Autoimmune Disease Aggregation in Families with Primary Sjögren's Syndrome

JUAN-MANUEL ANAYA, GABRIEL J. TOBON, PATRICIA VEGA, and JOHN CASTIBLANCO

ABSTRACT. ***Objective.*** Diverse autoimmune diseases may coexist in the same individual and in families, implying a common etiology. We examined the aggregation of autoimmune diseases among first-degree relatives (FDR) of patients with primary Sjögren's syndrome (pSS).

Methods. This was a population-based case-control family study in which 101 families of women classified as having pSS according to the revised American-European criteria and 124 families of matched controls without autoimmune disease were enrolled to investigate the presence of autoimmune diseases. We performed a genetic analysis that included familial correlation and recurrent risk ratios.

Results. In family cases, 38% had at least one FDR with an autoimmune disease, versus 22% in control families [odds ratio (OR) 2.2, 95% confidence interval (CI) 1.2–3.9, p = 0.01]. An autoimmune disease was registered for 7.3% of 876 patients' FDR as compared with 3.85% of 857 controls' FDR (OR 1.97, 95% CI 1.28–3.03, p = 0.002). The most frequent autoimmune diseases registered among the pSS patients' FDR were autoimmune thyroid disease (AITD), systemic lupus erythematosus, and rheumatoid arthritis, which disclosed aggregation. The proband phenotype (i.e., pSS) was correlated with AITD, systemic sclerosis, and all autoimmune diseases when considered together as a trait. Maternal transmission of the autoimmunity trait was observed in cases but not in controls.

Conclusion. Our results indicate that autoimmune diseases cluster within families of patients with pSS. This familial aggregation of autoimmune diseases adds further evidence that clinically different autoimmune phenotypes might share common susceptibility gene variants, which acting in epistatic pleitropy may represent risk factors for autoimmunity. (J Rheumatol 2006;33:2227–34)

Key Indexing Terms:
SJÖGREN'S SYNDROME AUTOIMMUNE DISEASES AUTOIMMUNE THYROID DISEASE
RHEUMATOID ARTHRITIS GENETICS INHERITANCE PATTERNS

Autoimmune diseases are chronic conditions initiated by the loss of immunological tolerance to self-antigens. The chronic nature of such diseases results in a significant effect not only on the quality of life, but also on medical care utilization, and direct and indirect economic costs. The estimated incidence of autoimmune diseases is about 90 per 100,000 person-years and their prevalence is about 3% of the population[1]. Almost all autoimmune diseases disproportionately affect middle-aged women and are among the leading causes of death for this group of patients. The older the patient, the lower the male:female ratio becomes[1].

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Although the etiology of autoimmune diseases is unknown, several factors are involved in the development of these diseases, including genetic and environmental ones[2,3]. Studies have established that each population holds a mutational pool in which most mutations individually (i.e., polymorphisms) will have small effects, but in combination with other alleles may favor or avoid autoimmune phenomena[3]. Such interplay within the genetic variants generates a change in the measurable risk of developing an autoimmune phenotype. This characteristic is one of the main reasons that autoimmune diseases are not inherited in a simple, classical Mendelian way, but have instead a complex or an as yet unknown mode of inheritance. Genetic contribution to autoimmune diseases is supported by the high rates of concordance, ranging from 15% to 60%, and by the high aggregation coefficients or recurrent risk ratios (λ_R)[4].

There is evidence indicating that some autoimmune diseases may aggregate within families. This includes not only cases of a single type of autoimmune disease (several members having the same trait) appearing among siblings, twins, and relatives of patients[5-8], but also several different ones (several family members with different autoimmune diseases)[9-20], thus indicating that autoimmune phenotypes could represent the pleiotropic outcome of nonspecific disease genes underlying similar immunogenetic mechanisms. The

hypothesis of a common origin for different autoimmune diseases is also supported by results of genome–wide scans showing that several loci may overlap in different autoimmune diseases[21,22], and by microarray expression profile studies disclosing a similar pattern of gene expression in different autoimmune diseases[23,24]. Finally, the multiple autoimmune syndrome (MAS), characterized by the presence of 3 or more autoimmune diseases in a single individual[25], is a clear example of how diverse phenotypes may be related to a single genotype.

