Maternal History of Autoimmune Disease and Later Development of Tourette Syndrome in Offspring

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Objective: In a nationwide prospective cohort study, we examined the possible association between maternal autoimmune disease (AD) and later diagnosis of Tourette syndrome (TS) in offspring.

Method: Data from national Danish health registers identified a cohort consisting of all children born in Denmark between 1990 and 2007 (n = 1,116,255), followed prospectively from birth until 2011, date of TS diagnosis, death, or emigration/disappearance, whichever came first. The incidence rate ratio (IRR) of TS, dependent on whether or not the mother had a prior diagnosis of AD, was estimated by Poisson regression with 95% CIs and adjusted for age, calendar time, place of birth, maternal and paternal age, parental psychiatric diagnoses other than TS, and parental TS.

Results: The cohort contributed a total of 13,000,162 person years and 2,442 participants with a diagnosis of TS (414 females and 2,028 males). Prior maternal AD was found in 110 of the 2,442 children with TS, corresponding to an increased risk of TS, with an adjusted IRR of 1.22 (95% CI = 1.01–1.48). Maternal history of a prior AD increased the risk of TS in males, with an adjusted IRR of 1.29 (95% CI = 1.05–1.58), but not in females, with an adjusted IRR of 0.89 (95% CI = 0.52–1.52).

Conclusion: Maternal AD was associated with a 29% increased incidence rate of TS in male offspring. This finding supports the hypothesis that neuroimmunological disorders may act as a component in the etiology of a subset of TS.

Key Words: Tourette syndrome, tics, autoimmune disease, neuroimmunology, cohort study

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Tourette syndrome (TS) is a neuropsychiatric disorder characterized by motor and vocal tics with an estimated population prevalence of 6 per 1,000 children.[1-3] In both clinical and community-based samples, comorbid conditions are highly prevalent, of which attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) are the most common.[4-8] Only 10% to 20% of children with TS have no comorbid psychiatric disorders.[9-11]

The exact etiology of TS is unknown and likely multifactorial. Twin and family studies provide evidence that polygenic hereditary factors are involved in the etiologies of most cases,[12,13] and some rare genetic variations may play a role in a smaller fraction of patients with TS.[14] However, at the same time, twin studies with concordance rates below 100% in monozygotic twins also document the importance of environmental risk factors for tics.[15] Environmental factors found to be associated with an increased risk of TS include adverse perinatal events,[16,17] exposure to androgens, psychological stress,[18] and infections,[19] as well as neuroimmunological dysregulation.[20,21] Immunological factors are thought to be etiologically important in several other neuropsychiatric disorders, including autism spectrum disorder (ASD),[22-28] schizophrenia,[29,30] and bipolar disorder.[31,32]

Supplemental material cited in this article is available online.

There is some evidence to suggest a possible immunological connection to TS. Group A β-hemolytic streptococci (GABHS) and other infections can trigger tics in some susceptible individuals,[19,33,34] although the validity of this GABHS-mediated presentation, referred to as pediatric autoimmune neuropsychiatric disorder associated with streptococcal Infection (PANDAS), is controversial and still under debate.[33] There is increasing evidence of immunological dysregulation in other developmental disorders, especially ASD.[22] In addition, immunological agents such as cytokines can play a role in neural plasticity, neuroprotection, and response to nonimmune stressors.[35,36]

In autoimmune disease (AD), the body fails to recognize its own cells, tissues, or organs, thus leading to an immune response against them. Factors thought to be involved in the pathogenesis of autoimmune diseases include genetic predisposition and a number of environmental factors, such as smoking, drug use, and viral and bacterial infections.[37,38]

Findings from studies examining the presence of TS-specific autoantibodies and antineuronal antibodies in patients with TS have been conflicting.[18,39,40] Other findings in favor of an autoimmune component in TS include a reduced number of T-regulatory cells,[41] lower IgA in PANDAS and TS,[42] and higher risk of family history of AD.[43] In a retrospective study, Murphy *et al.* identified 107 children and adolescents with tics and/or OCD, and information on maternal AD was obtained by interviewing the mothers. Among these mothers, 17.8% (n=18) reported diagnosis of AD. The study did not include a control group, but the identified prevalence of maternal AD was higher than that of

the general female population.[43] However, the study did not find a specific association between maternal AD and TS, although this may have been due to the small sample size. The study suggested that a diagnosis of maternal systemic lupus and autoimmune thyroiditis increased the risk of TS in offspring. The study did not consider the temporal relationship between maternal AD and TS.

Possible associations between AD in relatives and TS may be explained by various mechanisms. First, ADs and TS are heritable disorders and may share common genetic risk factors. Second, mothers who develop AD before giving birth may transfer autoantibodies to the fetus during pregnancy. These transferred antibodies may activate the immune system in the child and alter normal brain development. Third, AD is a chronic disease, and its presence in the mother may influence the mother–child relationship, increase stress levels, and thereby act as an environmental risk factor.

