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Familial Aggregation of Systemic Lupus Erythematosus, Rheumatoid Arthritis, and Other Autoimmune Diseases in 1,177 Lupus Patients From the GLADEL Cohort

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Objective. **To determine whether there is familial aggregation of systemic lupus erythematosus (SLE) and/or other autoimmune diseases in SLE patients and to identify clinical differences between patients with and those without familial autoimmunity.**

Methods. **We interviewed members of the Grupo Latinoamericano de Estudio del Lupus Eritematoso (GLADEL) inception cohort of 1,214 SLE patients to ascertain whether they had relatives with SLE and/or other autoimmune diseases. Identified relatives were studied. Familial aggregation was tested using reported highest and intermediate population prevalence data for SLE, rheumatoid arthritis (RA), or all autoimmune diseases, and studies were performed to identify the genetic model applicable for SLE.**

Results. **We identified 116 first-, second-, or third-degree relatives with SLE, 79 with RA, 23 with autoimmune thyroiditis, 3 with scleroderma, 1 with polymyositis, and 16 with other autoimmune diseases, related to 166 of the 1,177 SLE patients in the GLADEL cohort who agreed to participate. Forty-two SLE patients had 2 or more relatives with an autoimmune disease. We found a $\lambda_{sibling}$ of 5.8 and 29.0 for SLE and of 3.2–5.3 for RA, when comparing with their reported high or intermediate population prevalence, respectively. We also found familial aggregation for autoimmune disease in general ($\lambda_{sibling} = 1.5$) and determined that for SLE, a polygenic additive genetic model, rather than a multiplicative one, is applicable.**

Conclusion. **In SLE there is familial aggregation of SLE, RA, and autoimmune disease in general. A polygenic additive model applies for SLE. American Indian–white Mestizo SLE patients and those with higher socioeconomic level were more likely to have familial autoimmunity.**

Genetic factors participate in the etiopathogenesis of SLE (1,2). There can also be genetic overlap of SLE with other autoimmune diseases (3), and disease-predisposing genes for SLE or for other autoimmune diseases have been found by means of genome scan technology (2,3). There may also be a gene or genes that predispose to autoimmune disease in general (1,4). Whether there is familial aggregation proper, rather than the mere coincident occurrence, of SLE and/or other autoimmune disease in SLE patients has not been determined, mostly because of the large number of SLE patients, and the collaboration of their relatives, that would be required. The previously experienced extraordinary cooperation of patients in the Grupo Latinoamericano de Estudio del Lupus Eritematoso (GLADEL) cohort (5), as well as its size, encouraged us to attempt to overcome these difficulties in order to address this question. We also sought to identify any differences between SLE patients with and those without familial autoimmunity.

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PATIENTS AND METHODS

The GLADEL cohort. The general characteristics and composition of the GLADEL cohort have been described in detail elsewhere (5). Briefly, it was started in 1997 by establishing a common protocol, consensus definitions, and outcome measures. The 34 centers contributing to this cohort are distributed among 9 Latin American countries and were invited to participate on the basis of their academic profile and their staff expertise in SLE. To achieve a balanced representation among the participating centers despite the large numbers of SLE patients followed up at some of them, and to make this an inception cohort, each center enrolled 20–30 randomly selected SLE patients diagnosed in the last 2 years. After incorporating the initial 30 patients, each center continued to enter into the ARTHROS 2.0 database (or, subsequently, the improved ARTHROS 6.0 version) 1 randomly selected patient per month who had been diagnosed within the last 2 years. All data were submitted, via Internet, to a coordinating center where data were reviewed to ensure quality. GLADEL investigators, in addition to the authors, who enrolled patients in the present study are listed in Appendix A.

Autoimmune disease in relatives of SLE patients. To obtain information on the presence of autoimmune disease in the relatives of the SLE patients, an ad hoc questionnaire was added to the ARTHROS 6.0 database, to be administered personally to patients enrolled in the cohort who agreed to answer it. We were able to thus interview 1,177 (97%) of the 1,214 patients, after they had been given a list of autoimmune diseases to take home and discuss with their families (Table 1). Once identified, relatives with a probable autoimmune disease were personally interviewed and examined, if warranted. The interview included medical examination and, with the patient's permission, analysis of previous medical test findings (laboratory, imaging, etc.), clinical chart review, and interview with the treating physician. For relatives who lived a long distance away, telephone interviews were done. For these subjects also, previous medical test findings were analyzed, clinical charts were reviewed, and the treating physician was interviewed when available. When the relative was deceased, information was sought by review of available medical test findings, clinical chart review, and interview with the treating physician.

Table 1. Autoimmune diseases for which systemic lupus patients were asked about presence in relatives

System	Diseases
Endocrine	Hashimoto thyroiditis, primary myxedema, thyrotoxicosis, Addison's disease, type 1 diabetes mellitus
Hematologic	Pernicious anemia, hemolytic anemia, idiopathic thrombocytopenic purpura, idiopathic leukopenia, autoimmune neutropenia
Gastrointestinal	Autoimmune atrophic gastritis, autoimmune primary biliary cirrhosis, autoimmune active chronic hepatitis, ulcerative colitis, Crohn's disease
Neuromuscular	Myasthenia gravis, multiple sclerosis
Renal	Goodpasture's syndrome, idiopathic nephropathy (nephrotic or nephritic syndrome)
Cardiovascular	Rheumatic fever
Skin	Pemphigus vulgaris, psoriasis, cutaneous vasculitis
Ocular	Idiopathic uveitis
Systemic	Systemic lupus erythematosus, rheumatoid arthritis, scleroderma, polymyositis/dermatomyositis, mixed connective tissue disease, discoid lupus erythematosus, antiphospholipid syndrome, Sjögren's syndrome, Raynaud's phenomenon, systemic vasculitis

Study of familial aggregation. Familial aggregation (λ) was calculated for each degree of relatedness, using the formula $\lambda = K_{relative}/K$, where $K_{relative}$ is the prevalence for a degree of relatedness in the sample and K is the prevalence in the population (6). To determine familial aggregation, we used 3 population prevalence values covering the range of SLE prevalence reported in general populations (7), including the lower and higher extremes in Arctic Norway (0.0005 and 0.001, respectively) (8) and the rate in African Americans (0.005) (7).

