



Increased Risk of Atopic Diseases in the Siblings of Patients with Autism Spectrum Disorder: A Nationwide Population-Based Cohort Study

Ying-Xiu Dai^{1,2} · Ying-Hsuan Tai^{2,3,4} · Yun-Ting Chang^{1,2} · Tzeng-Ji Chen^{2,5} · Mu-Hong Chen^{2,6} 

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Abstract

Several studies have shown a strong association between atopic diseases and autism spectrum disorder (ASD). However, the risk of atopic diseases in individuals having ASD-affected siblings has never been investigated. This nationwide population-based cohort study included 2762 individuals with ASD-affected siblings and 11,048 controls. Diagnoses of atopic diseases, including asthma, atopic dermatitis, allergic rhinitis, and allergic conjunctivitis, were ascertained from 1996 or the birth data to the end of 2011. Individuals with ASD-affected siblings had a higher risk for asthma, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, and multiple atopic diseases compared with controls. In conclusion, individuals with ASD-affected siblings were more likely than were the controls to develop atopic diseases, suggesting shared familial mechanisms underlying the two conditions.

Keywords Atopy · Autism spectrum disorder · Cohort study · Epidemiology · Sibling · Taiwan's National Health Insurance Research Database

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impaired social communication and the presence of repetitive and stereotyped behaviors (Volkmar and McPartland 2014). Previous studies have reported a steady increase in the prevalence of ASD in

children in the United States over the past two decades (Xu et al. 2018). Although the pathogenesis underlying ASD remains unclear, data from twin and family studies suggest the presence of a genetic component in the etiology of ASD with the involvement of multiple gene loci (Weiss et al. 2009). However, genetic factors only contribute to a small effect in the development of ASD, suggesting gene-environment interactions in its etiology (Herbert 2010). The increase in ASD prevalence is paralleled by an alarming rise in the worldwide prevalence of atopic diseases, including asthma, atopic dermatitis, allergic conjunctivitis, and allergic rhinitis (Asher et al. 2006; Dai et al. 2018a, b). The affected individuals often begin with atopic dermatitis in infancy followed by allergic rhinitis and asthma in later life. This phenomena is known as the atopic March (Bantz et al. 2014).

Recently, the association between atopic diseases and ASD has been increasingly recognized (Billeci et al. 2015; Magalhaes et al. 2009). Our previous study revealed that children with ASD had increased risks of asthma (odds ratio [OR] 1.74, 95% confidence interval [CI] 1.51–1.99), allergic rhinitis (OR 1.70, 95% CI 1.51–1.91), and atopic dermatitis (OR 1.52, 95% CI 1.30–1.78) (Chen et al. 2013). Another study showed that the presence of atopic disease is

✉ Mu-Hong Chen
kremer7119@gmail.com

¹ Department of Dermatology, Taipei Veterans General Hospital, Taipei, Taiwan

² School of Medicine, National Yang-Ming University, Taipei, Taiwan

³ Department of Anesthesiology, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan

⁴ Department of Anesthesiology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

⁵ Department of Family Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

⁶ Department of Psychiatry, Taipei Veterans General Hospital, No. 201, Sec. 2, Shipai Rd, Beitou District, Taipei 11217, Taiwan, ROC

associated with an increased risk of ASD (HR 3.40, 95% CI 1.95–5.93) (Chen et al. 2014). This bidirectional association suggests a shared pathogenesis underlying ASD and atopic diseases. While many studies investigated the possible etiological association between atopic diseases and ASD (Billeci et al. 2015; Lee et al. 2016; Lin et al. 2014; Tonacci et al. 2017), the underlying mechanism remains elusive. There is evidence that maternal immune dysregulation, including atopic diseases, is associated with an increased risk of offspring ASD (Croen et al. 2005; Gong et al. 2019; Lyall et al. 2014). These findings suggest that atopic diseases may affect fetal brain development and contribute to ASD in some genetically susceptible individuals. However, interpretation of these findings is hampered by several limitations including small sample sizes, cross-sectional or case-control design, and lack of ASD diagnosis confirmed by psychiatrists.

