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Proband and Familial Autoimmune Diseases Are Associated With Proband Diagnosis of Autism Spectrum Disorders

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Abstract

Objective: There is evidence that parental autoimmune diseases (ADs) are associated with autism spectrum disorders (ASD) in offspring. The association between offspring ASD and ADs diagnosed in siblings and probands remains less clear. We examined whether proband and familial diagnoses of ADs were associated with increased odds of ASD in probands.

Method: The study is based on a nested case-control design that used data from a large national birth cohort (N = 1.2 million) in Finland. There were 4,600 cases of ASD and controls matched 1:4 on date of birth, sex, and residence. Data were accessed from national medical, birth, and central registries.

Results: Probands had a statistically significant increase in odds of ASD when they (adjusted odds ratio [OR] = 1.2), their mother (adjusted OR = 1.1), or their sibling (adjusted OR = 1.2) were diagnosed with an AD. With regard to specific ADs, we found a statistically significant increase in odds of ASD in probands diagnosed with autoimmune thyroiditis (adjusted OR = 2.7). Further analyses considering ADs by body system yielded a statistically significant increase in odds of ASD in probands with ADs associated with the central/peripheral nervous (adjusted OR = 4.8) and skin/mucous membrane (adjusted OR = 1.3) systems. Probands of mothers diagnosed with ear/eye (adjusted OR = 1.6) or respiratory (adjusted OR = 1.4) ADs, or siblings diagnosed with skin/mucous membrane ADs (adjusted OR = 1.3) also had increased odds of ASD.

Conclusion: The findings suggest that there may be common pathogenic, developmental mechanisms related to autoimmunity that are associated with the etiology of ASD.

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Keywords

autoimmune; familial; autism; proband; sibling

An immune component to autism spectrum disorder (ASD) is supported by findings of elevated pro-inflammatory cytokines and chemokines during pregnancies of ASD case offspring, and among children and adults with ASD.^{1–4} Studies also suggest that maternal or paternal autoimmune disorders (ADs) may increase the odds of ASD in offspring.^{5–9} Although findings vary among studies, some commonly identified ADs that have been related to ASD include maternal type 1 diabetes¹⁰ and hypothyroidism,^{5,6,11,12} and paternal ulcerative colitis and type 1 diabetes.¹³ Findings from many previous studies are limited by lack of inclusion of probands, parents, and siblings in the same study and by small sample sizes, which is a particularly important issue, given the low prevalence of many ADs.^{4,14,15} Extending these studies to siblings and probands also offers the potential to better understand shared genetic and environmental influences that may underlie relationships between ADs and ASD.^{3,7,8,11,15,16} These types of studies may also inform clinical evaluation and counseling when a family member is diagnosed with ADs.¹⁷

In the present study, we examined the association between proband and familial (mother, father, and siblings) diagnoses of AD, and odds of ASD in the proband. Given that the biological mechanisms by which ADs operate may vary by the body system affected, the ADs were classified according to this. We hypothesized that proband diagnosis of ASD would be associated with diagnosis of ADs of the central/peripheral nervous, endocrine, and gastrointestinal systems in first-degree relatives.

METHOD

Study Design

The Finnish Prenatal Study of Autism (FiPS-A) is a nested case-control study based on linkages of several nationwide Finnish registries. The FiPS-A has been described in detail previously.¹⁸ The sample includes all singleton live births in Finland between January 1, 1987, and December 31, 2005 (N = 1.2 million). The children were followed up until December 31, 2007, for the diagnosis of ASD (see Case Identification section below). The registries were linked using unique personal identity codes (PIC) assigned to each Finnish resident at birth, which remain the same throughout the lifespan. The FiPS-A has been authorized by the Ministry of Social Affairs and Health of Finland (STM/2593/2008). The ethics committee of the Finnish National Institute for Health and Welfare (THL) and hospital district of Southwest Finland and the Institutional Review Board of the New York State Psychiatric Institute have given approval for the study.

National Registries

All the data used in the study were collected from three national registries: the Finnish Hospital Discharge Register (FHDR), the Finnish Medical Birth Register (FMBR), and the Finnish Central Population Register (FCPR).

