Tic Symptom Profiles in Subjects with Tourette Syndrome from two Genetically Isolated Populations

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Background: *Tourette Syndrome (TS) has a complex etiology and wide variability in phenotypic expression. Identifying underlying symptom patterns may be useful for etiological and outcome studies of TS.*

Methods: *Lifetime tic and related symptom data were collected between 1996 and 2001 in 121 TS subjects from the Central Valley of Costa Rica and 133 TS subjects from the Ashkenazi Jewish (AS) population in the US. Subjects were grouped by tic symptoms using an agglomerative hierarchical cluster analysis. Cluster membership was tested for association with available ancillary information (age of onset, tic severity, comorbid disorders, medication treatment and family history).*

Results: *Cluster analysis identified two distinct groups in each sample, those with predominantly simple tics (cluster 1), and those with multiple complex tics (cluster 2). Membership in cluster 2 was correlated with increased tic severity, global impairment, medication treatment, and presence of comorbid obsessive-compulsive symptoms in both samples, and with family history of tics, lower verbal IQ, earlier age of onset, and comorbid obsessive-compulsive disorder and attention-deficit/hyperactivity disorder in the AS sample.*

Conclusions: *This study provides evidence for consistent and reproducible symptom profiles in two independent TS study samples. These findings have implications for etiological studies of TS.*

Key Words: Tourette Syndrome, cluster analysis, symptom profile, tics, obsessions, family history

Tourette Syndrome (TS) is a neuropsychiatric disorder that begins in childhood, and is composed of multiple motor and vocal tics (APA 1994). Although the epidemiology of TS appears to be similar throughout the world, with a hypothesized global prevalence of between 1 in 100 and 1 in 2000, the phenomenology of TS worldwide is less well understood (Apter et al 1993; Burd et al 1986; Caine et al 1988; Comings et al 1990; Hornse et al 2001; Kadesjo and Gillberg 2000; Robertson 2000; Scahill et al 2001). Not only can the pattern of symptom presentation vary greatly between individuals, there may also be important differences in expression and recognition of symptoms between cultures (Mathews et al 2001; Staley et al 1997). Severity of symptoms in TS can range from mild and non-impairing to severe and incapacitating, and in addition to the motor system abnormalities that define the disorder, TS is frequently associated with a number of psychiatric comorbidities, most commonly obsessive-compulsive disorder (OCD) and attention-deficit/hyperactivity disorder (ADHD), increasing the variability of expression of this disorder (Cath et al 2001; Chee and Sachdev 1994; Freeman et al 2000; Robertson 2000).

TS is etiologically complex, with multiple genetic and environmental factors likely to play a role in its development (Burd et al 1999; Comings 1995; Eapen et al 1993; Merette et al 2000; Montgomery et al 1982; Seuchter et al 2000; TSAICG 1999; Walkup 2001; Walkup et al 1996; van de Wetering and Heutink 1993). Studies aimed at identifying its underlying etiology have been underway for years, with only moderate success. For this reason, careful phenomenologic characterization of TS is crucial in attempts to understand it. For example, in complex neuropsychiatric disorders such as TS, even small changes in the definition of the phenotype can strongly influence the potential to identify the relevant genetic mutations (Lander and Schork 1994).

One approach to further characterizing neuropsychiatric disorders to aid in genetic and other etiological studies is the identification of symptom clusters or profiles through data reduction and classification methods such as cluster, factor, or latent class analysis. Such approaches have been successfully utilized for other neuropsychiatric disorders, including two that are frequently comorbid with TS and may be etiologically related, OCD and ADHD (Alsobrook et al 1999; Baer 1994; Burns et al 2001; Cavallini et al 2002; Feinstein et al 2003; Kumar and Steer 2003; Mataix-Cols et al 1999; McKay et al 1995; Molina et al 2001; Rohde et al 2001; Scholte et al 2002; Summerfeldt et al 1999; West et al 2003). For both of these disorders, classification techniques have identified a limited number of highly consistent symptom clusters that exist in both clinical and non-clinical study samples, and appear to differ in heritability and in treatment response (Alsobrook et al 1999; Baer 1994; Burns et al 2001; Cavallini et al 2002; Feinstein et al 2003; Kumar and Steer 2003; Mataix-Cols et al 1999; McKay et al 1995; Molina et al 2001; Rohde et al 2001; Scholte et al 2002; Summerfeldt et al 1999; West et al 2003). Although there have been a few attempts to further characterize the phenomenology of TS, only one study to date has systematically examined the underlying symptom structure in TS (Alsobrook and Pauls 2002; Jankovic 1997; Jankovic and Fahn 1986; Leckman et al 2001; Miguel et al 1995; Robertson 2000; Robertson and Stern 1998; Santangelo et al 1994; Walkup et al 1995). This study used a combination of cluster

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Received June 16, 2005; revised October 4, 2005; accepted December 16, 2006.

0006-3223/06/$32.00
doi:10.1016/j.biopsych.2006.02.009

analysis and principal components analysis (PCA) to identify groups of tics that tended to occur together in 85 TS subjects who were originally ascertained for family genetic studies (Alsobrook and Pauls 2002). Because the original tic variables were binary in nature (present or absent), and thus not ideal for standard PCA studies, and because there were many more tic variables (N = 29) than appropriate for PCA given the sample size, Alsobrook and Pauls used an initial hierarchical cluster analysis to create a smaller number of continuous variables. The results of the cluster analysis were then subjected to PCA. This study identified four primary symptom factors (aggressive phenomena, pure motor and phonic tics, compulsive phenomena, and tapping/absence of grunting), which accounted for 60% of the phenotypic variance in the sample, and differed in recurrence risks to family members and in relation to demographic variables such as age of onset and associated psychiatric comorbidities. As an example, high scores on the compulsive factor were associated with earlier age of onset of symptoms in the probands, and with the presence of ADHD and OCD in their relatives.

