Familial Autoimmunity in Systemic Sclerosis — Results of a French-based Case-Control Family Study

EUGÉNIE KOUMAKIS, PHILIPPE DIEUDÉ, JÉRÔME AVOUAC, ANDRÉ KAHAN, YANNICK ALLANORE, and Association des Sclérodermiques de France

ABSTRACT. ***Objective.*** To assess the prevalence of autoimmune diseases in first-degree relatives of patients with systemic sclerosis (SSc), and to compare those results with control families in order to identify patterns of autoimmune diseases in relatives.

Methods. A retrospective case-control postal questionnaire survey was performed in France to recruit patients with SSc belonging to an association of patients with SSc and unrelated age-matched and sex-matched controls. Each participant was asked to self-report on the existence of autoimmune diseases in their first-degree relatives. The prevalence of autoimmune diseases in the families of patients with SSc was compared with the corresponding prevalence in the families of controls.

Results. A total of 121 families out of 373 (32.4%) with a member having SSc reported at least 1 autoimmune disease in 1 or more first-degree relatives. The most frequent autoimmune diseases in SSc families when adjusted for family size were autoimmune thyroid disease (AITD; 4.9%), rheumatoid arthritis (4.1%), psoriasis (3.9%), and type 1 diabetes mellitus (2.9%). Compared with control families, AITD and connective tissue diseases (SSc, systemic lupus erythematosus, or Sjögren's syndrome) were more likely to occur in families with SSc ($p = 0.01$ and $p = 0.01$, respectively), with OR of 3.20 (95% CI 1.25–8.18) and 5.20 (95% CI 1.22–21.8). In contrast, inflammatory bowel disease was less likely to occur within families with SSc ($p = 0.02$, OR 0.29, 95% CI 0.11–0.80). In addition, the coexistence of more than 1 autoimmune disease in the index SSc case was associated with familial aggregation of autoimmune diseases.

Conclusion. Our results show that autoimmune diseases cluster within families of patients with SSc. This supports the notion that these diseases might arise on a shared genetic basis underlying several autoimmune phenotypes. (J Rheumatol First Release Jan 15 2012; doi:10.3899/jrheum.111104)

Key Indexing Terms:
FAMILIAL AGGREGATION
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Systemic sclerosis (SSc) is a complex systemic autoimmune disease in which both genetic and environmental factors contribute to disease susceptibility. Numerous genetic factors underlying susceptibility to SSc have been identified recently, the vast majority having to do with autoimmune pathways[1]. Most of these susceptibility loci have also been identified in other autoimmune diseases[2], supporting the existence of a genetic overlap between SSc and other autoimmune diseases and the concept of shared autoimmunity. Given the various overlap syndromes and the occurrence of more than 1 autoimmune disease in the same individual (polyautoimmunity), particular genetic loci may be involved in different spectra of autoimmune diseases, leading to the pleiotropic paradigm, whereas other genes may contribute to the specific phenotype, therefore favoring the heterogeneity of these disorders.

Clustering of multiple autoimmune diseases within families is increasingly recognized in a number of autoimmune disorders[3,4,5,6,7,8,9]. The coexistence of multiple autoimmune diseases within patients with SSc (polyautoimmunity) is well established[10,11,12]. In a cross-sectional study of 2 samples of patients with SSc from Canada and Colombia[11], 273 out of 719 patients (38%) had at least 1 coexisting autoimmune disease. The most frequently reported were autoimmune thyroid disease (AITD; 38%), rheumatoid arthritis (RA; 21%), Sjögren's syndrome (SS; 18%), and primary biliary cirrhosis (4%)[11]. These results were confirmed in a large white European cohort[12]: among 1132 patients with SSc, 239 (21%) developed at least 1 other autoimmune disease. However, there are few data regarding familial aggregation in SSc. Although a preliminary study on 1037 patients with SSc of Northern European descent suggested that first- and second-degree relatives of patients with SSc

From the Paris Descartes University, Rheumatology A Department, Cochin Hospital, APHP; and the Université Paris Diderot, Rheumatology Department, Hôpital Bichat Claude-Bernard, Paris, France.