There is still insufficient evidence as to whether AD in relatives is associated with TS; the current study is, to our knowledge, the first nationwide, population-based prospective study aimed at examining this possible association. To test the hypothesis of an immunological mechanism behind such an association, we included only mothers diagnosed with AD before the diagnosis of TS in the child.

METHOD

Materials

This study uses and merges data from a number of national Danish health registers. The National Patient Register (NPR)[44] was computerized in 1977 and holds information on all inpatient contacts to nonpsychiatric hospital departments. Since 1994, NPR has also included outpatient and emergency room contacts. The Danish Psychiatric Central Register (DPCR)[45] holds information on all inpatient admissions to psychiatric hospital departments since 1969, and, from 1995, also all outpatient contacts. Before 1994, the registers contain *International Classification of Diseases, Version 8 (ICD-8)*[46] diagnoses; from 1994 onward, *ICD-10*[47] diagnoses have been entered into both registers. Linkage between registers is possible by using the unique identification number assigned to every individual born in Denmark. The Civil Registration System (CRS)[48] contains unique identification numbers as well as the gender of the individual, date

TABLE 1 Baseline Characteristics of Cohort With Tourette Syndrome (TS)

	Participants With TS		Person-Years in Total Cohort (n = 13,000,162)	Incidence Rate of TS, per 10,000 Person-Years
	n	(%)		
Gender				
Male	2,028	(83.1)	6,666,244	3.04
Female	414	(16.9)	6,333,919	0.65
Parental psychiatric history				
Maternal history of any psychiatric disorder	340	(13.9)	1,184,620	2.87
Paternal history of any psychiatric disorder	252	(10.3)	955,848	2.64
Maternal history of Tourette syndrome	8	(0.3)	643	124.42
Paternal history of Tourette syndrome	9	(0.4)	953	94.44
Maternal autoimmune disease				
No maternal history of autoimmune disease	2,332	(95.5)	12,512,294	1.86
Maternal history of autoimmune disease	110	(4.5)	487,868	2.25
Place of birth				
Capital	408	(16.7)	1,759,337	2.32
Capital suburb	464	(19.0)	1,739,275	2.67
Provincial city >100,000 inhabitants	229	(9.4)	1,630,276	1.41
Provincial city 10,000–100,000 inhabitants	658	(26.9)	3,572,507	1.84
Rural area	683	(28.0)	4,298,767	1.59
Maternal age at child's birth, y				
0–19	54	(2.2)	251,757	2.14
20–24	450	(18.4)	2,038,325	2.21
25–29	955	(39.1)	5,018,399	1.90
30–34	702	(28.7)	4,052,951	1.73
35–39	232	(9.5)	1,428,063	1.63
40+	49	(2.0)	210,667	1.19
Paternal age at child's birth, y				
0–19	16	(0.7)	69,744	2.29
20–24	234	(9.6)	1,022,545	2.29
25–29	767	(31.4)	3,857,629	1.99
30–34	806	(33.0)	4,527,856	1.78
35–39	404	(16.5)	2,379,904	1.70
40+	215	(8.8)	1,142,485	1.88

of birth, place of birth, date of death, or other/lost to follow up in the register (e.g., emigration, if any), and the unique identification numbers of both parents.

Study Participants

We identified all persons born in Denmark between January 1, 1990, and December 31, 2006, with reference to both parents in the CRS. Using data from NPR (see Table S1, available online), 31 different ADs were identified in mothers of all children in the cohort. All children with TS (*ICD-10* code F95.2) identified in the national patient registers (NPR or DPCR) were defined as patients. In addition, we identified psychiatric diagnoses in parents. All individuals within the cohort were followed from the date of birth or January 1, 1995 (whichever came last) until December 31, 2010, date of first diagnosis with TS, or date of death, emigration, or disappearance (whichever came first). Follow-up begins in 1995 because of the inclusion of outpatient contacts in the registers. Cohort members were not older than 5 years at the start of follow-up.

Data Analyses

We used Poisson regression to estimate the incidence rate ratio (IRR) of TS, dependent on whether or not the mother had a diagnosis of AD on a date before the date of TS diagnosis in the offspring. Ninety-five percent CIs were calculated. The CIs of IRRs for individual ADs were calculated where cell sizes were larger than 10. We adjusted for the following confounders: age, calendar time (1995, 1996, 1997,…, 2010), place of birth (capital, capital suburb, provincial city of more than 100,000 inhabitants, provincial city of 10,000 to 100,000 inhabitants, rural area), maternal and paternal age at birth of the child (<25, 25–30, 30–35, >35 years), parental psychiatric diagnoses other than TS (yes/no), and parental TS (yes/no) before the child's own TS diagnosis. The analyses were performed using PROC GENMOD in SAS 9.3.[49]

RESULTS

The cohort consisted of 1,116,255 children contributing a total of 13,000,162 person-years and 2,442 participants with a diagnosis of TS (414 female and 2,028 male), corresponding to an incidence rate of 1.88 per 10,000 person-years in the total follow-up period. Participants with TS received their first diagnosis at mean age 9.64 years (SD = 2.98 years). Among children with TS, 13.9% of the mothers and 10.3% of the fathers had a history of a psychiatric disorder. The baseline characteristics of the participants with TS and the cohort are shown in Table 1.

