

# Tic symptom dimensions and their heritabilities in Tourette's syndrome

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

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

**Participants and methods** Lifetime tic symptom data were collected in 494 diagnosed individuals in two cohorts of TS patients from the USA ( $n = 273$ ) 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 carried out on 23 tic symptoms from the Yale Global Tic Severity Scale.

**Results** Three factors were identified explaining 49% of the total variance: factor 1, complex vocal tics and obscene behaviour; factor 2, body tics; and factor 3, head/neck tics. Using Sequential Oligogenic Linkage Analysis Routine, moderate heritabilities were found for factor 1 ( $h^2r = 0.21$ ) and factor 3 ( $h^2r = 0.25$ ). Lower heritability was found for overall tic severity ( $h^2r = 0.19$ ). Bivariate analyses indicated no genetic associations between tic factors.

## 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 individuals, 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 respect to comorbid neuropsychiatric symptoms, most frequently including obsessive-compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD) (Robertson *et al.*, 2009; Cath *et al.*, 2011). Although TS is known to have a genetic aetiology, the high variability in phenotypic expression and uncertainty with respect to 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

**Conclusion** These findings suggest that (i) three tic factors can be discerned with a distinct underlying genetic architecture and that (ii) considering the low tic heritabilities found, only focusing 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. *Psychiatr Genet* 25:112–118 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

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recently been used to reduce symptom heterogeneity, with promising results (Shytle *et al.*, 2003; Eapen *et al.*, 2004; Storch *et al.*, 2004; Mathews *et al.*, 2007; Grados and Mathews, 2008; Robertson *et al.*, 2008; Cavanna *et al.*, 2011a, 2011b). 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 Behavioural Symptoms (STOBS) (Pauls *et al.*, 1981), an interview that assesses the presence and severity of tics, obsessive-compulsive (OC) and ADHD symptoms. First, to obtain semicontinuous scores for the dichotomous items, a hierarchical CA was carried out 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: (i) aggressive and self-injurious behaviour, with temper fits and coprolalia; (ii) simple motor and phonic tics; (iii) compulsive behaviour such as throat clearing and repetitive actions; and (iv) finger tapping and absence of grunting. Shytle *et al.* (2003), using the Tourette's Disorder Scale that examined tics, mood, anxiety, attentional and impulsive and OC

symptoms, carried out principal components analysis in 60 patients from a university clinic, and identified four factors: (i) tics, (ii) OC behaviour, (iii) ADHD and (iv) aggressive behaviour (Shytle *et al.*, 2003). Using the STOBs, Mathews *et al.* (2007) reported a two-factor model to best fit the data derived from CA in two genetically isolated populations (Costa Ricans and Ashkenazi Jews) of 254 individuals with TS. The two-factor model observed was essentially the same in the two samples: (i) simple motor and vocal/phonic tics and (ii) 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 behavioural 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: (i) socially inappropriate behaviours and complex vocal tics, (ii) complex motor tics, (iii) simple tics, (iv) compulsive behaviours, and (v) touching self. Finally, 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 three factors through PCFA, including the following: (i) complex motor tics and paliphenomena; (ii) attentional, hyperactive and aggressive behaviours; and (iii) complex vocal tics and coprophomena, 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 significance of these factors with respect to the underlying genetic aetiology of TS has not been investigated as yet.

TS has a complex aetiology, with both genetic and unique environmental factors believed to determine its phenotype. With respect to the contribution of genetic factors, the heritability of TS as estimated from small clinical twin studies (Price *et al.*, 1985; Goetz and Tanner, 1990; Hyde *et al.*, 1992; Wolf *et al.*, 1996), from family studies (Pauls *et al.*, 1991; O'Rourke *et al.*, 2009) and, most recently, from genome-wide association studies (GWASs) (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 comorbidities, and only one study to date has investigated the heritability of tics relative to other behavioural 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 sub-phenotypes 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: (i) simple tics, (ii) chronic tics + OCD, (iii) TS + OC behaviour, (iv) TS + OCD, and (v) TS + OCD + ADHD combined. The second, fourth and fifth classes were heritable, with heritability estimates of 0.49, 0.18 and 0.65, respectively, suggesting that the classes containing the more complex behaviours were heritable, whereas the classes primarily containing tics were not (Grados and Mathews, 2008; Mathews and Grados, 2011). However, these studies did not explore tic symptoms at an item level, nor did they investigate genetic influences on the specific tic symptom factors.