Prior studies reported a higher recurrence risk of ASD among later-born siblings of ASD-affected children (Miller et al. 2018; Ozonoff et al. 2011). Individuals with ASD-affected siblings may share some genetic and environmental factors with their affected siblings, making them more susceptible to other mental and physical disorders (Jokiranta-Olkonemi et al. 2016; Spann et al. 2019). However, the risk of atopy among siblings of ASD probands has never been examined. Investigating atopic diseases among the siblings of ASD-affected children provides important information for clinical assessment, prevention, treatment, and etiologic research. This nationwide population-based study aims to examine the risk of developing atopic diseases, including atopic dermatitis, allergic rhinitis, allergic conjunctivitis, and asthma, among the siblings of probands with ASD.

Methods

Data Source

The National Health Insurance (NHI) is a mandatory national health insurance program, which covered more than 99.6% of all Taiwanese residents in 2017. The NHI Research Database (NHIRD) provides comprehensive information about the insured subjects, including details of demographics (date of birth, sex, and residential location) and claims data (outpatient and inpatient care, medical diagnoses, prescriptions, and operations). The NHIRD has been widely used in several studies investigating the association between atopy and ASD (Chen et al. 2014; Lee et al. 2016). To protect individual privacy, a unique identification number is assigned to each beneficiary and enciphered before the data is released for scientific purposes. The unique identification number was used to link all the healthcare records of each beneficiary. Family relationships were established by

analyzing the birth certificate and the dependent, insurance, and employment status. The methods of genealogy reconstruction using recorded family relationships in the NHIRD have been described previously (Chang et al. 2019; Chen et al. 2018, 2019; Cheng et al. 2018). The diagnostic codes used were based on the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM). This study was approved by the Institutional Review Board of Taipei Veterans General Hospital (2018-07-016AC).

Study Cohort and Controls

This cohort study included subjects who were born between 1980 and 2010 and had ASD-affected siblings. We excluded subjects with ASD diagnoses, invalid insurance status, unknown sex status, or unknown covariates. ASD was identified by ICD-9-CM code 299, and diagnoses that were made at least three times by board-certified psychiatrists during the observation period.

Matched Controls Without ASD-Affected Siblings

For each subject with ASD-affected siblings, four matched controls without ASD-affected siblings were randomly selected from the NHIRD Longitudinal Health Insurance Database. These subjects were matched for age, sex, and residence. Residence was classified into five levels of urbanization, with level 1 indicating the most urbanized area and level 5 the least urbanized area. The study subjects and controls were followed from 1996 or their birth date to the end of 2011.

Outcome

The primary outcome for the analysis was incidence of atopic diseases, including asthma (ICD-9-CM code 493), atopic dermatitis (ICD-9-CM code 691), allergic rhinitis (ICD-9-CM code 477), and allergic conjunctivitis (ICD-9-CM codes 372.05, 372.10, and 372.14). The diagnosis of atopic diseases was made at least three times by corresponding board-certified pediatricians, internal physicians, ophthalmologists, and dermatologists.

Sensitivity Analyses

To assess the robustness of our results, we performed sensitivity analyses to minimize the influence of potential bias in the study. First, to eliminate the comorbid effect of atopic diseases, sensitivity analysis was performed with adjustment of comorbid atopic diseases in model 1. For example, the relative risk (RR) of asthma was estimated after adjusting for atopic dermatitis, allergic rhinitis, and allergic conjunctivitis in the multivariate model. Second, the NHIRD only

contained claims data after 1996. The missing data before 1996 may lead to an underestimation of the incidence of atopic diseases. Therefore, we conducted a sensitivity analysis restricted to individuals born after January 1, 1996 in model 2. Third, detection bias may occur when an earlier diagnosis of atopic diseases was made in siblings with ASD probands due to increased awareness of atopic symptoms among parents in the case of atopic conditions in older siblings with ASD. To address this potential source of bias, we conducted a sensitivity analysis stratifying the subjects into older and younger siblings with ASD and atopic diseases in model 3.

Statistical Analysis

The t-test or Wilcoxon rank sum test was used to compare continuous variables between groups as appropriate, and the Pearson's test was used for categorical variables. We calculated the RRs of atopic diseases (asthma, allergic rhinitis, atopic dermatitis, and allergic conjunctivitis) in individuals

with ASD-affected siblings compared with the matched controls. Given an equal follow-up time for all subjects in each matched set, Breslow-Cox proportional hazards model was used to calculate the RR of atopic diseases between study and control cohorts (Breslow 1974; Cummings et al. 2003; D. K. Liddell et al. 1977). A two-sided p value < 0.05 was considered statistically significant. Data management and analyses were performed with SAS software (version 9.4; SAS Institute, Cary, NC).

