Title: Familiality of co-existing ADHD and tic disorders: evidence from a large sibling study

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Word count (abstract): 248
Word count (body of the manuscript): (without references): 3167
Tables: 2
Figures: 1

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Conflicts of interest:
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Tobias Banaschewski served in an advisory or consultancy role for Hexal Pharma, Lilly, Medice, Novartis, Otsuka, Oxford outcomes, PCM scientific, Shire and Viforpharma. He received conference attendance support and conference support or received speaker’s fee by Lilly, Medice, Novartis and Shire. He is/has been involved in clinical trials conducted by Lilly, Shire & Viforpharma. The present work is unrelated to the above grants and relationships.
Jan K Buitelaar has been in the past 3 years a consultant to / member of advisory board of / and/or speaker for Janssen Cilag BV, Eli Lilly, Shire, Lundbeck, Roche and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, royalties.
Aribert Rothenberger is member of an advisory board and speakers’ bureau of Lilly, Shire, Medice and Novartis. He got research and travel support and an educational grant from Shire and research support from the German Research Society.
Abstract

Background: The association of attention-deficit/hyperactivity disorder (ADHD) and tic disorder (TD) is frequent and clinically important. Very few and inconclusive attempts have been made to clarify if and how the combination of ADHD+TD runs in families.

Aim: To determine the first time in a large-scale ADHD sample whether ADHD+TD increases the risk of ADHD+TD in siblings and, also the first time, if this is independent of their psychopathological vulnerability in general.

Methods: The study included ADHD-index patients with co-existing TD (ADHD+TD, n=262) and without TD (ADHD-TD, n=947) as well as their 1606 full siblings (n=358 of the ADHD+TD index patients and n=1248 of the ADHD-TD index patients). We assessed psychopathological symptoms in index patients and siblings by using the strength and difficulties questionnaire (SDQ) and the parent and teacher Conners’ long version Rating Scales (CRS). For disorder classification the PACS-Interview was applied in n = 271 children. It was tested if the risk for ADHD, TD and ADHD+TD in siblings was associated with the related index patients’ diagnoses. In order to get an estimate for specificity we compared the four groups for general psychopathological symptoms.

Results: Co-existing ADHD+TD in index patients increased the risk of both comorbid ADHD+TD and TD in the siblings of these index patients. These effects did not extend to general psychopathology.

Interpretation: Co-existence of ADHD+TD may segregate in families (independent of further behavioral problems), probably because of the segregation of TD. This provides a new clinical aspect for psychoeducation in cases of ADHD+TD.

Keywords: ADHD, tic disorders, comorbidity, familiality, IMAGE, SDQ, CRS-L

What this study adds:
1. ADHD+TD segregates in families probably because of the segregation of TD.
2. This effect is not influenced by general psychopathology.
3. Both results provide a new clinical aspect for a better psychoeducation in these cases.
Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder with a strong impact on the affected individual’s life, including academic difficulties, impaired socialization, and strained parent-child relationships. Both genetic and environmental factors play a role in the etiology of ADHD. The disorder is accompanied by various psychiatric disorders. Research on familial underpinning of ADHD co-occurring with tic disorders (TD) is clinically important, since TD are commonly co-existing with ADHD. While about half of children with TD also meet criteria for ADHD, about 20% of children with ADHD are additionally suffering from TD.

O’Rourke et al., while reporting from earlier studies on ADHD+TD, stated “that the increased frequency of ADHD in relatives of TD probands” may be due to the enhanced risk for ADHD+TD. The risk for ADHD alone was not increased among relatives of TD patients. However, these studies were limited by small sample sizes and lacking of families with probands diagnosed with ADHD-only. Only Stewart et al. compared the relatives of four different groups with each other (ADHD+TD vs. TD-only vs. ADHD-only vs. healthy controls) and found that “comorbid ADHD+TD diagnoses in relatives were elevated in all case groups” and they concluded that “there is an increased risk of comorbid ADHD and TD in affected families.” Although this study suggests the existence of familiality of ADHD+TD, the small data base with limited sub-sample sizes demands further evaluation concerning (a) whether the pattern of ADHD+TD co-existence really runs in families and b) how disorder specific this might be. Since ADHD + TD is highly important in daily clinical practice (e.g. for psychoeducation, early prevention and treatment) it needs to be disentangled further. Therefore, it seems to be worthwhile elucidating the familiality of ADHD+TD. While taking an ADHD perspective, this study will extend the small empirical data base in order to better answer question (a) and add new knowledge to (b).