To test for the genetic model involved we used Risch's formula (6), i.e., $\lambda_{cousin} = \frac{1}{4}(\lambda_{offspring} + 3)$, by which, using the prevalence of an autoimmune disease in the various degrees of family relatedness, the type of inheritance (additive versus multiplicative) can be determined. We considered as first-degree relatives parents, siblings, and offspring; as second-degree relatives aunts, uncles, nephews, nieces, half-siblings, grandparents, and grandchildren; and as third-degree relatives first cousins. More distant relatives were not included.

The prevalences of rheumatoid arthritis (RA) used to determine familial aggregation in each degree of relatedness were those reported in general populations from Latin America (9–15) and Spain (16), i.e., from 0.001 to 0.005. We opted to exclude the highest prevalence of up to 6% found in native North American Indians (Yakima, Pima, and Chippewa) (17–19) for several reasons: 1) to our knowledge, in none of the Latin American countries studied has there ever been a report of such high RA prevalence in their American Indian populations; 2) those high prevalences may actually be the result of "bottlenecks" or founder effects; and 3) in reports that cite those high prevalences only single tribes were studied, suggesting relative inbreeding. This makes these groups quite different from the highly expanding populations of Latin America and unsuitable for comparison since they would tend to spuriously minimize potential familial aggregation in this and other studies.

The smaller numbers of other autoimmune diseases found in the relatives of our patients did not permit an individual analysis of each disease. We therefore combined all other autoimmune diseases in the relatives of SLE patients to determine if there was familial aggregation of autoimmunity in general, using the data reported by Jacobson and coworkers on the frequency of autoimmune diseases in the US in 1997 (20), and calculated their combined prevalence using data on the population of that country in 1997, as reported by the Census Bureau. We are aware of the potential limitations associated with use of these data, but found no other information on this. We found a $\lambda_{sibling}$ of 1.50, similar to the familial aggregation of autoimmune disease in general that has been found in patients with multiple sclerosis ($\lambda_{sibling}$ 1.65) (21).

Statistical analysis. We established 3 main groups from the SLE cohort: 1) patients who had at least 1 first-, second-, or third-degree relative with any autoimmune disease

Table 2. Autoimmune diseases in relatives of SLE patients in the GLADEL cohort, according to familial degree*

Disease in relatives	First-degree relatives			Second-degree relatives			Third-degree relatives (cousins)	Total relatives	Total patients
	Parents	Offspring	Siblings	Grandparents	Uncles/aunts	Nephews/nieces			
SLE	25	7	39	4	26	1	14	116	97
RA	19	0	13	21	19	0	8	80	67
ATD	12	0	4	1	4	2	0	23	18
SSc	0	0	1	1	1	0	0	3	3
PM	1	0	0	0	0	0	0	1	1

* SLE = systemic lupus erythematosus; GLADEL = Group Latinoamericano de Estudio del Lupus Eritematoso; RA = rheumatoid arthritis; ATD = autoimmune thyroid disease; SSc = systemic sclerosis (scleroderma); PM = polymyositis.

(SLE, RA, autoimmune thyroiditis, scleroderma, polymyositis) (n = 166), 2) patients who had at least 1 first-, second-, or third-degree relative with SLE (n = 97), and 3) patients who had at least 1 first-, second-, or third-degree relative with RA (n = 67). Each of these groups was compared with the remaining patients in the cohort interviewed for familial autoimmunity who did not have relatives affected with autoimmune disease (after excluding patients who had affected relatives only of fourth or more distant degree). Thus, we compared the first group with 996 patients who did not have relatives with any autoimmune disease (15 patients had to be excluded because they had distant relatives who were affected). The second group was compared with 1,075 patients who did not have relatives with SLE (5 patients excluded), and the third group with 1,109 patients who did not have relatives with RA (1 patient excluded). Statistical analysis of each set was done by cross-tabulation of categorical variables, and statistical significance was determined by Fisher's exact test (2-tailed) or chi-square statistic. We applied the Mann-Whitney U test to test continuous variables within each of the 3 groups. Multivariate models were obtained by logistic regression analyses using clinical, ethnic, and socioeconomic variables. All models were controlled by availability of medical insurance (without or partial versus complete coverage), disease duration (years), average value on the SLE Disease Activity Index (SLEDAI) (22), and value on the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index divided by disease duration (23). Distant relatives were excluded from the analyses. The probability of an SLE patient having familial autoimmunity (at least 1 relative with SLE, RA, or any autoimmune disease) was determined by calculating the exponential of the regression coefficients in terms of odds ratio, and 95% confidence intervals and *P* values were determined.