Results

There were 2762 individuals with ASD-affected siblings and 11,048 matched controls included in this study. Age, sex, and residence were well matched and did not have between-group differences (Table 1). Individuals with ASD-affected siblings had higher cumulative incidence of asthma (22.2% vs. 17.9%, $p < 0.0001$), atopic dermatitis (9.9 vs. 8.1, $p = 0.003$), allergic rhinitis (35.1% vs. 29.0%, $p < 0.0001$), and

Table 1 Demographic data and incidence of atopic diseases among individuals with ASD-affected siblings and controls

	With affected siblings (N = 2762)		Controls (N = 11,048)		p
Age, mean (SD)	12.8	4.7	12.8	4.7	0.954
Sex, n (%)					1.000
Male	1366	49.5	5464	49.5	
Female	1396	50.5	5584	50.5	
Level of urbanization, n (%)					1.000
1 (urbanized)	477	17.3	1908	17.3	
2	862	31.2	3448	31.2	
3	226	8.2	904	8.2	
4	201	7.3	804	7.3	
5 (rural)	996	36.1	3984	36.1	
Outcome					
No. of incident cases of atopic diseases, n (%)					
Asthma	622	22.2	1973	17.9	< 0.0001
Atopic dermatitis	276	9.9	897	8.1	0.003
Allergic rhinitis	983	35.1	3199	29.0	< 0.0001
Allergic conjunctivitis	550	19.6	1914	17.3	0.003
Age at atopic diseases diagnosis, median (IQR)					
Asthma	3.9	2.4–5.6	3.9	2.2–5.6	0.537
Atopic dermatitis	1.1	0.5–4.3	1.1	0.4–4.7	0.382
Allergic rhinitis	4.5	2.6–7.1	4.7	2.7–7.4	0.219
Allergic conjunctivitis	6.4	4.7–8.5	6.4	4.5–8.7	0.805
Numbers of atopic diseases, n (%)					< 0.0001
0	1353	49.0	6018	54.5	
1	686	24.8	2855	25.8	
2	499	17.8	1507	13.6	
3	193	7.0	558	5.1	
4	38	1.4	110	1.0	

SD Standard deviation, *IQR* interquartile range

allergic conjunctivitis (19.6% vs. 17.3%, $p = 0.003$) than the control group. In addition, individuals with ASD-affected siblings were more likely to have multiple atopic diseases than were the controls ($p < 0.0001$). There was no statistically significant difference between the two groups with respect to age of developing atopic diseases.

Breslow-Cox proportional hazards regression showed that individuals with ASD-affected siblings had a higher risk of developing asthma (RR 1.24, 95% CI 1.16–1.33), atopic dermatitis (RR 1.22, 95% CI 1.09–1.36), allergic rhinitis (RR 1.21, 95% CI 1.15–1.28), allergic conjunctivitis (RR 1.14, 95% CI 1.05–1.22), and multiple atopic diseases than did the controls (Table 2). Stratified by sex, the risk of developing atopic diseases remained increased in boys, while girls had significantly increased risks for asthma and allergic rhinitis but not for atopic dermatitis and allergic conjunctivitis. In sensitivity analysis with adjustment for comorbid atopic diseases, boys were still at an increased risk for developing all atopic diseases, but girls only had significantly increased risks for allergic rhinitis. When the analysis was restricted to individuals born after January 1, 1996, the risk of atopic diseases remained significantly increased in siblings of ASD probands. In model 3, the stratified analysis showed higher RRs of asthma, allergic rhinitis, and allergic conjunctivitis in individuals with younger ASD siblings than those with older ASD siblings. Although further research is needed to clarify these findings, this result suggests that such detection bias was unlikely in our study.

Discussion

In this nationwide population-based cohort study we found an increased risk of atopic diseases in individuals with ASD-affected siblings, which is in agreement with previous studies. Even if they were not affected by ASD, individuals with ASD-affected siblings had a modestly increased risk of developing these atopic diseases. After adjusting for comorbid atopic conditions, the risk of atopic diseases remained increased in boys with ASD-affected siblings, while girls only had a significantly increased risk for allergic rhinitis but not for asthma, atopic dermatitis, and allergic conjunctivitis. Atopic multimorbidity might explain the result of the sensitivity analysis. To investigate the relationship between these atopic diseases, we conducted a further analysis which showed that, in agreement with previous studies (Bantz et al. 2014; Paller et al. 2019), subjects with any one atopic disease had a significantly higher risk for another atopic comorbidity (data not shown). It was reasonably expected that the RRs of atopic diseases among subjects were greatly attenuated after adjustment for comorbid atopic diseases.