In this paper, we use cluster analysis to identify groups of individuals characterized by similar tic symptoms in TS samples from two genetically isolated populations; the Central Valley of Costa Rica (CVCR), and the Ashkenazi Jewish population in the United States. Unlike previous research, the examination of genetically isolated populations confers several advantages, including minimizing differences in symptom expression between subjects within a group due to cultural factors, and increasing the underlying genetic homogeneity of the sample, thus increasing the power to identify underlying biological components for any identified symptom cluster.

Methods and Materials

Subjects

The study sample consisted of 121 individuals who were recruited for a genetic study of TS in the Central Valley of Costa Rica (CVCR) between 1996 and 2001, and 133 individuals of Ashkenazi Jewish (AS) descent who were recruited in the US for a genetic study of TS during the same time period. Table 1 gives the characteristics of the two study samples. All subjects met DSM-IV criteria for TS. Subjects in Costa Rica were recruited from a variety of sources, including health care professionals, advertisements in the national newspaper and television, assessments done in the schools, and family members who had heard of the study. Subjects in the US were recruited primarily from TS specialty clinics. Informed consent (and assent, for children older than 5) was obtained for all subjects, and the studies were approved by the Institutional Review Board of the University of California, San Diego and by the Institutional Review Board of the Hospital Nacional de Niños, San José, Costa Rica.

Diagnostic Assessments

Diagnostic information regarding tics and related behaviors was systematically gathered using structured instruments. The Yale Self-Report Form (YSRF), a diagnostic instrument designed by the Tourette Syndrome Association International Consortium for Genetics, was administered to subjects and their parents by a psychiatrist with experience in the diagnosis of TS (CAM in the US and LDH in the CVCR) (TSAICG 1999). In addition to tic symptoms, the YSRF contains questions about obsessions and compulsions, as well as symptoms of inattention, impulsivity, and hyperactivity, derived from the Yale Brown Obsessive Compulsive Scale and the Connor's Parent Rating Scale for ADHD, revised (Conners 1998; Goodman et al 1989). Current and lifetime symptom prevalence was assessed. Each interview was videotaped for direct confirmation of tic symptoms. When available, medical records were obtained to elicit further medical and treatment history. In the AS sample, IQ was assessed using the Kaufman Brief Intelligence Test (KBIT) (Kaufman and Kaufman 1990). IQ data were not consistently available for the Costa Rican (CR) sample and thus are not included in the analyses. Diagnoses of TS, OCD, and ADHD were made using all available materials according to DSM-IV criteria by experienced clinicians (CAM, VIR, and TLL). Worst-ever tic severity was measured for both motor and vocal tics using a modification of the Yale Global Tic Severity Scale (YGTSS). In order to avoid circularity within the analyses, complexity of tics was removed from the measure, although frequency, forcefulness, and impact of the tics (degree of disruption) was retained, as was the measure of overall impairment (Leckman et al 1989).

Statistical Analysis

All statistical analyses were generated using SPSS 11.0 and Stata 8.2. Each study sample was analyzed separately. Individual tic symptoms were grouped into clusters using an agglomerative hierarchical cluster analysis (Ward's method for binary data was used because the tics were scored as 1 for present and 0 for absent). Subjects were clustered according to the presence or

Table 1. Characteristics of the TS Subjects from the Costa Rican (CR) and Ashkenazi (AS) Samples

	CR Sample (N = 121)	AS Sample (N = 133)	X^2 or F Statistic and p Value
Gender (percent male)	81	74	$X^2 = 1.9$; $p=.17$
Age at onset	6.3 years (SD=2.6)	5.6 (2.7)	$F = 1.2$; $p=.30$
Age at interview (range)	15.7 (SD=11.9) range = 5 to 73 years	22.5 (SD=15.0) range = 5 to 75 years	$F = 1.2$; $p=.21$
YGTSS motor tic severity	16.8 (SD=3.1)	20.9 (SD=2.9)	$F = 8.7$; $p<.0001$
YGTSS vocal tic severity	12.3 (SD=3.6)	17.3 (SD=4.5)	$F = 6.1$; $p<.0001$
YGTSS total severity score	54.1 (SD=13.9)	68.8 (SD=19.1)	$F = 1.9$; $p=.004$
Percent with OCD	4.2	61.4	$X^2 = 90.8$; $p<.0001$
Percent with ADHD	23.1	43.9	$X^2 = 12.2$; $p<.0001$
Percent with self-injurious behavior	14.1	42.9	$X^2 = 25.5$; $p<.0001$
Percent treated with medications	60	94	$X^2 = 52.4$; $p<.0001$
Percent treated with neuroleptics	31	64	$X^2 = 30.3$; $p<.0001$
Percent treated with multiple medications	31	83	$X^2 = 83.0$; $p<.0001$

ADHD=attention-deficit/hyperactivity disorder. OCD=obsessive-compulsive disorder, OCS= obsessive-compulsive symptoms, YGTSS= Yale Global Tic Severity Scale.

absence of 38 tic and related symptoms based on the Euclidean-squared cluster distances. For each sample, subjects were assigned membership into two through ten clusters, and these assignments were saved as new variables. ANOVA or chi square analyses were then conducted to examine the relationship between cluster membership for the two through ten clusters and tic severity, global impairment, number of obsessive compulsive symptoms, presence of comorbid OCD or ADHD, family history of tics or TS, age of onset, history of medication treatment, and IQ. These variables were chosen for analysis to provide information about the biological and clinical coherence and meaningfulness of the clusters. For example, IQ and history of medication treatment were included to provide an assessment of overall level of functioning, as was the measure of global impairment. Family history of tics and obsessive symptoms were included to assess potential genetic contributors to the clusters. Number of obsessive symptoms was included in addition to OCD because of the low proportion of subjects in the CR sample who met full DSM-IV criteria for OCD (Table 1). The model with the most consistent associations with these variables was chosen as the best-fit model in each sample. As a comparison, and to assess the stability of the derived symptom clusters, the cluster analysis was then re-run for each sample with the data clustered by tic symptoms rather than by subjects.