Hence, we are running this study by analyzing for the first time a large sample of ADHD affected children and their (partly also affected) siblings, who took part in the IMAGE study. Based on previous findings (see above) we expected as a directed hypothesis (a) higher frequency of ADHD+TD in the similarly stratified siblings group of index patients with ADHD+TD vs. the siblings group with ADHD-TD, supporting the assumption that ADHD+TD may run in families and (b) a higher level of broad band psychopathology symptoms in siblings of index children with ADHD + TD compared to siblings of index children with ADHD-TD. The latter could reflect an estimate of disorder related specificity of our segregational findings (non-directed hypothesis).

Methods and Materials

Sample

Families with at least one child with the combined subtype of ADHD (= index patient) and their full siblings (regardless of their possible ADHD-status) were recruited as part of the IMAGE (International Multi-center ADHD Genetics) study. IMAGE is a collaborative study that aims to identify genes that increase the risk of ADHD using linkage and association strategies. A detailed description of the IMAGE sample (including recruitment and exclusion criteria as well as ethical approval) has already been given in previous studies.

Our sample included 2815 individuals consisting of 1209 index patients suffering from ADHD and 1606 of their siblings. The higher number of siblings is due to the fact that some patients had more than one sibling who took part in the study.

The index patients (in total N=1209) were allocated to the group ADHD+TD (N=262) if they fulfilled the criteria for both ADHD and TD; if TD-criteria were not fulfilled, they were classified as group ADHD-TD (N=947).

The siblings of index patients (in total N=1606) were differentiated in those of index patients with ADHD-TD (N=1248) and siblings of index patients with ADHD+TD (N=358) regardless of their own diagnostic status. Further the 1606 siblings of index patients with ADHD (i.e. ADHD+TD and ADHD-TD; see above) were screened themselves for ADHD with Conners’ Rating Scales and SDQ. In case of scores indicative for a diagnosis of ADHD a PACS interview (see Assessment below) has been conducted.
and led to a diagnosis of ADHD in 131 siblings. Because the information about a TD diagnosis was taken from the PACS interview and this has been conducted only in those siblings for whom ADHD was assumed by screening, also the information about the occurrence of TD yes/no was available only for 271 siblings (i.e. not all TD siblings without ADHD might have been detected). Among those siblings 41 were identified as being affected with TD (see flow chart Fig. 1).

+++ figure 1 about here +++

Assessment
The clinical assessment of dimensional psychopathology was performed with the long versions of Conners’ Rating Scales (CRS) for parents and teacher and the Strengths and Difficulties Questionnaires (SDQ) for parents and teacher. Scores were indicative for a diagnosis of ADHD if T-scores were ≥ 63 on the Conners’ DSM-IV ADHD Total score and if the score on SDQ Hyperactivity scale exceeded the 90th percentile. In these cases the semi-structured interview PACS (Parental Account of Childhood Symptoms) was executed for the assessment of diagnostic categories. During the PACS parents were asked for detailed descriptions of what their children have done in specified situations over the previous week. Based on these reports, trained investigators verified the ADHD diagnosis according to DSM-IV criteria. The PACS-interview also allowed the examination of the existence of a TD. For this purpose the parents were asked if their child showed some kind of tic behavior. In case they affirmed this question, the parents were requested to specify what kind of tics they had observed (simple/complex motor/vocal tics or both) and when these tics first occurred. A diagnosis of TD was given if the child showed tics a couple of times a day or almost every day.