E. Koumakis, MD, Paris Descartes University, Rheumatology A Department, Cochin Hospital, APHP; P. Dieudé, MD, PhD, Université Paris Diderot, Rheumatology Department, Hôpital Bichat Claude-Bernard; J. Avouac, MD, PhD; A. Kahan, MD, PhD; Y. Allanore, MD, PhD, Paris Descartes University, Rheumatology A Department, Cochin Hospital, APHP.

Address correspondence to Dr. Y. Allanore, Service de Rhumatologie A, Hôpital Cochin, 27 rue du Faubourg Saint-Jacques, 75014 Paris, France. E-mail: yannick.allanore@cch.aphp.fr

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were more likely than controls to have other autoimmune conditions[13], data on the clustering of specific autoimmune phenotypes in families with SSc are scarce. To our knowledge and to date, only 2 studies have been reported on autoimmune disease familial aggregation of SSc probands[11,14]. A case-control study in a US cohort suggested a familial aggregation of systemic lupus erythematosus (SLE) and AITD in first-degree relatives of 1071 patients with SSc[14]. AITD was reported to be the second most frequent autoimmune disease in SSc relatives in a combined Canadian and Colombian cohort consisting of 719 patients[11]. However, this study did not include a control dataset. Moreover, the European population has not been investigated to date, and there are epidemiological discrepancies in the prevalence of autoimmune disease according to ethnicity together with heterogeneity of genetic bases according to origins.

Further characterization of the extent to which particular combinations of autoimmune diseases occur in a European population may offer insight into shared risk factors and shared pathophysiological pathways. As part of continuing studies in SSc, a retrospective case-control postal questionnaire survey was conducted with the participation of the Association des Sclérodermiques de France (ASF), in order to assess familial aggregation in SSc and to identify patterns of coexisting autoimmune diseases in first-degree relatives of patients with SSc.

MATERIALS AND METHODS

Study participants. Our study was performed in France. Our aim was to gather information on the existence of autoimmune diseases in patients with SSc (index case), in first-degree relatives of patients with SSc, in unrelated controls, and in their first-degree relatives. Patients with SSc were enrolled between December 2010 and June 2011 through the ASF. Information was obtained from the 1 index case per family with a standardized anonymous questionnaire adapted from a previously published study on the Multiple Autoimmune Disease Genetics Consortium collection[4]. Each patient was asked to report on the presence of autoimmune diseases in his/her relatives. Controls were selected by the index cases from a healthy brother-in-law or sister-in-law or neighbor or friend of the same age and sex, with no autoimmune disease[15]. The inclusion process is detailed in Figure 1. The questionnaire requested information about 17 autoimmune or immune-mediated disorders, including autoimmune hepatitis, AITD including Hashimoto's thyroiditis and Graves' disease, celiac disease, inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis, juvenile idiopathic arthritis, multiple sclerosis, primary biliary cirrhosis, pernicious anemia, psoriasis, psoriatic arthritis, RA, SS, SSc, SLE, type 1 diabetes mellitus, and vitiligo. Patients and controls with a positive family history of autoimmune disease were asked (1) to identify members of their family, including parents, siblings, and offspring, with a history of 1 or more of 17 diseases listed in the questionnaire; (2) to specify the number of relatives for each degree of relationship; and (3) to specify the number of relatives for each degree of relationship for whom they had medical information.

Statistical analysis. Descriptive statistics were used to summarize patients' characteristics. Control individuals with a personal history of any of the 17 listed diseases were excluded from the statistical analysis. The familial rates of autoimmune disease were calculated using the number of index cases and controls reporting at least 1 family member with 1 or more of the listed diseases. To calculate the prevalence of each autoimmune disease within SSc and control families, we used the number of affected individuals within first-degree relatives (index cases were excluded). The number of first-degree relatives within these families was used as the denominator. If several autoimmune diseases were reported in the same family member,

