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Familial risks of Tourette Syndrome and Chronic Tic Disorders: A population-based cohort study

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ABSTRACT

Importance: Chronic Tic Disorders (CTD), including Tourette Syndrome (TS), are assumed to be strongly familial and heritable. While gene-searching efforts are well underway, precise estimates of familial risk and heritability are lacking. Previous controlled family studies were small and typically conducted within specialist clinics, resulting in potential ascertainment biases. They were also underpowered to disentangle genetic from environmental factors contributing to the observed familiality. Twin studies have been either very small or based on parent-reported tics in population-based (non-clinical) twin samples.

Objective: To provide unbiased estimates of familial risk and heritability of TS/CTD at the population level.

Design and Setting: Population cohort, multigenerational, family study.

Participants: Using a validated algorithm, we identified 4,826 individuals diagnosed with TS/CTD (76% male) in the Swedish National Patient Register between 1969-2009.

Main outcome measure: Risks (Odds Ratios; OR) for TS/CTD in all biological relatives of probands, compared to relatives of unaffected individuals (matched on a 1:10 ratio) from the general population. Structural equation modeling was used to estimate the heritability of TS/CTD.

Results: The risk for TS/CTD amongst relatives of TS/CTD probands increased proportionally to the degree of genetic relatedness. The risks for first-degree relatives (OR= 18.69, 95% CI 14.53-24.05) were significantly higher than for second-degree relatives (OR= 4.58, 95% CI 3.22-6.52) and third-degree relatives (OR= 3.07, 95% CI 2.08-4.51). First-degree relatives at similar genetic distances (e.g. parents, siblings, offspring) had similar risks for TS/CTD, despite different degrees of shared environment. The risks for full siblings (50% genetic similarity; OR= 17.68, 95% CI 12.90-24.23) were significantly higher than that for maternal-half siblings (25% genetic similarity; OR= 4.41, 95% CI 2.24-8.67), despite similar environmental exposures. The

heritability of TS/CTD was estimated to be 0.77 (95% CI 0.70-0.85). There were no differences in familial risk or heritability between male and female patients.

Conclusions and relevance: TS/CTD clusters in families primarily due to genetic factors and appears to be amongst the most heritable neuropsychiatric conditions.

Keywords: Tourette syndrome, Chronic Tic Disorders, family study, genetic epidemiology

INTRODUCTION

Tourette Syndrome (TS) is thought to be a strongly familial and heritable neuropsychiatric disorder [1]. Controlled family studies have reported a 10- to 100-fold increase in the rates of TS in first-degree relatives of affected individuals, compared to control relatives [2-6]. Furthermore, chronic tic disorders (CTD) also occur more frequently among first-degree relatives of TS probands, compared to relatives of controls (7- to 22-fold increase), suggesting that TS and CTD share common etiological factors [1]. These previous family studies were carefully conducted but also had important limitations. First, the estimates of family risk have varied broadly, suggesting that previous studies may have been underpowered to provide precise estimates of familial transmission. Second, families were primarily recruited from specialist clinics, potentially resulting in the inclusion of more severe and impaired cases. Families with several affected members may have been more likely to volunteer for participation, thus inflating the familial risk. These possible biases can optimally be addressed by examining the familial structure of TS/CTD at the population level [7], recruiting patients from non-specialist clinics and randomly selecting control families from the general population. Third, studies conducted to date were underpowered to calculate risks for relatives with different degrees of genetic relatedness to the proband and different degrees of shared environmental exposures. Consequently, these studies could not disentangle genetic from environmental factors contributing to the observed familiality of TS/CTD. Fourth, previous family studies were too small to examine possible gender

differences in familiality and heritability; this is of critical importance given that TS/CTD is much more common in males than in females [8-12].

Twin studies are ideal to disentangle these aetiological factors, based on the different genetic resemblance of twins. To our knowledge, only two small twin studies of diagnosed TS/CTD cases have been published to date. Price and colleagues [13] recruited 30 identical (monozygotic (MZ)) and 13 same-sex non-identical (dizygotic (DZ)) twin pairs (mean age 18 years) from the Tourette Syndrome Association and found that 77% of MZ twins and 23% of DZ twins were concordant for tic disorders (TS or CTD). The MZ concordance rate reached 100% for TS or CTD when direct observational interviews were conducted on the same twin sample [14]. In another study of 16 pairs of MZ twins (mean age 13 years), 56% were concordant for TS and 94% were concordant for tic disorders but, because DZ twins were not included, no conclusions could be made about heritability [15]. Though the higher MZ concordance rates have been interpreted as implicating genetic factors as strongly contributing to the aetiology and familial transmission of TS/CTD, and gene-searching efforts are well underway [16-18], this evidence comes from small samples that may not represent broader TS and chronic tic populations.