Besides the multivariate logistic regression analysis, we constructed hierarchical log-linear models to probe and select the relevant interaction terms. We present 3 different models: one with the associated probability of having a relative with autoimmune disease, another with the associated probability of having a relative with SLE, and another with the associated probability of having a relative with RA (each binary, coded yes versus no). In these 3 models we included the same variables: the presence of avascular necrosis of bone (AVN) (binary, coded yes versus no), the use of high-dose prednisone (≥60 mg/day versus 0–59 mg/day), the ethnic group (Mestizo versus others), and the socioeconomic level (coded in 3 categories: low/medium-low versus medium versus medium-high/high). The variables and their interactions were selected using backward elimination, thus calculating the parsimonious models that were ordered by degree of complexity (generating class). Estimates of lambda parameters and their 95% confidence intervals were determined.

All statistical analyses were conducted with SPSS/PC, version 11.5 (Chicago, IL).

RESULTS

Familial autoimmunity. Through December 31, 2000, the GLADEL cohort has enrolled 1,214 patients, of whom 1,091 are female, 507 white, 537 American Indian–white Mestizo, 152 African–Latin American, and 18 of other ethnicities. Included are 316 patients from Argentina, 248 from Mexico, 207 from Brazil, 150 from Colombia, and 95 from Chile, with the rest from Cuba, Guatemala, Peru, and Venezuela.

Direct interview with the patients who agreed to participate in the present study (n = 1,177) revealed that 166 (14.1%) had relatives with an autoimmune disease, whether systemic or organ-specific. There were a total of 238 relatives with an autoimmune disease. The presence of the autoimmune disease was confirmed by direct personal interview with the affected relative in 162 instances and by telephone in 35 (14.7%); for 41 relatives, data were given only by the GLADEL patient, but the doctor deemed the information adequate. Among the relatives, there were 116 with SLE (9.9%), 79 with RA (6.7%), 23 with autoimmune thyroiditis (2.0%), 3 with scleroderma (0.3%), and 1 with polymyositis (0.08%) (Table 2). Sixteen had "other autoimmune diseases": 2 with autoimmune hemolytic anemia, 2 with primary antiphospholipid syndrome, and 1 each with polyarthritis and positive antinuclear antibodies but not yet diagnosed as SLE, type 1 diabetes mellitus and dwarfism, multiple sclerosis, primary Raynaud's phenomenon, nephrotic syndrome, primary Sjögren's syn-

Table 3. Prevalence of SLE in first-, second-, and third-degree relatives of SLE patients in the GLADEL cohort, and comparison with recorded prevalence of SLE in populations*

	Prevalence, %
SLE relatives	
First-degree	
Parents/offspring	2.7
Siblings	2.9
Second-degree (aunts/uncles/nieces/nephews)	1.95
Third-degree (cousins)	1.1
Populations	
European	0.010–0.081
African Caribbean	0.11–0.25
African American	0.375

* See Table 2 for definitions.

drome, myasthenia gravis, recent-onset polysynovitis not yet fulfilling criteria for RA, pernicious anemia, mixed connective tissue disease, rheumatic fever, psoriasis, and polyarteritis nodosa.

Of the 166 SLE patients who had relatives with autoimmune disease, 42 had more than 1 and the rest had only 1. Of the 97 patients who had at least 1 relative with SLE, 71 of these were first-degree relatives, 31 second-degree relatives, and 14 third-degree relatives. Fourteen patients had more than 1 relative with SLE. These findings provide insight with regard to the model of genetic susceptibility (6).

Unfortunately, the prevalence of SLE in general populations of Latin America, to which the SLE patients included in the GLADEL cohort belong, has received little study. The reported prevalence of SLE varies among populations, and because the GLADEL cohort is multiethnic and multinational, it would be too complex to try to consider the prevalence of SLE in each ethnic group and/or country to determine whether there is true familial aggregation. The alternative was to consider the highest recorded prevalence for SLE anywhere (0.375% in African Americans [7]). The prevalence of SLE we found in the first- and second-degree relatives of SLE patients was higher than those recorded in general populations (Table 3).

Table 4. Familial aggregation (λ) of systemic lupus erythematosus as calculated using 3 different putative prevalences in the general population (K)

	K		
Relationship	0.0005	0.001	0.005
Parents/offspring	54	27	5.4
Siblings	58	29	5.8
Aunts/uncles/ nieces/nephews	39	19.5	3.9
Cousins	22	11	2.2

Familial aggregation of SLE. Using a high putative SLE population prevalence (K) of 0.5% (higher than that reported [0.375%]), we obtained a $\lambda_{sibling}$ value of 5.8 (Table 4). We are aware that with this strict condition we were likely to obtain lower values of familial aggregation of SLE in SLE patients, but our aim was to determine without any doubt whether such aggregation exists ($\lambda > 1.0$). We also performed the analysis using an intermediate population prevalence ($K = 0.001$), as is more likely in Latin America (9–11). With it we found a $\lambda_{sibling}$ of 29.0. This value of familial aggregation is higher than those that have been found for other autoimmune diseases such as type 1 diabetes mellitus ($\lambda_{sibling}$ 15) or RA ($\lambda_{sibling}$ 8) (24). The differences in lambda values between relatives of various degrees can be used to determine the genetic model that best fits the data. According to Risch's formula (6), if the observed result for λ_{cousin} is similar to the expected one, the distribution fits a polygenic additive model. If the value decreases by a factor of >2 as relatedness becomes 1 degree more distant, a multiplicative model applies. Accordingly, we can expect a decrease from $\lambda_{sibling}$ (first-degree) 29.0 to λ_{aunt} (second-degree) <15.0 and to λ_{cousin} (third-degree) <7.2 (here and below, λ_{aunt} refers to $\lambda_{aunt/uncle/niece/nephew}$). In these analyses we obtained a λ_{aunt} value of 19.5 and a λ_{cousin} value of 11.0, which, although reflecting decreases, were decreases of less than a factor of 2 (Table 4). These data support the

