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Tic symptom dimensions and their heritabilities in Tourette's syndrome

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Abstract

Gilles de la Tourette's syndrome (TS) is both genotypically and phenotypically heterogeneous. Gene finding strategies have had limited success, possibly due to symptom heterogeneity.

Objectives—This study aimed at specifically investigating heritabilities of tic symptom factors in a relatively large sample of TS patients and family members.

Methods—Lifetime tic symptom data were collected in 494 diagnosed individuals, in two cohorts of TS patients from the US (n=273) and the Netherlands (n=221), and in 351 Dutch family members. Item-level factor analysis, using a tetrachoric correlation matrix in SAS (v9.2), was conducted on 23 tic symptoms from the Yale Global Tic Severity Scale (YGTSS).

Results—Three factors were identified explaining 49% of the total variance: factor 1) complex vocal tics & obscene behaviour; factor 2) body tics; and factor 3) head/neck tics. Using Sequential Oligogenic Linkage Analysis Routine (SOLAR) moderate heritabilities were found for factor 1 (h2 = 0.21) and factor 3 (h2 = 0.25). Lower heritability was found for overall tic severity (h2 = 0.19). Bi-variate analyses revealed no genetic associations between tic factors.

Conclusions—Thus, these findings suggest that 1) three tic factors can be discerned with a distinct underlying genetic architecture, and that 2) considering the low tic heritabilities found, only focussing on the narrow-sense TS phenotype and leaving out comorbidities that are part of the broader sense tic phenotype, may lead to missing heritability. Although these findings need replication in larger independent samples, they might have consequences for future genetic studies in TS.

Keywords

Tourette syndrome; tics; tic symptom factors; heritability; heterogeneity; factor analysis

Introduction

Gilles de la Tourette's syndrome (TS) is a chronic neuropsychiatric disorder characterized by the presence of both motor tics and vocal tics with onset in childhood (DSM-IV Task Force 1994). Tic symptoms are considerably variable within and across persons, especially during childhood, and may change in type, frequency and intensity over time (Cath et al. 2011). In addition to heterogeneity in tic presentation, TS also varies with regard to

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comorbid neuropsychiatric symptoms, most frequently including obsessive-compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD Cath et al. 2011; Robertson et al. 2009). Although TS is known to have a genetic etiology, the high variability in phenotypic expression and uncertainty with respect toof the relevant core phenotype(s) has, at least in part, complicated the identification of the responsible genes for susceptibility to the disorder (Scharf et al. 2013).

Data reduction methods such as factor analysis (FA), cluster analysis (CA) and latent class analysis (LCA) have recently been employed to reduce symptom heterogeneity with promising results (Cavanna et al. 2011a; Cavanna et al. 2011b; Eapen et al. 2004; Grados and Mathews 2008; Mathews et al. 2007; Robertson et al. 2008; Shytle et al. 2003; Storch et al. 2004). One of the earliest studies (Alsobrook and Pauls 2002) focused on 29 tic symptoms in 85 individuals with TS using the Schedule of Tourette and other Behavioral Symptoms (STOBS; Pauls et al. 1981), an interview which assesses presence and severity of tics, obsessive compulsive (OC) and ADHD symptoms. First, to obtain semi-continuous scores for the dichotomous items, a hierarchical CA was performed and identified 12 symptom clusters, which were transformed into sum scores and then used in a principal component factor analysis (PCFA). This resulted in four factors accounting for 61% of the variance: 1) aggressive & self injurious behaviour, with temper fits and coprolalia; 2) simple motor and phonic tics; 3) compulsive behaviour such as throat clearing and repetitive actions; and 4) finger tapping and absence of grunting. Shytle et al. (2003), using the Tourette's Disorder scale which examined tics, mood, anxiety, attentional and impulsive and OC symptoms conducted principal components analysis (PCA) in 60 patients from a university clinic, and identified 4 factors: 1)tics, 2) OC behavior, 3) ADHD, and 4) aggressive behavior (Shytle et al. 2003). Using the STOBS, Mathews et al. (2007) reported a 2-factor model to best fit the data derived from CA in two genetically isolated populations (Costa Rica & Ashkenazi Jews) containing 254 individuals with TS. The 2-factor model observed was essentially the same in the two samples: 1) simple motor and vocal/phonic tics; and 2) complex motor and vocal/phonic tics (Mathews et al. 2007; Mathews and Grados 2011).