Among the 2,442 children with TS, maternal history of AD before the diagnosis of the child was found in 110 cases. Individuals with maternal history of AD contributed a total of 487,867 person years to the cohort, and the unadjusted incidence rate of TS in this group was 2.25 per 10,000 person years, compared to 1.86 in children of mothers with no history of AD. Overall, this corresponded to an increased risk of TS in children of mothers with a history of AD, with an IRR of 1.22 (95% CI = 1.01–1.48; $p = .0479$), adjusted for gender, calendar time, age, place of birth, and maternal/paternal age at birth. However, this association in the total sample was driven mainly by the increased incidence of TS in male offspring. We found that maternal history of prior AD increased the risk of TS in males (adjusted IRR of 1.29 [95% CI = 1.05–1.58; $p = .015$]), but not in females (adjusted IRR of 0.89 [95% CI 0.52–1.52; $p = .678$]). The adjusted IRRs for TS dependent on maternal diagnosis of AD and stratified by gender are shown in Table 2.

The 4 most common maternal ADs of participants with TS were ulcerative colitis (IRR = 1.17; 95% CI = 0.74–1.86; n = 19; $p = .650$), rheumatoid arthritis (IRR = 1.21; 95% CI = 0.69–2.13; n = 13; $p = .467$), thyrotoxicosis (IRR = 0.58; 95% CI = 0.33–1.03; n = 12; $p = .068$), and multiple sclerosis (IRR = 1.54; 95% CI = 0.85–2.78; n = 11; $p = .139$). Several other ADs were associated with an increased IRR of TS in offspring, but estimates were based on very few cases. The frequency, distribution, and IRRs of the 110 ADs in individuals with TS are shown in Table 3.

DISCUSSION

We found that maternal diagnosis of an AD before the child being diagnosed with TS was associated with a 29% increased incidence rate of TS in male offspring when adjusted for the effect of calendar time, age, place of birth, parental psychiatric diagnoses other than TS, parental diagnoses of TS, and parental age at birth of the child.

This finding supports the hypothesis that TS may, in part, have an immunological etiology, at least in some individuals. This contrast results from the only previous study of this association.[43] Although the association was statistically insignificant, the study by Murphy *et al.* suggested that maternal systemic lupus and autoimmune thyroiditis could be associated with a greater risk of TS in offspring. In our

TABLE 2 Estimated Relative Risks (Incidence Rate Ratio [IRR]) for Tourette Syndrome (TS) in Offspring With a Maternal History of Autoimmune Disease Before Birth of Child

	IRR Estimates and 95% CIs		
		Gender[b]	
Diagnosis	Total TS Sample[a] (N = 2,442)	Females (n = 414)	Males (n = 2,028)
Diagnosis of maternal autoimmune disease	1.22 (1.01–1.48)	0.89 (0.52–1.52)	1.29 (1.05–1.58)
No diagnosis of maternal autoimmune disease (reference)	1	1	1

[a]*Adjusted for gender, calendar time, age, place of birth, parental psychiatric diagnoses other than TS, parental diagnoses of TS, and parental age at birth.*
[b]*Adjusted for calendar time, age, place of birth, parental psychiatric diagnoses other than TS, parental diagnoses of TS, and parental age at birth.*

TABLE 3 Specific Autoimmune Diseases in Mothers and Association With Tourette Syndrome (TS) in Offspring

Disease	Individuals With TS, n	IRR[a]	*p* Value
Thyrotoxicosis	12	0.58 (0.33–1.03)	.068
Autoimmune thyroiditis	4	1.26	—
Type 1 diabetes	10	0.77	—
Primary adrenocortical insufficiency	0	—	—
Celiac disease	6	2.71	—
Pernicious anemia	4	4.52	—
Autoimmune hemolytic anemia	0	—	—
Idiopathic thrombocytopenic purpura	<4	0.68	—
Multiple sclerosis	11	1.54 (0.85–2.78)	.139
Guillain Barré syndrome	<4	0.86	—
Iridocyclitis	5	0.92	—
Wegener's granulomatosis	0	—	—
Crohn's disease	9	0.91	—
Ulcerative colitis	19	1.17 (0.74–1.86)	.650
Primary biliary cirrhosis	<4	3.91	—
Autoimmune hepatitis	<4	0.72	—
Interstitial cystitis	<4	0.31	—
Pemphigoid	0	—	—
Pemphigus	0	—	—
Psoriasis	7	0.79	—
Alopecia areata	<4	1.53	—
Vitiligo	<4	1.10	—
Rheumatoid arthritis	13	1.21 (0.69–2.13)	.467
Juvenile arthritis	<4	1.72	—
Dermatopolymyositis	0	—	—
Polymyalgia rheumatica/ temporal arteritis	<4	2.20	—
Myasthenia gravis	0	—	—
Scleroderma	<4	1.44	—
Systemic lupus erythematosus	<4	1.21	—
Sjögren's syndrome	<4	2.40	—
Ankylosing spondylitis (morbus Bechterew)	<4	0.57	—

Note: IRR = incidence rate ratio.