Table 5. Prevalence of RA in first-, second-, and third-degree relatives of SLE patients in the GLADEL cohort, and comparison with recorded prevalence of RA in Latin American and Spanish populations*

	Prevalence, %	λ (K = 0.005–0.003)
SLE relatives		
Parents/offspring	1.6	3.2–5.3
Siblings	1.01	2.02–3.3
Grandparents	1.6	3.2–5.3
Aunts/uncles/nieces/nephews	1.10	2.1–3.5
Cousins	0.6	1.2–2.0
Population (ref.)		
Mexican: COPCORD (15)	0.4	
Mexican: Monterrey (12)	0.68	
Brazilian (14)	0.6	
Brazilian: COPCORD (15)	0.3	
Argentine: Tucumán (13)	0.2	
Chilean: COPCORD (15)	0.43	
Spanish (16)	0.5	

* The mean prevalence of RA in all Latin American populations is 0.44. COPCORD = Community Oriented Programme for the Control of Rheumatic Disease (see Table 2 for other definitions).

Table 6. Multivariate models obtained by logistic regression analysis to estimate the probability of an SLE patient in the GLADEL cohort having at least 1 relative with autoimmune disease, SLE, or RA*

Variable	Autoimmune disease			SLE			RA		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Avascular necrosis	7.0	2.2, 22.1	0.001	4.4	1.3, 15.5	0.02	5.6	1.4, 21.9	0.01
Ethnic group (Mestizo versus all others)	1.7	1.2, 2.5	0.003	1.6	1.0, 2.6	0.03	1.8	1.1, 3.1	0.03
Socioeconomic level									
Low/medium-low (referent)	1.0			1.0			1.0		
Medium	1.6	0.9, 2.9	0.11	1.9	0.9, 3.8	0.08	1.5	0.6, 3.6	0.33
Medium-high/high	2.1	1.2, 3.7	0.009	2.2	1.1, 4.3	0.02	1.8	0.8, 4.0	0.17

* All models were controlled for medical insurance (without or partial versus total coverage), disease duration (years), average SLE Disease Activity Index, and Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index value divided by disease duration). OR = odds ratio; 95% CI = 95% confidence interval (see Table 2 for other definitions).

notion of a polygenic additive model in SLE inheritance rather than a multiplicative one.

We also determined the prevalence of RA for each degree of relatedness to our SLE patients. For this we relied on better data on RA prevalence in Latin American populations (11–16) than those available for SLE. We found that the prevalence of RA in relatives of SLE patients was also higher than in general Latin American populations (1.01% in siblings and 1.6% in parents, versus 0.2–0.68% in the population) (Table 5). To determine the familial aggregation of RA in SLE patients, we calculated the lambda values using the RA prevalence in Latin American and Spanish populations (13–16). As seen in Table 5, familial aggregation of RA in SLE patients was also demonstrated ($\lambda_{sibling}$ 3.3, $\lambda_{parents}$ 5.3). The $\lambda_{sibling}$ value of 3.3 may be an underes-

Table 7. Models obtained by hierarchical log-linear analysis to probe interactions between categorical variables associated with the probability of having a relative with any autoimmune disease, systemic lupus erythematosus, or rheumatoid arthritis*

Interaction terms	*P*	Parameter†	λ	95% CI
Autoimmune disease model				
AD × AVN × SEL × HPD	0.04	1	0.0368	−0.3236, 0.3974
		2	0.1523	−0.1918, 0.4964
AVN × EG × SEL	0.02	1	0.2914	−0.0691, 0.6520
		2	−0.0728	−0.4170, 0.2712
AD × EG	0.0006	1	0.0440	−0.1960, 0.2841
SLE model				
AVN × HPD × SLE	0.02	1	0.1329	−0.1100, 0.3758
AVN × EG × SEL	0.03	1	0.2614	−0.1039, 0.6269
		2	−0.1249	−0.4652, 0.2154
EG × SLE	0.04	1	0.0712	−0.1717, 0.3141
SEL × HPD	0.006	1	0.0369	−0.3285, 0.4023
		2	−0.0342	−0.3746, 0.3060
RA model				
EG × SEL × RA	0.02	1	−0.1702	−0.5650, 0.2246
		2	−0.0567	−0.4088, 0.2953
AVN × EG × SEL	0.02	1	0.3412	−0.0536, 0.7360
		2	−0.0894	−0.4415, 0.2626
SEL × HPD × RA	0.02	1	−0.1773	−0.5722, 0.2174
		2	−0.1231	−0.4752, 0.2289
AVN × RA	0.02	1	0.5774	0.3213, 0.8336

* λ = difference between observed and expected natural log values; 95% CI = 95% confidence interval; AD = having a relative with autoimmune disease (yes versus no); AVN = avascular necrosis of bone (yes versus no); SEL = socioeconomic level (low/medium-low versus medium versus medium-high/high); HPD = high prednisone dose (≥60 mg/day); EG = ethnic group (Mestizo versus others); SLE = having a relative with systemic lupus erythematosus (yes versus no); RA = having a relative with rheumatoid arthritis (yes versus no).

† When SEL is included, a second parameter is necessary because there are >2 variables within this category.

timate and is more likely to be closer to the 5.3 found in parents/offspring.