Sjögren's syndrome (SS) is a late-onset autoimmune disease characterized by a lymphocytic and plasma cell infiltration of the exocrine glands, as well as by the production of autoantibodies leading to dryness of mucosa, mainly oral and lachrymal[26]. This disease can occur alone (primary, pSS) or in association with another autoimmune disease (secondary) including rheumatoid arthritis (RA)[27], systemic lupus erythematosus (SLE)[28], autoimmune hypothyroidism[12], and systemic sclerosis (SSc)[29]. Considering the interaction between autoimmune diseases summarized above and the growing evidence supporting a common genetic origin for these diseases, we examined the familial aggregation of autoimmunity within first-degree relatives (FDR) of patients with pSS.

MATERIALS AND METHODS

Patients and controls. This was a population-based case-control family study. Patients were women with pSS, all of whom fulfilled 4 or more of the diagnostic classification criteria proposed by the revised American-European Consensus Group[30], including a positive minor salivary gland biopsy. Patients belonged to our pSS cohort, a description of which has been reported[31]. They were seen as outpatients at the Clinica Universitaria Bolivariana, in Medellin, Colombia. Controls were selected from women attending the same clinic, of similar age (± 5 yrs), socioeconomic status, and ethnicity as the cases, with no evidence of autoimmune disease (Appendix 1). Exclusion criteria were preexisting autoimmune or hematological diseases and hepatitis B virus, hepatitis C virus, or human immunodeficiency virus infections. We enrolled 101 patients with pSS and 124 control individuals, all of whom were probands. FDR of patients with pSS or controls could not be accepted as cases or controls.

All individuals involved in this study were of Spanish ancestry and belonged to the population from the northwestern part of Colombia, South America (i.e., Paisa community). This population was established in the 16th and 17th centuries and flourished in relative isolation until the late 19th century. The admixture between Paisa and African or Amerindian populations has been historically documented as low[32], with an ancestral ethnic component of 85% Caucasian and 15% Amerindian. The African contribution has been estimated as being not significantly greater than 0. Thus, historical and genetic evidence supports the usefulness of this population for genetic studies[33,34].

Family collection. FDR of pSS patients and matched controls were interviewed following the methodology described by Priori, *et al*[16], using a standardized questionnaire that incorporated demographics and medical information including a checklist of 18 autoimmune diseases (Appendix 1). The diagnosis of autoimmune disease was considered reliable only if it was made by a certified physician (i.e., internist, endocrinologist, or rheumatologist) and confirmed by chart review or during discussion with the patient. Most FDR requiring medical care attended the same clinic as the patients. As for the families in our population, most of them are nuclear and at least 30% are multigenerational[35,36]. The great majority of households in our country still contain related persons[35,36]. In addition, all family members participating in this study were living in the same city and the families' size was large enough for establishing the robustness of our findings (Table 1). This research, accomplished in accordance with Resolution No. 008430 of 1993 from the Ministry of Health of the Republic of Colombia, was classified as research with minimal risk. The Ethics Committee of the Corporación para Investigaciones Biológicas approved the present study.

Table 1. Familial characteristics of patients with pSS and controls.

Characteristic	pSS n = 101	Controls n = 124
Age, yrs	54.3 ± 15.06	53.5 ± 12.8
Number of FDR*	876	857
Families with ≤ 5 FDR, (%)	20 (19.8)	7 (5.6)
Families with 6–10 FDR, (%)	39 (38.6)	47 (37.9)
Families with ≥ 11 FDR, (%)	42 (41.6)	70 (56.5)
Families with a FDR having at least one autoimmune disease		
No (%)	63 (62.4)	97 (78.2)
Yes (%)	38 (37.6)	27 (21.8)**
Number of FDRs with autoimmune disease		
0 (%)	63 (62.4)	97 (78.2)
1 FDR, (%)	25 (24.8)	22 (17.7)
≥ 2 FDRs, (%)	13 (12.9)	5 (4)†

FDR: first-degree relatives. * Data correspond to FDR excluding the proband offspring, who were not taken into account for the familial aggregation analysis. If considered, the total number of individuals taking into account the proband's offspring would be 980 for cases and 1433 for controls. ** OR 2.2; 95% CI 1.2–3.9, p = 0.01. † OR 3.5; 95% CI 1.21–10.23, p = 0.02.