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

## Participants and materials

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

### Participants

The study group included three samples, described in Table 1. Sample 1 (San Francisco) included 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. Participants from Costa Rica were recruited from a variety of sources including healthcare professionals,

**Table 1** Description of patients from three cohorts

	<i>n</i>	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

OCD, obsessive-compulsive disorder; YGTSS, Yale Global Tic Severity Score.

advertisements in the national newspaper and on television, and from advertising at primary and secondary schools. Ashkenazi participants were primarily recruited from TS specialty clinics. Sample 2 (Amsterdam) included 183 individuals with TS of Dutch Caucasian descent recruited between 2003 and 2007 in the Netherlands within the scope of genetic studies of TS. Sample 3 included 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 two 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 used widely by The Tourette Syndrome Association International Consortium for Genetics (TSAICC) (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, 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 specialty clinics Ashkenazi Jews to population-based advertisement Costa Rica. However, the very low rate of OCD in the Costa Rican sample might also reflect potential differences in both genetic underpinnings and phenotypic expression of these disorders in Costa Rica.

### Data management

Data from the University of California San Francisco and VU University Medical Center 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 because of item heterogeneity (i.e. ‘other complex motor tics’) and three tic items were

excluded as 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 carried out in TS-affected individuals from samples 1 and 2 on the 26 tic variables using the Polychor Macro in SAS (v9.2; SAS Institute Inc., Cary, North Carolina, USA). As 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 more than 1 were retained and the screeplot was examined to determine the best-fit model.

Subsequent confirmatory FAs were carried out using Mplus (v5.2a; Muthén & Muthén, Los Angeles, California, USA). One-factor through four-factor models were examined to determine the model with the most parsimonious fit. The FA estimation was based on weighted least-squares estimates using a diagonal weight matrix. Items were assigned to a factor if they had a loading 0.4 or more on that factor and items that were unstable across models (i.e. loaded on different factors from model to model) were excluded 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 less than 0.05 were used as accepted general indicators of good fit.

#### Creation of mean sum scores

As it is unclear to what extent the factor scores created by a particular dataset are generalizable to other samples, the mean sum scale scores for the resulting factors were calculated for the factors of the final model. The 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. As neither factor scale scores nor the total sum score were normally distributed, these variables were transformed using inverse normal transformations before calculating heritabilities. These scores were subsequently used in the heritability analyses.

#### Heritability analyses

After the best factor model fit was established, heritability analyses were carried out in the Dutch sample of

**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
$\chi^2$ (d.f.)	80.2 (1)	65.6 (1)	<sup>a</sup>	—
P-value	0.000	0.000	<sup>a</sup>	—

CFI, comparative fit index; RMSEA, root mean square error of approximation; TLI, Tucker–Lewis index; WRMR, weighted root mean square residual.

<sup>a</sup>Could not be computed.

probands and relatives with the aid of the quantitative factor sum scores using the Sequential Oligogenic Linkage Analysis Routine (SOLAR; Texas Biomedical Research Institute, San Antonio, Texas, USA) statistical package 6.2.2 (Almasy and Blangero, 1998). SOLAR uses a variance components approach that uses information from all available family members across generations using a default polygenic model and does not assume a specific inheritance model. The resultant heritability statistic ( $h^2_r$ ) 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 sex, 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 covariates in the analyses, and were reported in Table 4. Thus, we (i) dealt with the need to calculate heritabilities independent from other factor sum scores and we (ii) did not remove all variance because of shared genetic risk between the factors, which brought the risk of yielding a deflated estimate of heritability for each factor, making us unable to detect bivariate heritabilities. Further, age and sex were included as covariates in all analyses whenever there were indications that they contributed towards the variance explained (Table 4).

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

In addition, the degree of shared variance between the factor sum scores because of environmental factors ( $RhoE$ ) and genetic factors ( $RhoG$ ) was assessed in a pairwise manner (Almasy and Blangero, 1998), with age at assessment and sex as covariates in the analyses. The genetic correlation, which is the component of the overall correlation because of 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 White 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 patients 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

During the course of carrying out the EFA, three additional tic items were removed as they significantly cross-loaded on all factors, with a loading of more than 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 FAs yielded three 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 (i) complex vocal tics and obscene behaviour, (ii) body tics, and (iii) head/neck tics. Item loadings for the three-factor model are shown in Table 3.

### Heritability analyses

The heritability analyses showed significant genetic influences for factor 1 (complex vocal tics and obscene behaviour) and factor 3 (head tics). As age did not contribute towards the variance in factor 1, sex did not contribute towards variance in factor 3 and in total tic severity scores and neither age nor sex explained variance in factor 2, these covariates were excluded from the final heritability calculations in these factors (Table 4).

For factor 1,  $h^2_r = 0.21$  ( $P < 0.001$ ) when including the other factor mean scores as covariates and  $h^2_r = 0.18$  ( $P < 0.001$ ) without the other factors as covariates. For factor 3,  $h^2_r = 0.25$  ( $P < 0.001$ ) with the other factor mean scores as covariates and  $h^2_r = 0.18$  ( $P = 0.03$ ) without the other factor mean scores as covariates. There was no evidence for a genetic influence on factor 2 (body tics,  $h^2_r = 0.004$ ). Total tic severity had a heritability of  $h^2_r = 0.19$  ( $P = 0.001$ ) in the sample. As 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 showed no significant shared genetic influences between factor 1 and factor 3 ( $RhoG = 0.47$ ,  $P = 0.27$ ,  $SE = 0.27$ ), but did show shared environmental influences ( $RhoE = 0.5$ ,  $P < 0.001$ ,  $SE = 0.03$ ).