Three recent population-based studies have examined the heritability of parent-rated tics in children, resulting in modest heritability estimates. A Japanese study of 1896 twin pairs aged 3-15 (mean 11 years) reported modest heritability estimates (around 30%) for parent-rated

tics [19]. A British study including 854 pairs of 6-year old twins found evidence for strong familial effects on parent-rated tics (61%) but was unable to separate genetic from shared environmental sources of familial aggregation due to power issues [20]. A large nationally-representative sample of over 10,000 Swedish twins aged 9-12, reported heritability estimates for parent-rated tics of 56% [95% confidence intervals (CIs) 37-68], with the remaining variance due to non-shared environmental factors [21]. Although the assessment instrument varied across these studies, collectively, they suggest moderate heritability of parent-rated tics in young people, but it is unclear to what extent these findings can be extrapolated to clinically diagnosed tic disorders.

In an attempt to overcome some of these limitations and provide unbiased estimates of family clustering and heritability of TS/CTD at the population level, we linked and analyzed data from two Swedish population-based registers and tested three hypotheses: 1) TS/CTD will cluster in families at the population level; 2) the risk of TS/CTD will increase proportionally to the degree of genetic relatedness to the proband; 3) shared environment effects will be negligible. In exploratory analyses, we also examined possible gender differences in the patterns of familial clustering of TS/CTD.

METHODS

Swedish registers

Following approval from the Regional Ethics Committee in Stockholm, we linked two Swedish national registers, using the individual national registration numbers assigned at birth.

The Multi-Generation Register contains information about the identity of biological and adoptive parents of each individual born in Sweden since 1932 (with the mother as informant) or who immigrated to Sweden together with one or both parents before the age of 18 years and lived in Sweden at any time since 1961. Unless the biological/adoptive parents have actually lived in Sweden since 1947, when the national personal identification number was introduced, it is not possible to identify them. The father was defined either as the mother's husband at the time of birth, or the man acknowledged as father by unmarried mothers. With information on parents, it is possible to create family pedigrees for all individuals with relatives at increasing genetic and environmental distances from each index person.

The National Patient Register contains diagnostic information about patients treated in Sweden since 1969, with each consultation as a unique record in the register. Initially, it contained information on all inpatient care. From 2001, however, it also includes individuals with outpatient visits to specialist physicians (other than general practitioners) that resulted in one or more diagnoses according to the ICD-10 [22].

ICD diagnostic codes

The ICD codes for TS/CTD have been validated in Sweden (Rück et al, submitted). Briefly, we obtained a random sample of TS/CTD patient records from 3 Swedish counties (N=73), of which 64 contained sufficient information for analysis. Each file was carefully reviewed and blindly rated by two independent physicians. There was 100% of agreement between the two raters regarding the presence or absence of a chronic tic disorder (Kappa = 1, $p<0.001$). Overall, the ICD codes had excellent validity, with a positive predictive value (PPV) of 92% for both raters. The PPVs for ICD-8, ICD-9 and ICD-10 cases were 0.89, 0.86 and 0.97, respectively.

Further examination of specific ICD-10 sub-codes, revealed that the majority of patients who had F95.1 (CTD) codes in the register were diagnosed as TS (F95.2) by the raters (both motor and vocal tics were identified in the clinical histories). Unspecified tic disorder (F95.9) cases were diagnosed by the raters as either TS (F95.2), CTD (F95.1), unspecified tic disorder (F95.9) or transient tics (F95.0), suggesting that F95.9 is used more freely by clinicians. Consequently, we developed an algorithm to ensure that individuals who had transient tics as their only or final diagnostic code within the same year of the initial diagnosis were excluded from the analyses. Furthermore, individuals who received an initial diagnosis of transient, 'other' or unspecified tics were only included if they received at least an additional diagnosis of a tic disorder, except if the last available diagnosis was of transient tic disorder given within the same year of the initial diagnosis (Rück et al, submitted). We did not exclude any participants based

on comorbidities, as we preferred not to make assumptions about the hierarchical structure of mental disorders.

