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Familial Risk of Sjögren's Syndrome and Co-aggregation of Autoimmune Diseases in Affected Families

A Nationwide Population Study

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Objective. **To investigate familial aggregation of Sjögren's syndrome (SS) and the relative risks (RRs) of other autoimmune disease in relatives of patients with SS.**

Methods. **We identified 23,658,577 beneficiaries enrolled in the Taiwan National Health Insurance system in 2010, of whom 12,754 had SS. We identified 21,009,551 parent–child relationships and 17,168,340 pairs of full siblings. The familial risks of SS and other autoimmune diseases, tetrachoric correlation, and familial transmission were estimated.**

Results. **We identified 105 patients with SS who had an affected first-degree relative. The RR of SS was 18.99 (95% confidence interval [95% CI] 9.76–36.93) in siblings of patients with SS, 11.31 (95% CI 8.34–15.33) in offspring, and 12.46 (95% CI 9.34–16.62) in parents. Tetrachoric correlation coefficients were 0.53 (95% CI 0.41–0.65) for cotwins of affected individuals and 0.21 (95% CI 0.16–0.26) for full siblings. The familial transmission (heritability plus shared environmental contribution) was 0.54 (95% CI 0.44–0.77). In first-degree relatives of patients with SS, the RRs were 2.95 (95% CI 2.33–3.73) for rheumatoid arthritis, 6.25 (95% CI 5.15–7.58) for systemic lupus erythematosus, 2.39 (95% CI 0.77–7.41) for systemic sclerosis, 0.71 (95% CI 0.10–5.07) for idiopathic inflammatory myopathy, 1.97 (95% CI 1.29–3.02) for type 1 diabetes mellitus, 3.38 (95% CI 1.26–9.05) for multiple sclerosis, 1.67 (95% CI 0.83–3.33) for myasthenia gravis, 1.25 (95% CI 1.04–1.50) for psoriasis, 1.21 (95% CI 0.39–3.76) for inflammatory bowel disease, and 2.29 (95% CI 1.19–4.40) for vasculitis.**

Conclusion. **The risk of SS and other autoimmune diseases is increased in relatives of patients with SS, and more than one-half of phenotypic variance in SS can be explained by familial factors.**

Sjögren's syndrome (SS) is an autoimmune disease characterized by dry eyes and dry mouth and pathologic features such as lymphocytic infiltration and destruction of the lacrimal and salivary glands (1). In addition to exocrinopathy, SS may involve many organ systems and can cause heterogeneous clinical presentations, including arthritis (2) and renal disease (3). The prevalence of SS varies widely depending on the study design and the population studied. A recent report summarizing 3 population-based studies in Greece, Norway, and France estimated the prevalence of SS in Europe to be 0.04% (4). Using the National Health Insurance Research Database (NHIRD),

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which contains health information for almost all inhabitants of Taiwan, our group recently estimated that the prevalence of SS in Taiwan was 0.06% in 2005 (5).

Familial clustering of SS (6–14) as well as its coaggregation with other autoimmune diseases (15,16) have been suggested, but solid evidence for both notions is sparse. Several case reports have described concordance of SS in twins (6–9) and in families with ≥2 cases of SS (10–14). The tendency of SS to cluster within families suggests a role for familial factors such as genes and shared environment in the pathogenesis of the disease. Consequently, efforts to define the pathogenesis of SS have focused on genetic factors, and recent studies successfully identified susceptibility loci for SS (17–21). Environmental factors (such as viruses) and hormonal factors are also thought to participate in disease pathogenesis (22). Although these reports support the contribution of both genetic and shared environmental factors in the susceptibility to SS, they provide no quantitative estimates of the measures of familial risks of SS and the proportion of phenotypic variance that can be explained by familial factors (familial transmission). In addition, estimates of the respective risks of other autoimmune diseases in relatives of patients with SS have not been reported previously.

Therefore, using genealogy and linked health information derived from the NHIRD, we conducted this nationwide study comprising essentially the entire population of Taiwan in 2010 to determine familial aggregation of SS and to assess the relative contribution of familial factors to susceptibility to the disease. In addition, we also estimated the relative risks (RRs) of other autoimmune diseases associated with a family history of SS.