Statistical and genetic analysis. Data were managed and stored using the SPSS program (V9.05 for Windows, Chicago, IL). Results are presented as means ± standard deviation (SD), and in percentages. Comparisons between means were performed by the Student's t test, and those between percentages were done by the chi-square test and 2–sided Fisher's exact test, as appropriate. Crude odds ratios (OR) were calculated with 95% confidence intervals (CI). A p value of less than 0.05 was considered significant.

The Marker–Trait Associations in Pedigree Data (ASSOC) program in Statistical Analysis in Genetic Epidemiology (SAGE) software was used to assess whether or not the presence of an autoimmune disease affecting a proband correlated with the presence of an autoimmune disease affecting a FDR[37]. Probands were sampled in a nonrandom manner, and their selection was based on having or not having the disease trait of interest, assuming the correlation structure described by Elston, *et al*[38] and the regression model described by George and Elston[39]. For each family of size n, the proband is denoted by j=1 and the FDR by j=2, 3 . . . n; y_j denotes the disease status [affected ($y_j = 0$) or nonaffected ($y_j = 1$) with a specific autoimmune disease] for each family member. Additional test-specified covariates of the presented autoimmune diseases were included for each individual in a vector x_j. ASSOC implements maximum likelihood (ML) estimation of both components of variance and covariance coefficients. The model is described as $h(y_j)= h(ß^T x_j)+ G_j+F_j+F'_j+M_j+S_j+E_j$, where h is the transformation of the dependent variable and the predicted components are polygenic (G_j) and environmental (F_j, M_j, S_j, E_j) effects. The ML is determined under 2 hypotheses: H_1 assumes the general model including all the covariates specified, while H_0 excludes the test covariates. If L_1 and L_0 are the ML under H_1 and H_0, respectively, then the likelihood ratio statistic is $2|\ln(L_1)- \ln(L_0)|$. This joint test is asymptotically distributed as a chi-square test with the number of degrees of freedom equal to the number of test covariates.

Furthermore, familial aggregation (λ_R) was calculated for first-degree relatedness (parent/offspring and sibling/sibling pairs) using the formula $\lambda_R = K_{Relative}/K$, where $K_{Relative}$ (K_R) was the prevalence for a specific degree of relatedness in the sample, and K was the prevalence in the control pedigree samples or the mean prevalence in the population[40]. In other words, 2 approaches were taken to examine λ_R. First, a relative–pair comparison

between the prevalence of autoimmune diseases for the correspondent proband within each pedigree was calculated based on the pedigrees for both pSS and controls. Second, previously reported prevalences of autoimmune diseases were considered[9,11,41-47]. These were used to obtain the λ_R values using the calculated prevalence for each specific degree relative on the pSS affected proband pedigrees. Given the fact that information about the prevalence of autoimmune diseases in our population was not available, prevalences in the range of 0.1%–0.5% were chosen as reported in the literature[9,11,41-47]. Furthermore, 0.5% (5/1000 individuals) for each autoimmune disease and 2.5% (25/1000 individuals) for all autoimmune diseases taken together were selected as putative population prevalences as previously reported[9,11-41-47]. Finally, since there was a subgroup of autoimmune diseases in the pedigrees of patients with pSS that disclosed a low frequency, all autoimmune diseases were combined in order to determine the presence of autoimmune disease familial aggregation as a trait. These methods were extended to ascertain whether or not clustering of 2 or more autoimmune disorders in relatives of patients with pSS increased the probability or the risk for the presence of the disorder in the affected proband.

RESULTS

In this study 101 patients with pSS were examined. The mean age at onset was 45.4 ± 14.2 years and the mean duration of the disease was 6.1 ± 6.3 years. Anti-Ro and anti-La antibodies were registered in 78 (77.2%) and 39 (38.6%) patients, respectively (by ELISA, INOVA Diagnostics, Inc., San Diego, CA, USA). Not a single patient tested positive for anti-DNA and anti-Sm antibodies.

Of the 101 families of pSS cases, 38 (37.6%) had at least one FDR with an autoimmune disease compared with 27 (21.8%) of 124 control families (OR 2.2, 95% CI 1.2–3.9, p = 0.01) (Table 1). When families were stratified by the number of FDR, the risk of familial autoimmunity increased with the number of FDRs affected with an autoimmune disease (Table 1). No difference in age at diagnosis of pSS was found between patients with a family history of autoimmune disease (54.3 ± 15.06 years) and those without (53.5 ± 12.8 years).