Data Analyses

The risk of TS/CTD in relatives of probands with TS/CTD were compared with the risk in relatives of 10 randomly selected, unaffected control individuals matched by sex, birth year and county of residence at the time of the first recorded TS/CTD diagnosis of the proband. Relatives were also matched by sex and birth year. For instance, for each proband, we detected all possible proband-full sibling pairs, and randomly selected 10 control-full sibling pairs matched to probands-sibling pairs by sex and birth year. Because each proband may appear multiple times in different categories (e.g. parent, sibling and cousin) depending on family structure, the matching was done separately for each proband-relative pair to ensure adequate control of cohort/period effects and allow for equal time at risk for proband-relatives and control-relatives. The matching procedure was used for all available first-, second- and third degree relatives of each proband. We also examined potential gender effects by separately analyzing respective pairs of male-male, male-female, female-female and female-male probands and relatives.

Because the data were matched and the outcome dichotomous, we employed a conditional logistic regression model with the PROC PHREG procedure in SAS, version 9.3 [23]. Because several possibly correlated pairs of relatives from every family could be included in the

179 analysis, we adjusted for the non-independence of family members (e.g. several sibling pairs,
180 which share the same parents) by computing corrected (less narrow) confidence intervals with a
181 robust sandwich estimator (covsandwich option in PHREG).

182 By assuming that a continuous normally distributed liability underlies the observed
183 dichotomous diagnosis of TS/CTD, the tetrachoric correlations of TS/CTD between family
184 members can be estimated. These are often employed in twin and family studies to obtain
185 approximate heritability estimates using structural equation modeling. We fitted
186 liability-threshold models using full siblings and maternal half-siblings to decompose the
187 variance in liability of TS/CTD into additive genetic effects (A), shared environmental effects
188 (C), and non-shared environmental effects (E). Age and sex were adjusted for in the threshold of
189 TS/CTD. The genetic correlation was fixed to 0.5 for full siblings (they share on average 50% of
190 their segregating genes), and to 0.25 for maternal half-siblings (sharing 25% of their genes), and
191 we assumed that the family environment is shared between full siblings and maternal
192 half-siblings (Supplementary Materials). We began our model fitting with a full ACE model
193 allowing sex difference for the estimates of ACE. We then sought to simplify the model by
194 equating the ACE estimates between males and females, and then dropped the shared
195 environmental effects. Goodness of fit between the different models was assessed by a
196 likelihood-ratio test. Maximum likelihood estimation and univariate model fitting were
197 performed using the structural equation modeling package OpenMx in R.

198

199 **RESULTS**

200 *Sample characteristics*

201 Our algorithm resulted in the identification of 4,826 individuals diagnosed with TS/CTD (3,678
202 or 76.2% male; age mode = 10) between 1969-2009. Of the TS/CTD subjects, 73% had at least
203 one lifetime psychiatric comorbidity (Attention Deficit Hyperactivity Disorder 38%,
204 Obsessive-Compulsive Disorder 15%, Pervasive Developmental Disorders [PDD] 20%, Mental
205 Retardation [MR] 21%, Depression 16%, Anxiety disorders 12%, Other neurotic, stress-related
206 and somatoform disorders 14%, Substance use 10%).

207

208 *Familial risk of TS/CTD*

209 First-degree relatives of individuals with TS/CTD had significantly higher risk of having
210 TS/CTD than second-relatives and third-degree relatives. In turn, the odds ratios (ORs) for
211 second-degree relatives were higher than for third-degree relatives, though the confidence
212 intervals overlapped (**Table 1** and **Figure 1**). The pattern of results did not change substantially
213 when cases with PDD or MR were excluded from the analyses (Supplemental Figure 1).

214 Shared environmental influences on TS/CTD appeared to be considerably less
215 important. Full siblings, parents, and children of TS/CTD probands (all with 50% genetic
216 similarity but siblings assumed to have more shared environment as they grew up together in the

same family approximately during the same period of time) had comparable risks. Additionally, the risks for full siblings (50% genetic similarity) were significantly higher than that for maternal-half siblings (25% genetic similarity), despite similar shared environmental exposures. Furthermore, the risks did not differ significantly between maternal and paternal half-siblings (both with 25% genetic similarity but with maternal half-siblings sharing more environment as the vast majority (90%) of children in Sweden continue to live with their mother after parental divorce or separation; Supplementary Materials) [25]. Finally, first cousins (12.5% genetic similarity) had a 3-fold higher risk of having TS/CTD compared to controls, despite no or marginal shared environmental exposures with the TS/CTD proband.