[a] *CIs for the IRRs were calculated only for individual maternal autoimmune diseases with more than 10 cases of TS.*

study, the prevalence of systemic lupus, pernicious anemia, celiac disease, and autoimmune thyroiditis in mothers of children with TS was low; and although the estimated IRR for TS was greater than 1 for all 4 disorders, we did not calculate CIs because of low power (n < 10).

Our finding of an association between maternal AD and TS is consistent with evidence of associations between parental AD and other psychiatric disorders. In a prospective study, Eaton *et al.* found that prior parental history of AD was associated with a 1.3- to 3.8-times increased risk of schizophrenia in offspring.[50,51] In another population-based cohort study, Atladottir *et al.* found that maternal but not paternal rheumatoid arthritis and celiac disease diagnosed before delivery of the child was associated with an increased incidence of ASD in offspring,[23] suggesting that a combination of common genetic factors and a prenatal antibody exposure during pregnancy is of etiological importance. However, the ADs carrying the greatest risk for schizophrenia and ASD were based on few cases (n = 8 and n = 10, respectively). In a third study, Eaton *et al.* found that among 30 different ADs, only prior pernicious anemia in a parent or a sibling was associated with later development of bipolar disorder.[32]

In our study, no single diagnosis among the different maternal ADs (where n was >10) was significantly associated with TS. Maternal diagnosis of multiple sclerosis was found among those individuals with highest prevalence of TS, and the difference in incidence compared to nonexposed individuals reached nearly trend-level significance ($p = .139$). This finding suggests that the identified overall association between maternal AD and TS in offspring is not due to common genetic risk factors between AD and TS, as the 30 ADs are assumed to occur as a result of different genetic components. Most autoimmune diseases are linked to human leucocyte antigen (HLA) subtypes, in particular, by distinct HLA-DRB alleles,[37] and so far genetic susceptibility of TS has not been linked to the HLA-DRB locus.[52] The COL27A1 gene may possibly contribute to the risk of TS and, similarly, mutations in the SLITRK1 gene and histidine decarboxylase gene may be possible genetic markers for TS. One study found decreased expression of toll-like receptor 4 on monocytes in participants with TS, suggesting that some participants with TS may have impaired activation of the innate immune response to bacterial infections.[53] However, none of these have so far been linked to ADs, although very few studies have examined the possible genetic pleiotropy between ADs and TS.

Interestingly, maternal diagnosis of thyrotoxicosis tended to have a protective effect on the development of TS in offspring (IRR = 0.58; 95% CI = 0.33–1.03; n = 12; $p = .068$). This is consistent with the findings in the ASD study by Atladottir *et al.*, who noted an IRR of 0.58 (95% CI = 0.32–0.95),[23] but in contrast to findings from the study on schizophrenia, in which thyrotoxicosis was among the 5 ADs out of 30 to be more prevalent in both patients and their relatives with schizophrenia (IRR = 2.6 and 1.4, respectively).[51] In the study on bipolar disorder, no significant association with thyrotoxicosis was found in parents or siblings.[32] Genetic markers for thyrotoxicosis include polymorphisms in certain genes (especially CTLA-4, HLA-DRB-1, and tumor necrosis factor–α [TNF-α]),[54] and, in 1 study, a specific polymorphism in TNF-α tended to protect against TS.[55]

If the association between ADs and TS is not due to common genetic factors, then what are the possible explanations for our findings? Animal model studies have documented that transmission of antibodies can be associated with TS.[56] In mice, infections with GABHS may result in stereotypic movements, and infusion of immunoglobulin

(Ig)–G from GABHS-immunized mice into infection-naive mice produces similar behavioral changes in the recipients, and depletion of IgG promotes abolition of these motor behaviors.[57] Similarly, antibodies from sera of humans with TS have caused tic behavior in rats,[58] possibly by action of increased levels of antibodies against a specific nucleotide channel found in sera from patients with TS.[59] In humans, placental transfer of maternal IgG to the fetus is an important and effective mechanism, protecting the infant against infections early in life, before developing its own efficient humoral immune response. However, placental transferal of maternal autoantibodies may also harm the fetus.[60]