Subsequently, Robertson et al. (2008) reported the results of a hierarchical CA followed by PCFA on 32 tic and behavioral clusters derived from the National Hospital Interview Schedule (Robertson and Eapen 1996) in 410 individuals with TS (Robertson et al. 2008). Five factors were observed: 1) socially inappropriate behaviours and complex vocal tics; 2) complex motor tics; 3) simple tics; 4) compulsive behaviours; and 5) touching self. Lastly, Cavanna et al. (2011a) extended the cohort of Robertson et al. (2008) to encompass 639 individuals with TS, then used 12 clusters of symptoms acquired through the Hospital Anxiety and Depression Scale (HADS) and the Yale Global Tic Severity Scale (YGTSS), and identified 3 factors through PCFA, including: 1) complex motor tics and paliphenomena; 2) attentional, hyperactive, and aggressive behaviors; and 3) complex vocal tics and coprophenomena, accounting for 48.5% of the variance. The similarities across the studies, summarized by Mathews and Grados (2011) encompass: a subdivision between simple and complex tics, and the placement of compulsive versus inappropriate behaviour in separate classes. However, discrepancies existed at the level of the tic symptoms, and convergence has yet to be reached on the distinct tic symptom factors that define TS. Moreover, the

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significance of these factors with respect to the underlying genetic etiology of TS has not yet been investigated.

TS has a complex etiology, with both genetic and unique environmental factors thought to determine its phenotype. With respect to the contribution of genetic factors, the heritability of TS as estimated from small clinical twin studies (Goetz and Tanner 1990; Hyde et al. 1992; Price et al. 1985; Wolf et al. 1996), from family studies (O'Rourke et al. 2009; Pauls et al. 1991) and, most recently, from genome-wide association studies (GWAS; Davis et al. 2013) is up to 60%. However, in these studies heritability estimations were performed on the Tourette/tic phenotype as a whole, including its co-morbidities, and only one study to date has investigated the heritability of tics relative to other behavioral dimensions (Grados and Mathews 2008; Mathews and Grados 2011). In a large sample of 952 individuals from 222 TS families, LCA was used to identify TS subphenotypes, taking OCD and ADHD into account. A five-class solution was found to be the best model to fit the data, with the following classes: 1) simple tics; 2) chronic tics + OCD; 3) TS + OC behavior; 4) TS + OCD; and 5) TS + OCD + ADHD combined. The 2nd, 4th and 5th classes were heritable, with heritability estimates of 0.49, 0.18, and 0.65, respectively, suggesting that the classes containing the more complex behaviors were heritable, whereas the classes primarily containing tics were not (Grados et al. 2008; Mathews and Grados 2011). However, these studies did not explore tic symptoms at an item level, nor did they investigate genetic influences to the specific tic symptom factors.

Therefore, the aims of this study were: 1) to specifically identify tic symptom factos using an item-level approach; and 2) to explore the heritability of the identified factors and their genetic relationships to each other. We hypothesized that two symptom factors (i.e. simple versus complex tics) would be identified and the complex tic factor would be more heritable than the simple tic factor.

Methods and Materials

This study is a joint venture between the Departments of Psychiatry of the University of California San Francisco (UCSF) and VU University Medical Center (VUmc). The study was approved by the Medical/Ethical Review Boards of all participating centres and all study subjects gave written informed consent. For those individuals under the age of 18, parents provided informed consent and children provided assent for participation.

Participants

The study group consisted of three samples, described in Table 1. *Sample 1* (San Francisco) consisted of 121 TS affected individuals who were recruited for a genetic study of TS in the Central Valley of Costa Rica between 1996 and 2001, and 133 TS affected individuals of Ashkenazi Jewish descent who were recruited in the US for a genetic study of TS during the same time period. Subjects from Costa Rica were recruited from a variety of sources including health care professionals, advertisements in the national newspaper and on television, and from advertising at primary and secondary schools. Ashkenazi subjects were primarily recruited from TS specialty clinics. *Sample 2* (Amsterdam) consisted of 183 individuals with TS of Dutch Caucasian descent recruited between 2003 and 2007 in the

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Netherlands within the scope of genetic studies of TS. Sample 3 consisted of 351 relatives of the Dutch TS-affected probands, predominantly parents and siblings. Relatives were recruited through the probands at the outpatient services of GGZ Ingeest, a psychiatric institution specialized in the treatment of TS, and through the Dutch TS patient association. Families ranged in size between 2 and 27 individuals, with the largest family encompassing three generations.