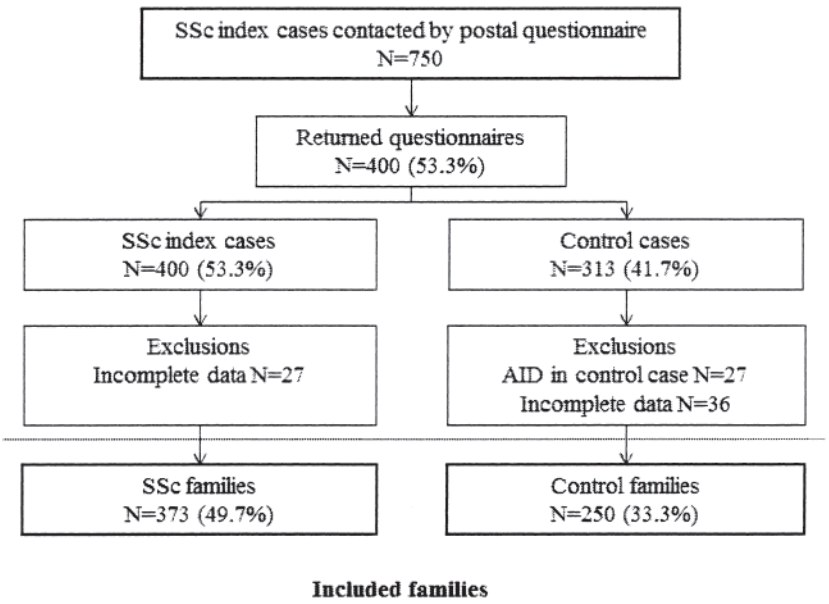

Figure 1. The recruitment of systemic sclerosis and control families through a postal questionnaire sent by the Association des Sclérodermiques de France. Unrelated controls were selected by index cases from a choice of healthy brother-in-law or sister-in-law or neighbor or friend of the same age and sex. Controls were excluded if they reported any of the 17 autoimmune diseases listed in the standard questionnaire.

this was counted separately as different cases corresponding to each autoimmune disease. The comparison of the adjusted prevalence of each autoimmune disease between SSc and control families was conducted by chi-square test or Fisher's exact test when appropriate, using the MedCalc statistical software (MedCalc 11.6.1, Mariakerke, Belgium). A standard measure of familial aggregation is the recurrence-risk ratio (denoted "λ") of disease in relatives of an index case, defined as the risk of disease in relatives of a random individual with disease, divided by the population prevalence of the disease. Hence, the recurrence-risk ratio of autoimmune disease in families (λ_R) was calculated for first-degree relatives using the formula $\lambda_R = K_{Relative}/K$, where $K_{relative}$ (K_R) was the prevalence in SSc families, and K was the prevalence in the control sample. We attempted to identify predictors of familial autoimmunity using a logistic regression analysis. OR were calculated with 95% CI. A p value < 0.05 was considered statistically significant.

RESULTS

Demographic characteristics of SSc index cases and controls (Table 1). Out of 750 questionnaires sent to patients with SSc by the ASF, 400 SSc families and 313 control families participated in the study (Figure 1). Twenty-seven SSc families were excluded because of incomplete response to autoimmune disease status within family members. Sixty-three control families were excluded because control index cases had a positive history of autoimmune disease or because of incomplete data regarding autoimmune disease status in family members. Of the 373 SSc index cases analyzed, 87.7% were women, 45.3% had limited cutaneous disease, and 54.7% had diffuse cutaneous disease. The mean age of patients with SSc was 61.1 ± 13.0 years. A total of 164 (44.0%) SSc index cases reported at least 1 coexisting autoimmune disorder; 35 (9.4%) reported 2, and 9 (2.4%) reported 3 or more. The most common diseases were SS (19.3%), AITD (13.1%), and RA (11.0%; Table 2). A total of 250 control cases were analyzed. The mean age of control individuals was 57.5 ± 13.4 years, and 211 (84.4%) were women. The sex distribution among the SSc and control cohorts interviewed was comparable (p = 0.27). As both cohorts were age-matched in the study, the age distribution of their relatives was also assumed to be comparable. The total number of first-degree relatives in families with AID was higher in the SSc group than in the control group, but there were no differences in the mean number of first-degree relatives, mean number of siblings, mean number of offspring per family, and in the percentage of medical information available in relatives between SSc and control groups (Table 1), suggesting limited ascertainment bias for the presence of autoimmune disease due to family size.