Diverse autoimmune diseases in pedigrees of patients and controls. Specific autoimmune diseases in FDR of both patients with pSS and controls are shown in Table 2. The percentage of FDR with at least one autoimmune disease in patients was 6.4% as compared with 3.85% in controls (OR 1.7, 95% CI 1.10–2.65, p = 0.01). There were 5 FDR of patients with pSS who presented more than one autoimmune disease, of whom 2 presented with MAS. Among controls not a single FDR presented more than one autoimmune disease (Table 2).

The general statistics of the pedigrees for the 101 patients with pSS and the 124 control individuals are shown in Table 3. In order to calculate the prevalence for each autoimmune disease the mean pedigree size, standard deviation, and total number of relative pairs were obtained. These analyses were restricted to FDR.

A sex-specific-relative type occurrence of autoimmune diseases in the case families was observed when compared with control families. Nine of 101 pSS patients had a mother affected by at least one autoimmune disease compared with only one father affected (OR 9.78, 95% CI 1.21–78.76, p = 0.01).

Table 2. Specific autoimmune diseases in FDR of patients with pSS and controls.

Autoimmune Diseases	In FDRs of pSS Patients	In FDRs of Controls
Primary Sjögren's syndrome	4	0
Systemic lupus erythematosus	8	1
Rheumatoid arthritis	15	10
Systemic sclerosis	2	0
Primary biliary cirrhosis	1	0
Vitiligo	4	3
Multiple sclerosis	1	0
Type 1 diabetes	3	1
Autoimmune hyperthyroidism	1	1
Autoimmune hypothyroidism	25	17
Total	64/876 (7.3%)*	33/857 (3.85%)
Number of FDR with at least one autoimmune disease*	56/876 (6.40%)**	33/857 (3.85%)

FDR: first-degree relative. * 5 FDR had more than one autoimmune disease (3 FDR had 2, one FDR had 3, and one FDR had 4). No FDR among controls had more than one, OR 1.97, 95% CI 1.28–3.03, p = 0.002. ** OR 1.7, 95% CI 1.10–2.65, p = 0.01.

Table 3. Pedigree general statistics for patients with pSS and controls.

Descriptors	Pedigrees	
	pSS	Controls
No. of pedigrees	101	124
Mean size ± SD	8.67 ± 3.63	6.91 ± 3.40
(Min, Max)	(3, 20)	(3, 19)
Pairs		
Parent/offspring	1340	1216
Sibling/sibling	2348	1863
Sister/sister	219	90
Brother/brother	113	119
Brother/sister	353	206

In the control group, there were 6 mothers and 2 fathers affected with one autoimmune disease (OR 3.1, 95% CI 0.61–15.68, p = 0.28).

Familial autoimmune disease correlation. By assessing whether or not the presence of pSS in the proband correlated with the presence of an autoimmune disease in an affected FDR, the correlation for the occurrence of each individual autoimmune disease was evaluated. Each model was weighted up every time a covariate (i.e., autoimmune disease) was added, thus assessing if the new trait would improve the likelihood of the primary phenotype by using the joint test, as described in Materials and Methods. A significant correlation was observed for autoimmune thyroid disease (AITD) (p = 0.0002) and also for SSc (p = 0.009). For RA at least one of the maximizations was not available and thus no joint test could be performed. Correlation was not observed for either SLE or vitiligo. When all the autoimmune diseases were considered together as a single trait, a significant genetic correlation was also observed (p = 0.004).

Familial aggregation (λ_R). For each pair of relatives (parent/offspring, sibling/sibling, and REL, representing the FDR specified pairs) the prevalence for each autoimmune disease, as well as for all autoimmune diseases taken together, is presented in Table 4. Previously reported prevalences were also taken into account[9,11,41-47]. These prevalences were used to calculate the familial aggregation according to different degrees of relatives (Table 5). Additionally, using the putative chosen prevalences [autoimmune disease individually (K = 0.5%) and all autoimmune diseases together (K = 2.5%)] λ_R

Table 4. Prevalence of autoimmune diseases in patients with pSS and controls according to relatedness.