Assessments

All participants were interviewed by trained research psychiatrists, psychologists or nurses, and TS diagnoses were established according to DSM IV-TR criteria (American Psychiatric association 1994). Data were collected using the STOBS. This scale has been widely used by the Tourette Syndrome Association International Consortium for Genetics (TSAICG, 2007), and contains 36 tic items (rated as: current/lifetime, not present), generating lifetime tic information. The YGTSS was used to assess severity in all participants and encompasses 10 severity items that measure the number, frequency, intensity, complexity, and interference of motor and phonic tics, with a separate impairment rating (Leckman et al. 1999). In the Dutch sample, tic diagnoses were confirmed using the Diagnostic Confidence Index (DCI; Robertson et al. 1999). The Yale-Brown Obsessive-Compulsive Scale (YBOCS; Goodman et al. 1989a; Goodman et al. 1989b; Storch et al. 2005) was used to assess worst ever (San Francisco) or present (Amsterdam) OC symptom severity. The different rates of OCD diagnoses between the three samples outlined in Table 1 seem to be related to the different sources of ascertainment in the various samples, ranging from Tourette's disorder speciality clinics (AJ) to population-based advertisement (CR). However, the very low rate of OCD in the Costa Rica sample might also reflect potential differences in both genetic underpinnings and phenotypic expression of these disorders in Costa Rica.

Data management

Data from the UCSF and VUmc were cleaned and merged to create a joint database. Tic items were coded as either "0" when an individual never had the symptom or as "1" if they had the symptom either in the past or in the present. The original dataset of 36 tic-related symptoms was reduced to 26 variables and these items were entered into the factor-analyses. Seven miscellaneous tic items were excluded from the analysis due to item heterogeneity (i.e. "other complex motor tics"), and three tic items were excluded since they represented compulsive goal-directed behaviours rather than "pure" motor or vocal tics (i.e. "injuring others").

Statistical Analysis

Factor analyses—Exploratory principal component factor analyses (EFA) were conducted in TS-affected individuals from samples 1 and 2 on the 26 tic variables using the Polychor Macro in SAS (v9.2). Since the data were dichotomous, tetrachoric correlation coefficient estimates were calculated and entered into the EFA. The solution was subjected to an oblique promax rotation to facilitate interpretation of the resulting factors (Stevens 2002). Only factors with an eigenvalue >1 were retained, and the screeplot was examined to determine the best-fit model.

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Subsequent confirmatory factor analyses were carried out using Mplus (v5.2a). One-through 4-factor models were examined to determine the model with the most parsimonious fit. The factor analysis estimation was based upon weighted least squares estimates using a diagonal weight matrix. Items were assigned to a factor if they had a loading 0.4 on that factor, and items that were unstable across models (i.e. loaded on different factors from model to model) were omitted from the confirmatory analyses.

Fit indices included were: Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), Root Mean Square Error of Approximation (RMSEA), and Weighted Root Mean square Residual (WRMR). Values of the CFI and of TLI approaching 0.95, values approaching 0.08 of the WRMR, and values of RMSEA <0.05 were used as accepted general indicators of good fit.

Creation of mean sum scores—Since it is unclear to what extent the factor scores created by a particular dataset are generalizable to other samples, mean sum scale scores for the resulting factors were calculated for the factors of the final model. Mean sum scores were created by dividing the number of items endorsed in the factor by the total number of items in the factor for each participant in samples 1, 2, and 3), resulting in scores between 0 and 1 (factor scale scores). A total symptom sum score was also created by summing all the tic items and dividing by the total number of symptoms. Since neither factor scale scores nor the total sum score were normally distributed, these variables were transformed using inverse normal transformations prior to calculating heritabilities. These scores were subsequently used in the heritability analyses.

Heritability analyses—After the best factor model fit was established, heritability analyses were conducted in the Dutch sample of probands and relatives with the aid of the quantitative factor sum scores using the Sequential Oligogenic Linkage Analysis Routine (SOLAR) statistical package 6.2.2. (Almasy and Blangero 1998). SOLAR employs a variance components approach that uses information from all available family members across generations using a default polygenic model, and does not assume a specifc inheritance model. The resultant heritability statistic (h2r) is based on a maximum-likelihood-based variance decomposition approach providing an estimate and a confidence interval (Fleming 2005). Factors that were deemed likely to affect heritability estimates of the factor sum scores, such as age at interview and gender, were included as covariates in all analyses. Heritabilities for each factor sum score were calculated both with and without including the other factor sum scores as co-variates in the analyses, and heritabilities are reported both with and without these co-variates. Thus, we 1) dealt with the need to calculate heritabilities independently of other factor sum scores, as well as 2) avoided to remove all variance due to shared genetic risk between the factors, with the risk of yielding a deflated estimate of heritability for each factor and the consequence of no detection of bivariate heritabilities.. Further, age and sex were included as co-variates in all analyses whenever there were indications that they contributed to the variance explained.