The FHDR includes all inpatient diagnoses since January 1, 1969, and outpatient diagnoses since January 1, 1998, for all hospitals in Finland. It contains the PIC for every patient, dates of admission and discharge, and diagnoses at discharge. The FHDR covers all medical diagnoses collected from all hospitals including health centers, military wards, prisons, and private hospitals. This does not include private outpatient clinics. The FHDR was used to identify ASD cases and their parents' and full siblings' psychiatric diagnoses. The register has been shown to have high validity.¹⁹ The diagnostic classification is based on the *International Classification of Diseases (ICD)*. The 8th revision (World Health Organization, 1967) was used from 1969 to 1986, the 9th revision (World Health Organization, 1977) from 1987 to 1995, and the 10th revision (World Health Organization, 1992) since January 1, 1996.

The FMBR was established in 1987 and is also maintained by THL. The register includes comprehensive and standardized data on every pregnancy, the prenatal period, and the neonatal period up to 7 days for all births in Finland. It includes the PIC of mothers and every liveborn child. The FMBR was used to identify mothers and control subjects as well as to obtain data on potential confounders.

The FCPR was established in 1969 and is maintained by the Finnish Population Register Centre. It is a computerized national register that contains basic information about Finnish citizens and foreign citizens living permanently in Finland. The data include name, PIC, address, municipality of residence, immigration and emigration, family relations, and date of birth and death. The FCPR was used to identify fathers and full siblings of probands.

Case Identification

The cases with ASD were identified according to *ICD-9* (299×) and *ICD-10* (F84×) codes. We included only the most recent ASD diagnosis, resulting in 19 cases with a diagnosis based on *ICD-9* codes, whereas the majority of cases were diagnosed based on *ICD-10* codes (n = 4,581). None were diagnosed based on *ICD-8* codes. The total number of children with ASD was 4,600 (3,660 boys and 940 girls), consisting of the 3 main subgroups: childhood autism (F84.0, n = 1111, mean age at diagnosis 5.5 years), Asperger syndrome (F84.5, n = 1744, mean age at diagnosis 10.0 years), and other pervasive developmental disorder (PDD/PDD-unspecified; F84.8/.9, n = 1745, mean age at diagnosis 7.6 years). The diagnoses of ASD in Finland are made in specialized clinics of child neurology, child and adolescent psychiatry, or pediatrics. The FHDR diagnosis of childhood autism has been validated previously.¹⁸ Asperger syndrome and PDD diagnoses were not validated by research assessments.

In general, diagnosis of psychiatric and medical conditions occur after careful diagnostic evaluations that include specialty physicians when necessary. In the Finnish health care system, all children are followed up annually at child health clinics before school age and continuing at school health units after starting school at the age of 6 years. Children requiring additional evaluation and follow-up care are evaluated at specialty pediatric clinics by a pediatrician. Adults are evaluated in health care clinics by general practitioners. If they require additional evaluation or follow-up care, they receive referrals to specialty physicians.

Identification of Controls

All ASD cases were matched to 4 controls by date of birth (± 30 days), sex, and place of birth (birth hospital or regional hospital district if a birth hospital control could not be found). Controls were excluded if they met criteria for ASD or profound/severe intellectual disability according to the FHDR. Overall, 18,058 control subjects were matched.

Identification of Autoimmune Diseases in Family Members (Mother, Father, and Full Siblings) and Probands

Register data on parents and full siblings have been available since January 1, 1969. If both parents were not able to be identified from the registries, the subject was excluded. Paternity was based on an individual's status as a husband of the mother at the time of the child's birth. If the mother was unmarried, paternity was confirmed by register data documenting the self-acknowledgement of the father, or positive DNA paternity testing. Paternity was established in 98.3% of the children by either of these measures at the registry level. Full siblings (cases, $n = 6,149$; controls, $n = 22,779$) were also identified.

The lifetime diagnoses of ADs (diagnosis was identified in the registry at any time during the individual's life) for family members (mother, father, and full siblings), ASD cases, and matched controls were obtained from the FHDR according to *ICD-8*, *ICD-9*, and *ICD-10*. The ADs were classified at three levels. First, they were classified as "any AD" separately for mothers, fathers, siblings, and probands. "Any AD" indicates that the family member has at least one AD diagnosis. Second, they were classified by the body system primarily affected. The 13 body systems, based on *ICD-10*, and the corresponding ADs, are listed in Supplement 1 (available online). Third, they were grouped by the most common ADs that previous clinical and epidemiologic studies identified as being associated with ASD, based on our review (Supplement 2, available online).