PATIENTS AND METHODS

Study population. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (approval no. 101-2178B) and by the National Health Research Institutes, which compiles data for the NHIRD. We constructed a cohort containing all beneficiaries enrolled in the Taiwan National Health Insurance (NHI) system in 2010, using data from the registry for beneficiaries, the registry for patients with catastrophic illness, and data sets of ambulatory care expenditures and details of ambulatory case orders, all of which are components of the NHIRD. Enrollment in the NHI system is mandatory by law in Taiwan. In 2010, >99.5% of the general population in Taiwan was covered by the insurance (23). The NHIRD contains registration information and data for original claims for reimbursement, including comprehensive information on personal details, socioeconomic status, family relationships, dates of clinical visits, medical diagnoses, medical expenditures, prescription details, examinations, and procedures. Data are updated biannually. All data for a given individual are linked by a unique national identification number that is associated with every record for that individual in the database. To ensure confidentiality, identification numbers were encrypted before being released for research, but the uniqueness of the encrypted identification is retained to ensure valid internal linkage.

Methods of identifying first-degree relatives and family ascertainment have been previously reported (see Supplementary material, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39127/abstract) (24). Briefly, lineal blood relatives and spouses can be directly identified using the indicators of relationships and unique national identification numbers. Full siblings of an individual are identified if they shared the same parents. Twins are full siblings with the same date of birth (±1 day), but twin zygosity cannot be derived from the database. To consider the correlation among individuals from the same family, we grouped individuals into families according to their relationships. In total, 21,009,551 parent–child relationships, 17,168,340 pairs of full siblings, and 342,066 twin pairs were identified, and these relationships were used to assemble 4,229,301 families, with a mean family size of 4.8 persons, spanning up to 5 generations.

Case definition of SS and other autoimmune diseases. The case definition for SS was a person with a catastrophic illness certificate for SS (International Classification of Diseases, Ninth Revision code 7102). The holders of a catastrophic illness certificate are entitled to a waiver of medical copayments. In order for a patient to receive a certificate for SS, the diagnosis must be supported by comprehensive clinical and laboratory assessments, and this information is required by the insurance administration for a review by commissioned expert panels to confirm the diagnosis before approval of waivers. The panel reviews the diagnosis, in compliance with the updated classification criteria. For instance, the preliminary European classification criteria for SS (25) and classification criteria by the American–European Consensus Group (26) were used in recent years to assist the review of certificate applications for SS. To eliminate patients with secondary SS, only those without a catastrophic illness certificate for rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis, or idiopathic inflammatory myopathy were included. We also identified patients with other autoimmune diseases including RA, SLE, systemic sclerosis, idiopathic inflammatory myopathy, type 1 diabetes mellitus, multiple sclerosis, myasthenia gravis, psoriasis, inflammatory bowel disease, and vasculitis (for full code lists, see Supplementary material, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39127/abstract).

Covariates. We considered age, sex, socioeconomic factors (place of residence, occupation, and income level), and family size as factors that might confound or modify the familial associations. A place of residence for each individual was categorized according to the level of urbanization (27). Occupations were classified into 5 categories, and income levels were categorized into sex-specific income quintiles (for additional details, see Supplementary material, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39127/abstract).

Statistical analysis. The prevalence of SS among individuals with affected first-degree relatives and the general population was calculated. Any individual with valid insurance registration in 2010 who met the case definition of SS between January 1, 1996 and December 31, 2010 was defined as a prevalent case. The number of individuals in the general population in Taiwan was used as the denominator for the prevalence of SS in 2010.