In order to identify those tics that were the most informative in determining cluster membership for the best-fit models, the tic symptoms that were the most significant in the univariate analyses for cluster membership were entered into a backwards-stepwise logistic regression for each sample. Variables were sequentially removed from the model if their p value was ≥ 0.1 until the best-fit model was reached. Tics that were not independently significant within the final model were then removed, and the two models (with and without these variables) were compared using a likelihood ratio test to determine the final model. Tics that were present in fewer than 10% of the sample were excluded from the analysis.

In addition to the cluster analyses, we performed exploratory principal components analyses (PCA) on our samples, as was done in the Alsobrook and Pauls study (Alsobrook and Pauls 2002). It should be noted that the factor structure derived from this earlier work had several methodological concerns that we attempted to address in our analyses. For example, one of the factors derived by Alsobrook and Pauls was defined by only two variables rather than the usually accepted minimum of three variables per factor, and notably the two variables used to define this factor were not symptom clusters but individual binary symptoms. Second, the criteria for retaining a variable to define a factor was set quite low (absolute value of $\geq .20$), although the generally accepted practice is to retain variables with factor

Table 2. Strength of Association Between Cluster Model and Relevant Clinical and Demographic Measures

	Number of Clusters								
AS Sample	2	3	4	5	6	7	8	9	10
Motor tic severity	**.016**	.056	NS	.031	.056	.055	.052	.020	.030
Phonic tic severity	**.0006**	.0027	.0031	.0079	.010	.021	.020	.019	.018
YGTSS Impairment	**<.00001**	<.00001	.0001	.0002	.0004	.0006	.0011	.0022	.0042
OCD	**.014**	.053	NS	NS	NS	NS	NS	NS	NS
Number OCS	**<.00001**	<.00001	<.00001	.0001	.0001	.0001	.0001	<.00001	<.00001
ADHD	**.044**	.059	NS	NS	NS	NS	NS	NS	NS
Age at onset	**.043**	**.030**	NS	NS	NS	NS	NS	NS	NS
Med treatment	NS	NS	NS	NS	NS	NS	NS	NS	NS
Neuroleptic tx	.011	.025	.026	.021	**.005**	.019	.034	.052	.032
Multiple meds	**.05**	NS	NS	NS	NS	NS	NS	NS	NS
Verbal IQ	**.028**	NS	NS	NS	NS	NS	NS	NS	NS
Performance IQ	NS	NS	NS	NS	NS	NS	NS	NS	NS
Total IQ	NS	NS	NS	NS	NS	NS	NS	NS	NS
Family history of tics	NS	NS	NS	NS	NS	NS	NS	NS	NS
Bilineal family hx of tics	**.001**	.006	.007	.010	.015	.029	.044	NS	NS

	Number of Clusters								
CR Sample	2	3	4	5	6	7	8	9	10
Motor tic severity	.0007	.003	**.0005**	.0014	.0023	.0026	.0048	.0048	.0086
Phonic tic severity	**.0008**	.0013	.0039	.0048	.0101	.0174	.2743	.0056	.0086
YGTSS Impairment	**.0003**	.0007	.0014	.0037	.0074	.0117	.0204	.0349	NS
OCD	NS	NS	**.042**	NS	NS	NS	NS	NS	NS
Number OCS	.029	**.010**	.027	NS	.038	NS	NS	NS	NS
ADHD	NS	NS	NS	NS	NS	NS	NS	NS	NS
Age at onset	NS	NS	NS	NS	NS	NS	NS	NS	NS
Med treatment	**.006**	.017	.042	NS	NS	NS	NS	NS	NS
Neuroleptic tx	**.002**	.006	.017	.030	.040	.026	.035	.052	.004
Multiple meds	**.047**	NS	**.045**	.046	.045	NS	NS	NS	NS
Family history of tics	NS	NS	.040	NS	**.026**	.038	.053	NS	NS
Bilineal family hx of tics	NS	NS	NS	NS	NS	NS	NS	NS	NS

Values given are the p values associated with a one-way analysis of variance (motor tic severity, phonic tic severity, global tic severity, and age at onset), or chi square analysis (OCD, ADHD, and family history of tics), as appropriate. NS, not statistically significant. The most significant p values are in bold type, and the best-fit models for each sample are bracketed. AS, Ashkenazi sample; CR, Costa Rican sample; ADHD, attention-deficit/hyperactivity disorder; OCD, obsessive-compulsive disorder; OCS, obsessive-compulsive symptoms; YGTSS, Yale Global Tic Severity Scale.

loadings of ≥.40 (Rummel 1970). We conducted two factor analyses in each sample using the more commonly accepted and somewhat more stringent criteria. The first PCA factored a matrix of polychoric correlations between the individual binary tic symptoms. In the second PCA, analysis was limited to factoring 10 and 7 tic clusters derived from the cluster analysis in the AS and CR samples respectively, following Alsobrook and Pauls' approach.

Results

Cluster Analysis: AS Sample

The best-fit model for the AS sample was comprised of two clusters. This model was the most strongly associated with motor and phonic tic severity, global impairment, presence of OCD, ADHD, bilineal family history of tics, verbal IQ, and treatment with multiple medications. It was the second best predictor of age at onset, after the three-cluster model, and history of neuroleptic treatment, after the six-cluster model (Table 2). History of medication treatment in general, performance IQ, total IQ, and family history of tics were not significantly associated with any of the nine models.