Since neither factor sum scores nor the total symptom sum score were normally distributed, these variables were transformed using inverse normal transformations prior to calculating heritabilities. The heritability of tic severity based on YGTSS was also examined.

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In addition, the *degree of shared variance* between the factor sum scores due to environmental factors (RhoE) and genetic factors (RhoG) was assessed in a pair-wide fashion (Almasy & Blangero 1998), with age at assessment and gender as covariates in the analyses. The genetic correlation, which is the component of the overall correlation that is due to pleiotropy (i.e., the effect of a gene or set of genes on both traits simultaneously), was obtained from the kinship information contained in the pedigrees. In contrast, the environmental correlation was obtained from the estimate of the individual-specific error (Almasy and Blangero 1998).

Results

Clinical characteristics of the sample

Participants in Samples 1 (Costa Rica/Ashkenazi Jewish TS patients) and 2 (Dutch Caucasian TS patients) were all diagnosed with TS (97%) or chronic tics (3%). OCD was diagnosed in 61.4% of the Ashkenazi Jews, in 4.2% of the Costa Rican, and in 32.5% of the Dutch patients. A total of 107 (29.4%) Dutch family members (Sample 3) were diagnosed with TS or chronic tics, and OCD was diagnosed in 4.5% of the Dutch family members.

Factor analyses

In the course of conducting the EFA, three additional tic items were removed since they significantly cross-loaded on all factors, with a loading of >0.3. These items were: turning or stretching, whistling, and uttering syllables. Fit indices for the 1-, 2-, 3- and 4-factor models are summarized in Table 2. The factor analyses yielded 3 factors to best fit the data, explaining 49% of the overall variance, with factor 1 explaining 29.3%, factor 2 explaining 11.8% and factor 3 explaining 7.8% of the variance. These factors were: 1) complex vocal tics & obscene behaviour; 2) body tics; and 3) head/neck tics. Item loadings for the 3-factor model are displayed in Table 3.

Heritability analyses (table 4)

The heritability analyses showed significant genetic influences for factor 1 (complex vocal tics & obscene behaviour) and factor 3 (head tics). As age did not contribute to the variance in Factor 1, and since sex did not contribute to variance in factor 3 and in total tic severity scores, and since neither age nor sex explained variance in factor 2, these covariates were removed from final heritability calculations in these factors.

For factor 1, H2r =0.21 (p<0.001) when including the other factor mean scores as covariates and h2r=0.18 (p<0.001) without the other factors as co-variates. For factor 3, h2r=0.25 (p<0.001) with the other factor mean scores as co-variates and h2r=0.18 (p=0.03) without the other factor mean scores as co-variates. There was no evidence for a genetic influence on factor 2 (body tics; h2r=0.004). Total tic severity had a heritability of h2r=0.19 (p=0.001) in the sample. Since there was no evidence for a genetic influence on factor 2, we only computed bivariate heritabilities for the relationship between factor 1 and factor 3. The bivariate genetic analyses revealed no significant shared genetic influences between factor 1 and factor 3 (RhoG=0.47; p=0.27, SE=0.27), but did reveal shared environmental influences (RhoE=0.5; SE=0.03; p<0.001).

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Discussion

This study has specifically set out to detect specific “pure” tic symptom dimensions and their heritabilities instead of examining the broader sense TS phenotype, which includes the most prevalent comorbidities with OCD and ADHD. This is the first study that focusses on symptom-based tic dimensions instead of the phenotype TS as a unitary condition (including its co-morbidities), and is one of the largest factor analytic studies in TS patients and family members to date. The approach is in line with the growing body of studies that aims to decrease the symptom heterogeneity of TS (Cavanna et al. 2011a; Mathews and Grados 2011; Robertson et al. 2008).