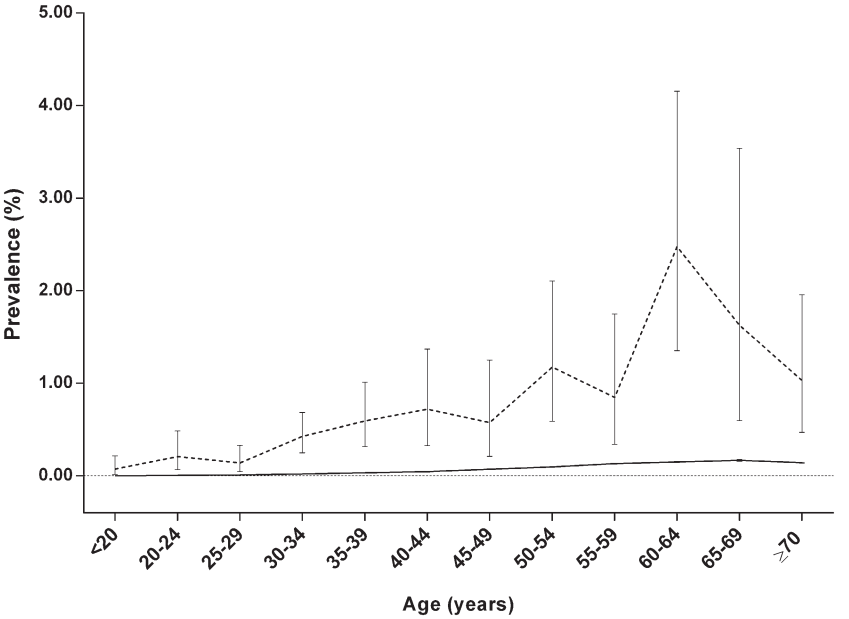

Figure 1. Age-specific prevalence of Sjögren's syndrome in individuals with a first-degree relative with Sjögren's syndrome (broken line) and in the general population (solid line) in Taiwan in 2010. Bars show 95% confidence intervals.

The recurrence risk for SS was defined as the likelihood of a diagnosis of SS in an individual with an affected first-degree relative with a diagnosis of SS. We calculated the recurrence risk for a specific type of relative (parents, offspring, sibling, and twins) of patients with SS as the prevalence of SS in individuals with a specific type of affected relative (28). The adjusted prevalence ratio was used as a measure for the RR of SS (29) and was calculated as the prevalence of SS among individuals with affected relatives divided by the prevalence of SS in the general population. The RR estimated in this study is equivalent to the relative recurrence ratio, but for simplicity we refer to it as RR throughout. The marginal Cox proportional hazards model with an equal followup time for all subjects (30), adjusted for age, sex, socioeconomic factors, and family size, was used to estimate the RRs and 95% confidence intervals (95% CIs). We used the robust sandwich estimator to calculate corrected 95% CIs to account for possible case clustering within families (31). This approach has been applied previously in other diseases and validated (32). We also estimated tetrachoric correlation coefficients to measure the degree of similarity in different types of relatives. We assumed that a continuous normally distributed liability underlies the diagnosis of SS.

Heritability was defined as the proportion of phenotypic variance that is attributable to genetic factors, and familial transmission was defined as the sum of heritability and the proportion attributable to shared environmental factors. Each of these values can be calculated using a polygenic liability model (33–35). The familial transmission in this study was estimated as the function of the difference of normal deviation of the threshold from the mean liability between individuals with affected siblings and the normal population (for details, see Supplementary material, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39127/abstract).

The original model assumes zero common environmental variance, and therefore familial transmission equals heritability. We consider this assumption not to be applicable in the case of SS, however, considering known environmental factors that may predispose to the disease and be shared among family members (22). In a previous study by our group, we further used spouses as a control to separate shared environmental component and heritability (24). However, because SS predominantly affects females and its prevalence is low, it was not possible to identify enough affected spouse pairs to produce reliable estimates. Therefore, we reported only familial transmission. Next, for patients with SS, we calculated the probability of not having a family history of SS (sporadic cases) according to the formula based on the polygenic liability model developed by Yang et al (36). We restricted family history to first-degree relatives and assumed an average of 2 siblings in a family.

We further estimated the extent of familial coaggregation of other autoimmune diseases in affected families. RRs and 95% CIs for RA, SLE, systemic sclerosis, idiopathic inflammatory myopathy, type 1 diabetes mellitus, multiple sclerosis, myasthenia gravis, inflammatory bowel diseases, psoriasis, and vasculitis were estimated as the adjusted prevalence ratio of specified autoimmune diseases between individuals with a first-degree relative with SS and the general population. We estimated the RR for other autoimmune diseases using a marginal Cox proportional hazards regression model with an equal followup time for all subjects. The RRs were adjusted for age, sex, and family size, and were considered case clustering within families by using the robust sandwich estimate. Two-tailed *P* values less than or equal to 0.05 were considered significant. All analyses were performed using SAS version 9.3.

