Title: Proband and familial autoimmune diseases are associated with proband diagnosis of autism spectrum disorders

Running Head: Familial autoimmune diseases and autism

[a]Joint first authorship

Marisa N. Spann, Ph.D.,[a] Department of Psychiatry, Columbia University, Vagelos College of Physicians and Surgeons, 622 West 168th Street, PH Room 1540, New York, NY 10032

Laura Timonen-Soivio, M.D.,[a] Department of Child Psychiatry, University of Turku and Turku University Central Hospital, Lemminkäisenkatu 3/ Teutori (3rd floor), 20014 Turku, Finland; Department of Child Neuropsychiatry, Helsinki University Central Hospital, Ratapihantie 11, Helsinki, Finland

Auli Suominen, M.Sc, Department of Child Psychiatry, University of Turku and Turku University Central Hospital, Lemminkäisenkatu 3/ Teutori (3rd floor), 20014 Turku, Finland

Keely Cheslack Postava. Ph.D., Department of Psychiatry, Columbia University Vagelos College of Physicians and Surgeons and New York State Psychiatric Institute, 1051 Riverside Drive, Unit 23, New York, NY, USA

Ian W. McKeague, Ph.D., Department of Biostatistics, Columbia University Mailman School of Public Health, 722 West 168th Street, New York, NY, USA

Andre Sourander, M.D., Department of Psychiatry, Columbia University Vagelos College of Physicians and Surgeons, New York State Psychiatric Institute, 1051 Riverside Drive, Unit 23, New York, NY, USA; Department of Child Neuropsychiatry, Helsinki University Central Hospital, Ratapihantie 11, Helsinki, Finland; Department of Epidemiology, Columbia University Mailman School of Public Health, 722 West 168th Street, New York, NY, USA

Alan S. Brown, M.D., Department of Psychiatry, Columbia University Vagelos College of Physicians and Surgeons and New York State Psychiatric Institute, 1051 Riverside Drive, Unit 23, New York, NY, USA; Department of Epidemiology, Columbia University Mailman School of Public Health, 722 West 168th Street, New York, NY, USA

Corresponding Author:

Dr. Marisa N. Spann

Department of Psychiatry

Columbia University, Vagelos College of Physicians and Surgeons

622 West 168th Street, PH Room 1540

 New York, NY 10032

Email: mns2125@cumc.columbia.edu

Phone: (646) 774-5824

Social Media Text: https://www.columbiapsychiatry.org/profile/alan-brown-md;

https://www.columbiapsychiatry.org/profile/marisa-spann-phd;

http://pregnancy.bmedcumc.org/perinatalpathways_staff/

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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 utilized 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. We accessed data 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.

Conclusions: The findings suggest that there may be common pathogenic, developmental mechanisms

related to autoimmunity that are associated with the etiology of ASD.

LAY SUMMARY

We examined whether familial diagnoses of autoimmune diseases were associated with ASD in probands. The study is based on a large national birth cohort in Finland. Probands had a statistically significant increase in odds of ASD when they, their mother, or their sibling were diagnosed with an AD. The findings suggest that there may be common pathogenic, developmental mechanisms related to autoimmunity that are associated with the etiology of ASD.

INTRODUCTION

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] Though findings vary between studies, some commonly identified ADs that have been related to ASD include maternal type I diabetes[10] and hypothyroidism,[5,6,11,12] and paternal ulcerative colitis and type I 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 until December 31, 2007 for the diagnosis of ASD (see "case identification" 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 the 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 on all births in Finland. It includes the PIC of mothers and every live born 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 includes 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 (299x) and ICD-10 (F84x) codes. We included only the most recent ASD diagnosis resulting in 19 cases with a diagnosis based on ICD-9 codes, while 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 three 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 annually at child health clinics before school age and continuing at school health units after starting school at the age of six. 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 four 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 has 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 anytime 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 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 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, $\geq$ 35), maternal, paternal, and sibling psychiatric diagnoses (yes/no), infant

weight for gestational age (< 2 standard deviations; SD below the mean, $\geq$ 2 SD above the mean),

infant gestational age (< 37 weeks, $\geq$ 37 weeks), and number of previous births (0, $\geq$ 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's χ^2-test or Fisher's 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 less than 0.05)

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: 1) cases diagnosed with ADs before their diagnosis of ASD, and 2) cases

diagnosed with ADs after their diagnosis of ASD. Since the present study utilized 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, $\alpha = 0.05/34 = 0.001$). Note that for many of the specific ADs, there were insufficient

numbers of cases or controls (fewer than 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: (1) lifetime diagnosis of an AD in the mother, (2) proband sex, and (3) 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.