Covariates

The demographic variables considered as potential confounds were maternal socioeconomic status (SES) based on family employment categories (SES; upper white collar workers, lower white collar workers, blue collar workers, or others), smoking status during pregnancy (yes/no), maternal and paternal age (15–24, 25–34, 35), maternal, paternal, and sibling psychiatric diagnoses (yes/no), infant weight for gestational age (< 2 SDs; SD below the mean, 2 SDs above the mean), infant gestational age (< 37 weeks, 37 weeks), and number of previous births (0, > 1). The data on these variables were obtained from the FMBR and the FHDR. These demographic variables were selected as potential confounds because in previous studies they were found to have an association with ASD.^{20–26} To further evaluate whether these variables were confounds for the existing sample, we performed bivariate analyses (Pearson χ^2 -test or Fisher exact test) to test the significance of associations between these variables and ASD case or control status of the probands. We also assessed whether these variables had a statistically significant association with familial (maternal, paternal, and sibling, separately) or proband diagnosis of ADs among controls. The variables that had a statistically significant association with both ADs in the controls and ASD (two-sided p values of $< .05$) were included as covariates in adjusted statistical models for the

primary hypotheses. We have applied this approach to identify covariates in prior studies.
16,27

Statistical Analysis

For the primary analyses, lifetime diagnosis of ADs in the mother, father, or siblings and the probands themselves was the exposure of interest. This was a dichotomous (yes/no) indicator of any AD. The outcome was the ASD case or control status of the probands.

The generalized estimating equation method with an exchangeable correlation structure was used to examine the associations between familial ADs (paternal, maternal, and full sibling) and ASD in this matched case-control design. The log-offset term was chosen to account for the different follow-up times for each family member and the number of siblings. The method was applied to account for the dependence between cases and matched controls and the siblings within the same family. The associations between ADs and ASD in the probands were quantified using conditional logistic regression.

Post hoc analyses were conducted using conditional logistic regression to assess combinations of the presence or absence of an AD in parents as predictors of ASD in the proband. AD diagnoses of parents were classified into four categories: neither parent (reference group), both parents, only mother, and only father. Further analyses were conducted for associations between AD and ASD within probands by two strata: cases diagnosed with ADs before their diagnosis of ASD; and cases diagnosed with ADs after their diagnosis of ASD. Because the present study used lifetime diagnoses of ADs, we performed this analysis to ensure that the timing of AD diagnoses did not alter associations with proband ASD.

The models were first fitted as unadjusted. All models, excluding post hoc analyses, were then repeated, adjusting for the covariates as described above. To account for multiple testing, we applied a Bonferroni correction for the analyses of body system and specific ADs and ASD (for 34 independent regression tests, $\alpha = 0.05/34 = 0.001$). It should be noted that for many of the specific ADs, there were insufficient numbers of cases or controls (<5 cases or controls with ADs) to permit statistical analysis.

We conducted additional analyses to determine whether the proband's sex modified the associations between proband (or familial) diagnosis of an AD and ASD in the proband. The statistical model included the following: lifetime diagnosis of an AD in the mother; proband sex; and an interaction term for lifetime maternal diagnosis of an AD by proband sex. The model was repeated replacing diagnosis of an AD in the mother with the father, siblings, and proband. For all models, the outcome was the ASD case or control status of the probands.

Results are reported using odds ratios (ORs) with 95% confidence intervals (95% CIs). Statistical analyses were carried out using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

ADs and ASD in Probands

There was a statistically significant increase in odds of ASD among probands who had a diagnosis of an AD (Table 1). Upon further analyses, a statistically significant increase in odds of ASD was present among probands diagnosed with ADs primarily targeting the central/peripheral nervous and skin/mucous membrane (Table 2). Furthermore, there was a statistically significant increase in odds of ASD among probands with a diagnosis of autoimmune thyroiditis (Table 3).

Familial ADs and ASD in Probands

There was a statistically significant increase in odds of ASD among probands of mothers, fathers, and siblings who were diagnosed with an AD (Table 1). The association between ADs diagnosed in the mothers and siblings (but not the fathers), and ASD in the proband remained statistically significant after adjustment for covariates.

Subgroup analyses of ADs affecting different body systems revealed a statistically significant increase in odds of ASD in probands whose mothers were diagnosed with ADs associated with the ear/eye and respiratory systems, as well as probands whose siblings had diagnoses of ADs associated with the skin/mucous membrane system (Table 4). There was no statistically significant association between paternal diagnoses of ADs of specific body systems and odds of ASD in the proband.

With regard to specific diagnoses, statistically significant increases in odds of proband ASD were found in those with mothers diagnosed with autoimmune thyroiditis, asthma, and iritis/uveitis (Table S1, available online). No statistically significant difference in odds was observed for ASD in probands whose fathers or siblings were diagnosed with any of the specific ADs in our analyses.