Measurements
To assess the psychopathological profile of the children (index patients and their related siblings) parents and teachers had to complete the long versions of Conners’ Rating Scales – Revised (CPRS-R-L and CTRS-R-L respectively) and the Strengths and Difficulties Questionnaire (SDQ-P and SDQ-T respectively). The CPRS-R-L is a well-established instrument to assess childhood behavior problems. We focused on five of its seven main scales (oppositional, social problems, anxious-shy, psychosomatic, perfectionism) as well as on its DSM-IV scales, (DSM-IV inattention, DSM-IV hyperactivity-impulsivity and DSM-IV total score) to examine the symptomatology of the children. The SDQ is a brief behavioral screening questionnaire with five primary scales (hyperactivity, conduct problems, peer problems, emotional problems and prosocial problems) which were all considered. All subjects had an estimated full-scale IQ above 80.

Data analyses
All data were statistically analyzed with SAS (Statistical Analysis System). To analyze the familial occurrence for each of the three conditions under investigation (ADHD, TD, ADHD+TD) we calculated the relative risk of sibling’s diagnoses in relation to both index patient-groups (ADHD-TD and ADHD+TD). The odds ratio served as a measure for the degree to which the relative risks of sibling’s diagnosis differed between both patient-groups. The method used was PROC GENMOD.

To analyze the level of psychopathological symptoms a mean score was calculated for each Conners’ and SDQ scale named above. Because of some missing data from questionnaires and PACS interview the number of cases varied between the different psychopathological variables. An analysis of variances was conducted, including two factors: “proband-status” (index patients vs. siblings) and “disorder” (ADHD-TD vs. ADHD+TD). Index patients and siblings derived from the same families, so their data were partly dependent of each other. But they did not form a sample of matched pairs with one sibling being assigned to each index patient, because number of participating siblings per
family varied. Therefore we employed PROC GENMOD for generalized linear models – a SAS procedure able to handle partly dependent data. Additionally, follow-up comparisons analyzed patient-groups and sibling-groups separately. The comparison of both index patients groups was accomplished with t-tests for descriptive purposes. For the case of inhomogeneous variances the degrees of freedom were approximated by the Welch-Satterthwaite equation. For comparison of the sibling-groups we used PROC GENMOD.

Results

Group characteristics

Patients suffering from ADHD without TD (ADHD-TD: mean age 10.7 ± 2.8 years) did not differ in age from patients with ADHD+TD (mean age 11.1 ± 2.7 years, p = .06). Additionally, there were no differences in IQ between the two groups (ADHD-TD: mean IQ = 99.8 ± 16.2 vs. ADHD+TD: mean IQ = 100.0 ± 15.6, p = .88). However, in the group of children with ADHD-TD the proportion of girls (14.5%) exceeded their proportion in the ADHD+TD-group (6.8%, p < .01).

Siblings of index patients with ADHD-TD had a mean age of 10.8 ± 3.4 years and a mean IQ of 101.7 ± 13.3. This did not differ from the mean age and IQ of the siblings whose related index patient suffered from ADHD+TD (mean age 10.7 ± 3.4 years, p = .42, and mean IQ 102.9 ± 13.3, p = .41). Also, there was no significant difference in gender between both groups (siblings of ADHD index patients 49.9% female vs. siblings of ADHD+TD index patients 52.0% female, p = .53).

Frequency of disorder

This analysis included different subsamples (see Fig. 1) of siblings, because information about the occurrence of a TD diagnosis was not available for all. Therefore each subsample of siblings of ADHD-TD patients and each corresponding subsample of siblings of ADHD+TD patients were compared in terms of age, gender and IQ. No significant differences between the quasi-experimental-conditions were found in any of siblings’ subsamples.

+++ table 1 about here +++

For the first analysis of familial transmission the relative risk for ADHD did not differ between siblings of index patients with ADHD+TD and siblings of index patients suffering from ADHD without TD (p = .38, see table 2, crosstab 1).
For the second analysis, the relative risk for TD tended to differ between siblings of index patients with ADHD+TD and siblings of index patients suffering from ADHD without TD (p=.07, see table 2, crosstab 2).
For the third analysis, siblings of index patients with ADHD+TD had a statistically significant 2.43-fold higher risk for ADHD+TD than siblings of index patients with ADHD (p=.04, see table 2, crosstab 3).