Familial autoimmunity within SSc families. A total of 121 (32.4%) of 373 SSc families reported at least 1 case of a first-degree relative with an autoimmune disease, whereas 252 (67.6%) families had no history of autoimmunity other than SSc. Within these 121 families, data were collected for 823 first-degree members, including 215 children, 366 siblings, and 242 parents. The number of autoimmune diseases reported was 192, in a total of 178 first-degree relatives. Out of the 373 SSc families included in our study, 9 (2.4%) were multiplex SSc families, reporting at least 2 cases of SSc (index case included). One family reported 3 cases of SSc (including the index case) and 1 case of SS, and the index case reported a personal history of RA and SS. In addition to SSc, 36 families (9.7%) reported 2 or more autoimmune diseases, 15 (4.0%) reported 3 or more autoimmune diseases, and 6 (1.6%) reported 4 or more autoimmune diseases in first-degree relatives. The distribution of autoimmune diseases in first-degree relatives among SSc and control cohorts investigated is summarized in Table 3. We estimated the familial prevalence for each individual disease using the first-degree relatives of SSc families reporting at least 1 autoimmune disease in first-degree relatives. AITD was the most common autoimmune disease in SSc family members

Table 1. Characteristics of systemic sclerosis index cases and controls.

Characteristics	Index Cases, n = 373	Controls, n = 250	p
Women, n (%)	327 (87.7)	211 (84.4)	0.27
Mean age, yrs (SD)	61.1 (13.0)	57.5 (13.4)	0.98
No. families with at least 1 autoimmune disease (%)	121 (32.4)	49 (19.6)	0.0006
No. first-degree relatives	823	318	
Mean no. first-degree relatives (SD)	6.8 (2.9)	6.5 (2.5)	0.18
Mean no. offspring (SD)	1.8 (1.3)	2.1 (1.1)	0.10
Mean no. siblings (SD)	3.0 (2.3)	2.4 (2.1)	0.08
No. first-degree relatives with available medical history (%)	679 (82.5)	271 (85.0)	0.35

Table 2. Prevalence of associated autoimmune diseases within systemic sclerosis (SSc) index cases (n = 373).

Concomitant Autoimmune Diseases	Index SSc Cases, n (%)
No.	
≥ 1	164 (44.0)
≥ 2	35 (9.4)
≥ 3	9 (2.4)
Disease type, n (%)	
Sjögren's syndrome	72 (19.3)
Autoimmune thyroid disease	49 (13.1)
Rheumatoid arthritis	41 (11.0)
Vitiligo	18 (4.8)
Systemic lupus erythematosus	13 (3.5)
Psoriasis	12 (3.2)
Primary biliary cirrhosis	8 (2.1)
Pernicious anemia	5 (1.3)
Celiac disease	4 (1.1)
Inflammatory bowel disease	3 (0.8)
Autoimmune hepatitis	3 (0.8)
Type 1 diabetes mellitus	2 (0.5)
Psoriatic arthritis	1 (0.3)
Juvenile idiopathic arthritis	0
Multiple sclerosis	0

Table 3. Prevalence of specific autoimmune diseases adjusted to family size in first-degree relatives (FDR) of systemic sclerosis (SSc) index cases and matched controls. Data correspond to the total number of FDR with each autoimmune disease, and the percentages are the family size-adjusted prevalences of autoimmune diseases in FDR. Familial aggregation (λ_R) was calculated using the formula $\lambda_R = K_{relative}/K$, where $K_{relative}$ is the prevalence of autoimmune diseases in FDR of patients with SSc, and K is the prevalence of FDR of control cases. Autoimmune thyroid disease includes Hashimoto's thyroiditis and Graves' disease. Connective tissue diseases include Sjögren's syndrome, systemic lupus erythematosus, and SSc.