Covariates

All of the demographic variables, except for maternal smoking during pregnancy, were statistically significantly associated with proband ASD (Table S2, available online). Proband AD diagnosis was statistically significantly associated with familial diagnosis of a psychiatric disorder, earlier gestational age at birth, maternal SES, and sex. Any diagnosis with an AD in at least two family members was statistically significantly associated with maternal age at the proband's birth, smoking during pregnancy, SES, and familial psychiatric diagnosis.

Post Hoc Analyses

The odds ratios for ASD in the proband were numerically similar regardless of whether both parents or only one parent was diagnosed with an AD (Table S3, available online). A statistically significant increase in odds of ASD in the proband was observed regardless of whether the diagnosis of ADs of the endocrine, respiratory, and skin/mucous membrane systems was made before or after the ASD diagnosis (data available upon request). The interaction between diagnosis of an AD by sex of the proband in association with odds of

proband ASD was not statistically significant (data available upon request). There was also no statistically significant interaction between any familial AD and sex of the proband in association with the proband's diagnosis of ASD (data available upon request).

DISCUSSION

Results of the present study using data from a Finnish national birth cohort indicate increased odds for ASD diagnosis among those with an AD diagnosis themselves, or with first-degree relatives with an AD diagnosis. To our knowledge, the associations between proband ASD and familial ADs (considering each first-degree relative separately), as well as proband ASD and ADs affecting several individual body systems, are novel findings.

With regard to specific ADs, we first consider the association between ADs and ASD in the proband. To our knowledge, no previous population registry-based study has reported associations between proband ASD diagnosis among those also with diagnoses of asthma and autoimmune thyroiditis. Although a previous large case-control study found no association between proband diagnosis of asthma and ASD, asthma diagnosis was based on maternal self-report.²⁸ Interestingly, our group has previously reported that maternal thyroid peroxidase antibody (TPO-Ab), an autoantibody involved in autoimmune thyroiditis, was associated with increased odds of childhood autism.¹⁶ Maternal TPO-Ab can cross the placenta,²⁹ and can lead to deficiencies in offspring thyroid function and motor and intellectual abilities.^{29,30}

Separate analyses of ADs affecting specific body systems investigated in probands revealed increased odds for ASD associated with central/peripheral nervous system ADs. This is particularly significant, given the extensive previous findings reporting altered brain structure and function in individuals with ASD.^{31,32} ADs of the central and peripheral nervous system can directly affect brain and spinal cord tissues and cells through autoantibody activation, including T-helper type 1 cytokines (eg, interleukin-12 and γ), which cause inflammation.^{33,36} This pathway can alter brain structure (myelination, volume) and function (synaptic connectivity) and may translate to alterations in behavior, cognition, and sensorimotor functions.^{33–36} Because ASD is associated with altered structure and function of motor (somato-motor and sensory cortex, cerebellum, and basal ganglia) and social cognition (eg, portions of the frontal lobe and temporal parietal junction) brain networks, this is a promising area for further study.^{31,32}

The lack of association between gastrointestinal system ADs and ASD in our study was surprising, given that children with ASD are at increased risk for gastrointestinal symptoms, such as irritable bowel syndrome, functional constipation, and incontinence.^{37,38} However, the previous literature regarding associations between specific gastrointestinal system ADs and ASD have been inconsistent. For example, the present and two prior studies found no association between celiac disease and odds of ASD diagnosis.³⁹ In contrast, a previous clinical study of children with ASD found a higher prevalence of celiac disease compared with the country's pediatric population.⁴⁰ There may be biological factors that mediate associations between gastrointestinal ADs and ASD that could account for the inconsistent findings from epidemiological and clinical studies. For example, although a study us the

Swedish biopsy registry did not find an association with celiac disease and ASD, individuals with normal mucosa but celiac disease serology (positive immunoglobulins A or G endomysium, transglutaminase, or gliadin) were four times more likely to have ASD.⁴¹ Similarly, in utero exposure to inflammation due to a gastrointestinal AD in the mother could also affect the maternal—fetal dyad's shared gut microbiome placing offspring at greater odds for gastrointestinal difficulties in general.^{7,8,13} Additional research focused on biological indicators of gastrointestinal health in the mother and probands and the association with ASD should be considered.