Gender effects

Analyses by gender of the proband and gender of the relative revealed a higher number of male-male dyads, but the risks and tetrachoric correlations (which are not affected by sample size) were approximately similar for male-male, male-female, female-male and female-female dyads (**Table 2**).

Heritability estimates

Tetrachoric correlations were approximately double for full siblings than for maternal half-siblings (**Table 1**). There was no evidence of quantitative sex differences in the liability to

TS/CTD. In the full ACE model, the variance in liability of TS/CTD was largely attributable to additive genetic factors (0.72, 95% CI 0.42-1.00]), with negligible effect of shared environment (0.03, 95% CI 0.00-0.16]. The remaining variance was attributable to non-shared environmental influences and measurement error (0.25, 95% CI 0.08-0.43]. The best fitting model included additive genetic factors (0.77, 95% CI 0.70-0.85) and non-shared environmental factors (0.23, 0.15-0.30). The shared environment component could be dropped without any significant loss of fit (**Table 3**).

DISCUSSION

Extending previous, much smaller, family studies primarily conducted in specialist clinical settings, TS/CTD was significantly more prevalent among biological relatives of TS/CTD probands than in relatives of matched population controls. Further, the risk of TS/CTD in relatives increased significantly with increasing genetic relatedness to the proband. The pattern of results was similar in male and female patients. The heritability of TS/CTD was estimated to be approximately 77%, with the remaining variance being attributable to non-shared environmental influences and measurement error.

Together with the previous family and twin literature, largely derived from clinical samples of European origin, our data confirm that TS/CTD runs in families primarily due to genetic factors. Previous twin studies of strictly diagnosed TS/CTD [13,15] were too small to provide robust heritability estimates, whereas population-based (non-clinical) studies of

parent-rated tics [19-21] estimated the genetic contribution to range between 30-60% but were limited by the lack of clinician-based diagnostic assessments. Recent efforts to estimate the heritability of TS from genotyped data employing genome-wide complex trait analysis methods have also estimated the heritability of TS to be around 60%[17]. Our estimates suggest that TS/CTD may be even more heritable than previously thought.

Although we cannot conclusively rule out shared environmental factors, these appear to make a much smaller contribution to the etiology of the disorder. Instead, unique or non-shared environmental influences may confer increased risk to developing TS/CTD. A range of environmental risk factors for TS/CTD has been tentatively identified, including older paternal age and a number of peri-natal adversities (e.g., severe maternal stress, severe nausea and vomiting, smoking during the pregnancy as well as low birth weight and delivery complications low Apgar scores at birth) [26-28]. However, longitudinal, genetically informed studies are still rare; such studies should be prioritized alongside gene-searching efforts. The identification of genetic differences in susceptibility to particular environments (gene by environment interactions) in TS/CTD will be an important challenge for the future. Finally, the possibility of gene-environment correlations should also be investigated, as it is plausible that genetic factors could influence the specific environmental experiences of children vulnerable to developing TS/CTD [29].

While chronic tic disorders are clearly more prevalent in males, both in clinical and epidemiological samples [8-10,12,30], our results suggest that the familial risk for TS/CTD is comparable in male and female probands, regardless of the sex of the relative. The implication for molecular genetic research would be that when specific genes associated with TS/CTD are identified, they will be associated with TS/CTD in both sexes and that they will have similar effect sizes in males and females. However, these findings do not preclude the role of gender-specific factors during embryonic and fetal development in the causation of the disorder [31,32]. Female sex may be a protective factor against TS/CTD; whether females require a greater familial etiologic load to manifest the phenotype, as has been suggested in Autism Spectrum Disorder [33], is an interesting question for the future.

Strengths and limitations

Strengths of the present study include the large population-based sample of TS/CTD cases diagnosed in Sweden over 40 years, all their relatives, as well as carefully matched, randomly selected controls. This ensured minimal risk of selection, recall, and report biases for both TS/CTD and control families. Further, this is the first study to have sufficient power to examine the familial risk of TS/CTD across relatives at varying genetic and environmental distances from the probands. Another important strength was careful selection of probands based on our

validation of the ICD codes in the Swedish National Patient Register, which resulted in an algorithm designed to minimize the risk of false positive diagnoses.