Autoimmune Diseases, n (%)	FDR* of SSc Patients, n = 823	FDR of Controls, n = 318	p	Familial Aggregation (λ_R)
Autoimmune thyroid disease	40 (4.9)	5 (1.6)	0.01**	3.1
Connective tissue disease	26 (3.2)	2 (0.6)	0.01**	5.0
Rheumatoid arthritis	34 (4.1)	11 (3.5)	0.76	1.2
Psoriasis	32 (3.9)	16 (5.0)	0.49	0.8
Type 1 diabetes mellitus	24 (2.9)	10 (3.2)	1.0	0.9
Hashimoto's thyroiditis	26 (2.8)	3 (0.9)	0.04**	3.0
Graves' disease	11 (1.9)	2 (0.6)	0.18	3.1
Vitiligo	11 (1.3)	4 (1.3)	1.0	1.1
Sjögren's syndrome	10 (1.2)	1 (0.3)	0.31	3.9
Systemic sclerosis	9 (1.1)	1 (0.3)	0.30	3.5
Inflammatory bowel disease	7 (0.9)	9 (2.8)	0.02**	0.3
Systemic lupus erythematosus	7 (0.9)	0.00	0.20	NA
Multiple sclerosis	6 (0.7)	3 (0.9)	0.71	0.8
Psoriatic arthritis	5 (0.6)	1 (0.3)	1.0	1.9
Primary biliary cirrhosis	2 (0.2)	1 (0.3)	1.0	0.8
Juvenile idiopathic arthritis	2 (0.2)	0	1.0	NA
Pernicious anemia	1 (0.1)	1 (0.3)	0.48	0.4
Celiac disease	1 (0.1)	1 (0.3)	0.48	0.4
Autoimmune hepatitis	0.00	0.00	NA	NA
No. FDR with at least 1 autoimmune disease	192 (23.3)	64 (20.1)	0.28	1.2

* FDR include parents, siblings and offspring. ** $p < 0.05$. NA: not available.

(4.9%), followed by RA (4.1%), psoriasis (3.9%), and type 1 diabetes mellitus (2.9%).

Characteristics of the control cohort and comparison of familial autoimmunity between SSc and control families. In the control cohort, 49 families (19.6%) had 1 or more first-degree relatives with 1 or more autoimmune diseases. A total of 66 autoimmune diseases were reported in 64 first-degree relatives. The most commonly reported autoimmune diseases in the controls' families were psoriasis (5.0%), RA (3.5%), type 1 diabetes mellitus (3.1%), and IBD (2.8%).

The family size-adjusted prevalences of connective tissue disorders (SS, SLE, or SSc) and of AITD (Hashimoto's thyroiditis or Graves' disease) were higher in SSc families than in controls' families: 3.2% versus 0.6% (p = 0.01, OR 5.20, 95% CI 1.22–21.8) and 4.9% versus 1.6% (p = 0.01, OR 3.20, 95% CI 1.25–8.18), respectively (Tables 3 and 4). There was no difference between SSc and control families for the prevalence of each specific disease when analyzed separately, except for Hashimoto's thyroiditis, which was overrepresented in SSc families (2.8% vs 0.9%; p = 0.035, OR 3.4, 95% CI 1.03–11.40) and IBD, which occurred less frequently in SSc families (0.9% vs 2.8%; p = 0.02, OR 0.29, 95% CI 0.11–0.80).

Table 4. Estimated risk of AITD, connective tissue diseases, and IBD in first-degree relatives (FDR) of patients with systemic sclerosis (SSc).

Disease Type	FDR of SSc Families, n = 823	FDR of Control Families, n = 318	OR (95% CI)
AITD, n (%)	40 (4.9)	5 (1.6)	3.20 (1.25–8.18)
Connective tissue disease, n (%)	26 (3.2)	2 (0.6)	5.20 (1.22–21.8)
IBD, n (%)	7 (0.9)	9 (2.8)	0.29 (0.11–0.80)

AITD: autoimmune thyroid disease; IBD: inflammatory bowel disease.