RESULTS

Prevalence of SS in individuals with an affected first-degree family member versus the general population. The study population comprised 23,658,577 individuals enrolled in the NHI system in Taiwan in 2010. There

Table 1. Baseline characteristics of the individuals with relatives affected by SS and the general population*

Variable	Women			Men		
	At least 1 affected relative (n = 10,416)	General population (n = 11,926,513)	*P*	At least 1 affected relative (n = 11,569)	General population (n = 11,732,064)	*P*
Age, mean ± SD years	33.2 ± 16.9	37.9 ± 20.4	<0.001	33.4 ± 16.3	37.1 ± 20.6	<0.001
Patients with SS	95 (0.91)	11,462 (0.10)	<0.001	10 (0.09)	1,292 (0.01)	<0.001
Place of residence			<0.001			<0.001
Urban	6,901 (66.25)	7,197,968 (60.35)		7,166 (61.94)	6,737,087 (57.42)	
Suburban	2,664 (25.58)	3,209,020 (26.91)		3,051 (26.37)	3,372,637 (28.75)	
Rural	707 (6.79)	1,087,991 (9.12)		793 (6.85)	1,098,656 (9.36)	
Unknown	144 (1.38)	431,534 (3.62)		559 (4.83)	523,684 (4.46)	
Income level			<0.001			<0.001
Quintile 1	1,499 (14.39)	1,960,003 (16.43)		1,690 (14.61)	2,117,136 (18.05)	
Quintile 2	1,549 (14.87)	1,839,576 (15.42)		1,389 (12.01)	1,495,341 (12.75)	
Quintile 3	2,138 (20.53)	3,161,293 (26.51)		2,398 (20.73)	3,135,633 (26.73)	
Quintile 4	2,196 (21.08)	2,252,173 (18.88)		2,534 (29.86)	2,294,886 (19.56)	
Quintile 5	2,875 (27.60)	2,274,656 (19.07)		2,986 (25.81)	2,163,222 (18.44)	
Unknown	159 (1.53)	438,812 (3.68)		572 (4.94)	525,846 (4.48)	
Occupation			<0.001			<0.001
Dependent of insured individual	3,835 (36.82)	4,924,319 (41.29)		3,952 (34.16)	4,285,015 (36.52)	
Civil servant, teacher, military personnel, and veterans	706 (6.78)	401,734 (3.37)		660 (5.70)	582,717 (4.97)	
Non–manual labor worker and professional	3,469 (33.30)	3,031,660 (25.42)		4,323 (37.37)	3,325,548 (28.35)	
Manual labor worker	1,534 (14.73)	2,612,534 (21.91)		1,498 (12.95)	2,272,550 (19.37)	
Other	872 (8.37)	956,266 (8.02)		1,136 (9.82)	12,66234 (10.79)	

* Except where indicated otherwise, values are the number (%). SS = Sjögren's syndrome.

were 12,754 individuals (11,462 women and 1,292 men) with SS in the general population of Taiwan in 2010, which is equivalent to a prevalence of 0.05% (0.10% in women and 0.01% in men). In the general population of Taiwan in 2010, 21,985 individuals (0.09%) had at least one first-degree relative with SS. Among these individuals, 105 had SS (prevalence 0.48%). The mean ± SD age of the patients with SS was lower in those with a family history (46.6 ± 16.2 years) than in those without a family history (57.0 ± 14.2 years; $P < 0.001$, by Student's *t*-test). For individuals with an affected first-degree relative, the age-specific prevalence of SS was significantly higher than that in the general population (Figure 1). Other characteristics of the study population are shown in Table 1.

Relative risks of SS in individuals with affected first-degree relatives. Table 2 shows the prevalence (recurrence risk) of SS in individuals with an affected first-degree relative, according to different relationships and sexes of the affected individuals and their families. Overall, having an affected first-degree relative with SS was associated with an adjusted RR of 12.37 (95% CI 9.54–16.05) for the disease. Individuals with female and male affected relatives had respective RRs for SS of 13.24 (95% CI 10.15–17.27) and 10.06 (95% CI 4.91–20.61), suggesting that the sex of the affected relative did not influence the RR.