Some studies have suggested that, in subsets of patients with TS, immunologically mediated changes in striatal dopamine may be an etiologically important mechanism for the development of this disorder.[20] A subset of patients with TS have a sudden post-infectious onset of tics, and GABHS infection is thought to be a likely candidate involved.[61] In addition, patients with TS are more prone to GABHS infections and develop a stronger immunological response to these infections.[62,63] In an earlier study, Murphy *et al.* found that exacerbations in the severity of symptoms in patients with OCD or tics were associated with higher streptococcal titers.[64] A cross-sectional study found that children with TS were more likely to have anti–basal ganglia antibodies,[65] and in PANDAS, antibodies may attack brain cells due to molecular similarities and may be the mechanism behind this association.[66] Alternatively, infections with GABHS and other bacteria and viruses may act via modulation of cytokines. GABHS is a potent inducer of interferon-γ (IFN-γ) and most proinflammatory cytokines.[35,67] In some studies, penicillin has been shown to play a synergistic role in symptom improvement by specifically conjugating to IFN-γ and reducing IFN-γ activity,[68,69] and anecdotal reports of symptom improvement in PANDAS after 2 to 6 weeks of antibiotic treatment[19] suggest that penicillin may decrease antibacterial load.[70] Patients with TS and/or OCD have increased levels of some proinflammatory cytokines (TNF-α, interleukin-12), increased gene expression of interleukin-2 in basal ganglia,[71] elevated synthesis of antineuronal antibodies, and decreased number of regulatory T-cells[20,21]; in addition, serum level of interleukin-2 is associated with tic severity.[72] Patients with TS have elevated gene expression of the inflammatory factor protein tyrosine phosphatase receptor–N. However, the exact immunological mechanisms involved in TS remain unclear.

Our study has some limitations, as do other register-based studies. Diagnoses in the registers are clinical diagnoses, not the result of a systematic, well-described, uniform assessment. In addition, not all tic disorders require attending a hospital department, and some children may have been diagnosed with tics by the general practitioner and were thus not registered or included in the present study. Several studies have found good specificity of diagnoses in Danish registers but lower sensitivity.[73,74] Missed true cases could bias our results and lead to an underestimation of the association. On the other hand, patients diagnosed at hospital departments may represent more severe cases, and the results may therefore not be generalizable to populations with less severe symptoms. Similarly, the low mean age of included mothers may have biased our results, as mothers diagnosed with AD at a relatively young age were more likely to be captured. Again, this may bias our results by underestimating the association. Furthermore, as we did not adjust for comorbid psychiatric disorders in offspring (e.g., ADHD or OCD), the estimated association with maternal AD may therefore not solely be driven by TS. Although the population of Denmark, compared to those of most other European countries, is relatively homogenous in terms of ethnic and racial differences, our results may be biased by not adjusting for such differences. Finally, the finding of an association between maternal AD and TS in male but not in female offspring may be due to a smaller sample of females with TS (n = 414), but also there may be true gender-related differences in neuroimmune-related processes in TS.

In conclusion, the results from this large, nationwide, prospective, population-based study extend previous research and offer additional support for a possible neuroimmunological component in the etiology of TS. &