Second, we consider the relationship between ASD among probands and familial diagnosis of ADs. Consistent with a previous study,¹² we found an association between maternal asthma and proband ASD. However, our results showing a statistically significant increase in odds of proband ASD associated with maternal autoimmune thyroiditis are not consistent with results of a prior study.⁷ Nonetheless, as previously mentioned, we demonstrated in a prior study an association between maternal TPO-Ab and increased odds of childhood autism.¹⁶ Maternal iritis/uveitis was associated with offspring ASD in our study, but not in three prior studies.^{8,15,42} The prior studies were limited by having only one case and/or control subject with the iritis/uveitis diagnosis. With regard to sibling AD diagnoses and risk for proband ASD, skin/mucous membrane system ADs in siblings were associated with increased odds of ASD in the proband. This has not been demonstrated previously.⁷

Third, we consider possible mechanisms that could explain the associations between familial diagnosis of ADs and ASD among probands. Shared environmental factors, occurring in utero and/or postnatally, may be antecedents of ASD. The plausibility of in utero environmental factors is supported by the greater number of associations between ADs and ASD for mothers, as compared to fathers, in our and two other studies,^{43,44} and the fact that maternal autoantibodies can pass through the placenta.⁴⁵ This may be particularly relevant to the association between maternal autoimmune thyroiditis and ASD, and our prior finding, cited above, that maternal TPO-Ab documented in maternal sera is related to increased odds of childhood autism.¹⁶ With regard to neurodevelopment, maternal transfer of brain-reactive autoantibodies results in increased stem cell proliferation in the embryonic neocortex, as well alterations in neuronal size, and neuronal death in brain areas including the hippocampus, cerebellum, and frontal cortex.^{46–48} The presence of several maternal brain-reactive autoantibodies are also associated with increases in ADs as well as autism severity ratings of social deficits and motor stereotypies as well as language and cognitive impairment.^{16,46,49}

Furthermore, we consider genetic vulnerability, given that ADs are heritable diseases^{1,4} and autism has a strong genetic component.⁵⁰ Although we did not assess this directly, ADs of different types aggregate within families.³ Our findings indicating that an amalgamation of different ADs in immediate family members are related to ASD in probands support the plausibility of a common autoimmune mechanism in families with a history of ADs.^{4,16} The prevalence of one or more specific ADs clustering in a family is quite high (46%) for probands with ASD.^{4,16} Furthermore, several common ADs share regulatory the human leukocyte antigen system of genes that are involved in recognition of self and modulating immune responsiveness.^{3,51}

This study has several strengths. First, we applied a comprehensive analytic approach to evaluate the association between ADs and ASD in offspring, including all immediate family members and probands. Other studies have not included siblings and/or probands. Moreover, the cases and controls were derived from a large, population-based national birth cohort including virtually all childhood ASD cases diagnosed in Finland through medical registries that cover the entire population. The sample size therefore was among the largest and most representative of those investigating this question, yielding increased statistical power. Furthermore, in comparison to many other birth cohort studies relating ADs and ASD, the present study featured an extensive number of ADs evaluated for associations. Finally, we used stringent criteria to determine statistical significance by adjusting for multiple comparisons with the Bonferroni correction.

Some limitations of the present study should be noted. First, there may be some children with ASD and families with ADs that were not identified in the registries because they never received medical attention or other factors. However, universal health coverage, together with the comprehensive medical and psychiatric registries drawn on in this study, increased the likelihood of detecting diagnoses of ADs and ASD. Second, the children diagnosed with ASD and/or ADs may have received more medical care. We found no difference in odds of ASD between cases diagnosed with an AD before versus after the ASD diagnosis. Third, some ADs are quite rare in the population. The sample of exposed cases and controls for certain classes of ADs, including those of the gynecological and central/peripheral nervous system in the proband, were small, leading to reduction in the effect sizes. Thus, future cohort studies with larger numbers of exposed individuals with these and other rare ADs are necessary. Fourth, given the small number of exposed cases and controls resulting in a wide confidence interval in the analyses between central/peripheral nervous system ADs and ASD, these findings should be interpreted with caution. Fifth, although we were able to adjust for potential confounding through the inclusion of many covariates in the statistical models, residual factors related to family lifestyle or health may still confound the association of ADs and odds of ASD. Sixth, we are not able to determine whether paternity was confirmed by marriage, by acknowledgement of the father, or by DNA testing, as this was established at the registry level.