In SS, the degree of genetic distance between family relatives is associated with the RRs. The RRs of SS were 661.75 (95% CI 278.09–1,574.70) in cotwins of patients with SS, 18.99 (95% CI 9.76–36.93) in siblings, 11.31 (95% CI 8.34–15.33) in offspring, and 12.46 (95% CI 9.34–16.62) in parents. In addition, the RRs increased with the number of types of affected first-degree relatives. Compared with the general population, individuals with 1 type of affected first-degree relative had an RR of 12.71 (95% CI 9.80–16.49), and those with 2 or more affected first-degree relatives had an RR of SS of 70.36 (95% CI 10.28–481.60).

Familial transmission and tetrachoric correlation of SS. Overall, the tetrachoric correlation coefficient for first-degree relatives was 0.22 (95% CI 0.19–0.24) (Table 2). The tetrachoric correlation coefficients were estimated to be 0.53 (95% CI 0.41–0.65) for twins and 0.21 (95% CI 0.16–0.26) for full siblings. Using a polygenic liability model, we estimated that the familial transmission for SS was 0.54 (95% CI 0.44–0.77). Given the parameters estimated previously, 84.0% of SS patients were expected to be sporadic cases.

Table 2. Relative risks (RRs) and tetrachoric correlation for Sjögren's syndrome in different kinships*

Type of affected relative, sex of affected relative, sex of individual	No. of cases	Prevalence, %	RR (95% CI)†	Tetrachoric correlation coefficient (95% CI)
Any relative				
Female				
Female	88	0.94	13.75 (10.36–18.26)	0.24 (0.21–0.26)
Male	8	0.08	10.37 (5.21–20.62)	0.17 (0.10–0.24)
All	96	0.48	13.24 (10.15–17.27)	0.22 (0.19–0.24)
Male				
Female	7	0.67	8.92 (4.28–18.61)	0.17 (0.09–0.24)
Male	2	0.17	21.15 (2.97–150.36)	0.21 (0.08–0.33)
All	9	0.41	10.06 (4.91–20.61)	0.17 (0.10–0.23)
All				
Female	95	0.91	13.24 (10.13–17.31)	0.24 (0.21–0.26)
Male	10	0.09	11.57 (5.90–22.67)	0.18 (0.12–0.24)
All	105	0.48	12.37 (9.54–16.05)	0.22 (0.19–0.24)
Parent				
Female, mother				
Female	39	0.55	13.12 (9.55–18.02)	0.17 (0.13–0.20)
Male	5	0.06	14.26 (5.97–34.07)	0.14 (0.06–0.22)
All	44	0.29	13.04 (9.68–17.57)	0.15 (0.12–0.18)
Male, father				
Female	3	0.38	8.47 (2.72–26.36)	0.11 (0.01–0.21)
Male	0	0	NA	NA
All	3	0.17	7.37 (2.37–22.92)	0.09 (0.01–0.18)
All				
Female	42	0.53	12.65 (9. 32–17.17)	0.17 (0.13–0.20)
Male	5	0.05	12.71 (5.32–30.36)	0.13 (0.05–0.21)
All	47	0.28	12.46 (9.34–16.62)	0.15 (0.12–0.18)
Offspring				
Female, daughter				
Female	33	2.65	11.79 (8.43–16.50)	0.32 (0.28–0.36)
Male	3	0.29	8.94 (2.90–27.54)	0.26 (0.15–0.37)
All	36	1.59	11.41 (8.28–15.74)	0.31 (0.27–0.34)
Male, son				
Female	4	2.74	11.79 (4.49–30.99)	0.28 (0.18–0.39)
Male	0	0	NA	NA
All	4	1.58	10.44 (3.98–27.41)	0.27 (0.17–0.36)
All				
Female	37	2.66	11.79 (8.59–16.19)	0.33 (0.29–0.37)
Male	3	0.27	8.04 (2.61–24.78)	0.25 (0.14–0.36)
All	40	0.31	11.31 (8.34–15.33)	0.25 (0.14–0.36)
Sibling				
Female, sister				
Female	14	1.36	21.78 (10.77–44.12)	0.24 (0.18–0.30)
Male	0	0	NA	NA
All	14	0.63	18.92 (9.37–38.40)	0.21 (0.16–0.26)
Male, brother				
Female	0	0	NA	NA
Male	2	1.77	153.48 (20.90–1,127.20)	0.39 (0.25–0.53)
All	2	0.93	19.72 (2.89–1,34.54)	0.21 (0.09–0.34)
All				
Female	14	1.23	19.09 (9.42–38.68)	0.23 (0.17–0.29)
Male	2	0.15	20.13 (2.81–144.30)	0.20 (0.08–0.32)
All	16	0.65	18.99 (9.76–36.93)	0.21 (0.16–0.26)
Twin				
Female, twin sister				
Female	4	36.36	756.32 (332.32–1,721.27)	0.57 (0.43–0.70)
Male	0	0	NA	NA
All	4	28.57	723.05 (314.11–1,664.39)	0.55 (0.43–0.68)
Male, twin brother				
Female	0	0	NA	NA
Male	0	0	NA	NA
All	0	0	NA	NA
All				
Female	4	33.33	695.68 (296.16–1,634.17)	0.55 (0.42–0.69)
Male	0	0	NA	NA
All	4	23.53	661.75 (278.09–1,574.70)	0.53 (0.41–0.65)