The results were reported using odds ratios (ORs) with 95% confidence intervals (95% CIs). The statistical analyses were carried out using SAS 9.4 (SAS Institute, Cary, NC, USA).

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). Lastly, 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 S2, 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 S1, 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 were 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 on 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 on 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. While 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 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 (e.g., interleukins-12 and 23, tumor necrosis factor, interferon-y), 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] Since ASD is associated with altered structure and function of motor (somato-motor and sensory cortex, cerebellum, and basal ganglia) and social cognition (e.g., 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 of 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, while a study utilizing 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 is not consistent with results of a prior study.[7] However, 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 only having one case and/or control subject with the iritis/uveitis diagnosis. With regards 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 ours 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 and language and cognitive impairment.[16,46,49]

Further we consider genetic vulnerability given that ADs are heritable diseases[1,4] and autism has a strong genetic component.[50] While 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 variants in the DNaseI hypersensitivity sites of the genome (approximately 42%) that control DNA transcription and variants in the human leukocyte antigen system of genes that are involved in recognition of self and modulating immune responsiveness.[3,51]

The 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 which 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 attention and careful evaluation from medical professionals compared to the controls with no ASD or ADs. However, 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 via DNA testing, as this was established at the registry level.

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.

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Table 1. Associations between Familial Autoimmune Diseases and Autism Spectrum Disorder in the Probands								
	Diagnostic Classification		Unadjusted			Adjusted		
ADs	Case (n=4,600) n (%)	Controls (n=18,058) n (%)	OR	CI (95%)	*p-value*	OR	CI (95%)	*p-value*
Proband[a, b]	738 (16.04)	2255 (12.49)	1.34	1.23-1.47	**<0.0001**	1.21	1.11-1.32	**<0.0001**
Any Familial[c]	1752 (38.09)	6008 (33.27)	1.14	1.10-1.19	**<0.0001**	1.02	0.97-1.07	0.35
Maternal[d]	875 (19.02)	2901 (16.06)	1.19	1.11-1.27	**<0.0001**	1.13	1.06-1.21	**0.0005**
Paternal[e]	604 (13.13)	2116 (11.72)	1.12	1.03-1.22	**0.0086**	1.08	0.99-1.18	0.07
Sibling[f, g]	747 (12.15)	2330 (10.23)	1.24	1.14-1.35	**<0.0001**	1.16	1.06-1.26	**0.001**

Note:

Abbreviations: ADs, autoimmune diseases; n, number with ADs; OR, odds ratio; CI, confidence interval; SES, maternal socioeconomic status.

Familial category includes maternal, paternal, and sibling ADs

[a]Conditional logistic regression results reported

Adjusted for:

[b]SES, gestational age, and maternal and familial psychiatric diagnosis

[c]SES, gestational age, weight for gestational age, maternal age, previous births, and maternal, paternal, and sibling psychiatric diagnosis

[d]SES, gestational age, weight for gestational age, maternal age, and maternal psychiatric diagnosis

[e]gestational age, paternal age, and paternal psychiatric diagnosis

[f]SES, maternal and paternal age, previous births, and sibling psychiatric diagnosis

[g]counts for siblings (n = 6149 cases) and (n = 22,779 controls)

Statistically significant values of p-value (p)<0.05 are shown in bold

Table 2. Associations between Proband Autoimmune Diseases Categorized by Body System and Autism Spectrum Disorder in the Probands								
ADs by Body System	Probands		Unadjusted			Adjusted		
	Case (n=4,600) n (%)	Controls (n=18,058) n (%)	OR	CI (95%)	*p-value*	OR	CI (95%)	*p-value*
Blood	23 (0.50)	67 (0.37)	1.34	0.83-2.16	0.22	1.31	0.82-2.10	0.25
Central/Peripheral Nervous System	9 (0.20)	7 (0.04)	5.03	1.87-13.51	**0.001**	4.77	1.83-12.44	**0.001**
Coronary/Heart	1 (0.02)	6 (0.03)	---	---	---	---	---	---
Connective Tissue	27 (0.59)	94 (0.52)	1.12	0.73-1.72	0.59	1.07	0.69-1.65	0.76
Ear/Eye	7 (0.15)	22 (0.12)	1.24	0.53-2.91	0.61	1.23	0.52-2.93	0.64
Endocrine	63 (1.37)	173 (0.96)	1.42	1.07-1.89	**0.01**	1.37	1.02-1.84	**0.04**
Gastrointestinal	33 (0.72)	81 (0.45)	1.59	1.06-2.39	**0.02**	1.59	1.07-2.36	**0.02**
Gynecologic	0 (0.00)	0 (0.00)	---	---	---	---	---	---
Metabolic (Liver, Kidney)	4 (0.09)	9 (0.05)	---	---	---	---	---	---
Respiratory	319 (6.93)	1044 (5.78)	1.20	1.06-1.35	**0.004**	1.14	1.01-1.29	**0.04**
Skin/Mucous Membrane	366 (7.96)	1061 (5.88)	1.35	1.20-1.51	**<0.0001**	1.31	1.17-1.47	**<0.0001**
Systemic/Multi-Organ/Vascular	3 (0.07)	20 (0.11)	---	---	---	---	---	---
Note:								