In conclusion, we identified several novel associations between proband and familial ADs and ASD (in the proband) in a large national birth cohort. Our findings suggest that immune-related pathways common to ADs may be involved in the relationship between ADs and ASD. These findings offer the potential for an improved understanding of the role of immune or autoimmune etiologies of ASD, which may facilitate preventive and clinical interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1
Associations Between Familial Autoimmune Diseases (ADs) and Autism Spectrum Disorder in the Proband

ADs	Diagnostic Classification		Unadjusted			Adjusted		
	Cases (n = 4,600) n (%)	Controls (n = 18,058) n (%)	OR	95% CI	p	OR	95% CI	p
Proband ^{a,b}	738 (16.04)	2,255 (12.49)	1.34	1.23–1.47	<.0001	1.21	1.11–1.32	<.0001
Any Familial ^c	1,752 (38.09)	6,008 (33.27)	1.14	1.10–1.19	<.0001	1.02	0.97–1.07	.35
Maternal ^d	875 (19.02)	2,901 (16.06)	1.19	1.11–1.27	<.0001	1.13	1.06–1.21	.0005
Paternal ^e	604 (13.13)	2,116 (11.72)	1.12	1.03–1.22	.0086	1.08	0.99–1.18	.07
Sibling ^{f,g}	747 (12.15)	2,330 (10.23)	1.24	1.14–1.35	<.0001	1.16	1.06–1.26	.001

Note: Familial category includes maternal, paternal, and sibling ADs. Statistically significant values of $p < .05$ are shown in boldface type, n = number with ADs; OR = odds ratio.

^aConditional logistic regression results reported.

^bAdjusted for maternal socioeconomic status (SES), gestational age, and maternal and familial psychiatric diagnosis.

^cAdjusted for SES, gestational age, weight for gestational age, maternal age, previous births, and maternal, paternal, and sibling psychiatric diagnosis.

^dAdjusted for SES, gestational age, weight for gestational age, maternal age, and maternal psychiatric diagnosis.

^eAdjusted for gestational age, paternal age, and paternal psychiatric diagnosis.

^fAdjusted for SES, maternal and paternal age, previous births, and sibling psychiatric diagnosis.

^gAdjusted for counts for siblings (n = 6149 cases) and controls (n = 22,779).

TABLE 2

Associations Between Proband Autoimmune Diseases (ADs) Categorized by Body System and Autism Spectrum Disorder in the Probands

ADs by Body System	Probands		Unadjusted			Adjusted		
	Cases (n = 4,600) n (%)	Controls (n = 18,058) n (%)	OR	95% CI	p	OR	95% CI	p
Blood	23 (0.50)	67 (0.37)	1.34	0.83–2.16	.22	1.31	0.82–2.10	.25
CNS/PNS	9 (0.20)	7 (0.04)	5.03	1.87–13.51	.001	4.77	1.83–12.44	.001
Coronary/Heart	1 (0.02)	6 (0.03)	—	—	—	—	—	—
Connective Tissue	27 (0.59)	94 (0.52)	1.12	0.73–1.72	.59	1.07	0.69–1.65	.76
Ear/Eye	7 (0.15)	22 (0.12)	1.24	0.53–2.91	.61	1.23	0.52–2.93	.64
Endocrine	63 (1.37)	173 (0.96)	1.42	1.07–1.89	.01	1.37	1.02–1.84	.04
Gastrointestinal	33 (0.72)	81 (0.45)	1.59	1.06–2.39	.02	1.59	1.07–2.36	.02
Gynecologic	0 (0.00)	0 (0.00)	—	—	—	—	—	—
Metabolic (Liver, Kidney)	4 (0.09)	9 (0.05)	—	—	—	—	—	—
Respiratory	319 (6.93)	1,044 (5.78)	1.20	1.06–1.35	.004	1.14	1.01–1.29	.04
Skin/Mucous Membrane	366 (7.96)	1,061 (5.88)	1.35	1.20–1.51	<.0001	1.31	1.17–1.47	<.0001
Systemic/Multisystem/Vascular	3 (0.07)	20 (0.11)	—	—	—	—	—	—

Note: Adjusted for maternal socioeconomic status, gestational age, and maternal and familial psychiatric diagnosis. Dash (—) indicates insufficient number of observations for statistical comparison. Statistically significant values of $p < .05$ are shown in boldface type; $p < .001$ meets significance based on Bonferroni correction. CNS = central nervous system; n = number with ADs; OR = odds ratio; PNS = peripheral nervous system.