Autoimmune Disease	K_{ss}*			K_{CI}			Reported K [Population][ref]
	P/O (N)	SIB (N)	REL (N)	P/O (N)	SIB (N)	REL (N)	
pSS	0.15 (2)	0.09 (2)	0.10 (4)	0.00 (0)	0.00 (0)	0.00 (0)	0.01 [Caucasian][41]
T1D	0.07 (1)	0.09 (2)	0.08 (3)	0.08 (1)	0.00 (0)	0.03 (1)	0.34 [UK-Caucasian][42]
							0.19 [North Americans][44]
							0.48 [UK, USA–Caucasian][9]
AITD	0.97 (13)	0.55 (13)	0.68 (26)	0.66 (8)	0.54 (10)	0.58 (18)	Graves
							0.65 [UK–Caucasian][46,47]
							0.80 [USA–Caucasian][9,44]
							Hashimoto
							0.80 [UK–Caucasian][47]
							1.15 [USA–Caucasian][44]
SLE	0.30 (4)	0.17 (4)	0.21 (8)	0.00 (0)	0.05 (1)	0.03 (1)	0.024 [USA–Caucasian][1]
							0.027 [UK–Caucasian][10]
RA	0.37 (5)	0.43 (10)	0.39 (15)	0.41 (5)	0.27 (5)	0.32 (10)	0.46 [South Americans–Brazil][45]
							0.55 [UK–Caucasian][10,43]
							0.86 [USA–Caucasian][9,44]
SSc	0.15 (2)	0.00 (0)	0.05 (2)	0.00 (0)	0.00 (0)	0.00 (0)	0.004 [USA–Caucasian][44]
PBC	0.07 (1)	0.00 (0)	0.03 (1)	0.00 (0)	0.00 (0)	0.00 (0)	0.003 [USA–Caucasian][1]
VIT	0.00 (0)	0.17 (4)	0.10 (4)	0.16 (2)	0.05 (1)	0.10 (3)	0.40 [USA–Caucasian][1,9]
MS	0.00 (0)	0.04 (1)	0.03 (1)	0.00 (0)	0.00 (0)	0.00 (0)	0.06 [USA–Caucasian][9]
All	1.94 (26)	1.45 (34)	1.56 (64)	1.32 (16)	0.91 (17)	1.06 (33)	2.5 [UK–Caucasian][10]

T1D: type 1 diabetes mellitus; AITD: autoimmune thyroid diseases; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; SSc: systemic sclerosis; PBC: primary biliary cirrhosis; VIT: vitiligo; MS: multiple sclerosis. * Data are given in percentages. Prevalences are disclosed between relative pairs: P/O: parent/offspring; SIB: sibling/sibling; REL: first-degree relatives. K_{SS}: prevalence for autoimmune disease in pSS patient pedigrees. K_{CI}: prevalence in control pedigrees. K: prevalence in the general population. N: number of observed relative-pairs in the pedigrees.

Table 5. Familial aggregation (λ_R) of autoimmune diseases (AID) in pSS families.

AID	$\lambda_R = K_{SS}/K_{CI}$			$\lambda_R = K_{SS}/K$		
	$\lambda_{P/O}$	λ_{SIB}	λ_{REL}	$\lambda_{P/O}$	λ_{SIB}	λ_{REL}
pSS	NA	NA	NA	0.30	0.18	0.21
T1D	0.91	NA	2.43	0.14	0.18	0.16
AITD	1.47	1.03	1.17	1.94	1.10	1.36
SLE	NA	3.17	6.47	0.60	0.34	0.42
RA	0.91	1.59	1.21	0.74	0.86	0.78
SSc	NA	NA	NA	0.30	0.00	0.10
PBC	NA	NA	NA	0.14	0.00	0.06
VIT	NA	3.17	1.08	0.00	0.34	0.21
MS	NA	NA	NA	0.00	0.08	0.06
Autoimmune disease*	1.47	1.59	1.57	0.78	0.58	0.67