Familial aggregation (λ_R). Familial aggregation was calculated for each autoimmune disease using the prevalence of autoimmune diseases in SSc families and in control families (Table 3). Familial aggregations of SS ($\lambda_R = 3.9$), SSc ($\lambda_R = 3.5$), Graves' disease ($\lambda_R = 3.1$), and Hashimoto's thyroiditis ($\lambda_R = 3.0$) were the conditions most observed in families of patients with SSc. Familial aggregation of SLE could not be calculated because there were no cases in control families. However, familial aggregation of connective tissue diseases reached 5.0 in SSc families.

Characteristics of SSc patients with familial autoimmunity.

When we compared patients with SSc who did have first-degree relatives with at least 1 autoimmune disease with those who did not, we found no difference in age and sex, but we found an interesting association between having familial autoimmunity and multiple autoimmune diseases in the index SSc case (p = 0.005) and a personal history of Hashimoto's thyroiditis (p = 0.02) in univariate analysis. In multivariate logistic regression analysis, the probability of familial autoimmunity was found to be strongly and persistently associated with the presence of multiple autoimmune diseases in the index case (p = 0.004). The occurrence of any autoimmune disease in first-degree members was 1.9 times more likely when index SSc cases also reported a coexisting autoimmune disease (OR 1.9, 95% CI 1.2–3.0, p = 0.004; data not shown).

DISCUSSION

These French SSc and control datasets were investigated to determine whether a number of autoimmune diseases were more prone to occur in first-degree relatives of patients with SSc than in control families. Prevalence was adjusted to family size in order to avoid sample size bias. Although the familial aggregation of specific autoimmune phenotypes has previously been suspected[11,14], ours is the first study, to our knowledge, confirming familial clustering of AITD and connective tissue diseases in a concurrent case-control study and in a European population. We found higher frequencies of AITD and connective tissue disorders (SLE, SSc, or SS) in first-degree relatives of patients with SSc than in control families. First-degree relatives were at higher risk of developing any autoimmune disease when the index case reported multiple autoimmune diseases. In contrast, we found that having a relative with SSc conferred a lower risk of developing IBD.

The coexistence of autoimmune diseases in general within families has been studied in RA and in other systemic autoimmune diseases, most commonly in SLE and SS[6,9,16]. For example, a study examining the aggregation of autoimmune diseases among first-degree relatives of patients with primary SS showed that AITD, SLE, and SSc clustered within families of patients with primary SS[9]. While the specific familial aggregation of SSc has been addressed[17,18], there are very few data on coexisting systemic autoimmune diseases other than SSc. In our study, the recurrence-risk ratio of connective tissue diseases (SSc, SLE, or SS) in SSc families was 5.0. In a large sample study investigating 1071 patients with SSc and 4612 first-degree relatives, Arora-Singh and colleagues observed a higher prevalence of SLE than in a control sample[14]. The most striking increase for familial prevalence was observed in SLE (OR 16.98), followed by hyperthyroidism (OR 2.76). It is noteworthy that attempts to constitute a concurrent control group failed and the authors therefore used data from a former epidemiological study not investigated for the purpose of Arora-Singh's study[19]. This limited the extent of comparison because of (1) missing information on a number of autoimmune diseases such as SS and primary biliary cirrhosis in the control dataset, and (2) a lower mean age of control index cases (42.8 years) compared with the mean age of SSc index cases (58.1 years), leading to potential bias in the prevalence of autoimmune disease cases in first-degree relatives. Nevertheless, the data from our current study partly confirm these findings. Further, individual and familial aggregation of systemic autoimmune diseases is supported by the recent data of genetic studies. Indeed, shared autoimmunity has appeared as a critical component of the genetic basis of autoimmune diseases. Outside the MHC region, shared susceptibility genes between SLE and SSc identified to date include polymorphisms of genes involved in innate immune pathways (*IRF5*)[20,21], T cell differentiation and activation (*STAT4*, *PTPN22*)[4,22,23,24,25], and immune intracellular signaling pathways (*BANK1*, *BLK*, *TNFAIP3*)[26,27,28,29].