Characteristics of SLE patients with familial autoimmunity. When we compared SLE patients who did and those who did not have relatives with autoimmune disease, we found no difference by sex but found an interesting association between having a relative with autoimmune disease and increased years of education ($P = 0.006$). A higher percentage of Mestizo SLE patients had relatives with autoimmune disease (54.9%) compared with non-Mestizo patients (41.1%) ($P = 0.001$). SLE patients from Chile also had a higher percentage of relatives with autoimmune disease (15.2%) than SLE patients not from Chile (6.9%) ($P = 0.001$) and the same was true for SLE patients from Mexico versus those not from Mexico (25.0% versus 17.9%; $P = 0.04$), but this was not found for any other Latin American country. These associations between having a relative with autoimmune disease and ethnicity or nationality remained significant when only relatives with SLE ($P = 0.02$ and $P = 0.001$, respectively) or with RA ($P = 0.02$ and $P = 0.02$, respectively) were considered. We could not determine the role of family size.

When we adjusted the SLICC/ACR index (23) for disease duration, we did not find differences between SLE patients with and those without relatives with autoimmune disease, SLE, or RA. Mean values on the SLEDAI (22) and Mexican SLEDAI (25) were also not significantly different between groups. There were no differences between patients with SLE relatives, RA relatives, and/or familial autoimmunity in terms of age at disease onset or at diagnosis or the number of ACR classification criteria for SLE fulfilled (26).

In multivariate logistic regression analyses, the probability of an SLE patient having familial autoimmunity was found to be strongly and persistently associated with the presence of AVN, as well as with ethnic group (Mestizo) and higher socioeconomic level, independent of the availability of medical insurance, disease duration, average SLEDAI score, and SLICC/ACR index adjusted by disease duration (Table 6). The same pattern (presence of AVN, Mestizo ethnicity, and higher socioeconomic level) was found to be associated with a higher probability of having a relative with SLE or RA (Table 6).

Results of the hierarchical log-linear analysis are shown in Table 7. In the 3 models, the variables autoimmune disease, SLE, and RA appear in the highest-order interaction terms. Also in these models, AVN stood out for all 3 diseases, albeit in different generating class. For example, in the first model, constructed for autoimmune disease, the highest-order interaction included autoimmune disease, AVN, socioeconomic level, and high prednisone dose. In the second model, for SLE, the highest-order interaction included SLE, AVN, and high-dose prednisone. In the third model, for RA, the highest-order interaction did not include AVN, but only the presence of RA, ethnic group, and socioeconomic level. The interaction of AVN and high-dose prednisone was found to be relevant in the autoimmune disease and SLE models.

DISCUSSION

In the present study we determined that there is familial aggregation of SLE and of RA in SLE patients, since the prevalence of these diseases among members of the families of the GLADEL cohort were higher than those found in the corresponding populations, even when the calculations were made considering the highest population prevalence. Although these familial aggregations in SLE had been suspected (27), they had not actually been proven. Familial aggregation of autoimmune disease has also been found in multiple sclerosis, including a trend toward the presence of relatives with SLE in multiple sclerosis "multiplex" families (21). The familial aggregation of SLE that we found in the GLADEL cohort (λ 29) when considering an intermediate population prevalence, as is most likely in Latin America, is similar to, or even higher than, that found among patients with other autoimmune diseases (24) and was still important (λ 5.8) when we considered a high-prevalence population.

Interestingly, the familial aggregation of RA found in SLE patients is similar to that reported in RA families (24). The lower prevalence of RA in siblings than in parents of lupus patients in our cohort may reflect the young age of siblings of patients who have SLE of recent onset, since the mean age at onset of RA is higher than that for SLE.

There were other autoimmune diseases among the relatives of our SLE patients, providing evidence of familial aggregation when all autoimmune diseases were investigated; the $\lambda_{sibling}$ of 1.50 was similar to that found for general autoimmunity in relatives of multiple sclerosis patients (λ 1.65) (21). The striking variety of autoimmune disease found among first-, second-, and third-degree relatives of our SLE patients is an intriguing finding whose significance remains to be investigated.

It had already been known that SLE patients may have relatives with the disease (28–31), and studies of multiplex families have been helpful in the identification

of genes involved in predisposition to lupus (32). It was important, however, to rule out coincidence in the make-up of such families, as we did in this study. Healthy relatives of SLE patients may also have antinuclear antibodies (ANAs), including anti–double-stranded DNA (anti-dsDNA), at a significantly higher prevalence than controls (33), although autoantibodies within families of SLE patients are not always directed against the same nuclear antigens (34) and relatives of SLE patients who have antinucleosome, but not anti-dsDNA, antibodies are usually ANA-free (33). In multiplex SLE families, however, both the autoantibodies and the organ involvement present in the affected members tend to be similar (35). This is also the case in different ethnic groups in which antibody profiles and organ involvement tend to be similar in affected members of multiplex families within the group, thus indicating an important genetic role for autoantibody profiles; this is supported by the findings of a study of monozygotic twins concordant for SLE (36).

It is also of interest that lymphocytotoxic autoantibodies have been found in both consanguineous and nonconsanguineous family members of SLE patients (37,38), particularly those living in the same household, whose SLE proband had active disease at the time of the study (38). This suggests that caution should be exercised in the interpretation of our findings as being merely genetic, since environmental factors, shared by families, may also apply (1), and even genetically identical siblings (e.g., monozygotic twins) can be discordant for SLE (36,39). Relatives of SLE patients, particularly those belonging to multiplex families, may also have immune dysregulation, with increased production of interleukin-10 (40). In addition, it has been observed that SLE patients may have comorbidity with other autoimmune conditions such as autoimmune thyroiditis (41), and it has previously been suggested that there is an increased prevalence of other autoimmune diseases among relatives of SLE patients, or of SLE among relatives of patients with other autoimmune conditions (21). The number of affected individuals, however, is not large enough to permit ascertainment, in smaller studies, of whether the occurrence of SLE or other autoimmune conditions in more than 1 member of a family is merely coincidental.