K_{SS}: prevalence for autoimmune disease in pSS patient pedigrees. K_{CI}: prevalence in control pedigrees. K: chosen prevalence in the general population, λ_R: recurrent risk ratio ($\lambda_R = K_{SS}/(K_{CI}$ or K)], where R is the specific relative pair used (P/O: parent/offspring; SIB: sibling/sibling; REL: first-degree relatives); the ratio was calculated by a comparison between prevalence of pSS (K_{SS}) in patients depending on its first-degree relative disease or by using the mean reported population prevalence for AID (Data for calculations were obtained from Table 4). NA: Data not applicable. Because prevalences were not observed for K_{CI}, a proper appreciation of λ_R could not be accomplished. Nevertheless, if taking these results into consideration, the λ_R would disclose a high aggregation for those AID that were observed in patient but not in control pedigrees. * When taken together, the chosen population prevalence (K) for AID was considered to be 25/1000 individuals, and for each individual AID 5/1000 individuals.

were calculated (Table 5). Values supporting familial aggregation ($\lambda_R > 1.0$) were observed for both groups using both the pedigrees and the putative published prevalences data. Familial aggregation of AITD ($\lambda_R = 1.23 \pm 0.22$), SLE ($\lambda_R = 4.82 \pm 2.33$), RA ($\lambda_R = 1.24 \pm 0.34$), type 1 diabetes mellitus (T1D, $\lambda_R = 1.67 \pm 1.07$), vitiligo ($\lambda_R = 2.13 \pm 1.48$), and all autoimmune diseases taken together ($\lambda_R = 1.55 \pm 0.06$) was clearly observed in the families of patients of pSS. Estimation of the complete familial aggregation was reached by calculating the average of $\lambda_{P/O}$, λ_{SIB}, and λ_{REL} values as shown in Table 5. Representative pedigrees are depicted in Figure 1.

DISCUSSION

The results of this study confirm clustering of autoimmune diseases in families of patients with pSS. Although evidence has been reported for the familial clustering of autoimmune diseases in RA[14], SLE[16,17], polymyositis[13], juvenile RA[15], multiple sclerosis[10], vitiligo[9], pemphigus[11], and T1D[19,20], this is the largest report for pSS. Such results when confirmed within different populations allow a more complete and homogeneous comprehension of the pathogenic mechanism of autoimmune diseases. Bloch and Bunim first suggested a shared immunopathological mechanism for SS, SLE, SSc, and AITD, as well as a possible familial aggregation of these diseases in patients with pSS[48]. They described the clinical and immunological characteristics of 57 SS cases and some

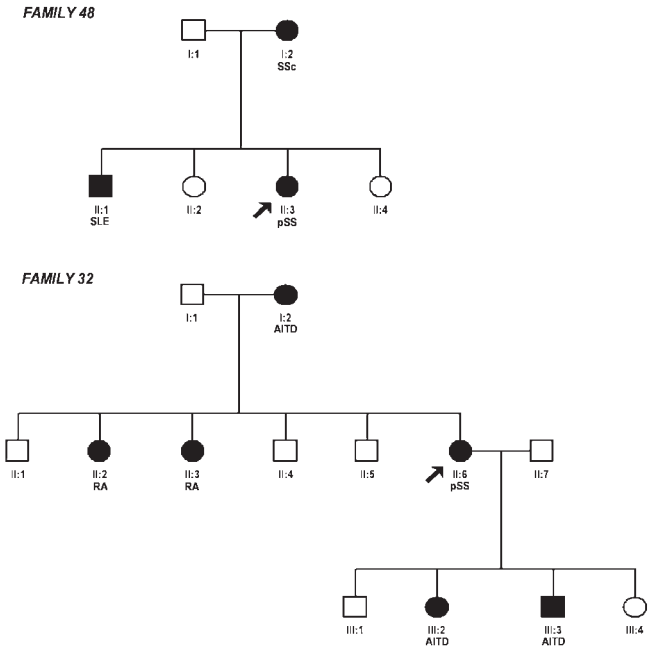

Figure 1. Representative pedigrees observed in families with pSS. Each numbered pedigree structure is given considering each of the autoimmune diseases found. Family 32 extended pedigree shows the clustering of autoimmune diseases through various generations; for analysis purposes only first and second generation individuals were considered. SLE: systemic lupus erythematosus, pSS: Sjögren's syndrome, RA: rheumatoid arthritis, AITD: autoimmune thyroid disease, SSc: systemic sclerosis.

immunological abnormalities among their relatives. However, most of these patients (70%) had secondary SS[48]. As was mentioned, SS may coexist with RA[27], SLE[28], AITD[12], and SSc[29].