For the most part, presence or absence of complex tics determined membership in either cluster 1 or cluster 2 (Table 3). Individuals assigned to cluster 1 were less likely to display tics such as picking, walking in patterns, copropraxia, holding unusual postures, bending or gyrating, rotating or spinning, self injurious behaviors or behaviors that could injure others, coughing, whistling, coprolalia, or word tics. Individuals assigned to cluster 2 were characterized by complex mouth tics, touching the head to the shoulder, throwing the head back, shoulder jerking and shrugging, arm or hand tics, writing tics, leg and foot tics, abdominal tensing, animal or bird noises, other phonic tics, echolalia, and palilalia. Presence of simple tics such as eye movements, nose movements, head shaking, throat clearing, and sniffing did not discriminate between membership in cluster 1 and cluster 2, nor did complex behaviors such as tapping,

Table 3. Associations of Specific Tic Symptoms with Cluster Membership for the Two-Cluster Model in the AS and CR Samples

	AS			CR		
	Cluster 1	Cluster 2		Cluster 1	Cluster 2	
Simple eye tics	89.3%	100%	$P=.02$	**83.6%**	98.4%	$P=.004$
Eye gestures	34.5%	57.5%	$P=.011$	**41.8%**	65.6%	$P=.009$
Nose movements	86.9%	93.6%	NS	47.3%	65.6%	$P=.044$
Mouth movements	61.9%	[87.2%]	$P=.002$	42.9%	[72.3%]	NS
Touching head to shoulder	42.9%	[72.3%]	$P=.001$	38.2%	[84.4%]	$P<.0001$
Throwing head back	34.5%	[70.2%]	$P<.0001$	32.7%	70.3%	$P<.0001$
Head shaking	45.2%	44.7%	NS	1.8%	3.1%	NS
Shoulder jerking	31.0%	[80.9%]	$P<.0001$	21.8%	[46.9%]	$P=.004$
Shoulder shrugging	29.8%	[78.7%]	$P<.0001$	16.4%	[50.0%]	$P<.0001$
Arm or hand movements	75%	[93.6%]	$P=.008$	20.0%	[62.5%]	$P<.0001$
Complex arm movements and writing tics	58.3%	[95.7%]	$P<.0001$	41.8%	39.6%	NS
Leg and foot movements	66.7%	[95.7%]	$P<.0001$	32.7%	{73.4%}	$P<.0001$
Walking in patterns	**19.1%**	44.7%	$P=.002$	**5.5%**	21.9%	$P=.011$
Abdominal tensing	38.1%	{70.2%}	$P<.0001$	10.9%	{59.4%}	$P<.0001$
Other motor tics	54.8%	74.5%	$P=.026$	32.7%	46.9%	NS
Touching	17.9%	36.2%	$P=.019$	9.1%	17.2%	NS
Tapping	11.9%	23.4%	NS	7.3%	12.5%	NS
Picking	**4.8%**	27.7%	$P<.0001$	1.8%	3.1%	NS
Evening up	23.8%	34.0%	NS	1.8%	4.7%	NS
Reckless behaviors	0%	2.1%	NS	0%	3.1%	NS
Copropraxia	**11.9%**	48.9%	$P<.0001$	**0%**	7.8%	$P=.034$
Unusual postures	**13.1%**	46.8%	$P<.0001$	**5.5%**	23.4%	$P=.006$
Bending or gyrating	**2.4%**	21.3%	$P<.0001$	0%	14.1%	$P=.004$
Rotating or spinning	**6.0%**	36.2%	$P<.0001$	0%	3.1%	NS
Sudden impulsive behaviors	**23.8%**	61.7%	$P<.0001$	**9.1%**	25.0%	$P=.023$
Behaviors that could injure others	**6.0%**	27.7%	$P=.001$	**1.8%**	10.9%	$P=.048$
Self injurious behaviors	**25%**	55.3%	$P=.001$	**5.5%**	18.8%	$P=.029$
Coughing	**25%**	61.7%	$P<.0001$	40.0%	50.0%	NS
Throat clearing	67.9%	76.6%	NS	76.4%	76.6%	NS
Sniffing	41.7%	63.8%	$P=.015$	65.5%	62.5%	NS
Whistling	**2.4%**	29.8%	$P<.0001$	16.6%	31.3%	NS
Animal or bird noises	28.6%	[70.2%]	$P<.0001$	20.0%	35.9%	NS
Other phonic tics	65.5%	[95.7%]	$P<.0001$	21.8%	{68.8%}	$P<.0001$
Syllables	19.1%	36.2%	$P=.03$	1.8%	4.7%	NS
Coprolalia	**11.9%**	68.1%	$P<.0001$	**9.1%**	26.6%	$P=.014$
Words	**7.1%**	48.9%	$P<.0001$	**1.8%**	14.1%	$P=.016$
Echolalia	**17.9%**	70.2%	$P<.0001$	**5.5%**	25%	$P=.004$
Palilalia	**20.2%**	63.8%	$P<.0001$	**1.8%**	12.5%	$P=.02$

Numbers represent percentage of individuals in the cluster with that symptom. Symptoms whose presence determines cluster membership are denoted by brackets, and symptoms whose absence determines cluster membership are denoted by bold type. AS, Ashkenazi sample; CR, Costa Rican sample; YGTSS, Yale Global Tic Severity Scale; ADHD, attention-deficit/hyperactivity disorder; OCD, obsessive-compulsive disorder; OCS, obsessive-compulsive symptoms.

evening up, or reckless behaviors. Individuals in cluster 2 (complex tics) had increased motor and phonic tic severity, increased global impairment, increased rates of comorbid OCD and ADHD, an earlier age of onset, lower verbal IQ, more treatment with neuroleptics, more treatment with multiple medications, and were more likely to have a bilineal family history of tics compared with individuals in cluster 1.