Level of psychopathology

The two-factorial analyses of variance revealed a significant main effect for “proband-status” with regard to all of the psychopathological symptoms. In contrast, no main effect for “disorder” was found except for prosocial behavior rated by parents. The interaction effect was significant on four scales of the CPRS-R-L (oppositional: p < .01, social problems: p < .01, anxious-shy: p < .01, perfectionism: p = .01) and on three scales of the SDQ-P (conduct problems: p = .01, peer problems: p = .01, emotional problems: p = .01). In teacher ratings the interaction only reached significance on the CTRS-R-L DSM-IV total score (p = .05) (see table 2).
The pairwise comparisons showed significant differences between index-patients with ADHD-TD and those with ADHD+TD on most of the psychopathological measures. Parents rated ADHD+TD children as more impaired than children suffering from ADHD-TD. In contrast to the parents’ assessment, teachers rated patients with ADHD as showing significantly more severe symptoms of psychopathology than patients suffering from ADHD+TD. For parent as well as teacher ratings effect-sizes were small ranging
Discrimination of ADHD and TD among children is not always easy. Children with ADHD and TD may share some symptoms, such as hyperactivity, impulsive behavior, and difficulties in controlling their behavior. However, the severity and frequency of these symptoms can vary between children with pure ADHD and children with ADHD+TD. In this study, we investigated the familial risk for ADHD and TD in relatives of ADHD+TD patients.

**Methods**

We conducted a genetic analysis of ADHD and TD in siblings of ADHD+TD patients. We included 239 probands (mean age 13.8) and 692 first-degree relatives in total. The number of cases in each proband group varied between 41-75 and between 114-219 in the relative groups. Stewart et al. reported that ADHD+TD was increased not only in relatives of the ADHD+TD group but also in relatives of the TD-only and ADHD-only case groups supporting the assumption of a cross-disorder vulnerability and familiality of ADHD+TD. However, in Stewart et al. (see adaptation of their data in O'Rourke et al. table 1) the first-degree relatives of the ADHD+TD proband groups vs. the ADHD-only group show higher frequencies for TD as well as ADHD+TD. Including our data, it seems probable that TD might be the essential factor for the familiality of both TD and ADHD+TD; i.e. if TD is added to ADHD (in the ADHD+TD groups) it does not seem to increase the risk of ADHD. In other words, in this case ADHD is the leading vulnerability marker. In contrast, and this is our main finding, there was a significantly higher risk of ADHD+TD (and a tendency for TD) among siblings of patients with ADHD+TD. This suggests that the familiality of ADHD+TD may exist probably driven by TD.

**Frequency of disorder**

We found that the familial risk for ADHD was not different in both sibling groups, i.e. if TD is added to ADHD (in the ADHD+TD groups) it does not seem to increase the risk of ADHD. In other words, in this case ADHD is the leading vulnerability marker. In contrast, and this is our main finding, there was a significantly higher risk of ADHD+TD (and a tendency for TD) among siblings of patients with ADHD+TD. This suggests that the familiality of ADHD+TD may exist probably driven by TD.

To our knowledge there is only one study which examined the occurrence of ADHD+TD in relatives of ADHD+TD patients. It included 239 probands (mean age 13.8) and 692 first-degree relatives in total. The number of cases in each proband group varied between 41-75 and between 114-219 in the relative groups. Stewart et al. reported that ADHD+TD was increased not only in relatives of the ADHD+TD group but also in relatives of the TD-only and ADHD-only case groups supporting the assumption of a cross-disorder vulnerability and familiality of ADHD+TD. However, in Stewart et al. (see adaptation of their data in O'Rourke et al. table 1) the first-degree relatives of the ADHD+TD proband groups vs. the ADHD-only group show higher frequencies for TD as well as ADHD+TD. Including our data, it seems probable that TD might be the essential factor for the familiality of both TD and ADHD+TD; i.e. if TD is added to ADHD (in the ADHD+TD groups) it does not seem to increase the risk of ADHD. In other words, in this case ADHD is the leading vulnerability marker. In contrast, and this is our main finding, there was a significantly higher risk of ADHD+TD (and a tendency for TD) among siblings of patients with ADHD+TD. This suggests that the familiality of ADHD+TD may exist probably driven by TD.