ASD often co-occurs with other psychiatric and medical conditions, posing a lifelong burden on those affected.

Siblings of ASD probands share some genetic and environmental factors, which make them more prone to psychiatric and physical conditions. Jokiranta-Olkoniemi et al. (2016) showed that siblings of ASD probands had increased risks of psychiatric or neurodevelopmental disorder, with the largest association being childhood-onset disorders, including ASD (adjusted RR 11.8, 95% CI 9.4–14.7), tic disorders (adjusted RR 4.3, 95% CI 2.3–8.2), attention-deficit/hyperactivity disorder (adjusted RR 3.7, 95% CI 2.9–4.7), learning and coordination disorders (adjusted RR 3.2; 95% CI 2.8–3.6), intellectual disability (adjusted RR 3.1, 95% CI 2.3–4.2), conduct and oppositional disorders (adjusted RR 2.8, 95% CI 2.2–3.5), and emotional disorders with onset specific to childhood (adjusted RR 2.6, 95% CI 1.9–3.4). Increased risks of schizophrenia, affective disorders, anxiety disorders, and personality disorders were also observed among siblings of ASD probands. Physical conditions associated with siblings of ASD probands have seldom been studied. One recent study showed that proband diagnosis of ASD was associated with autoimmune diseases diagnosed in siblings (adjusted OR 1.2, 95% CI 0.7–1.9) (Spann et al. 2019). In the present study, we found increased risks of atopic diseases in individuals with ASD-affected siblings, which has never been reported before. However, with the relatively small effect size observed in our study, the results should be interpreted cautiously. Our findings suggest a shared familial risk of ASD and atopic diseases. Potential shared pathophysiologic mechanisms, including genetic background, common immunological pathways, and environmental factors may account for this association.

The genetic components of ASD are complex and heterogeneous with highly variable phenotypic expression (Persico and Napolioni 2013). Genetic links between atopic diseases and ASD have recently been discovered. GATA-3 is a gene involved in the regulation of the development and differentiation of various cell lines, including serotonergic and sympathetic neurons (Moriguchi et al. 2006; Tamauchi et al. 2004; Tsarovina et al. 2004). GATA-3 expression is also associated with the development of ASD in humans and animal models (Trottier et al. 1999). Additionally, GATA-3 plays a critical role in the differentiation of Th2 cells from naïve CD4+ cells. It has been shown to be essential for the gene expression of the cytokines IL-4, IL-5, and IL-13 that mediate allergic inflammation (Barnes 2008). Another candidate gene is adrenoceptor beta 2 (ADBR2), a gene encoding beta-2-adrenergic receptor. The Glu27 allele of ADRB2 may confer increased risk of ASD (Cheslack-Postava et al. 2007); ADRB2 polymorphisms is also associated with atopic diseases (Mohamed-Hussein et al. 2018; Roguedas et al. 2006). Macrophage migration inhibitory factor (MIF) is an essential immunoregulatory cytokine. The MIF gene has been associated with both ASD and atopic diseases (Bacher et al. 1996; Mizue et al. 2005; Renner et al. 2005; Yasuda et al.

Table 2 Relative risk for atopic diseases among individuals with ASD-affected siblings and controls