TABLE 3
Associations Between Proband Autoimmune Diseases (ADs) and Autism Spectrum Disorder in the Proband

Specific ADs	Proband		Unadjusted			Adjusted		
	Cases (n = 4,600) n (%)	Controls (n = 18,058) n (%)	OR	95% CI	p	OR	95% CI	p
Blood								
ITP/purpura/immune thrombocytopenia	7 (0.15)	23 (0.13)	1.19	0.51–2.77	.69	1.15	0.51–2.60	.74
CNS/PNS								
Guillain-Barré syndrome	1 (0.02)	2 (0.01)	—	—	—	—	—	—
Multiple sclerosis	3 (0.07)	0 (0.00)	—	—	—	—	—	—
Myasthenia gravis	1 (0.02)	1 (0.01)	—	—	—	—	—	—
Connective Tissue								
Ankylosing spondylitis	2 (0.04)	1 (0.01)	—	—	—	—	—	—
Dermatomyositis/polymyositis	0 (0.00)	0 (0.00)	—	—	—	—	—	—
Mixed connective tissue disease	0 (0.00)	1 (0.01)	—	—	—	—	—	—
Rheumatoid arthritis	3 (0.07)	5 (0.03)	—	—	—	—	—	—
Sjögren syndrome	3 (0.07)	7 (0.04)	—	—	—	—	—	—
Ear/Eye								
Iritis/uveitis	6 (0.13)	17 (0.09)	1.38	0.54–3.50	.50	1.37	0.51–3.64	.53
Endocrine								
Autoimmune thyroiditis	18 (0.39)	26 (0.14)	2.71	1.48–4.94	.001	2.67	1.46–4.89	.001
Diabetes mellitus type 1	40 (0.87)	140 (0.78)	1.12	0.79–1.58	.53	1.09	0.77–1.56	.62
Graves disease	0 (0.00)	3 (0.02)	—	—	—	—	—	—
Hypothyroidism	16 (0.35)	25 (0.14)	2.50	1.34–4.69	.004	2.54	1.38–4.69	.003
Hypothyroidism	0 (0.00)	4 (0.02)	—	—	—	—	—	—
Gastrointestinal								
Celiac disease	25 (0.54)	53 (0.29)	1.85	1.15–2.97	.01	1.81	1.15–2.86	.01
Crohn's disease	3 (0.07)	7 (0.04)	—	—	—	—	—	—
Ulcerative colitis	7 (0.15)	23 (0.13)	1.19	0.51–2.77	.69	—	—	—
Respiratory								
Asthma	319 (6.93)	1,044 (5.78)	1.20	1.06–1.35	.004	1.14	1.01–1.29	.04
Skin/Mucous Membrane								

Specific ADs	Proband		Unadjusted			Adjusted		
	Cases (n = 4,600) n (%)	Controls (n = 18,058) n (%)	OR	95% CI	p	OR	95% CI	p
Alopecia areata	5 (0.11)	5 (0.03)	3.91	1.13–13.51	.03	—	—	—
Psoriasis	6 (0.13)	28 (0.16)	0.84	0.35–2.02	.70	0.68	0.26–1.78	.43
Systemic/MultiorganA/ascular PSS/CREST/scleroderma	1 (0.02)	2 (0.01)	—	—	—	—	—	—
Systemic lupus erythematosus	0 (0.00)	0 (0.00)	—	—	—	—	—	—

Note: Adjusted for maternal socioeconomic status, gestational age, and maternal and familial psychiatric diagnosis. Dash (—) indicates insufficient number of observations for statistical comparison. Statistically significant values of $p < .05$ are shown in boldface type; $p < .001$ meets significance based on Bonferroni correction. CREST = calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; CNS = central nervous system; ITP = idiopathic thrombocytopenic purpura; n = number with ADs, OR = odds ratio; PNS = peripheral nervous system; PSS = progressive systemic sclerosis.

TABLE 4

Associations Between Familial Autoimmune Diseases Categorized by Body System and Autism Spectrum Disorder Cases and Matched Controls

ADs by Body System	Maternal					
	Cases (n = 4,600) n (%)	Controls (n = 18,058) n (%)	Unadjusted		Adjusted ^a	
			OR	95% CI	OR	95% CI
Blood	9 (0.20)	35 (0.19)	1.0	0.5–2.1	1.04	0.5–2.2
CNS/PNS	24 (0.52)	89 (0.49)	1.1	0.7–1.7	1.0	0.6–1.6
Coronary/Heart	4 (0.09)	16 (0.09)	—	—	—	—
Connective Tissue	95 (2.07)	311 (1.72)	1.2	1.0–1.5	1.1	0.9–1.4
Ear/Eye	80 (1.74)	197 (1.09)	1.6 ^{***}	1.2–2.1	1.6 ^{***}	1.2–2.1
Endocrine	123 (2.67)	387 (2.14)	1.3 [*]	1.0–1.5	1.1	0.9–1.4
Gastrointestinal	90 (1.96)	329 (1.82)	1.1	0.9–1.4	1.0	0.8–1.2
Gynecologic	162 (3.52)	520 (2.88)	1.2 [*]	1.0–1.5	1.2 [*]	1.0–1.4
Metabolic	59 (1.28)	151 (0.84)	1.5 ^{**}	1.1–2.1	1.3 [§]	1.0–1.7
Respiratory	199 (4.33)	530 (2.93)	1.5 ^{***}	1.3–1.7	1.4 ^{***}	1.2–1.6
Skin/Mucous Membrane	221 (4.80)	833 (4.61)	1.0	0.9–1.2	1.0	0.9–1.2
Systemic/Multiorgan	82 (1.78)	314 (1.74)	1.03	0.8–1.3	0.9	0.7–1.2