The factor analysis yielded a 3-factor model: 1) complex vocal tics & obscene behaviour; 2) body tics; and 3) head/neck tics. These factors follow the somatosensory map with greater resolution than previous studies and arguably coincide with the homunculus of the brain. This outcome is positioned between Mathews’ 2-factor model: 1) simple motor and vocal/phonic tics; and 2) complex motor and vocal/phonic tics, and Robertson’s 5-factor model of 1) socially inappropriate behaviours and other complex vocal tics; 2) complex motor tics; 3) simple tics; 4) compulsive behaviours; and 5) touching self, sharing features with both models. It is noteworthy that Robertson et al. make the same distinction of pure tic factors into complex and simple tics as Mathews et al. do, but use different statistical methods to approach the same conclusion (LCA versus FA). The first factor (complex vocal tics & obscene behaviour) in this study is similar to Robertson’s first factor, denoting a level of convergence across the studies.

The 3-factor model found in this study, combined with the apparent lack of genetic relationship between the heritable factors (factor 1 and 3), brings forward the notion of unique differences in genetic architecture underlying the separate tic symptom dimensions, and argues against a one-tic factor model as the phenotype of choice in genetic studies. In fact, when dropping the other tic factors as co-variates from the heritability models, heritability estimates for factors 1 and 3 decreased which corroborates the specific heritability contributions to each tic symptom factor. The low heritability estimates of tic severity (lower than the actual tic symptom dimensions) are in accordance with this notion. These findings are also consistent with the previous study that examined heritabilities for TS and related disorders (Mathews and Grados 2011). In that study, heritability estimates up to 0.65 have been found when including OCD and ADHD co-morbidity, whereas tic-only heritabilities were significantly lower. Moreover, in a recent study in which Genetics-of Complex-Trait-Analysis (GCTA) was conducted using all genome-wide common variant SNP data derived from a Genome-Wide Association Study (GWAS) in TS, heritability estimates were found of 0.58 (Davis et al. 2013; Mathews and Grados 2011). GWAS data had been collected in TS patients with broadly defined phenotypes including comorbid OCD and ADHD. Genetic correlations of 0.41 were found between tics and OCD, indicating that - within TS patients-tics and OC symptoms share a substantial part of their genetic etiology. Apparently, in line with clinical notions, only part of the heritability is captured when a narrowly defined tic phenotype is used. This argues against using a pure tic phenotype as the phenotype of interest in genetic studies and indicates that within TS families, a broad

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phenotype that also includes co-morbidity with OCD and possibly with ADHD should be taken into account.

There are several limitations of this study, including the relatively small number of available families for the heritability analyses, and the small number of multigenerational families relative to sib pair and trio families. Many of the parents and other relatives of the tic patients were unaffected with TS, and had few tic symptoms, potentially lowering the heritability estimates for the quantitative tic phenotypes. Further, the contribution of age and sex to the variation differed within the different tic factors. For factor 1, when the other factors were included as covariates, age but not sex could be dropped from the model, suggesting a sex effect specifically for factor one (the complex tic factor). As expected from the population prevalences of tics, males were over-represented in our study samples (table 1) which might be an explanation for the sex contribution to the variability in factor 1.. However, following this line of reasoning, it is somewhat surprising that this sex contribution did not hold for factor 3. We do not have an adequate explanation for this. The age effect on the variability within factor 3 (head/neck tics) might be explained by overrepresentation of young individuals to head/neck tics, since in general tics onset with mild head/neck tics (Leckman et al. 1999). Finally, this study has examined only tic symptoms; because of relatively small sample sizes, we were unable to conduct factor analyses to simultaneously examine the structure of tic, OC and ADHD symptoms in our TS families, which might have led to a substantial proportion of missing heritability concerning the “broader sense” TS phenotype..

Conclusions and future directions

In sum, this study suggests that the tics in TS are composed of 3 factors, of which 2 seem to be clearly heritable, with unique genetic factors contributing to these factors. Taking these separate tic dimensions into account while performing genetic studies might fine-tune and inform future genetic studies. At the same time, only including tic symptoms in genetic analyses, rather than including OC and ADHD symptoms, may lead to an incomplete and partial picture of the actual TS phenotype and is likely to lead to missing heritabilty. Future studies should extend the item-level symptom based approach as taken in this study on tics by including comorbid OC and ADHD symptoms into a single dataset, and perform item-level based factor analyses, to unravel the factor analytic structure of the broad sense tic phenotype, which in genetic analyses may lead to more successful discovery of the genetic mechanisms underlying TS (Paschou et al. 2007). In extension to this, several exciting meta-analytic endeavours are currently carried out across diagnoses with the help of various genetic consortia that all participate in the psychiatric genetic consortium (Sullivan 2010), to investigate genetic commonalities across disorders and associate these with symptom profiles. Hopefully these joint efforts will bring about more etiology-driven classification to inform future genetic, neurobiological and treatment studies.