	Total			Male			Female		
	RR (95% CI)		<i>P</i>	RR (95% CI)		<i>P</i>	RR (95% CI)		<i>P</i>
Primary model									
Asthma	1.24	1.16–1.33	< 0.0001	1.22	1.11–1.34	< 0.0001	1.28	1.15–1.42	< 0.0001
Atopic dermatitis	1.22	1.09–1.36	0.001	1.27	1.09–1.47	0.002	1.16	0.98–1.37	0.077
Allergic rhinitis	1.21	1.15–1.28	< 0.0001	1.19	1.11–1.27	< 0.0001	1.25	1.16–1.35	< 0.0001
Allergic conjunctivitis	1.14	1.05–1.22	0.001	1.21	1.09–1.34	0.0002	1.06	0.95–1.18	0.316
Multiple atopic diseases									
1	0.96	0.90–1.02	0.190	0.94	0.86–1.03	0.184	0.98	0.89–1.07	0.610
2	1.30	1.20–1.41	< 0.0001	1.30	1.17–1.45	< 0.0001	1.31	1.16–1.48	< 0.0001
3	1.39	1.21–1.59	< 0.0001	1.41	1.18–1.69	0.000	1.35	1.09–1.67	0.007
4	1.40	1.03–1.92	0.033	1.38	0.90–2.09	0.136	1.44	0.91–2.30	0.123
Model 1^a									
Asthma	1.12	1.04–1.20	0.002	1.12	1.02–1.23	0.017	1.11	0.99–1.23	0.072
Atopic dermatitis	1.14	1.02–1.27	0.025	1.21	1.04–1.41	0.014	1.06	0.89–1.25	0.528
Allergic rhinitis	1.13	1.07–1.19	< 0.0001	1.10	1.03–1.18	0.008	1.17	1.09–1.27	< 0.0001
Allergic conjunctivitis	1.05	0.98–1.14	0.178	1.12	1.01–1.24	0.036	0.99	0.89–1.11	0.877
Multiple atopic diseases									
1	0.93	0.87–0.99	0.028	0.92	0.84–1.01	0.091	0.94	0.86–1.03	0.182
2	1.04	0.95–1.13	0.455	1.05	0.94–1.18	0.399	1.03	0.89–1.18	0.723
3	1.28	1.00–1.63	0.046	1.30	0.98–1.74	0.071	1.23	0.78–1.92	0.374
4	1.00	1.00–1.00	1.000	1.00	1.00–1.00	1.000	1.00	1.00–1.00	1.000
Model 2^b									
Asthma	1.20	1.11–1.30	< 0.0001	1.19	1.08–1.32	0.001	1.21	1.07–1.37	0.002
Atopic dermatitis	1.24	1.11–1.40	0.0003	1.29	1.10–1.51	0.002	1.19	1.00–1.42	0.049
Allergic rhinitis	1.19	1.12–1.26	< 0.0001	1.17	1.08–1.27	< 0.0001	1.20	1.10–1.32	< 0.0001
Allergic conjunctivitis	1.10	1.00–1.20	0.050	1.13	1.00–1.28	0.060	1.06	0.93–1.22	0.386
Multiple atopic diseases									
1	0.91	0.84–0.99	0.024	0.89	0.80–1.00	0.047	0.93	0.83–1.05	0.239
2	1.29	1.17–1.41	< 0.0001	1.27	1.12–1.44	0.0002	1.31	1.14–1.50	0.0002
3	1.31	1.12–1.53	0.001	1.34	1.09–1.63	0.005	1.27	0.99–1.63	0.064
4	1.47	1.05–2.06	0.025	1.55	0.99–2.41	0.054	1.37	0.82–2.30	0.230
Model 3^c									
Older siblings with ASD									
Asthma	1.07	0.97–1.18	0.168	1.10	0.97–1.23	0.129	1.03	0.87–1.20	0.766
Atopic dermatitis	1.24	1.08–1.42	0.002	1.34	1.12–1.59	0.001	1.12	0.90–1.38	0.318
Allergic rhinitis	1.06	0.98–1.14	0.135	1.05	0.96–1.15	0.325	1.07	0.95–1.20	0.249
Allergic conjunctivitis	1.01	0.91–1.13	0.823	1.04	0.90–1.19	0.614	0.98	0.82–1.17	0.821
Multiple atopic diseases									
1	0.93	0.85–1.02	0.114	0.91	0.81–1.03	0.128	0.96	0.84–1.09	0.503
2	1.12	1.00–1.25	0.057	1.17	1.02–1.35	0.028	1.03	0.85–1.25	0.750
3	1.04	0.85–1.26	0.732	1.01	0.79–1.30	0.934	1.08	0.78–1.49	0.663
4	1.90	1.31–2.76	0.001	1.95	1.23–3.09	0.005	1.80	0.95–3.42	0.072
Younger siblings with ASD									
Asthma	1.45	1.32–1.59	< 0.0001	1.40	1.24–1.58	< 0.0001	1.52	1.32–1.74	< 0.0001
Atopic dermatitis	1.16	0.97–1.37	0.101	1.15	0.91–1.44	0.253	1.17	0.90–1.52	0.239
Allergic rhinitis	1.36	1.27–1.46	< 0.0001	1.32	1.21–1.45	< 0.0001	1.40	1.27–1.55	< 0.0001
Allergic conjunctivitis	1.23	1.11–1.35	< 0.0001	1.38	1.21–1.58	< 0.0001	1.09	0.94–1.25	0.245
Multiple atopic diseases									
1	1.00	0.91–1.09	0.940	1.01	0.89–1.14	0.892	0.99	0.87–1.11	0.810