**Level of psychopathology**

Parallel to the analysis of the index patients’ categorical psychopathology by diagnoses, we assessed the dimensional psychopathological profile in the patients’ siblings in order to get a rough estimate of specificity. In contrast to the comparisons of affected index children (ADHD-TD showed less symptoms than ADHD+TD), we did not find any differences comparing the values of siblings of ADHD-TD patients vs. siblings of ADHD+TD patients which all were within the normal range. Thus, the assumption of higher general psychopathological vulnerability in siblings of index patients with ADHD+TD (as a first hint of familiality) was not supported on the basis of dimensional psychopathology and underlines that TD adds little to psychic problems when it co-exists with ADHD.

For parent as well as teacher ratings the effect sizes while comparing patients with ADHD-TD and those with ADHD+TD were small. This could be due to the uncertainty of these non-expert raters in differentiating the children’s behavior because there can exist some mimicry of symptoms in ADHD and TD concerning hypermotricity, inattention and impulsiveness. Teachers’ ratings were found somewhat opposite to parents’ ratings. Although there are several reports about different outcomes of parents’ versus teachers’ ratings of ADHD core-symptoms, this issue is still not resolved. Further, it is clinically a well-known fact that children with TD (including those with ADHD+TD) are very often able to control their symptoms at school and “let them out” when they are at
home. Therefore specifically hyper-motor behaviour and impulsivity might be hidden at school and quite obvious at home. Thus, when comparing teacher and parent ratings of ADHD-TD versus ADHD+TD patients, environmental/informant influences might explain the difference.

**Limitations**

There are some limitations of the study that need to be mentioned. The gender ratio differed between both index patients groups. Among the patients suffering from ADHD+TD there was a higher percentage of boys compared with the ADHD-TD group. Although this seems to be a natural fact of ADHD+TD, this might have somewhat biased the results towards externalizing behaviors, because ratings of psychopathological symptoms are not independent of gender. As we analyzed index patients and siblings sharing family environment only interpretations referring to familiality but not heritability and/or genetic background are possible.

Further, our study design included only two index patient-groups (ADHD-TD and ADHD+TD). In order to comment on more specific modes of familiality it would be necessary to additionally include a TD-only and a healthy control-group.

**Conclusions**

Our results suggest that ADHD+TD may run in families and that the vulnerability for this might be related to TD. The TD-specificity of our finding is supported by the fact, that TD-only ran also in families and that general psychopathology did not show familiality effects. It remains to be clarified if this familial TD-effect may be influenced by obsessive-compulsive symptoms (which often exist together with ADHD as well as TD), because there is some evidence that association between TD and ADHD “may be due to a genetic association between OCD and ADHD and in part to shared environmental factors”.

Unfortunately, our data set did not allow to test this hypothesis. Whether our significant interaction effect between ‘proband status’ and ‘disorder’ for perfectionism (CPRS-R-L) reflects a signal in this direction remains to be left open. Also, our findings do not allow to firmly conclude if ADHD+TD should best be seen as an additive combination of two separate nosologies or if it should be considered a distinct subtype within a heterogeneous disorder, but recent research at different levels of investigation suggests merely the additive variant. Finally, the issue that familiality of ADHD+TD may be driven by TD (independent of further behavioral problems) provides a new clinical aspect for psychoeducation in these cases.