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Table 1

Description of patients from 3 cohorts.

	n	Age(SD)	Male Sex (%)	Mean YGTSS scores (SD)	OCD diagnosis (%)
Sample 1:					
Ashkenazi	138	22.5 (15)	74%	20.9 (2.9)	61.4%
Costa Rica	222	15.7 (11.9)	81%	29.1 (3.4)	4.3%
Sample 2:					
Dutch patients	183	27.9 (15.2)	70%	20.1 (10)	30%
Dutch relatives					
- Parents	219	51.4 (11)	45%	2.15 (1)	3%
- Siblings	63	23.4 (14.7)	40%	6.5 (8)	7%
- Offspring	36	16.3 (6.8)	60%	5.8 (8)	14%

SD: standard deviation; YGTSS: Yale Global Tic Severity Score; OCD: Obsessive Compulsive Disorder.

Psychiatr Genet. Author manuscript; available in PMC 2016 November 21.

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Table 2

Factor analyses fit indices for the 1-, 2-, 3- and 4-factor solutions.

Number of factors	1	2	3	4
CFI	0.743	0.845	0.896	0.853
TLI	0.790	0.872	0.914	0.879
RMSEA	0.080	0.062	0.051	0.061
WRMR	1.664	1.401	1.233	1.349
χ^2 (df)	80.2 (1)	65.6(1)	*	-
p-value	0.000	0.000	*	-

CFI: comparative fit index; TLI: Tucker-Lewis Index; RMSEA: Root Mean Square Error of Approximation; WRMR: Weighted Root Mean square Residual.

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Table 3

Factor loadings of the 3-factor Model

	Factor 1 Complex vocal tics & obscene behavior	Factor 2 Body tics	Factor 3 Head/Neck tics
Obscene Language	**0.82500**	−0.00229	0.22562
Complex vocal tics, Words	**0.80594**	0.04781	0.09589
Rude or obscene gestures	**0.70991**	0.04988	0.21085
Complex vocal tics, Palilalia	**0.69911**	0.04461	0.28079
Complex vocal tics, Echolalia	**0.67048**	0.15882	0.22461
Animal or bird noises	**0.50527**	0.22318	−0.00630
Unusual positions	**0.48007**	0.18690	0.39825
Single movements with leg, foot or toe	0.30532	**0.68584**	0.23252
Bend or rotate	0.31212	**0.66593**	0.00281
Complex movements with leg, foot or toe	0.18820	**0.64382**	0.11020
Single Movements with the stomach	0.03216	**0.61452**	0.32418
Single movements with arm or hand	0.32899	**0.57490**	0.18583
Complex movements with arm or hand	0.23168	**0.53576**	0.20332
Eye blinking, eye squeezing	−0.18261	0.17901	**0.65403**
Looking surprised or amazed	0.03576	0.10441	**0.64670**
Single shoulder movements	0.19017	0.20764	**0.63803**
Coughing or sniffing	0.08302	−0.24348	**0.60898**
Throat clearing	0.26087	−0.47085	**0.60722**
Complex shoulder movements	0.15120	0.28644	**0.59055**
Touch shoulder with chin, lift chin	0.21821	0.15633	**0.58832**
Widen nostrils, smile	−0.03045	0.37437	**0.53980**
Throw head backwards	0.10547	0.28644	**0.52498**
Lift nose, bite tongue	0.21111	0.27436	**0.48558**

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Table 4

Heritability estimates of tic factors and tic severity with age and sex as covariates, and with and without other factors as co-variates

Number of factors	h2r	SE	*p*	kurtosis	covariate(s)
Factor 1 (Complex)	**0.21**	0.06	0.0006	0.56	age *, sex, factor 2, factor 3
Factor 1 (Complex)	0.18	0.06	0.003	0.67	age, sex *
Factor 2 (Body)	0.004	0.07	0.48	−0.2	age *, sex *, factor 1, factor 3
Factor 2 (Body)	0	na	0.5	−0.27	age, sex *
Factor 3 (Head)	**0.25**	0.11	0.02	0.11	age, sex *, factor 1, factor 2
Factor 3 (Head)	0.18	0.09	0.03	−0.28	age, sex *
Tic Severity (YGTSS)	**0.19**	0.09	0.027	−0.43	age, sex *

*Covariates did not contribute significantly to the proportion of variance, and was removed from the final model.