Reveille, *et al* examined the presence of autoimmune diseases in family members of 51 patients with pSS[18]. As in our study, they observed that AITD, RA, and SLE were the most common autoimmune diseases among relatives. Multiple sclerosis and SSc were also registered, although less frequently. No aggregation analysis was performed. However, they investigated the relationships of human leukocyte antigen (HLA) genes and heavy chain immunoglobulin haplotypes to disease and autoantibody expression in 6 large kindreds, each having one or more members with pSS[18]. Segregation analyses suggested a Mendelian dominant genetic effect common among the many autoimmune diseases and serologic reactions that were not linked to HLA or Gm. The presence of autoantibodies in FDR of patients with pSS was examined by Arnett, *et al*, who observed that the presence of anti-Ro and anti-La antibodies could well be another marker of familial autoimmunity in pSS and SLE[49].

No case of pSS was recorded among FDR of our control group. When the families were stratified by the number of FDR, the risk of familial autoimmunity increased with the number of affected FDR (Table 1). Other studies have shown a similar result for SLE[16]. Likewise, the 6.1% of affected FDR of SLE cases reported by Priori, *et al*[16] matches the 6.4% presented in this study. The prevalence of autoimmune diseases among FDR of control individuals was 3.85%, a figure similar to the reported prevalence of such disorders in the general population[1] and in FDR of controls in other studies of familial autoimmunity[10,11].

Familial aggregation (λ_R) of AITD, SLE, RA, T1D, vitiligo, and all autoimmune diseases taken together was observed in this study (Table 5). The λ_R obtained indicates the frequency of an autoimmune trait being present in the sampled pedigree depending on its distribution, while the different weighted models (i.e., correlation) indicate how a trait explains the presence of an autoimmune disease in the proband when a FDR is affected by an autoimmune disease.

Foster, *et al* documented autoimmune diseases and autoantibodies in 207 relatives of 42 index cases with pSS[12]. AITD was the most common autoimmune disease registered[12,13]. In our study, AITD, mainly hypothyroidism, was also the most common disease encountered among FDR of patients with pSS, as has also been reported in familial studies of multiple sclerosis[10], vitiligo[9], juvenile RA[15], and SLE[16]. AITD not only aggregates in the families of patients with pSS but may also coexist with other autoimmune diseases[9,16,17,28,50].

A significant familial correlation was noticed for AITD and SSc, implying that the presence of each one of these diseases would be associated with the proband disease phenotype (i.e., pSS). The observed familial correlation for SSc could be explained by its familial distribution, since the disease had

been present at all times in parents (mothers) of affected probands, while no SSc cases had been observed among FDR of controls. More important, when all the autoimmune diseases were considered together as a trait, a significant correlation became apparent. This finding supports previous analysis suggesting that autoimmune diseases might be the consequence of the pleiotropic effects of a single major gene on a polygenic background[2,14,18]. The lack of genetic information (i.e., genotypes) prevents us from drawing conclusions about the specific role of loci in the susceptibility to autoimmune diseases. Nonetheless, the strong suggestions given in previous studies allow us to point out the major histocompatibility complex (MHC), including both HLA and non-HLA[4,51], as one of the central loci contributing to pSS and autoimmune diseases. However, not all autoimmune diseases share the same genetic susceptibility or allelic spectrum. Thus, the genetic risk factors for autoimmune diseases may well consist of 2 forms: those that are common to many autoimmune diseases and those that are specific for a given disorder (Figure 2).

The next most commonly registered autoimmune diseases in FDR of patients with pSS were RA and SLE. Familial correlation was not obtained for these diseases because at least one of the maximizations was not available and thus no joint test could be performed. However, λ_{REL} was observed for both SLE and RA, but was significantly higher for SLE (Table 5). Both pSS and SLE share similar susceptibility gene polymorphisms including HLA and non-HLA variants[4,21,52,53], which may account for the observed aggregation. Shared genetic factors are, in fact, the most likely cause for familial aggregation; however, it is important to keep in mind that shared environmental factors can also explain this aggregation. For a specified relative type, a λ_R greater than 1 suggests familial aggregation of the disease, but does not indicate whether genetic and/or environmental factors are causing the aggregation[54]. Thus, a major strength of this study was the inclusion of origin- and ethnic-matched control families whose environmental conditions were similar to those of the patient's families.