To our knowledge, no previous study has adequately addressed the question of true familial aggregation of autoimmune disease (SLE, RA, or other) in SLE that could indicate the effect of genetic and/or shared environmental factors that cause it. If and when such a study is done, the investigators should take into account the fact that our study of relatives was based on their clinical diagnoses of autoimmune disease rather than on their fulfillment of classification criteria as is commonly done (in, for instance, the classification of patients as having SLE for enrollment in the GLADEL cohort).

Familial aggregation of autoimmune diseases other than SLE in SLE patients may have several explanations: it could indicate on the one hand the participation of a gene or genes that predispose to or favor the development of autoimmune disease in general (1,4,42–45), and/or on the other hand that these families also carry predisposing genes for each of the diseases their members express. These could include genes belonging to the major histocompatibility complex (HLA), CTLA-4 (43), complement genes, the RUNX family genes recently shown to be related to SLE, RA, and psoriasis (44), and/or the possible human equivalent of the *Pia* loci that cause susceptibility, in rats, to autoimmunity induced by the environmental agent pristane (46). One hundred sixty-six (14.1%) of our SLE patients had relatives with an autoimmune disease (SLE, RA, autoimmune thyroiditis, or other), and 42 of these 166 (25%) had at least 2 relatives with an autoimmune disease (the same or different ones); 1 patient had 5 affected relatives (4 first-degree [2 with RA, 1 with SLE, 1 with autoimmune thyroiditis] and 1 third-degree [RA]). In an earlier, smaller study of patients with SLE (47), family histories of autoimmune disease, including SLE (18%), RA (11%), and Hashimoto thyroiditis (2%), were also found. Studies in autoimmune mice have also shown a high susceptibility not only to the primary disease (e.g., type 1 diabetes in NOD mice), but to several autoimmune diseases or their autoantibody marker(s) (48).

The prospective nature and the multinational character of the GLADEL cohort also permitted us to seek differences between patients who had familial autoimmunity and those who did not. In multivariate logistic regression analyses, we found a significantly higher frequency of familial autoimmunity in SLE patients of the Mestizo ethnic group than the other ethnic groups. A higher socioeconomic level also was statistically significantly and independently associated with a higher probability of having relatives with SLE and/or other autoimmune diseases. Stepwise logistic regression analyses revealed that AVN was consistently and powerfully associated in the 3 models (autoimmune disease, SLE, and RA).

In the hierarchical log-linear analysis, we confirmed the association of the presence of AVN in the SLE patients who had relatives with SLE, RA, and/or

autoimmune disease, in interaction with the use of high-dose prednisone, ethnic group, and socioeconomic level at different orders of interaction terms. High-dose prednisone and AVN interacted in 2 models (SLE and autoimmune disease). The fact that the Mestizo ethnic group and the highest socioeconomic level appeared in these models could indicate a role of both genetic and environmental factors in the probability of an SLE patient having relative(s) with SLE, RA, and/or any autoimmune disease. We also found that familial autoimmunity was significantly associated with higher education, perhaps indicating that more educated patients could better identify their relatives with familial autoimmunity, which would imply that there may be some degree of underreporting of familial autoimmunity in our study, particularly by those patients at lower socioeconomic and/or education levels. Some of these differences could also be due to different sharing of environmental risk factors by different families, which could alter the frequency of autoimmune disease in some of them.

Obviously, the number, sex, and ages of possible family members who can develop autoimmune disease would affect the frequency of autoimmune disease in families. However, as clearly shown in Table 4, the main factor influencing familial aggregation (λ) of autoimmune disease in our SLE patients was the degree of relatedness, which, in turn, would influence age since siblings would be younger than parents or aunts/uncles. Thus, we sought to determine the applicable genetic model for SLE by using the prevalence for relatives of each degree. Our calculations indicated that an additive model best fits the data for SLE. This is different from other autoimmune diseases, such as type 1 diabetes mellitus, where a multiplicative model has been proposed (49). This information may help in predicting the best type of approach to the identification of SLE-related genes. A pure additive model is similar to a single-gene model, and therefore, extended pedigrees would be more useful than sibling pairs to identify the genetic components (6). Studies with larger numbers of sibling pairs are therefore needed in order to approach a situation similar to that provided by extended pedigrees. This model suggests that to develop SLE, regardless of the environmental factors involved, an individual would have to have the susceptibility variants from 1 or more genes, whereas epistatic effects (genetic interactions) may be of lesser importance.

Our results regarding the familial aggregation of RA in SLE support the notion of their genetic overlap. This could also occur with other autoimmune diseases, as suggested in a genome-wide screen of multiplex RA families (3). However, the fact that RA is a more complex disease, in which an environmental component appears to be of major importance (50), must also be taken into consideration.

Our findings of familial aggregation not only of SLE, but also of RA and autoimmune disease in general, in SLE patients, together with the findings reported by us and others of autoantibodies and immune dysregulation in SLE relatives and of comorbid autoimmune conditions in individual patients, may indicate that the occurrence of the so-called overlap syndromes, i.e., the association of SLE with RA ("rhupus") (51), of Sjögren's syndrome with RA, SLE, or primary biliary cirrhosis (52,53), or of primary biliary cirrhosis with the CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias) variant of scleroderma (Reynolds' syndrome) (54) represent the same process at the individual versus the family level. These, as well as observations using animal models of autoimmune disease (4,48), provide clues regarding the interplay of autoimmunity-predisposing genes.

This publication is dedicated to the memory of Dr. Donato Alarcón-Segovia, whose teachings and ideals were an example and guidance to all of us.