Cluster Analysis: CVCR Sample

In contrast to the AS sample, two models provided a good fit for the data in the CR sample: a two-cluster and a four-cluster solution. The two-cluster solution was the best predictor of phonic tic severity, global impairment, history of medication treatment, and history of neuroleptic treatment, and was the second best predictor of motor tic severity, history of multiple medications, and number of obsessive-compulsive symptoms. This model was almost identical to the best-fit model for the AS sample in terms of symptom profile (Table 3). As with the AS sample, individuals assigned to cluster 2 (complex tics) in the two-cluster model had increased motor and phonic tic severity, increased global impairment, increased numbers of obsessive symptoms, and increased history of treatment with medications, including neuroleptics and multiple medications, compared with individuals assigned to cluster 1.

The four-cluster model was the most strongly associated with motor tic severity and presence of OCD, and was also significantly associated with phonic tic severity, global impairment, number of obsessive-compulsive symptoms, family history of tics, and history of medication treatment (Table 2). Age at onset, presence of ADHD, and bilineal family history of tics were not significantly associated with any of the nine models. For this model, cluster membership could be described as the presence of multiple simple tics (cluster 1), presence of complex phonic tics (cluster 2), presence of posturing, rotating, or bending tics (cluster 3), and lack of simple tics or few tics (cluster 4) (Table 4). Individuals assigned to cluster 1 were less likely to have tics such as touching the head to the shoulder, shoulder jerking and shrugging, walking in patterns, and muscle tensing. Most tic symptoms, including eye, nose, and mouth movements, other simple motor tics, throat clearing, and sniffing, were frequently endorsed by individ-

Table 4. Associations of Specific Tic Symptoms with Cluster Membership for the Four-Cluster Model in the CR (Costa Rican) Sample

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	
Eye movements	91.7%	88.9%	100%	**68.4%**	$P<.0001$
Raising eyebrows	52.8%	{100%}	60.0%	**21.1%**	$P=.001$
Nose movements	86.1%	66.7%	80.0%	**31.6%**	$P<.0001$
Mouth movements	69.4%	77.8%	63.6%	**5.3%**	$P<.0001$
Touching head to shoulder	**27.8%**	66.7%	{87.3%}	57.9%	$P<.0001$
Throwing head back	44.4%	{88.9%}	67.2%	**10.5%**	$P<.0001$
Head shaking	2.8%	0%	3.6%	0%	NS
Shoulder jerking	19.4%	33.3%	{49.1%}	26.3%	$P=.026$
Shoulder shrugging	**16.7%**	77.8%	45.5%	**15.8%**	$P<.0001$
Arm or hand movements	27.8%	{88.9%}	58.2%	**5.3%**	$P<.0001$
Complex arm movements and writing tics	47.2%	66.7%	34.6%	31.6%	NS
Leg and foot movements	47.2%	{100%	69.1%	5.3%	$P<.0001$
Walking in patterns	5.6%	33.3%}	{20.0%}	5.3%	$P=.054$
Abdominal tensing	**11.1%**	44.4%	61.8%	**10.5%**	$P<.0001$
Other simple motor tics	44.4%	22.2%	50.9%	**10.5%**	$P=.011$
Touching	8.3%	11.1%	18.2%	10.5%	NS
tapping	8.3%	{22.2%}	10.9%	5.3%	NS
picking	2.8%	0%	3.6%	0%	NS
Evening up	2.8%	0%	5.5%	0%	NS
Reckless behaviors	0%	0%	3.6%	0%	NS
copropraxia	0%	11.1%	7.3%	0%	NS
Unusual postures	5.6%	0%	{27.3%}	5.3%	$P=.008$
Bending or gyrating	**0%**	11.1%	14.6%	**0%**	$P=.037$
Rotating or spinning	0%	0%	3.6%	0%	NS
Sudden impulsive behaviors	11.1%	22.2%	25.5%	5.3%	NS
Behaviors that could injure others	2.8%	22.2%	9.1%	0%	NS
Self injurious behaviors	5.6%	33.3%	16.4%	5.3%	NS
coughing	52.8%	{88.9%}	43.6%	**15.8%**	$P=.002$
Throat clearing	86.1%	88.9%	74.6%	57.9%	NS
sniffing	72.2%	88.9%	58.2%	52.6%	NS
whistling	19.4%	{77.8%}	23.6%	10.5%	$P=.001$
Animal or bird noises	16.7%	55.6%	32.7%	26.3%	NS
Other phonic tics	13.9%	44.4%	{72.7%}	36.8%	$P<.0001$
syllables	2.8%	11.1%	3.6%	0%	NS
coprolalia	13.9%	77.8%	18.2%	0%	$P<.0001$
words	2.8%	77.8%	3.6%	0%	$P<.0001$
echolalia	5.6%	88.9%	14.6%	5.3%	$P<.0001$
palilalia	2.8%	55.6%	5.5%	0%	$P<.0001$

Percentages represent percentage of individuals in the cluster with that symptom. Symptoms whose presence determines cluster membership are denoted by brackets, and symptoms whose absence determines cluster membership are denoted by bold type.

uals assigned to this cluster, compared to those assigned to the other clusters. Individuals assigned to cluster 2 were more likely to have eyebrow raising, throwing the head back, arm and hand movements, leg and foot movements, bending or gyrating, coughing, whistling, coprolalia, word tics, echolalia, and palilalia than were members of the other clusters. Individuals in cluster 3 were characterized by a higher frequency of touching the head to the shoulder, holding unusual postures, bending or gyrating, rotating or spinning, and other phonic tics. Individuals in cluster 4 exhibited a lower frequency of the majority of tics, but were more specifically characterized by a relative absence of eye movements, raising the eyebrows, nose and mouth movements, throwing the head back, shoulder shrugging arm and hand tics, leg and foot tics, walking in patterns, abdominal tics, other simple motor tics, coughing, and coprolalia. The presence of complex motor tics/behaviors, including writing tics, touching, tapping, picking evening up, reckless behaviors, copropraxia, rotating or spinning, sudden impulsive behaviors, behaviors that could injure others, and self injurious behaviors did not tend to discriminate between the clusters. Of note, these behaviors were relatively uncommon in all of the clusters.