Registers also have limitations. Individuals diagnosed with TS/CTD in the National Patient Register probably represent only a fraction of all cases in the Swedish population. Many individuals with mild tics may not seek help and, thus, may never be diagnosed or treated. Furthermore, the National Patient Register only includes patients seen by specialist physicians (e.g. pediatricians, neurologists or psychiatrists); those diagnosed in primary care by general practitioners or other professionals (e.g. nurses) are not included. Finally, outpatients were only included in the register from 2001. Thus, the register may only include the more severe and complex forms of TS/CTD (in our cohort, over 70% of patients had at least one lifetime psychiatric comorbidity) and our results may not generalize to milder forms of the disorder. However, the incomplete coverage of TS/CTD cases in the Register should be constant across the families of probands and the families of comparison subjects, thus not influencing our estimates. It is theoretically possible that having a relative with TS/CTD increases the chance of seeking help/receiving a diagnosis, though our findings suggest small or negligible shared environmental effects, which would argue against this possibility. Another limitation is that longitudinal registers are subject to 'left truncation' or missing data before the date the register started, which may result in greater prevalence of TS/CTD in younger generations. However, since we matched for birth year and time at risk, such losses would be similar for both case and

311 control dyads and not affect family risks. Despite the very large sample size, our study could not
312 distinguish between TS and CTD because our validation study suggested that clinicians in
313 Sweden often use these diagnostic codes indistinctly. Finally, our results may not generalize to
314 non-European populations; it has been suggested that ethnic differences in allelic frequencies
315 may explain the low prevalence of TS/CTD in non-European populations [10].
316
317 *Conclusions*
318 With these caveats in mind, our results indicate that TS/CTD is a strongly familial disorder
319 within the Swedish population and the observed pattern of familiality is consistent with a likely
320 genetic etiology. Our heritability estimates place TS/CTD amongst the most heritable
321 neuropsychiatric conditions.
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436 **Table 1.** Risks of TS/CTD in relatives of probands diagnosed with TS/CTD in Sweden (1969-2009) compared with relatives of matched controls, and
437 tetrachoric correlations.
438

Relation to proband	Average degree of genetic similarity	Number of dyads	Concordant pairs (expected)	Concordant pairs (observed)	Matched odds ratio (95% CI)	Tetrachoric correlation (Standard Error)
First-degree relatives						
Full siblings	50%	59,518	16.4	112	17.68 (12.90-24.23)	0.40 (0.01)
Parents	50%	95,675	3.2	24	21.08 (11.19-39.68)	0.30 (0.02)
Offspring	50%	16,572	3.1	24	24.74 (12.42-49.30)	0.30 (0.02)
Total	50%	171,765	22.8	160	18.69 (14.53-24.05)	
Second-degree relatives						
Maternal half-siblings	25%	15,767	5.2	16	4.41 (2.24-8.67)	0.22 (0.03)
Paternal half-siblings	25%	18,372	3.0	8	3.19 (1.27-8.00)	0.13 (0.04)
Uncles or aunts	25%	126,251	3.3	13	5.49 (3.04-9.89)	0.15 (0.03)
Nephews or nieces	25%	30,638	3.4	13	5.24 (2.83-9.72)	0.15 (0.03)
Total	25%	349,310	15.9	57	4.58 (3.22-6.52)	
Third-degree relatives						
First cousins	12.5%	238,822	21.8	56	3.07 (2.08-4.51)	0.11 (0.01)

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Table 2. Gender effects: Risks (OR, 95% Confidence Intervals and Tetrachoric correlations) for the presence of TS/CTD in relatives of probands diagnosed with TS/CTD.

	Male-male pairs			Male-female pairs			Female-female pairs			Female-male pairs		
Relation to proband	**Concordant pairs, observed**	**Matched OR (95% CI)**	**TC (SE)**	**Concordant pairs, observed**	**Matched OR (95% CI)**	**TC (SE)**	**Concordant pairs, observed**	**Matched OR (95% CI)**	**TC (SE)**	**Concordant pairs, observed**	**Matched OR (95% CI)**	**TC (SE)**
First-degree relatives, total	84	16.75 (11.95-23.50)	0.34 (0.01)	31	23.42 (13.26-41.38)	0.32 (0.02)	14	17.48 (7.45-41.02)	0.33 (0.03)	31	21.65 (12.36-37.92)	0.32 (0.02)
Second-degree relatives, total	35	4.78 (3.00-7.64)	0.12 (0.02)	9	4.51 (2.29-8.90)	0.09 (0.03)	4	5.53 (1.58-19.37)	0.12 (0.04)	9	3.86 (1.97-7.57)	0.09 (0.03)
Third-degree relatives	32	2.69 (1.71-4.24)	0.11 (0.02)	12	4.88 (2.60-9.18)	0.13 (0.03)	0	-	-	12	4.29 (2.31-7.96)	0.13 (0.03)

OR, Odds Ratios; CI, Confidence Interval; TC, Tetrachoric correlation; SE, Standard Error.