A predominant inheritance of the autoimmunity trait from mothers was evident in patients with pSS, as was previously observed in this[18] and other autoimmune diseases[16,19], indicating a preferential transmission of susceptibility alleles from mothers to offspring. Maternal transmission of autoimmunity could be influenced by the high preponderance of autoimmune diseases in women as compared with the general population; however, this higher than expected frequency of maternal transmission of the autoimmunity trait would warrant further studies of mitochondrial DNA, genomic imprinting, maternal-offspring compatibility, and indirect genetic effects in pSS and other autoimmune diseases.

Our study shows aggregation of autoimmune diseases in families of patients with pSS. Results indicate that autoimmunity might aggregate as a trait favoring a common immunogenetic origin for diverse autoimmune phenotypes, and emphasize the importance of the autoimmunity family history as a substantial risk factor for the development of pSS and other autoimmune diseases.

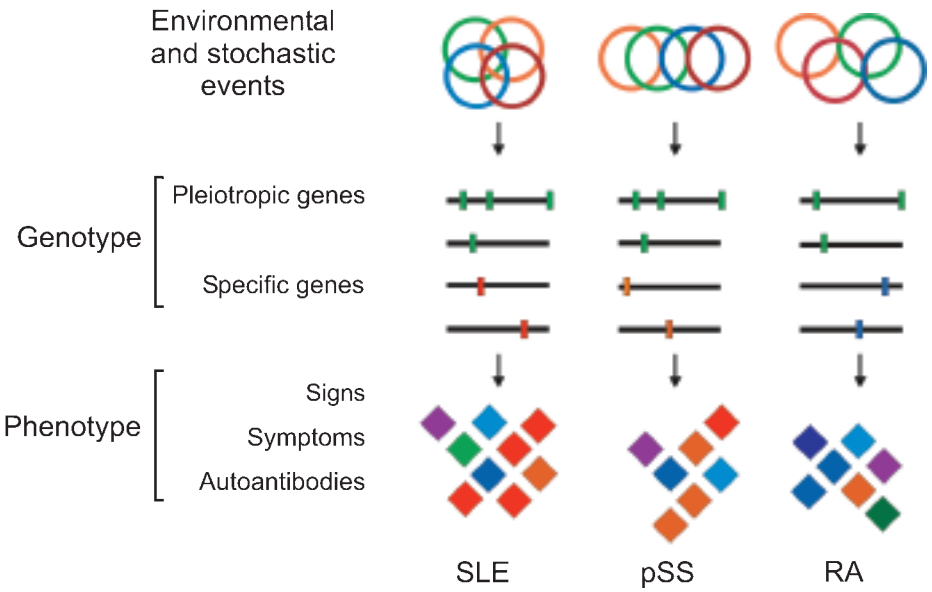

Figure 2. The common origin for diverse autoimmune diseases hypothesis. Autoimmune diseases are the result of multiple interactions of polymorphic genes and environmental or stochastic factors leading to loss of immunological tolerance to self-antigens and then to tissue damage. The genetic risk factors for autoimmune diseases may well consist of 2 forms: those common to many autoimmune diseases acting in epistatic pleitropy and those specific for a given disorder. SLE: systemic lupus erythematosus, SS: Sjögren's syndrome, RA: rheumatoid arthritis.

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Appendix 1. List of autoimmune diseases investigated in our study.

No.	Autoimmune Disease	Ref.
1	Diabetes mellitus type 1	1
2	Systemic lupus erythematosus	2
3	Antiphospholipid syndrome	3
4	Rheumatoid arthritis	4
5	Sjögren's syndrome	5
6	Mixed connective tissue disease	6
7	Ankylosing spondylitis	7
8	Scleroderma	8
9	Dermato-polymyositis	9–10
10	Crohn's disease or ulcerative colitis	11
11	Megaloblastic anemia	12
12	Hypothyroidism (Hashimoto)	13
13	Hyperthyroidism (Graves)	14
14	Psoriasis	15
15	Vitiligo	15
16	Primary biliary cirrhosis	16
17	Autoimmune Hepatitis	17
18	Multiple sclerosis	18
19	Other	19

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19. This was a free question asked by the physicians and included vasculitis, coeliac disease, Addison's disease, primary glomerulonephritis.

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