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REFERENCES

1. Alarcon-Segovia D, Alarcon-Riquelme ME. Etiopathogenesis of systemic lupus erythematosus: itineraries of three troikas. In: Lahita RG, editor. Systemic lupus erythematosus. 4th ed. San Diego: Elsevier; 2004. p. 93–107.
2. Alarcon-Riquelme ME. Family studies in systemic lupus erythematosus. Rheumatology (Oxford) 2002;41:364–6.
3. Jawaheer D, Seldin MF, Amos CI, Chen WV, Shigeta R, Monteiro J, et al. A genomewide screen in multiplex rheumatoid arthritis families suggests genetic overlap with other autoimmune diseases. Am J Hum Genet 2001;68:927–36.
4. Bergsteindottir K, Yang HT, Petterson U, Holmdahl R. Evidence of common autoimmune disease genes controlling onset, severity, and chronicity based on experimental models of multiple sclerosis and rheumatoid arthritis. J Immunol 2000;164:1564–8.
5. Pons-Estel B, Catoggio LJ, Cardiel MH, Soriano ER, Gentiletti S, Villa AR, et al, and the Grupo Latino americano de Estudio del Lupus. The GLADEL multinational Latin American prospective inception cohort of 1,214 patients with systemic lupus erythematosus: ethnic and disease heterogeneity among "Hispanics." Medicine (Baltimore) 2004;83:1–17.

6. Risch N. Linkage strategies for genetically complex traits. I. Multilocus models. Am J Hum Genet 1990;46:222–8.
7. Petri M. Epidemiology of systemic lupus erythematosus. Best Pract Res Clin Rheumatol 2002;16:547–58.
8. Nossent HC. Systemic lupus erythematosus in the arctic region of Norway. J Rheumatol 2001;28:539–46.
9. Cardiel MH, Rojas-Serrano J. Community based study to estimate prevalence, burden of illness and help seeking behavior in rheumatic diseases in Mexico City: a COPCORD study. Clin Exp Rheumatol 2002;20:617–24.
10. Ferraz MB. Epidemiology and community studies: Latin America. Baillieres Clin Rheumatol 1995;9:1–9.
11. Reyes-Llerena GA, Guibert-Toledano M, Hernandez-Martinez AA, Gonzalez-Otero ZA, Alcocer-Varela J, Cardiel MH. Prevalence of musculoskeletal complaints and disability in Cuba: a community based study using the COPCORD core questionnaire. Clin Exp Immunol 2000;18:736–42.
12. Sauza del Pozo J, Martinez E, Salas R, Garcia D. Prevalencia de la artritis reumatoidea en la población mexicana [abstract]. Rev Mex Reumatol 1991;6:55.
13. Spindler A, Bellomio V, Berman A, Lucero E, Baigorria M, Paz S, et al. Prevalence of rheumatoid arthritis in Tucuman, Argentina. J Rheumatol 2002;29:1166–70.
14. Marques Neto J, Texeira Goncalves H, de Oliveira Barros L, Lobato Cunha M, Radominski S, de Oliveira S, et al. Estudo multicentrico do prevalência da artrite reumatóide do adulto em amostras da populaçâo brasileira. Rev Brasileira Reumatol 1993; 33:169–73.
15. Bennett K, Cardiel MH, Ferraz MB, Riedmann P, Goldsmith CH, Tugwell P, for the The PANLAR-COPCORD Working Group Community screening for rheumatic disorder: cross cultural adaptation and screening characteristics of the COPCORD Core Questionnaire in Brazil, Chile, and Mexico. J Rheumatol 1997;24: 160–8.
16. Carmona L, Villaverde V, Hernandez-Garcia C, Ballina J, Gabriel R, Laffon A, and the EPISER Study Group. The prevalence of rheumatoid arthritis in the general population of Spain. Rheumatology (Oxford) 2002;41:88–95.
17. Willkens RF, Blandau RL, Aoyama DT, Beasley RP. Studies of rheumatoid arthritis among a tribe of Northwestern Indians. J Rheumatol 1976;3:9–14.
18. Harvey J, Arnett FC, Bias WB, Hsu SH, Stevens MB. Heterogeneity of HLA-DR4 in the rheumatoid arthritis of a Chippewa band. J Rheumatol 1981;8:797–803.
19. Del Puente A, Knowler WC, Pettit DJ, Bennett PH. High incidence and prevalence of rheumatoid arthritis in Pima Indians. Am J Epidemiol 1989;129:1170–8.
20. Jacobson DL, Gange SJ, Rose NR, Graham NM. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin Immunol Immunopathol 1997;84: 223–43.
21. Broadley SA, Deans J, Sawcer SJ, Clayton D, Compston DA. Autoimmune disease in first degree relatives of patients with multiple sclerosis: a UK survey. Brain 2000;123:1102–11.
22. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH, and the Committee on Prognosis Studies in SLE. Derivation of the SLEDAI: a disease activity index for lupus patients. Arthritis Rheum 1992;35:630–40.
23. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum 1996;39:363–9.
24. Vyse TJ, Todd JA. Genetic analysis of autoimmune disease. Cell 1996;85:311–8.
25. Guzman J, Cardiel MH, Arce-Salinas A, Sanchez-Guerrero J, Alarcon-Segovia D. Measurement of disease activity in systemic lupus erythematosus: prospective validation of 3 clinical indices. J Rheumatol 1992;19:1551–8.
26. Tan EM, Cohen AS, Fries J, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–7.
27. Hochberg MC. The application of genetic epidemiology to systemic lupus erythematosus. J Rheumatol 1987;14:867–9.
28. Giles I, Isenberg D. Lupus in the family: analysis of a cohort followed from 1978 to 1999. Lupus 2001;10:38–44.
29. Eroglu GE, Kohler PF. Familial systemic lupus erythematosus: the role of genetic and environmental factors. Ann Rheum Dis 2002;61:29–31.
30. Cooper GS, Dooley MA, Treadwell EL, St Clair EW, Gilkeson GS. Risk factors for development of systemic lupus erythematosus: allergies, infections, and family history. J Clin Epidemiol 2002;55: 982–9.
31. Sato EI, Atra E, Gabriel A Jr, Masi AT. Systemic lupus erythematosus: a family study of 25 probands. Clin Exp Rheumatol 1991;9:455–61.
32. Prokunina L, Castillejo-Lopez C, Oberg F, Gunnarsson I, Berg L, Magnusson V, et al. A regulatory polymorphism within the PDCD1gene is associated with susceptibility to systemic lupus erythematosus in humans. Nat Genet 2002;32:666–9.
33. Mohan C, Liu F, Xie C, Williams RC Jr. Antisubnucleosome reactivities in systemic lupus erythematosus (SLE) patients and their first degree relatives. Clin Exp Immunol 2001;123:119–26.
34. Van der Linden MW, Westendorp RG, Zidane M, Meheus L, Huizinga TW. Autoantibodies within families of patients with systemic lupus erythematosus are not directed against the same nuclear antigens. J Rheumatol 2001;28:284–7.
35. Quintero-del-Rio AI, Bacino D, Kelly J, Aberle T, Harley JB. Familial systemic lupus erythematosus: a comparison of clinical manifestations and antibody presentation in three ethnic groups. Cell Mol Biol 2001;47:1223–7.
36. Reichlin M, Harley JB, Lockshin MD. Serologic studies of monozygotic twins with systemic lupus erythematosus. Arthritis Rheum 1992;35:457–64.
37. DeHoratius RJ, Messner RP. Lymphocytotoxic antibodies in family members of patients with systemic lupus erythematosus. J Clin Invest 1975;55:1254–8.
38. DeHoratius RJ, Alarcon-Segovia D, Messner RP, Fishbein E. Lymphocytotoxic antibodies in Mexican patients with systemic lupus erythematosus and their families: relationship of disease activity in the probands to antibody cytotoxicity in their relatives Rev Invest Clin 1981;33:161–4.
39. Deapen D, Escalante A, Weinrib L, Horwitz D, Bachman B, Roy-Burman P, et al. A revised estimate of twin concordance in systemic lupus erythematosus. Arthritis Rheum 1992;35:311–8.
40. Llorente L, Richaud-Patin Y, Couderc J, Alarcon-Segovia D, Ruiz-Soto R, Alcocer-Castillejos N, et al. Dysregulation of interleukin-10 production in relatives of patients with systemic lupus erythematosus. Arthritis Rheum 1997;40:1429–35.
41. Pyne D, Isenberg DA. Autoimmune thyroid disease in systemic lupus erythematosus. Ann Rheum Dis 2002;61:70–2.
42. Levin L, Tomer Y. The etiology of autoimmune diabetes and thyroiditis: evidence for common genetic susceptibility. Autoimmun Rev 2003;2:377–86.
43. Ueda H, Howson JM, Esposito L, Heward J, Snook H, Chamberlain G, et al. Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. Nature 2003;423:506–11.
44. Alarcon-Riquelme ME. A RUNX trio with a taste for autoimmunity. Nat Genet 2003;35:299–300.
45. Ban Y, Tomer Y. The contribution of immune regulatory and thyroid specific genes to the etiology of Graves' and Hashimoto's thyroiditis. Autoimmunity 2003;36:367–79.
46. Olofsson P, Holmberg, Patterson U, Holmdahl R. Identification