Figures 1 and 2 show the results of the cluster analyses using the tic symptoms as the units of clustering rather than the subjects. This approach was used as the first step in the Alsobrook and Pauls analysis, and was done here both as a comparative measure, and to assess the robustness of the symptom structure identified above (Alsobrook and Pauls 2002). Although the tic symptoms assessed were not identical in the two studies, there was substantial overlap, allowing for comparison.

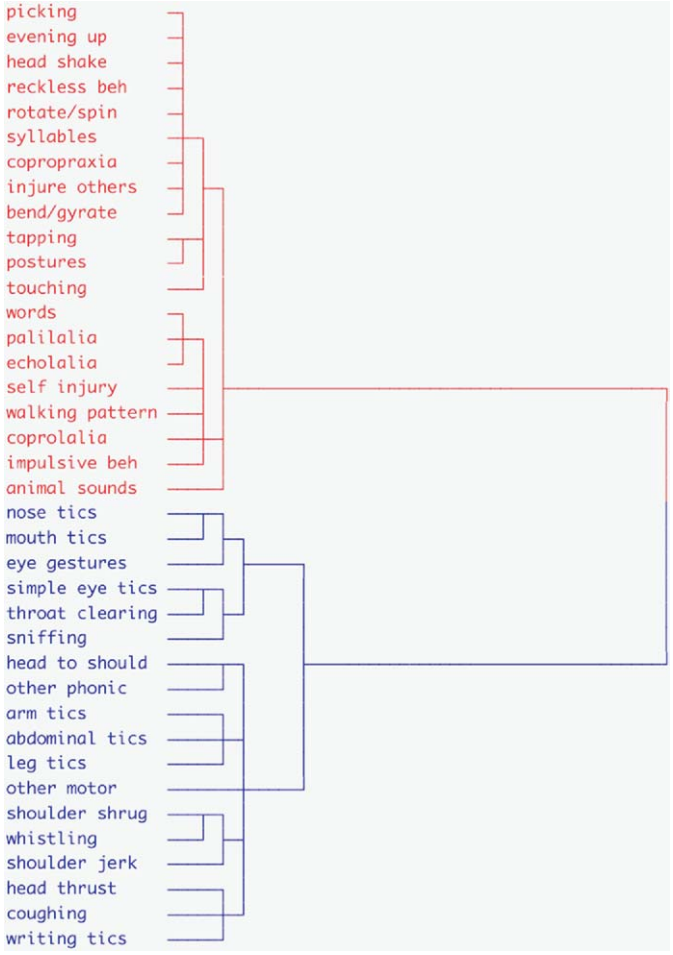

Figure 1. Hierarchical agglomerative cluster analysis using Ward's method of tic symptoms in 121 subjects with TS from the CVCR (Central Valley of Costa Rica). In this analysis, tic variables were used as the clustering units, rather than subjects. The red cluster is comprised primarily of complex tics, and the blue cluster is comprised primarily of simple tics.

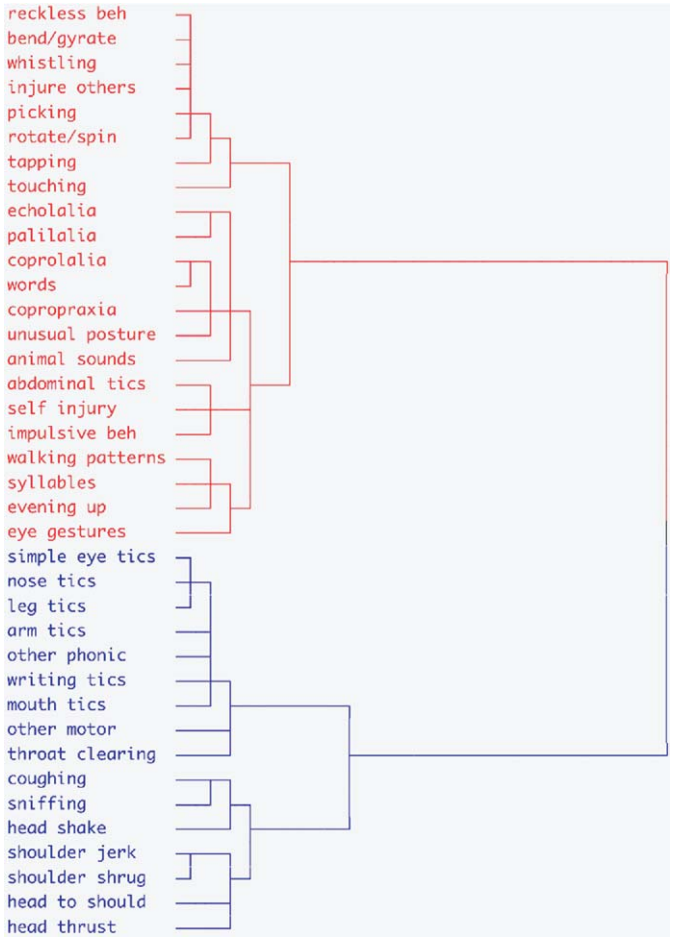

Figure 2. Hierarchical agglomerative cluster analysis using Ward's method of tic symptoms in 133 TS subjects of Ashkenazi Jewish descent. In this analysis, tic variables were used as the clustering units, rather than subjects. The red cluster is comprised primarily of complex tics and the blue cluster is comprised primarily of simple tics.