As observed by Anaya, *et al* in SS[9], the autoimmune disease reported most frequently in first-degree relatives of patients with SSc was AITD: 4.9% in SSc families compared with 1.6% in controls' relatives (p = 0.01, OR 3.20, 95% CI 1.25–8.18). Increased rates of AITD in family members of patients with SSc have been reported in a study by Hudson, *et al*, in which AITD was the second most frequent autoimmune disease in first-degree relatives after RA[11]. Arora-Singh and colleagues[14] observed a higher prevalence of hypothyroidism and hyperthyroidism in SSc relatives than in the control sample (OR 2.51 and 2.76, respectively). Our results are consistent with this observation, strongly suggesting a specific relationship between SSc and AITD, which may be related to genetic bases. Reported data on the *PTPN22* R620W polymorphism support, for example, its pleiotropic role in both systemic autoimmune diseases and AITD[4,23,30].

Intriguingly, we found a protective association between having a relative with SSc and the occurrence of IBD (OR 0.29, 95% CI 0.11–0.80). To date, concomitant immune-mediated diseases reported in patients with IBD include psoriasis, celiac disease, and multiple sclerosis[2,8,31,32]. Familial associations of Crohn's disease and ulcerative colitis with other autoimmune conditions have also been suggested[33]. Genome-wide association studies investigating the genetic loci implicated in IBD have highlighted more than 50 risk loci[34], a substantial proportion of which have also been associated with autoimmune diseases[34]. Interestingly, some of these overlapping genes can have contrasting risk profiles in different diseases. For example, polymorphisms of the *IRF5* gene have been found to confer risk of IBD, SSc, SLE, and RA[35,36], whereas the associations of the *PTPN22* R620W and *IL23R* variants shared between IBD and RA occur in opposite directions[35,37,38,39]. Further studies will be needed to clarify these findings, but together these results emphasize that polyautoimmunity must be

taken into account for the definition of phenotype in genetic studies.

The questionnaire-based design of our study did not allow us to assess the influence of disease phenotype on familial aggregation. However, the results of our previous study suggested that individual aggregation of autoimmune diseases within SSc patients was associated with milder disease[12].

Our study has some limitations. SS, SLE, and SSc tended to be more frequent in SSc relatives, but our study was underpowered to obtain statistical differences. A larger cohort will be necessary to confirm these results for each individual disease. In this population-based case-control family design, ascertainment bias should be considered, because affected relatives of the cases are more likely to be reported than affected relatives of controls[40]. Efforts were made to reduce confounding factors, such as the choice of controls, which differed from the cases only by disease status. Accuracy of self-reported autoimmune diseases was another limitation. Although a detailed questionnaire was sent to avoid confusion and/or inaccuracies in the diagnosis of autoimmune diseases, we did not have a face-to-face history with physical and laboratory examinations to confirm relatives' diagnoses. However, it is noteworthy that when medical records are available, confirmation rates of self-reported autoimmune diseases in the literature are relatively high (80%–100%) for SLE, thyroiditis, SSc, and SS, but tend to be much lower in RA[41]. Indeed, we observed high rates of RA in SSc families (4.1%), which were also frequently reported in the control dataset (3.5%), reflecting a potential bias due to confusion between osteoarthritis and RA. However, the study protocol was explained during patients' meetings at several times, and since we used the same approach in both SSc and control families, this bias should be minimized. In addition, the comparison between groups revealed no difference in the familial prevalence of RA, consistent with the results reported by Arora-Singh, *et al*[14].

Our findings highlight that patterns of autoimmune diseases, such as SSc and other systemic autoimmune diseases, but also SSc and organ-specific autoimmune diseases such as AITD, occur in excess within SSc families, whereas other autoimmune diseases are less frequent than in the general population. This supports the concept of shared autoimmunity, a common genetic background with pleiotropic effects leading to various autoimmune phenotypes within the same family. Deciphering the common genetic components of different patterns of complex autoimmune diseases may help in understanding their pathophysiology, and will hopefully lead to new prevention and therapeutic progress. In addition, these results should push geneticists and clinicians to perform more in-depth phenotyping of patients with autoimmune diseases and to analyze some clusters of diseases, and also to take into account polyautoimmunity in statistical analyses.

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