and isolation of dominant susceptibility loci for pristane-induced arthritis. J Immunol 2003;171:407–16.
47. Pistiner M, Wallace DJ, Nessim S, Metzger AL, Klinenberg JR. Lupus erythematosus in the 1980s: a survey of 570 patients. Semin Arthritis Rheum 1991;21:55–64.
48. Johansson AC, Lindqvist B, Johannesson M, Holmdahl R. Genetic heterogeneity of autoimmune disorders in the nonobese diabetic mouse. Scand J Immunol 2003;57:203–13.
49. Cordell HJ, Todd JA, Bennet ST, Kawaguchi Y, Farrall M. Two-locus maximum lod score analysis of a multifactorial trait: joint consideration of IDDM2 and IDDM4 with IDDM1 in type 1 diabetes. Am J Hum Genet 1995;57:920–34.
50. Gregersen P. Genetics of rheumatoid arthritis: confronting complexity. Arthritis Res 1999;1:37–44.
51. Panush RS, Edwards LN, Longley S, Webster E. "Rhupus" syndrome. Arch Intern Med 1988;148:1633–6.
52. Alarcon-Segovia D, Ibanez G, Velazquez-Forero F, Hernandez-Ortiz J, Gonzalez Jimenez Y. Sjögren's syndrome in systemic lupus erythematosus: clinical and subclinical manifestations. Ann Intern Med 1974;81:577–83.
53. Alarcon-Segovia D, Diaz-Jouanen E, Fishbein E. Features of Sjögren's syndrome in primary biliary cirrhosis. Ann Intern Med 1973;79:31–6.
54. Hirakata M, Akizuki M, Miyashi K, Matsushima H, Okano T, Homma M. Coexistence of CREST syndrome and primary biliary cirrhosis: serologic studies of two cases. J Rheumatol 1988;15: 1166–70.

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