Table 2 (continued)

	Total			Male			Female		
	RR (95% CI)		<i>P</i>	RR (95% CI)		<i>P</i>	RR (95% CI)		<i>P</i>
2	1.45	1.31–1.61	< 0.0001	1.39	1.21–1.61	< 0.0001	1.52	1.30–1.77	< 0.0001
3	1.81	1.51–2.17	< 0.0001	1.96	1.55–2.48	< 0.0001	1.63	1.23–2.17	0.001
4	1.04	0.64–1.69	0.862	0.85	0.41–1.78	0.663	1.28	0.67–2.42	0.457

ASD Autism spectrum disorder, CI confidence interval, RR relative risk

^aAdjusted for comorbid atopic diseases

^bRestricted to individuals born after January 1, 1996

^cSubjects stratified into older and younger siblings with ASD and atopic diseases

2014). These studies provided genetic evidence underlying the association between atopic diseases and ASD.

The observed association between maternal atopy in pregnancy and ASD risk in offspring suggests an interaction between genetic vulnerability and environmental factors. Croen et al. (2005) investigated the association between maternal autoimmune diseases, allergies, and asthma in pregnancy and ASD risk in offspring. These authors found that maternal asthma in pregnancy was associated with greater than twofold elevated risk for ASD in the offspring. In a second study examining allergy among parents of children aged 1–6 years and ASD among their children 5 years later, Larsson et al. (2009) found that the presence of maternal eczema was associated with the risk of developing ASD.

In addition to the shared genetic components, environmental factors might play a role in the observed associations in our study. Previous studies have suggested that the abnormal brain development in ASD is affected by prenatal environmental factors. For example, maternal stress and smoking increase the risk of both ASD and atopic diseases in the offspring (Larsson et al. 2009; Tanaka et al. 2007). Another example of environmental association between these two diseases is air pollution. It has recently been reported that air pollutants, such as volatile organic compounds, are associated with increased risks of ASD and atopic diseases (Boutin-Forzano et al. 2005; Karimi et al. 2017).

The strengths of this study include a cohort study design with a large sample size and reliable ASD diagnosis made by psychiatrists. However, this study has some limitations. First, the incidence of ASD and atopic diseases might be underestimated in our study since only those who sought medical services could be included in the NHIRD. Second, the NHIRD lacks information on genetics and several environmental factors, including maternal smoking, prenatal stress, birth complications, breastfeeding history, and family socioeconomic status, which are potential confounders. Third, the possibility of misclassification of diagnoses may exist. However, ASD and atopic diseases were diagnosed by board-certified psychiatrists and corresponding specialists, thus yielding a better diagnostic validity relative to the self-reported questionnaire. Finally,

because almost all our subjects were Taiwanese, the external validity of our findings remains uncertain. In comparison with other countries, Taiwan has relatively lower prevalence rates of atopic diseases and ASD. The prevalence rate of ASD in Taiwan was 28.7/10,000 compared with 60–70/10,000 in western countries (Chien et al. 2011; Fombonne 2005, 2009). In Taiwan, the prevalence rates of atopic dermatitis, allergic rhinitis, and asthma were 6.7%, 26.3%, and 11.9%, respectively (Hwang et al. 2010), while the corresponding rates for other countries were 0.3–20.5%, 1.5–36.8%, and 1.4–39.7% (Asher et al. 2006). These epidemiological differences could be related to aspects of genetics, lifestyle, indoor or outdoor environment, and awareness of disease, thus potentially limiting the generalizability of our results.

In conclusion, siblings of ASD probands have a higher risk for atopic diseases compared with controls. These findings provide further support for shared familial mechanisms underlying ASD and atopic diseases, which may facilitate preventive and clinical interventions.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Research Involving Human Participants and/or Animals This study does not involve any human participants or animal.

Informed Consent The institutional review board of Taipei Veterans General Hospital approved this retrospective study and waived the patient informed consent requirement (2017-08-005CC).

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