* 95% CI = 95% confidence interval; NA = not applicable.
† Adjusted for age, sex, place of residence, quintile of income level, occupation, and family size.

Table 3. Relative risks (RRs) of other autoimmune diseases in individuals with first-degree relatives with Sjögren's syndrome*

	With affected relatives		General population		
	No. of cases	Prevalence, %	No. of cases	Prevalence, %	RR (95% CI)†
Rheumatoid arthritis					
Female	50	0.48	29,527	0.25	2.87 (2.18–3.78)
Male	18	0.16	7,887	0.07	3.21 (2.02–5.09)
All	68	0.31	37,414	0.16	2.95 (2.33–3.73)
Systemic lupus erythematosus					
Female	96	0.92	16,822	0.14	6.24 (5.10–7.65)
Male	13	0.11	1,984	0.02	6.31 (3.65–10.88)
All	109	0.50	18,806	0.08	6.25 (5.15–7.58)
Systemic sclerosis					
Female	2	0.02	1,493	0.01	2.12 (0.53–8.50)
Male	1	0.01	395	0.003	3.24 (0.46–22.91)
All	3	0.01	1,888	0.01	2.39 (0.77–7.41)
Idiopathic inflammatory myopathy					
Female	1	0.01	1,259	0.01	1.10 (0.16–7.86)
Male	0	0	548	0.005	NA
All	1	0.005	1,807	0.01	0.71 (0.10–5.07)
Type 1 diabetes mellitus					
Female	10	0.10	5,406	0.05	1.69 (0.91–3.14)
Male	13	0.11	4,852	0.04	2.26 (1.31–3.89)
All	23	0.10	10,258	0.04	1.97 (1.29–3.02)
Multiple sclerosis					
Female	4	0.04	961	0.01	4.86 (1.81–13.00)
Male	0	0	287	0.002	NA
All	4	0.02	1,248	0.01	3.38 (1.26–9.05)
Myasthenia gravis					
Female	6	0.06	3,466	0.03	2.12 (0.95–4.73)
Male	2	0.02	2,248	0.02	1.03 (0.26–4.12)
All	8	0.04	5,714	0.02	1.67 (0.83–3.33)
Psoriasis					
Female	51	0.64	67,857	0.58	1.29 (0.98–1.70)
Male	74	0.49	45,447	0.38	1.22 (0.97–1.54)
All	125	0.57	113,304	0.48	1.25 (1.04–1.50)
Inflammatory bowel disease					
Female	1	0.01	1,026	0.01	1.26 (0.18–8.97)
Male	2	0.02	1,686	0.01	1.18 (0.29–4.72)
All	3	0.01	2,712	0.01	1.21 (0.39–3.76)
Vasculitis					
Female	6	0.06	1,837	0.02	4.07 (1.83–9.07)
Male	3	0.03	2,907	0.02	1.22 (0.39–3.79)
All	9	0.04	4,744	0.02	2.29 (1.19–4.40)

* 95% CI = 95% confidence interval; NA = not applicable.
† Adjusted for age, sex, place of residence, quintile of income level, occupation, and family size.