Abbreviations: ADs, autoimmune diseases; n, number with ADs; OR, odds ratio; CI, confidence interval; SES, maternal socioeconomic status

Adjusted for SES, gestational age, and maternal and familial psychiatric diagnosis

--- insufficient number of observations for statistical comparison

Statistically significant values of p<0.05 are shown in bold; p<0.001 meets significance based on Bonferroni correction

Table 3. Associations between Proband Autoimmune Diseases and Autism Spectrum Disorder in the Proband								
Specific ADs	Proband		Unadjusted			Adjusted		
	Case (n=4,600) n (%)	Controls (n=18,058) n (%)	OR	CI (95%)	*p-value*	OR	CI (95%)	*p-value*
Blood								
ITP/Purpura/Immune Thrombocytopenia	7 (0.15)	23 (0.13)	1.19	0.51-2.77	0.69	1.15	0.51-2.60	0.74
Central/Peripheral Nervous System								
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	0.50	1.37	0.51-3.64	0.53
Endocrine								

Autoimmune Thyroiditis	18 (0.39)	26 (0.14)	2.71	1.48-4.94	**0.001**	2.67	1.46-4.89	**0.001**
Diabetes Mellitus Type 1	40 (0.87)	140 (0.78)	1.12	0.79-1.58	0.53	1.09	0.77-1.56	0.62
Graves Disease	0 (0.00)	3 (0.02)	---	---	---	---	---	---
Hypothyroidism	16 (0.35)	25 (0.14)	2.50	1.34-4.69	**0.004**	2.54	1.38-4.69	**0.003**
Hyperthyroidism	0 (0.00)	4 (0.02)	---	---	---	---	---	---
Gastrointestinal								
Celiac Disease	25 (0.54)	53 (0.29)	1.85	1.15-2.97	**0.01**	1.81	1.15-2.86	**0.01**
Crohn's Disease	3 (0.07)	7 (0.04)	---	---	---	---	---	---
Ulcerative Colitis	7 (0.15)	23 (0.13)	1.19	0.51-2.77	0.69	---	---	---
Respiratory								
Asthma	319 (6.93)	1044 (5.78)	1.20	1.06-1.35	**0.004**	1.14	1.01-1.29	**0.04**
Skin/Mucous Membrane								
Alopecia Areata	5 (0.11)	5 (0.03)	3.91	1.13-13.51	**0.03**	---	---	---
Psoriasis	6 (0.13)	28 (0.16)	0.84	0.35-2.02	0.70	0.68	0.26-1.78	0.43
Systemic/Multi-organ/Vascular								
PSS/CREST/Scleroderma	1 (0.02)	2 (0.01)	---	---	---	---	---	---
Systemic Lupus Erthyematosus	0 (0.00)	0 (0.00)	---	---	---	---	---	---

Note:

Abbreviations: ADs, autoimmune diseases; n, number with ADs; OR, odds ratio; CI, confidence interval; SES, maternal socioeconomic status CNS, Central Nervous System; Thyroiditis, THY; PNS, Peripheral Nervous System; Progressive Systemic Sclerosis, PSS; Idiopathic Thrombocytopenic Purpura, ITP

Adjusted for SES, gestational age, and maternal and familial psychiatric diagnosis

--- insufficient number of observations for statistical comparison

Statistically significant values of p<0.05 are shown in bold; p<0.001 meets significance based on Bonferroni correction