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REFERENCES

1. Kraft JT, Dalsgaard S, Obel C, Thomsen PH, Henriksen TB, Scahill L. Prevalence and clinical correlates of tic disorders in a community sample of school-age children. Eur Child Adolesc Psychiatry. 2012;21:5-13.
2. Khalifa N, von Knorring AL. Prevalence of tic disorders and Tourette syndrome in a Swedish school population. Dev Med Child Neurol. 2003; 45:315-319.
3. Scahill L, Dalsgaard S, Bradbury K. The prevalence of Tourette syndrome and its relationship to clinical features. In: Martino D, Leckman JF, eds. Tourette Syndrome. New York: Oxford University Press; 2013.
4. Cavanna AE, Rickards H. The psychopathological spectrum of Gilles de la Tourette syndrome. Neurosci Biobehav Rev. 2013;37:1008-1015.
5. Lebowitz ER, Motlagh MG, Katsovich L, *et al*. Tourette syndrome in youth with and without obsessive compulsive disorder and attention deficit hyperactivity disorder. Eur Child Adolesc Psychiatry. 2012;21: 451-457.
6. Coghill D, Spiel G, Baldursson G, *et al*. Which factors impact on clinician-rated impairment in children with ADHD? Eur Child Adolesc Psychiatry. 2006;15(Suppl 1):I30-I37.
7. Rothenberger A, Roessner V. The phenomenology of attention-deficit/ hyperactivity disorder in Tourette syndrome. In: Martino D, Leckman JF, eds. Tourette Syndrome. New York: Oxford University Press; 2013.
8. Ferrao Y, De Alvarenga PG, Hounie AG, De Mathis MA, De Rosario MC, Miguel EC. The phenomenology of obsessive-compulsive symptoms in Tourette syndrome. In: Martino D, Leckman JF, eds. Tourette Syndrome. New York: Oxford University Press; 2013.
9. Khalifa N, Von Knorring A-L. Psychopathology in a Swedish population of school children with tic disorders. J Am Acad Child Adolesc Psychiatry. 2006;45:1346-1353.
10. Mol Debes NM, Hjalgrim H, Skov L. Validation of the presence of comorbidities in a Danish clinical cohort of children with Tourette syndrome. J Child Neurol. 2008;23:1017-1027.
11. Cath DC, Ludolph AG. Other psychiatric comorbidities in Tourette syndrome. In: Martino D, Leckman JF, eds. Tourette Syndrome. New York: Oxford University Press; 2013.
12. Pauls DL. An update on the genetics of Gilles de la Tourette syndrome. J Psychosom Res. 2003;55:7-12.
13. Paschou P. The genetic basis of Gilles de la Tourette Syndrome. Neurosci Biobehav Rev. 2013;37:1026-1039.
14. Ercan-Sencicek AG, Stillman AA, Ghosh AK, *et al*. L-histidine decarboxylase and Tourette's syndrome. N Engl J Med. 2010;362:1901-1908.
15. Walkup JT. Epigenetic and environmental risk factors in Tourette syndrome. In: Cohen DJ, Goetz CG, Jankovic J, eds. Tourette Syndrome. Philadelphia: Lippincott, Williams and Wilkins; 2001.
16. Hoekstra PJ, Dietrich A, Edwards MJ, Elamin I, Martino D. Environmental factors in Tourette syndrome. Neurosci Biobehav Rev. 2013;37: 1040-1049.
17. Hoekstra PJ. Perinatal adversities and Tourette syndrome. In: Martino D, Leckman JF, eds. Tourette Syndrome. New York: Oxford University Press; 2013.
18. Martino D. Immunity and stress response in Tourette syndrome. In: Martino D, Leckman JF, eds. Tourette Syndrome. New York: Oxford University Press; 2013.
19. Murphy TK. Infections and tic disorders. In: Martino D, Leckman JF, eds. Tourette Syndrome. New York: Oxford University Press; 2013.
20. Murphy T, Kurlan R, Leckman J. The immunobiology of Tourette's disorder, pediatric autoimmune neuropsychiatric disorders associated with streptococcus, and related disorders: a way forward. J Child Adolesc Psychopharmacol. 2010;20:317-331.
21. Martino D, Zis P, Buttiglione M. The role of immune mechanisms in Tourette syndrome [Epub ahead of print]. Brain Res. May 15, 2014; http://dx.doi.org/10.1016/j.brainres.2014.04.027.
22. Gesundheit B, Rosenzweig JP, Naor D, *et al*. Immunological and autoimmune considerations of autism spectrum disorders. J Autoimmun. 2013;44:1-7.
23. Atladottir HO, Pedersen MG, Thorsen P, *et al*. Association of family history of autoimmune diseases and autism spectrum disorders. Pediatrics. 2009;124:687-694.
24. Comi AM, Zimmerman AW, Frye VH, Law PA, Peeden JN. Familial clustering of autoimmune disorders and evaluation of medical risk factors in autism. J Child Neurol. 1999;14:388-394.
25. Careaga M, Van de Water J, Ashwood P. Immune dysfunction in autism: a pathway to treatment. Neurotherapeutics. 2010;7:283-292.
26. Onore C, Careaga M, Ashwood P. The role of immune dysfunction in the pathophysiology of autism. Brain Behav Immun. 2012;26:383-392.
27. Sweeten TL, Bowyer SL, Posey DJ, Halberstadt GM, McDougle CJ. Increased prevalence of familial autoimmunity in probands with pervasive developmental disorders. Pediatrics. 2003;112:e420.
28. Molloy CA, Morrow AL, Meinzen-Derr J, *et al*. Familial autoimmune thyroid disease as a risk factor for regression in children with autism spectrum disorder: a CPEA Study. J Autism Dev Disord. 2006;36:317-324.
29. Horvath S, Mirnics K. Schizophrenia as a disorder of molecular pathways. Biol Psychiatry. 2015;77:22-28.
30. Benros ME, Mortensen PB, Eaton WW. Autoimmune diseases and infections as risk factors for schizophrenia. Ann N Y Acad Sci. 2012; 1262:56-66.
31. Vonk R, van der Schot AC, Kahn RS, Nolen WA, Drexhage HA. Is autoimmune thyroiditis part of the genetic vulnerability (or an endophenotype) for bipolar disorder? Biol Psychiatry. 2007;62:135-140.
32. Eaton WW, Pedersen MG, Nielsen PR, Mortensen PB. Autoimmune diseases, bipolar disorder, and non-affective psychosis. Bipolar Disord. 2010;12:638-646.
33. Macerollo A, Martino D. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS): An evolving concept. Tremor Other Hyperkinet Mov. 2013;3. pii: tre-03-167-4158-7.
34. Vitaliti G, Trifiletti RR, Falsaperla R, Parano E, Spalice A, Pavone P. A new clinical feature associated with familial early-onset of dystonic-guttural tics: an unusual diagnosis of PANDAS. J Pediatr Neurosci. 2014;9:79-81.
35. Gabbay V, Coffey BJ, Guttman LE, *et al*. A cytokine study in children and adolescents with Tourette's disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33:967-971.
36. Leckman JF, Katsovich L, Kawikova I, *et al*. Increased serum levels of interleukin-12 and tumor necrosis factor-alpha in Tourette's syndrome. Biol Psychiatry. 2005;57:667-673.
37. Davidson A, Diamond B. Autoimmune diseases. N Engl J Med. 2001;345: 340-350.
38. Vojdani A. A potential link between environmental triggers and autoimmunity. Autoimmune Dis. 2014;2014:437231.
39. Muller N, Kroll B, Schwarz MJ, *et al*. Increased titers of antibodies against streptococcal M12 and M19 proteins in patients with Tourette's syndrome. Psychiatry Res. 2001;101:187-193.
40. Loiselle CR, Wendlandt JT, Rohde CA, Singer HS. Antistreptococcal, neuronal, and nuclear antibodies in Tourette syndrome. Pediatr Neurol. 2003;28:119-125.
41. Kawikova I, Leckman JF, Kronig H, *et al*. Decreased numbers of regulatory T cells suggest impaired immune tolerance in children with Tourette syndrome: a preliminary study. Biol Psychiatry. 2007;61:273-278.
42. Kawikova I, Grady BP, Tobiasova Z, *et al*. Children with Tourette's syndrome may suffer immunoglobulin A dysgammaglobulinemia: preliminary report. Biol Psychiatry. 2010;67:679-683.
43. Murphy TK, Storch EA, Turner A, Reid JM, Tan J, Lewin AB. Maternal history of autoimmune disease in children presenting with tics and/or obsessive-compulsive disorder. J Neuroimmunol. 2010;229:243-247.
44. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull. 1999;46:263-268.
45. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. Scand J Public Health. 2011;39(7 Suppl):54-57.
46. World Health Organization. International Classification of Diseases: Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD-8). Vol. 8, rev. Geneva: World Health Organization; 1967.
47. World Health Organization W. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Geneva: World Health Organization; 1992.
48. Pedersen CB, Gøtzsche H, Møller JØ, Mortensen PB. The Danish Civil Registration System—a cohort of eight million persons. Dan Med Bull. 2006;53:441-449.
49. SAS Institute Inc. SAS (release 9.3). Cary, NC: SAS Institute Inc.; 2011.
50. Eaton W, Mortensen PB, Agerbo E, Byrne M, Mors O, Ewald H. Coeliac disease and schizophrenia: population based case control study with linkage of Danish national registers. BMJ. 2004;328:438-439.
51. Eaton WW, Byrne M, Ewald H, *et al*. Association of schizophrenia and autoimmune diseases: linkage of Danish national registers. Am J Psychiatry. 2006;163:521-528.
52. Schoenian S, Konig I, Oertel W, *et al*. HLA-DRB genotyping in Gilles de la Tourette patients and their parents. Am J Med Genetics. 2003; 119B:60-64.