Co-aggregation of other autoimmune diseases. Table 3 shows the adjusted RRs (95% CIs) for other autoimmune diseases in individuals with affected first-degree relatives compared with the general population. The RR in individuals with a first-degree relative with SS was 2.95 (95% CI 2.33–3.73) for RA, 6.25 (95% CI 5.15–7.58) for SLE, 2.39 (95% CI 0.77–7.41) for systemic sclerosis, 0.71 (95% CI 0.10–5.07) for idiopathic inflammatory myopathy, 1.97 (95% CI 1.29–3.02) for type 1 diabetes mellitus, 3.38 (95% CI 1.26–9.05) for multiple sclerosis, 1.67 (95% CI 0.83–3.33) for myasthenia gravis, 1.25 (95% CI 1.04–1.50) for psoriasis, 1.21 (95% CI 0.39–3.76) for inflammatory bowel disease, and 2.29 (95% CI 1.19–4.40) for vasculitis.

DISCUSSION

This study is the first to investigate the risk of SS in individuals with affected first-degree relatives and to estimate the familial transmission of SS in a general population. We observed that the prevalence of SS in relatives of patients with the disease is 12-fold higher than that in the general population, and that genetic distance is associated with the magnitude of risk. The familial transmission of SS was 0.54. Despite this, most cases of SS are expected to be sporadic, based on the polygenic liability model. Furthermore, the prevalence of other autoimmune diseases is

higher among individuals with an affected first-degree relative.

Our results have several implications. First, the study provides quantitative estimates for absolute risks and RRs, familial transmission, and the proportion of sporadic cases of SS, which are valuable for clinical counseling. Second, these data may help in the planning of future genetic studies to determine candidate susceptibility genes. Third, the co-aggregation of SS and certain other autoimmune diseases suggests an overlapping pathogenesis that deserves further elucidation.

Formal evidence for familial aggregation and the magnitude of any familial or genetic contribution are rarely reported. Concordance of SS in several twin pairs has been reported previously (6–9), generally with very similar phenotypes (e.g., pathologic findings and serologic and clinical presentations). For example, a pair of monozygotic twins with SS exhibited nearly identical and clonally restricted anti-Ro/SSA autoantibodies (9). In addition, several studies in families that include a member with SS have been reported (10,11,13,14,37,38). However, previous studies have not included twin concordance rates, tetrachoric correlation coefficients, and familial transmission.

Our study provides several lines of evidence supporting the importance of familial factors, including both genes and environment, in susceptibility to SS. First, the age-specific prevalence of SS was significantly higher in first-degree relatives of SS patients in all age bands compared with the general population, and the adjusted RR associated with a family history was high (12-fold higher than that in the general population). Second, the RR and tetrachoric correlation coefficient varied according to genetic distance, and sibling RRs are higher than parental and offspring RRs despite the same genetic distance, suggesting contributions of both genes and shared environmental factors to disease susceptibility. Finally, using a polygenic liability model, we estimated that 54% of phenotypic variance can be explained by familial factors.

Under the polygenic liability model, however, most cases of SS are expected to be sporadic rather than familial. This phenomenon seems counterintuitive but appears to be the norm for many common complex diseases (36). For example, a theoretical estimate showed that the probability of sporadic cases of RA was 78–84%, depending on the parameters used (36). Real-world epidemiologic data also support this notion. A prospective inception cohort study recruited 204 RA patients with complete family histories, and 162 of the patients (79.4%) were identified as having sporadic RA (39). A similar phenomenon exists in SLE (36), despite one study showing no phenotypic differences between sporadic and familial cases (40).

Collectively, our results provide useful information for counseling patients and their family members. Full information on familial absolute risks and RRs, familial transmission, and the probability of sporadic cases should be provided and fully explained to prevent misconception and undue distress. Given both a low absolute risk (<1%) and a high probability of sporadic cases, decisions based solely on family history to screen for the disease in asymptomatic family members of the affected patients do not seem to be justified. Nonetheless, further studies should be undertaken to test the utility of family history as a tool to identify at-risk individuals.

