorder, other psychiatric disorders, and self-injurious behaviors. Medical records were also collected to document the developmental and family histories as well as a previous medical and psychological examinations and interventions. All patients (except for two) gave consent and were videotaped to further document the specific characteristics of their tic symptoms.

RESULTS

Twelve consanguineous families with at least one affected family member with TS were enrolled. In five families, the parents were first cousins. Figure 1 presents the largest of these pedigrees. The remainder were either second cousins (N = 6) or third cousins (N = 1).

The 11 remaining pedigrees are presented as supplemental materials. In all pedigrees, both TS and OCD were diagnosed in at least one additional family member.

Five of index cases were male, with the mean age of 14.6 ± 6.1 years (age range from 8 through 31 years). Mean scores for motor and vocal tics severity (according to Y-GTSS) were 19.0 (SD = 3.7) and 13.4 (SD = 5.3), respectively; mean score for the impairment severity was 38.3 (SD = 10.3). Coprolalia was present in 91.7% of our patients, and copropraxia was observed in one of the cases.

The mean age of onset for the development of vocal and motor tics were 7.2 years (SD = 2.9) and 8.4 years (SD = 2.9), respectively. The difference between the mean age of onset for vocal versus motor tics was statistically significant (paired $t = 2.34$, $df = 11$, $P = 0.04$). The mean age of onset of coprolalia was 10.2 years (SD = 3.9).

Various self-injurious behaviors were noted in 91.7% of our patients. We included behaviors such as skin scratching as well as more injurious acts such as skin picking, resulting in excoriation, bleeding, or inflammation.

The most frequent comorbidities in our Tourette sample were OCD and ADHD (6 and 5 patients, respectively). Severity of obsessive-compulsive symptoms for all index cases was ascertained with the 10-item severity scale of the Y-BOCS (mean total score = 22.3 ± 5.2). The mean age of onset of OCD was 5.8 years (SD = 1.6). The most frequently encountered obsessions and compulsions involved aggressive, sexual, and religious content (55.5%) as well as obsessions of symmetry combined with ordering and arranging compulsions (44.4%). Two probands were diagnosed with Bipolar disorder, one with Down syndrome and one with Asperger disorder.

DISCUSSION

Lander and Botstein⁴ proposed a method, referred to as “homozygosity mapping,” that consists of searching for a region of the genome that is autozygous in the inbred individuals affected by a given disease. In an effort to pursue this genetic strategy, we identified 12 consanguineous Iranian TS kindred. Remarkably, the illness was uniformly severe in these index cases accompanied with coprolalia and frequent self-injurious behaviors. The severe phenotypes seen in the probands may represent a referral bias in a developing country in which overt tic behaviors are stigmatizing to the individual and the family. However, in each of the three referral sites, coprolalia was rarely part of the initial presentation of probands from nonconsanguineous families.

Age of Onset of Vocal Tics

The mean age of onset for vocal tics was earlier than for motor tics in 8 of the 12 cases and simultaneous in two others. This is unusual, as motor tics are typically the first manifestation of TS in a majority of referred and nonreferred cases. For example, Shapiro et al.,¹⁴ in their exhaustive characterization of 658 referred cases, found that only 17% in which the initial tic symptom was vocal in character. An identical percentage was also observed in a population-based study of Swedish school-age children.¹⁵ We also note that Lichter et al.¹⁶ reported the paternal transmission of TS to be associated with an earlier onset of vocal tics relative to motor tics.

Coprolalia and Self-Injurious Behaviors

Coprolalia, which is the least understood and perhaps most unusual symptom of TS, occurs in less than one-third of clinical populations.^{14,17–21} To some extent, this may be culturally determined, as only 4% have true coprolalia in Japan,²¹ and some countries show higher

figures than in the United States or Europe.²⁰ It is also clear that the presence of vocal tics, particularly coprolalia, is associated with higher ratings of severity on scales such as the YGTSS.^{11,22}

SIB occurs in up to 60% of patients with TS, although estimates vary depending on the definition of self-injury.^{23–27} A variety of self-injurious behaviors have been reported in individuals with TS, including compulsive skin picking, self-hitting, lip and other self-biting, bruxism, head banging, and eye damage from self-poking. In one genetic study of over 300 subjects, mild to moderate SIB in TS was correlated with the presence of OC symptoms particularly the presence of aggressive obsessions. In contrast, severe SIB in TS was correlated with variables related to impulse dysregulation and the presence of episodic rage attacks. They also found that individuals who had TS plus at least one other psychiatric comorbidity had a fourfold increase in SIB, and there was a positive linear relationship between the number of psychiatric comorbidities and the presence of SIB. More recently, Cheung et al.²⁷ found that TS patients with SIB and other potentially life-threatening symptoms were significantly more likely to have a personal history of OCD, complex phonic tics, coprolalia, and copropraxia. The clinical profile of our 12 cases is consistent with these earlier observations in larger populations of clinically referred cases.

Limitations

The primary limitations of this study relate to the method of data collection used. Clinical data were collected retrospectively from subjects and their family members, leading to potential bias, including recall and ascertainment biases. In addition, longitudinal data were not available. As a result, it was not possible to assess whether the SIBs were temporally related to the presence of obsessive or impulsive symptoms. In addition, the ongoing genetic studies have not been completed, and there is no definitive evidence that these cases are the result of recessive inheritance as yet.

Progress to Date

The ongoing genetic studies have not been completed, and there is no definitive evidence that these cases are the result of recessive inheritance as yet. Thus far, the results show some promise based on a genomewide analysis of linkage by using homozygosity mapping although no chromosome segment was homozygous in all affected subjects. Several chromosomal intervals are currently under study, and genotyping of additional markers in these intervals has been completed. Several potential candidate genes are under active investigation, but the results, thus far, are not definitive.

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FIG. 1.

Pedigree of one of the consanguineous kindreds identified. Square and round symbols indicate males and females, respectively. Affected individuals are identified using the following symbols: Tourette syndrome (right half filled) symbols, chronic vocal tic disorder (right upper quadrant filled), chronic motor tic disorder or transient tic disorder (right lower quadrant filled), obsessive compulsive disorder (left lower quadrant filled), and attention deficit hyperactivity disorder (left upper quadrant filled). Unaffected subjects are indicated by unfilled symbols, and deceased subjects are indicated by a diagonal line. The proband is indicated by an arrow.