53. Weidinger E, Krause D, Wildenauer A, *et al*. Impaired activation of the innate immune response to bacterial challenge in Tourette syndrome. World J Biol Psychiatry. 2014;15:453-458.
54. Khalilzadeh O, Noshad S, Rashidi A, Amirzargar A. Graves' ophthalmopathy: a review of immunogenetics. Curr Genomics. 2011;12:564-575.
55. Liu S, Yi M, Wang M, Sun Y, Che F, Ma X. Association of IL8 -251A/T, IL12B -1188A/C and TNF-alpha -238A/G polymorphisms with Tourette syndrome in a family-based association study in a Chinese Han population. Neurosci Lett. 2011;495:155-158.
56. Hornig M, Lipkin WI. Immune-mediated animal models of Tourette syndrome. Neurosci Biobehav Rev. 2013;37:1120-1138.
57. Yaddanapudi K, Hornig M, Serge R, *et al*. Passive transfer of streptococcus-induced antibodies reproduces behavioral disturbances in a mouse model of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection. Mol Psychiatry. 2010;15:712-726.
58. Yeh CB, Wu CH, Tsung HC, Chen CW, Shyu JF, Leckman JF. Antineural antibody in patients with Tourette's syndrome and their family members. J Biomed Sci. 2006;13:101-112.
59. Yeh CB, Shui HA, Chu TH, Chen YA, Tsung HC, Shyu JF. Hyperpolarisation-activated cyclic nucleotide channel 4 (HCN4) involvement in Tourette's syndrome autoimmunity. J Neuroimmunol. 2012;250:18-26.
60. Palmeira P, Quinello C, Silveira-Lessa AL, Zago CA, Carneiro-Sampaio M. IgG placental transfer in healthy and pathological pregnancies. Clin Dev Immunol. 2012;2012:985646.
61. Mell L, Davis R, Owens D. Association between streptococcal infection and obsessive-compulsive disorder, Tourette's syndrome, and tic disorder. Pediatrics. 2005;116:56-60.
62. Bombaci M, Grifantini R, Mora M, *et al*. Protein array profiling of tic patient sera reveals a broad range and enhanced immune response against Group A Streptococcus antigens. PLoS One. 2009;4:e6332.
63. Leslie DL, Kozma L, Martin A, *et al*. Neuropsychiatric disorders associated with streptococcal infection: a case-control study among privately insured children. J Am Acad Child Adolesc Psychiatry. 2008;47:1166-1172.
64. Murphy TK, Sajid M, Soto O, *et al*. Detecting pediatric autoimmune neuropsychiatric disorders associated with streptococcus in children with obsessive-compulsive disorder and tics. Biol Psychiatry. 2004;55:61-68.
65. Martino D, Chiarotti F, Buttiglione M, *et al*. The relationship between group A streptococcal infections and Tourette syndrome: a study on a large service-based cohort. Dev Med Child Neurol. 2011;53:951-957.
66. Snider LA, Swedo SE. PANDAS: current status and directions for research. Mol Psychiatry. 2004;9:900-907.
67. Miettinen M, Matikainen S, Vuopio-Varkila J, *et al*. Lactobacilli and streptococci induce interleukin-12 (IL-12), IL-18, and gamma interferon production in human peripheral blood mononuclear cells. Infect Immun. 1998;66:6058-6062.
68. Brooks BM, Hart CA, Coleman JW. Differential effects of beta-lactams on human IFN-gamma activity. J Antimicrob Chemother. 2005;56:1122-1125.
69. Brooks BM, Thomas AL, Coleman JW. Benzylpenicillin differentially conjugates to IFN-gamma, TNF-alpha, IL-1beta, IL-4 and IL-13 but selectively reduces IFN-gamma activity. Clin Exp Immunol. 2003;131:268-274.
70. Sela S, Neeman R, Keller N, Barzilai A. Relationship between asymptomatic carriage of Streptococcus pyogenes and the ability of the strains to adhere to and be internalised by cultured epithelial cells. J Med Microbiol. 2000;49:499-502.
71. Morer A, Chae W, Henegariu O, Bothwell AL, Leckman JF, Kawikova I. Elevated expression of MCP-1, IL-2 and PTPR-N in basal ganglia of Tourette syndrome cases. Brain Behav Immun. 2010;24:1069-1073.
72. Bos-Veneman NG, Bijzet J, Limburg PC, Minderaa RB, Kallenberg CG, Hoekstra PJ. Cytokines and soluble adhesion molecules in children and adolescents with a tic disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34:1390-1395.
73. Linnet KM, Wisborg K, Secher NJ, *et al*. Coffee consumption during pregnancy and the risk of hyperkinetic disorder and ADHD: a prospective cohort study. Acta Paediatr. 2009;98:173-179.
74. Madsen KM, Hviid A, Vestergaard M, *et al*. A population-based study of measles, mumps, and rubella vaccination and autism. N Engl J Med. 2002;347:1477-1482.