**Acknowledgements**

The International Multisite ADHD Genetics (IMAGE) project is a multi-site, international effort. Funding support for the IMAGE project was provided by NIH grants R01MH62873 and R01MH081803 to S.V. Faraone and the genotyping of samples was provided through the Genetic Association Information Network (GAIN). The dataset used for the analyses described in this manuscript were obtained from the database of Genotypes and Phenotypes (dbGaP) found at http://www.ncbi.nlm.nih.gov/gap through dbGaP accession number #20726-2. Samples and associated phenotype data for the IMAGE Project were provided by the principal investigators Stephen V. Faraone, Philip Asherson, Tobias Banaschewski, Jan Buitelaar, Richard P. Ebstein, Michael Gill, Ana Miranda, Fernando Mulas, Robert D. Oades, Herbert Roeyers, Aribert Rothenberger, Joseph Sergeant, Edmund Sonuga-Barke, and Hans-Christoph Steinhausen, the chief investigators at each site, Rafaela Marco, Nanda Rommelse, Wai Chen, Henrik Uebel, Hanna Christiansen, Ueli C. Mueller, Cathelijne Buschgens, Barbara Franke, and Margaret Thompson, as well as the statistical analysis team, M. Daly, C. Lange, N. Laird, J. Su, and B. Neale. This project also received funding from the European Union’s Seventh Framework Programme for research, technological development and demonstration under grant agreements n° 602805 (AGGRESSOTYPE), n° 603016 (MATRICS) and n° 278948 (TACTICS).
References


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<td>55.8</td>
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<td>13.7</td>
<td>61.1</td>
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<td>52.9</td>
<td>11.5</td>
<td>52.6</td>
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<td>hyperactivity</td>
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<td>7.7</td>
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<td>3.1</td>
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<td>2.7</td>
<td>2.3</td>
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<td>2.0</td>
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<td>3.3</td>
<td>2.7</td>
<td>-0.97</td>
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<td>2.0</td>
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<td>2.84**</td>
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**Table 1**: Psychopathological profile

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<thead>
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<th>Measure</th>
<th>Description</th>
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<tr>
<td>CRS</td>
<td>Conners’ Rating Scales – Revised (Conners, Sitarenios et al. 1998; Conners, Sitarenios et al. 1998)</td>
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<tr>
<td>SDQ</td>
<td>Strengths and Difficulties Questionnaire (Woerner, Becker et al. 2004)</td>
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</tbody>
</table>

M: mean, SD: standard deviation, t: test statistic (t-test), Z: test statistic (PROC GENMOD)

** p ≤ .01, * p ≤ .05, + p ≤ .10
<table>
<thead>
<tr>
<th>patients</th>
<th>siblings</th>
<th>relative risk</th>
<th>odds ratio (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>crosstab 1</td>
<td>no ADHD (^a)</td>
<td>ADHD (^a)</td>
<td>0.88</td>
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<tr>
<td>ADHD</td>
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<td>98</td>
<td>ns</td>
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<tr>
<td>ADHD+TD</td>
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<td>33</td>
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<tr>
<td>crosstab 2</td>
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<td>ADHD+TD</td>
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<td>14</td>
<td>0.29</td>
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<tr>
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<td>ADHD+TD</td>
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<tr>
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<td>14</td>
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<tr>
<td>ADHD+TD</td>
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<td>0.35</td>
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</tbody>
</table>

Table 2: Frequency of siblings’ ADHD and/or TD diagnoses independently of further diagnoses based on Parental Account of Children’s Symptoms (PACS) interview.  
Note: Siblings were screened for a previous ADHD diagnosis, clinical suspicion of ADHD, an average T-score of the DSM-IV total symptom score (N-scale) greater than 63 on the Conners scales or scores >90th percentile on the SDQ-hyperactivity scale. Only in verified cases the semi-structured PACS interview was performed leading to diagnosis based on operational DSM-IV criteria for ADHD and/or TD.  
\(^a\) independently of TD status of the siblings  
\(^b\) independently of ADHD status of the siblings  
Data in cells: absolute frequencies, * p ≤ .05, + p ≤ .10, ns: non-significant  
crosstab 1 and 2: two-tailed; non-directed hypothesis  
crosstab 3: one-tailed, directed hypothesis