Recent genome-wide association studies (GWAS) identified an expanding array of candidate genes that are associated with an increased risk of SS (41). Recently, 2 GWAS in SS were undertaken (20,21). One of these studies analyzed 395 patients with SS and 1,975 population controls of European descent and showed strong associations with genes within the HLA region (20). Several candidate genes outside the regions that were previously identified, such as *STAT4* and *IFR5* (18,19), did not exceed the significance limit. Another study genotyped 597 patients with primary SS and 1,090 healthy controls of Han Chinese ethnic origin and demonstrated a new susceptibility locus and also confirmed previously reported loci (21).

GWAS have also been very successful in identifying candidate genes for other autoimmune disorders, such as RA, SLE, type 1 diabetes mellitus, and multiple sclerosis. The similarity of the magnitude of the sibling risk between SS (15-fold) and type 1 diabetes mellitus (15-fold), RA (8-fold), SLE (30-fold), and multiple sclerosis (20-fold) (42) suggests that it should be possible to identify specific genetic risk factors for SS both within and outside the HLA region, in a relatively small GWAS (~2,000 cases), as was done for the aforementioned autoimmune diseases (43–45). Our results therefore may be useful for planning further GWAS to identify specific susceptibility genes for SS.

Apart from genetic factors, shared environmental factors may also contribute to familial clustering of SS. For example, Epstein-Barr virus (EBV) infection, with subsequent activation of epithelial cells and the immune system, has been proposed as a plausible environmental factor contributing to the development of SS (46). EBV most commonly spreads via bodily fluids (primarily saliva), and family members of infected patients are potentially at higher risk of infection.

Therefore, both genetic factors and shared environmental factors may contribute to the phenotypic variance in SS.

First-degree relatives of patients with SS have an increased risk of other autoimmune diseases, and the magnitude of the risk was particularly high for SLE. This tendency for familial co-aggregation of autoimmune diseases with SS was also suggested previously, but the magnitude of the risk associated with specific diseases has not been reported. A multicenter hospital-based study in Italy comprising 140 patients with SS and 109 in-patient controls without a history of autoimmune disease showed that patients with SS had a 5-fold risk of having a first-degree relative with autoimmune diseases (including 1 with SS) (16). Our results suggest that some autoimmune diseases share part of the pathogenesis of SS, but the magnitude of overlapping factors contributing to disease manifestation is different. Sjögren's syndrome appears to share many of these factors with SLE and RA, which is expected, because SLE and RA often coexist with SS. A high prevalence of sicca syndrome in patients with type 1 diabetes mellitus was reported previously (47), but a link between type 1 diabetes mellitus and SS was demonstrated only recently (48). The coexistence of multiple sclerosis (49) and vasculitis (50) with SS has also been reported. Currently, however, there are no data on familial co-aggregation of these diseases in families in which a member is affected by SS. Our data could be of value when counseling families of patients with SS.

The present study has some limitations. First, the classification of cases was based purely on the diagnosis recorded in the registry of patients with catastrophic illnesses or based on records in primary care. The NHIRD is primarily a health insurance database and lacks full information on clinical findings, laboratory testing, and examinations; therefore, formal classification criteria for SS could not be applied. Nevertheless, issuance of a catastrophic illness certificate requires strong medical evidence for a diagnosis of SS that is agreed upon by an expert panel, and applications for these certificates are submitted almost exclusively by rheumatologists. Therefore, any misclassification is unlikely to unduly affect our conclusion. Second, patients with less severe disease may not have received a certificate and thus will not have been identified as cases. Third, the estimate for probability of sporadic cases was based on data derived from first-degree relatives. In this study, therefore, sporadic cases are limited to patients with no first-degree relative. Fourth, our model cannot effectively separate contributions from genetic and shared environmental factors. Finally, whether these results apply to different populations and settings outside of Taiwan requires further study.

In conclusion, this population-wide study confirms that in Taiwan, SS clusters within families, and that both genetic and environmental factors contribute to susceptibility to the disease. Relatives of patients with SS tend to have an increased risk of other autoimmune diseases. These findings may also be useful when counseling families of patients with SS. In addition, these results may help inform the design of future studies of familial and genetic risks of SS.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Yu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Kuo, Zhang, Doherty.

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