In both the AS and CR samples, the tic variables fell into two major clusters; complex tics and simple body tics. In all but a few cases, the tic symptoms contained in the complex tic cluster and those in the simple tic cluster corresponded to those seen in the Alsobrook and Pauls analysis. For example, picking, touching, tapping, echolalia, palilalia, coprolalia, self-injury, and impulsive behaviors or temper fits were contained in the complex tic cluster in all three dendograms. Tensing of body parts was also contained in this cluster in the AS and Alsobrook and Pauls sample, although not in the CR sample. Similarly, hopping was seen in the complex tics cluster in the Alsobrook and Pauls sample, and a similar tic, walking in patterns, was found in this cluster in both the AS and TS samples. For all three samples, simple eye tics, nose and other facial tics, head tics, arm tics, simple noises, arm (finger and hand tics), leg tics, and throat clearing were contained in the simple tics cluster. Coughing was the only symptom that did not fit into this pattern: it was clustered with the complex tics in the

Table 5. Best-fit Model for Tics that Best Determined Membership into Cluster 2 for the Two-Cluster Model, AS (Ashkenazi) Sample

	Odds Ratio (95% CI)	SE	Z	*p*
Echolalia	138.6 (2.55–7536.0)	282.6	2.42	.016
Other phonic tics	89.1 (1.4–5695.8)	189.0	2.12	.034
Coughing	384.9 (5.4–27344.9)	837.3	2.74	.006
Shoulder shrug	1446.1 (5.3–398310.6)	4145.4	2.54	.011
Coprolalia	2820.0 (15.1–525818.1)	7522.2	2.98	.003
Animal sounds	55.3 (2.1–1435.2)	91.9	2.42	.016
Impulsive behaviors	20.6 (1.0–441.7)	32.3	1.94	.053

LR chi^2 = 152.2, $p<0.00001$, pseudo $R^2=0.89$. Tics that were removed from the model included head thrusts, writing tics, abdominal tensing, whistling, leg and foot tics, and posturing.

Alsobrook and Pauls sample and with the simple tics in our samples.

Determinants of Cluster Membership

The tics that were the most significant determinants of cluster membership in the univariate analyses were similar between the two samples, and included head thrusts, shoulder shrugging, arm tics, leg tics, abdominal tensing, other phonic tics, posturing, and echolalia for both samples, with the addition of eye tics for the CR sample and coprolalia, coughing, whistling, and animal sounds for the AS sample. Two tics, echolalia, and other phonic tics, were key determinants of membership in cluster 2 of the two-cluster model for both samples (Tables 5 and 6). In addition, coprolalia, coughing, shoulder shrugs, animal sounds, and impulsive behaviors were important determinants in cluster membership for the AS sample, while blinking, abdominal tensing, arm tics, leg and foot tics, and head-to-shoulder tics were important determinants in cluster membership for the CR sample. These tics accounted for 89% and 72% of the variance in cluster membership in the AS and CR samples, respectively. Echolalia and other phonic tics alone accounted for one-third of the variance in cluster membership for each sample (29% for the AS sample, and 25% for the CR sample).

Exploratory Factor Analyses

For both the AS and the CVCR samples, the matrix of polychoric correlations between the individual binary tic symptoms was found not to be amenable to PCA due to a very large number of low correlations between symptoms, and thus factor analysis was not possible using the tics as binary variables. In the second PCA, which used a smaller number of continuous variables derived from the cluster analysis, we extracted three factors in the AS sample and two factors in the CR sample. These factors resembled the complex and simple tic clusters identified by cluster analyses using subjects rather than tic symptoms (data not shown). Because these results do not add substantially to the results of the cluster analyses, we have focused primarily on the results of the cluster analysis, which is remarkably similar in our samples, and also corresponds to the results of the cluster analysis reported by Alsobrook and Pauls.

Discussion

This study provides additional evidence that tics and related symptoms in individuals with TS are comprised of two primary clusters–a complex symptom cluster and a simple tic cluster. These clusters were found to be remarkably similar in two very diverse and genetically isolated populations, and were also comparable to the underlying structure seen in the hierarchical cluster analysis performed previously (Alsobrook and Pauls 2002). Individuals with membership in the complex cluster had increased tic severity, an increase in the rates of comorbid OCD and ADHD, an increase in family history of tics, and an earlier age of onset compared with those in the simple tics cluster. Traditionally, the optimal number of clusters is chosen based purely on the statistical properties of the clusters with respect to the variables used to define them. We have chosen to assess cluster coherence and clinical/biological relevance on the basis of ancillary information about individuals assigned to the clusters, and have therefore identified a two-cluster solution as the optimal solution in each sample. Measures of tic severity, global impairment, IQ, presence of comorbid syndromes such as obsessive-compulsive symptoms and ADHD, family history of tics, and history of medication treatment all have clinical relevance, and perhaps also have etiological relevance. In our study, cluster membership was highly correlated with these measures, suggesting that they also have clinical and/or biological meaning.