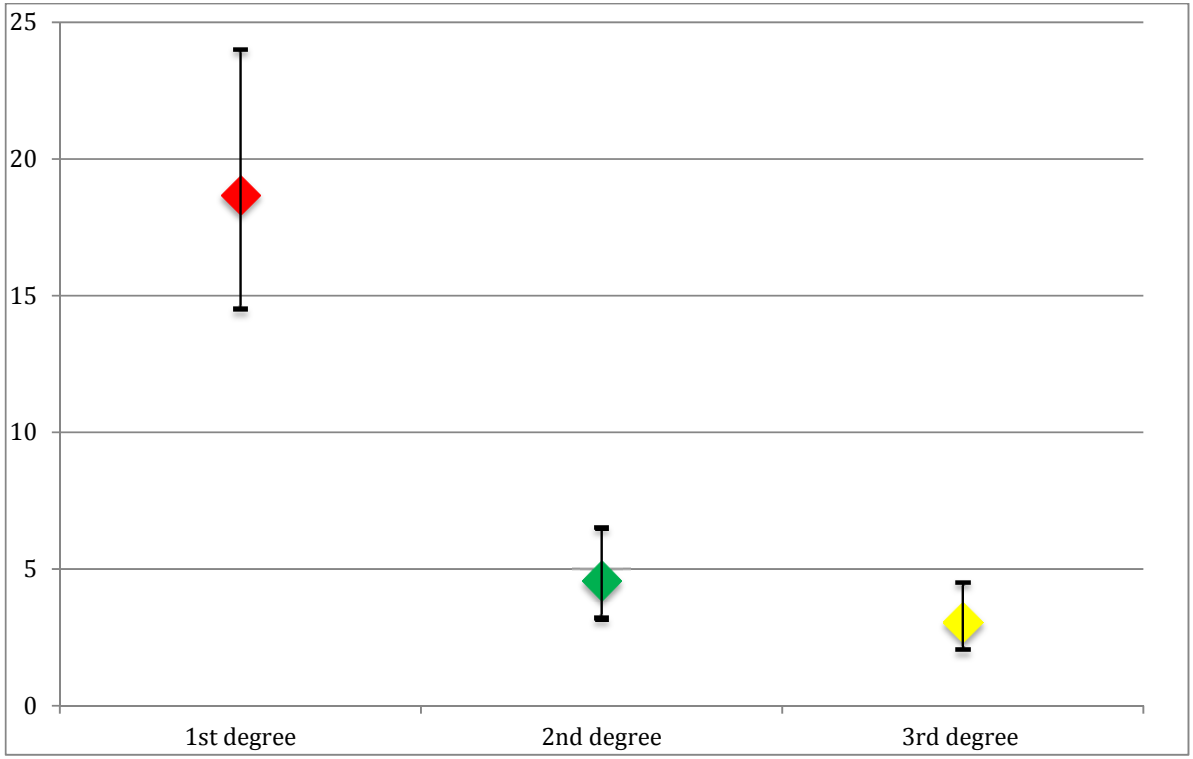
Table 3. Model fitting results based on the family data.

Models	**-2 LL**	χ^2	**Δ df**	***p-value***	**AIC**	**Compared to**
I. ACE model with sex difference	142638.2				-30358610	
II. ACE model without sex difference	142642.5	4.3	2	0.12	-30358610	Model I
III. AE model without sex difference [a]	142642.6	0.1	1	0.70	-30358611	Model II

[a] Best fitting model.

Notes: - 2LL = minus twice the log likelihood; χ^2 = differences in -2LL statistic between submodel and full model; Δ df = change in degrees of freedom between submodel and full model; p=probability; AIC = Akaike Information Criterion.

Figure 1. Risks (OR and 95% CI) for TS/CTD among first, second and third degree relatives of TS/CTD probands in the Swedish National Patient Register (1969-2009) compared to matched population controls.



Legend: First-degree relatives included full siblings, parents, and children. Second-degree relatives included maternal and paternal half siblings, grandparents and grandchildren, uncles/aunts, and nephews/nieces. Third-degree relatives consisted of first cousins.