	Paternal						Sibling					
	Cases (n = 4,600) n (%)	Controls (n = 18,058) n (%)	Unadjusted		Adjusted ^b		Cases (n = 6,149) n (%)	Controls (n = 22,779) n (%)	Unadjusted		Adjusted ^c	
			OR	95% CI	OR	95% CI			OR	95% CI	OR	95% CI
6 (0.13)	15 (0.08)	1.6	0.6–4.0	—	—	—	22 (0.36)	72 (0.32)	1.2	0.7–1.9	1.2	0.7–1.9
17 (0.37)	65 (0.36)	1.0	0.6–1.7	0.9	0.5–1.6	4 (0.07)	18 (0.08)	18 (0.08)	—	—	—	—
5 (0.11)	22 (0.12)	0.9	0.3–2.4	—	—	5 (0.08)	8 (0.04)	8 (0.04)	2.4	0.8–7.4	—	—
64 (1.39)	232 (1.28)	1.1	0.8–1.4	1.0	0.8–1.4	40 (0.65)	111 (0.49)	111 (0.49)	1.4 [§]	1.0–2.0	1.3	0.9–1.8
58 (1.26)	238 (1.32)	1.0	0.7–1.3	1.0	0.7–1.3	19 (0.31)	46 (0.20)	46 (0.20)	1.6 [§]	0.9–2.7	1.7 [§]	1.0–2.9
68 (1.48)	195 (1.08)	1.4 [*]	1.0–1.8	1.3 [§]	1.0–1.7	82 (1.33)	232 (1.02)	232 (1.02)	1.4 [*]	1.1–1.8	1.2	1.0–1.6
90 (1.96)	301 (1.67)	1.2	0.9–1.5	1.1	0.9–1.4	37 (0.60)	121 (0.53)	121 (0.53)	1.2	0.8–1.8	1.1	0.7–1.6
—	—	—	—	—	—	8 (0.13)	24 (0.11)	24 (0.11)	1.3	0.6–2.9	—	—

	Paternal					Sibling					
	Cases (n = 4,600) n (%)	Controls (n = 18,058) n (%)	Unadjusted		Adjusted ^b	Cases (n = 6,149) n (%)	Controls (n = 22,779) n (%)	Unadjusted		Adjusted ^c	
			OR	95% CI				OR	95% CI	OR	95% CI
	48 (1.04)	125 (0.69)	1.5 [*]	1.1–2.1	1.3	4 (0.07)	20 (0.09)	—	—	—	—
	137 (2.98)	486 (2.69)	1.1	0.9–1.3	1.1	280 (4.55)	916 (4.02)	1.2 [*]	1.0–1.4	1.1	1.0–1.3
	172 (3.74)	650 (3.60)	1.0	0.9–1.2	1.0	362 (5.89)	1020 (4.48)	1.4 ^{***}	1.2–1.6	1.3 ^{***}	1.1–1.4
	96 (2.09)	315 (1.74)	1.2	1.0–1.5	1.2	14 (0.23)	35 (0.15)	1.6	0.8–2.9	1.5	0.8–2.8

Note: Dash (—) indicates insufficient number of observations for statistical comparison. Statistically significant values are shown in boldface type. ADs = autoimmune diseases; CNS = central nervous system; n = number with ADs; OR = odds ratio; PNS = peripheral nervous system.

^a Adjusted for maternal socioeconomic status (SES), gestational age, weight for gestational age, maternal age, and maternal psychiatric diagnosis.

^b Adjusted for gestational age, paternal age, and paternal psychiatric diagnosis.

^c Adjusted for SES, maternal and paternal age, previous births, and sibling psychiatric diagnosis

* $p < .05$;

** $p < .01$;

*** $p < .001$ (Bonferroni-corrected significance level);

§ $p < .10$.