The similarity of the cluster profiles and the consistency of the correlations with tic severity and psychiatric comorbidity are particularly striking given the differences in symptom presentation between the study groups. Subjects in the CVCR sample were, in general, much less severely affected than were subjects in the AS group. The CVCR subjects endorsed fewer tic symptoms (only 30 tics were endorsed by at least 10% of subjects, compared with 40 tics in the AS sample) and noted less impairment from their tics. They endorsed many fewer complex or compulsive tics, including bending and gyrating, tic patterns, rotating or spinning, writing tics, nail biting, speech abnormalities, and rude gestures, and had a much lower incidence of OCD, ADHD, and self-injurious behavior. In addition, subjects in the CVCR were less often treated with medications, including neuroleptics, and less often required multiple medications than did those in the AS sample. The similarities in model structure between three very different study populations (the two in our study and that described previously by Alsobrook and Pauls), despite substantial differences in ascertainment methods, cultural expression of symptoms, levels of comorbidity, and treatment patterns, suggests that these symptom clusters represent biologically relevant substructure within TS.

These findings have potential implications for studies examining the etiology of TS, particularly for genetic studies. Family studies of TS have consistently shown that multiple TS-like phenotypes can be identified in TS families, including TS, TS + OCD, OCD alone, and a variety of other tic and related syndromes (Comings and Comings 1990a, 1990b, 1990c; McMahon et al 1996; Pauls et al 1990; Robertson and Gourdie 1990; Walkup et al 1996). However, the appropriate phenotype for genetic

Table 6. Best-fit Model for Tics that Best Determined Membership into Cluster 2 for the Two-Cluster Model, CR (Costa Rican) Sample

	Odds Ratio (95% CI)	SE	Z	*p*
Echolalia	56.3 (1.5–2087.3)	103.7	2.19	.029
Other phonic tics	44.6 (5.5–360.7)	47.6	3.56	<.0001
Blinking	762.7 (3.0–195918.0)	2159.1	2.34	.019
Head to shoulder	33.9 (4.8–239.7)	33.8	3.53	<.0001
Abdominal tensing	47.2 (5.0–446.2)	54.1	3.36	.001
Arm tics	7.0 (1.2–40.7)	6.3	2.17	.030
Leg and foot tics	10.5 (1.8–62.8)	9.6	2.59	.010

LR chi^2 = 117.9, $p=<0.00001$, pseudo $R^2=0.72$. Tics that were removed from the model included head thrusts, eye gestures, posturing, and shoulder shrugs.

studies of TS has been debated for many years, and to date, no clear causative loci for TS have been identified (Barr et al 1999; Heutink et al 1990, 1995; Merette et al 2000; Pakstis et al 1991; Simonic et al 2001; TSAICG 1999). The fact that, in our samples, simple tics did not distinguish between individuals in the two clusters (the primary difference between the clusters identified in this study was the presence or absence of complex tics and related symptoms) suggests that there is an underlying core phenotype for TS that consists of multiple simple tics, and a second TS-plus phenotype that consists of multiple simple tics plus complex tics and other complex (compulsive and/or impulsive) behaviors. We hypothesize that the core TS phenotype identified here is likely to arise from a common underlying etiology (e.g., a gene of major effect) and that the TS-plus phenotype arises with the contribution of additional genetic and/or environmental factors in some individuals. The findings from the Alsobrook and Pauls study support this hypothesis, and suggest that a second genetic factor may be important in development of cluster 2 symptoms. In their sample of TS patients and family members, the compulsive factor (subsumed under cluster 2 in our study) was associated with an increased risk of both OCD and ADHD in first-degree relatives, while none of the factors were significantly associated with an increased risk of TS (Alsobrook and Pauls 2002). Under this hypothesis, genetic studies of TS are most likely to be successful if they initially focus on the core TS phenotype regardless of the presence of additional complex symptoms, followed by the subsequent examination of individuals with more complex phenotypes such as those with comorbid OCD and ADHD, rather than dividing individuals with and without complex tics into separate groups for study. In such genetic studies, the presence and/or number of complex symptoms of the type seen in cluster 2 of our study could then be used as a covariate in a secondary genetic analysis following the identification of areas of interest in the entire sample, either to refine the linkage area in the same way that age of onset has been used as a covariate to refine the genetic studies of schizophrenia, for example, or to identify epistatic genetic effects (Glidden et al 2003). Similarly, genetic factors common to both clusters may interact with specific environmental factors (e.g., prenatal maternal smoking, exposure to stimulants) to cause symptom patterns such as those seen in cluster 2. In this case, the interaction between specific genetic loci of interest and putative environmental risk factors could be examined, as has been done for depression in the context of life stress and the serotonin transporter gene (Caspi et al 2003). In a separate study, we have identified maternal prenatal smoking as a strong risk factor for comorbid OCD and increased tic severity in TS subjects, both of which are highly correlated with membership in cluster 2 in this study (Mathews in press). Although we do not have the power to examine the relationship between specific environmental factors such as prenatal maternal smoking and cluster membership in these samples, we plan to do so in future samples, and to incorporate these findings into our genetic studies in the ways discussed above.

Limitations

The primary limitation of this study is the relatively small sample size in comparison to the large number of variables examined. We have accommodated this problem to the degree possible by choosing hierarchical cluster analysis as our principal tool, primarily because it is an exploratory approach that is less sensitive to small sample sizes than factor analysis, and also because it can easily accommodate binary variables. Small sample sizes also limit our ability to assess the relationship between cluster membership and potential environmental contributors, as mentioned above. An additional limitation is the indirect nature of the outcome data. Because these data were collected for genetic studies, we do not have optimal assessments of many potentially relevant clinical outcomes, such as treatment response or remission in adulthood. This study should be replicated in a much larger dataset, ideally one for which longitudinal data are available.

This study was supported by grants from the NINDS (R0I 444653 and R01 NS40024), the NIMH (K02 MH01375), and the NCRR (K23 RR15533).

We thank the patients and families participating in the study, and the Tourette Syndrome Association, Roxana Romero and Gila Klein for their assistance in collecting the data.

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