TABLE S1 *International Classification of Diseases (ICD), Revision 8* and *ICD-10* Codes for the Included Autoimmune Diseases

Disease	*ICD-8*	*ICD-10*
Thyrotoxicosis, Morbus Basedowi	242.00	E05.0
Autoimmune thyroiditis, Hashimoto's	245.03	E06.3
Diabetes mellitus, type 1	249	E10
Primary adrenocortical insufficiency	255.10-255.12; 255.18; 255.19	E27.1
Celiac disease	269.00	K90.0
Pernicious anemia	281.00; 281.01; 281.08; 281.09	D51.0
Autoimmune hemolytic anemia	283.90; 283.91	D59.1
Idiopathic thrombocytopenic purpura	446.49	D69.3
Multiple sclerosis	340	G35
Guillain Barré syndrome	354	G61.0
Iridocyclitis	364	H20
Wegener's granulomatosis	446.29	M31.3
Crohn's disease	563.01	K50
Ulcerative colitis	563.19	K51
Primary biliary cirrhosis	571.90	K74.3
Autoimmune hepatitis	571.93	K73
Interstitial cystitis	595.03	N30.1
Pemphigoid	694.05	L12
Pemphigus	694 except 694.05	L10
Psoriasis	696.09; 696.10; 696.19	L40; not L40.4
Alopecia areata	704.00	L63
Vitiligo	709.01	L80.9
Rheumatoid arthritis	712.19; 712.39; 712.59	M05; M06
Juvenile arthritis	712.09	M08
Dermatopolymyositis	716	M33
Polymyalgia rheumatica/temporal arteritis	446.30; 446.31; 446.39	M31.5 M31.6; M35.3
Myasthenia gravis	733.09	G70.0
Scleroderma	734.00-734.02; 734.08; 734.09	M34
Systemic lupus erythematosus	734.19	M32.1 M32.9
Sjögren's syndrome	734.90	M35.0
Ankylosing spondylitis (Mb. Bechterew)	712.49	M45.9