Table 4. Associations between Familial Autoimmune Diseases Categorized by Body System and Autism Spectrum Disorder Cases and Matched Controls																			
ADs by Body System	Maternal							Paternal								Sibling				
			Unadjusted		Adjusted[a]					Unadjusted		Adjusted[b]						Unadjusted		Adjusted[c]
	Case (n=4,600) n (%)	Controls (n=18,058) n (%)	OR	CI (95%)	OR	CI (95%)		Case (n=4,600) n (%)	Control (n=18,058) n (%)	OR	CI (95%)	OR	CI (95%)		Case (n=6,149) n (%)	Controls (n=22,779) n (%)	OR	CI (95%)	OR	CI (95%)
Blood	9 (0.20)	35 (0.19)	1.0	0.5-2.1	1.04	0.5-2.2		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
CNS/PNS	24 (0.52)	89 (0.49)	1.1	0.7-1.7	1.0	0.6-1.6		17 (0.37)	65 (0.36)	1.0	0.6-1.7	0.9	0.5-1.6		4 (0.07)	18 (0.08)	---	---	---	---
Coronary/Heart	4 (0.09)	16 (0.09)	---	---	---	---		5 (0.11)	22 (0.12)	0.9	0.3-2.4	---	---		5 (0.08)	8 (0.04)	2.4	0.8-7.4	---	---
Connective Tissue	95 (2.07)	311 (1.72)	1.2	1.0-1.5	1.1	0.9-1.4		64 (1.39)	232 (1.28)	1.1	0.8-1.4	1.0	0.8-1.4		40 (0.65)	111 (0.49)	1.4^	1.0-2.0	1.3	0.9-1.8
Ear/Eye	80 (1.74)	197 (1.09)	1.6***	1.2-2.1	1.6***	1.2-2.1		58 (1.26)	238 (1.32)	1.0	0.7-1.3	1.0	0.7-1.3		19 (0.31)	46 (0.20)	1.6^	0.9-2.7	1.7^	1.0-2.9
Endocrine	123 (2.67)	387 (2.14)	1.3*	1.0-1.5	1.1	0.9-1.4		68 (1.48)	195 (1.08)	1.4*	1.0-1.8	1.3^	1.0-1.7		82 (1.33)	232 (1.02)	1.4*	1.1-1.8	1.2	1.0-1.6
Gastrointestinal	90 (1.96)	329 (1.82)	1.1	0.9-1.4	1.0	0.8-1.2		90 (1.96)	301 (1.67)	1.2	0.9-1.5	1.1	0.9-1.4		37 (0.60)	121 (0.53)	1.2	0.8-1.8	1.1	0.7-1.6
Gynecologic	162 (3.52)	520 (2.88)	1.2*	1.0-1.5	1.2*	1.0-1.4		---	---	---	---	---	---		8 (0.13)	24 (0.11)	1.3	0.6-2.9	---	---
Metabolic	59 (1.28)	151 (0.84)	1.5**	1.1-2.1	1.3^	1.0-1.7		48 (1.04)	125 (0.69)	1.5*	1.1-2.1	1.3	0.9-1.8		4 (0.07)	20 (0.09)	---	---	---	---
Respiratory	199 (4.33)	530 (2.93)	1.5***	1.3-1.7	1.4***	1.2-1.6		137 (2.98)	486 (2.69)	1.1	0.9-1.3	1.1	0.9-1.3		280 (4.55)	916 (4.02)	1.2*	1.0-1.4	1.1	1.0-1.3

Skin/Mucous Mem.	221 (4.80)	833 (4.61)	1.0	0.9-1.2	1.0	0.9-1.2		172 (3.74)	650 (3.60)	1.0	0.9-1.2	1.0	0.9-1.2		362 (5.89)	1020 (4.48)	**1.4*****	1.2-1.6	**1.3*****	1.1-1.4
Systemic/Multi-Org.	82 (1.78)	314 (1.74)	1.03	0.8-1.3	0.9	0.7-1.2		96 (2.09)	315 (1.74)	1.2	1.0-1.5	1.2	0.9-1.5		14 (0.23)	35 (0.15)	1.6	0.8-2.9	1.5	0.8-2.8

Note:

Abbreviations: ADs, autoimmune diseases; n, number with ADs; OR, odds ratio; CI, confidence interval; SES, maternal socioeconomic status; CNS, Central Nervous System; PNS, Peripheral Nervous System; Mem., Membrane; Org., Organ

Adjusted for:

[a]SES, gestational age, weight for gestational age, maternal age, and maternal psychiatric diagnosis

[b]gestational age, paternal age, and paternal psychiatric diagnosis

[c]SES, maternal and paternal age, previous births, and sibling psychiatric diagnosis

--- insufficient number of observations for statistical comparison

Statistically significant values are shown in bold

p<0.10^, p<0.05*, p<0.01**, p<0.001(Bonferroni corrected significance level)***