**Table 3** Factor loadings of the three-factor model

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

The values in bold are the resultant heritabilities reported and discussed in the paper.

**Table 4** Heritability estimates of tic factors and tic severity with age and sex as covariates, and with and without other factors as covariates

Number of factors	h <sup>2</sup> r	SE	P	Kurtosis	Covariate(s)
Factor 1 (complex)	<b>0.21</b>	0.06	0.0006	0.56	Age <sup>a</sup> , sex, factor 2, factor 3
Factor 1 (complex)	0.18	0.06	0.003	0.67	Age, sex <sup>a</sup>
Factor 2 (body)	0.004	0.07	0.48	−0.2	Age <sup>a</sup> , sex <sup>a</sup> , factor 1, factor 3
Factor 2 (body)	0	NA	0.5	−0.27	Age, sex <sup>a</sup> , factor 1, factor 2
Factor 3 (head)	<b>0.25</b>	0.11	0.02	0.11	Age, sex <sup>a</sup> , factor 1, factor 2
Factor 3 (head)	0.18	0.09	0.03	−0.28	Age, sex <sup>a</sup>
Tic severity (YGTSS)	<b>0.19</b>	0.09	0.027	−0.43	Age, sex <sup>a</sup>

Bold values emphasize allocation of symptoms into 3 distinct groups following the factor analysis.

YGTSS, Yale Global Tic Severity Scale.

<sup>a</sup>Covariate did not contribute significantly towards the proportion of variance, and was excluded from the final model.

## Discussion

This study specifically aimed 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 to focus on symptom-based tic dimensions instead of the phenotype TS as a unitary condition (including its comorbidities), 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 (Robertson *et al.*, 2008; Cavanna *et al.*, 2011a; Mathews and Grados, 2011).

The FA yielded a three-factor model: (i) complex vocal tics and obscene behaviour, (ii) body tics, and (iii) 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’ two-factor model: (i) simple motor and vocal/phonic tics, and (ii) complex motor and vocal/phonic tics; and Robertson’s five-factor model: (i) socially inappropriate behaviours and other complex vocal tics, (ii) complex motor tics, (iii) simple tics, (iv) compulsive behaviours, and (v) touching self, sharing features with both models. It is noteworthy that Robertson and colleagues make the same distinction of pure tic factors into complex and simple tics as Mathews and colleagues do, but use different statistical methods to approach the same conclusion (LCA vs. FA). The first factor (complex vocal tics and obscene behaviour) in this study is similar to Robertson’s first factor, denoting a level of convergence across the studies.

The three-factor model found in this study, combined with the apparent lack of genetic relationship between the heritable factors (factors 1 and 3), leads to 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 excluding the other tic factors as covariates from the heritability models, heritability estimates for factors 1 and 3 decreased, which corroborates the specific heritability contributions towards 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 comorbidity, whereas tic-only heritabilities were significantly lower. Moreover, in a recent study in which Genetics-of Complex-Trait-Analysis (GCTA) was carried out using all genome-wide common variant SNP data derived from a GWAS in TS, heritability estimates of 0.58 were found (Mathews and Grados, 2011; Davis *et al.*, 2013). 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 aetiology. 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 phenotype that also includes comorbidity 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 multi-generational 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 towards 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 excluded 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 towards 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 effect of age on the variability within factor 3 (head/neck tics) might be explained by over-representation of young individuals to head/neck tics as in general tics onset with mild head/neck tics (Leckman *et al.*, 1999). Finally, this study has examined only tic symptoms; because of the relatively small sample sizes, we could not carry out FAs to simultaneously examine the structure of tic, OC and ADHD symptoms in our TS families, which might have led to a considerable proportion of missing heritability in the 'broader sense' TS phenotype.

### Conclusion and future directions

In sum, this study suggests that the tics in TS are composed of three factors, of which two seem to be clearly heritable, with unique genetic factors contributing

towards 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 heritability. Future studies should extend the item-level symptom-based approach as adopted in this study on tics by including comorbid OC and ADHD symptoms in a single dataset, and carry out item-level-based FAs 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 addition, several exciting meta-analytic endeavours on GWAS results of individual disorders (i.e.: Tourette's disorder, OCD, schizophrenia, anorexia nervosa), brought together in the Psychiatric Genetics Consortium are currently carried out (Sullivan, 2010). Hopefully, these joint efforts will yield more aetiology-driven classification to inform future genetic, neurobiological and treatment studies.

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### Conflicts of interest

There are no conflicts of interest.

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