Autoimmune diseases and autoantibodies in the first degree relatives of patients with systemic sclerosis

Rajpreet K. Arora-Singh a,1, Shervin Assassi a,*,1, Deborah J. del Junco b, Frank C. Arnett a, Marilyn Perry a, Uzma Irfana, Roozbeh Sharifa, Tony Mattarc, Maureen D. Mayesa

a Division of Rheumatology and Immunogenetics, University of Texas Health Science Center at Houston, Houston, TX, USA
b Center for Clinical and Translational Sciences, University of Texas Health Science Center at Houston, Houston, TX, USA
c Computer Task Force Inc., Troy, MI, USA

Objective: To determine aggregation of autoimmune diseases in the first degree relatives (FDR) of patients with systemic sclerosis (SSc) and to investigate frequencies of antinuclear antibodies (ANA) and other autoantibodies in the FDRs and spouses of patients with SSc.

Methods: Information on FDRs including history of autoimmune disease was obtained from unrelated SSc probands in the Scleroderma Family Registry and DNA Repository. FDRs were contacted to verify any reported autoimmune diseases. The prevalence of autoimmune disease in probands’ families was compared with the corresponding prevalence in controls from the literature. Furthermore, sera from probands’ FDRs and spouses in addition to unrelated controls were investigated for the presence of antinuclear antibodies (ANA).

Results: We investigated 4612 FDRs of 1071 SSc probands. SSc probands with anti-centromere antibodies (ACA) and limited disease type were more likely to report familial autoimmunity (p = 0.0022 and p = 0.041, respectively). The four most prevalent autoimmune diseases among SSc probands’ FDRs were hypothyroidism (4%), Rheumatoid arthritis (1.5%), hyperthyroidism (1.3%) and systemic lupus erythematosus-SLE (0.4%). Compared to control families, SLE, hypothyroidism and hyperthyroidism were more common in SSc probands’ families. The most striking increase for familial prevalence was observed in SLE (OR = 16.98, 95% CI = 1.02–227.82, p = 0.004), ANA was present in 14.2% of probands’ FDR’s and 8.6% of spouses and did not differ from the prevalence of ANA among controls (p = 0.124 and p = 0.477, respectively). Only two FDRs of probands had ACA while none had anti-topoisomerase antibodies.

Conclusion: Our study implies varying degrees of risk for familial autoimmunity among subtypes of SSc and provides further support for common genetic and potentially environmental factors leading to SSc and SLE.© 2010 Published by Elsevier Ltd.

1. Introduction

Systemic sclerosis (SSc) is a chronic multi-system autoimmune disease of unknown etiology. Familial recurrence has been shown to be greater than expected by chance. A positive family history is the strongest risk factor yet identified for SSc [1].

Diverse autoimmune diseases may coexist in the same individual and in families, implying a common etiology. The presence of antinuclear antibodies (ANA) is the serological hallmark of connective tissue diseases, and the majority of patients with SSc and other connective tissue diseases have ANAs. Two previous studies have examined ANA positivity in family members and/or spouses of SSc patients with contradicting results. Maddison et al. reported higher frequency of ANA positivity among FDRs and spouses of patients with SSc [2] while Barnett et al. did not find an increased frequency of ANAs among family members or spouses of SSc patients [3]. A study, investigating the spectrum of polyautoimmunity and familial autoimmunity in a cross-sectional population of 719 SSc patients from two cohorts (Canada and Columbia) reported that 273 (38%) patients with SSc had another autoimmune disease. Furthermore, 260 patients reported FDRs with autoimmune disease. The prevalence of autoimmune diseases was determined by self- or other
report. The reported diagnoses were confirmed by medical record review or patient interview only in the Columbian cohort. The prevalence rates of rheumatoid arthritis (RA) (3.4% vs. 28.7%), autoimmune thyroid disease (1.4% vs. 14%) and systemic lupus erythematosus (SLE) (0.7 vs. 4.9%) were significantly lower in the Columbian cohort than in the Canadian sample. This difference might be explained by the different methods of case confirmation in these two populations [4].

The hypothesis of a common origin for different autoimmune diseases is supported by results of genetic studies showing that several susceptibility loci may overlap in different autoimmune diseases, and by gene microarray expression studies disclosing a similar transcriptional pattern in different autoimmune diseases. For example, the PITPN22 gene has been associated with the development of rheumatoid arthritis, SLE, type 1 diabetes mellitus, Hashimoto’s thyroiditis and SSc [5–10]. Similarly, STAT4 has been implicated in susceptibility to RA, SLE, primary biliary cirrhosis (PBC), and Sc [11–13].

The aims of this study were to examine the aggregation of autoimmune diseases in the FDR’s of SSc patients as verified by physicians or medical record review and to investigate the prevalence of antinuclear antibodies in these individuals in comparison to healthy controls and spouses of patients with SSc.

2. Methods

2.1. Study participants

We investigated 1071 unrelated patients with SSc (probands), 4612 FDRs (parents and siblings only) of SSc patients, and 637 controls (including spouses). All SSc probands and controls in addition to a portion of FDR’s were enrolled in the Scleroderma Family Registry and DNA Repository (Registry). The SSc probands either met the 1980 American College of Rheumatology preliminary criteria for the classification of SSc [14] or had at least three of the five CREST syndrome features (calcinosis, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias) [15]. Children of SSc probands were excluded because of their low expected lifetime prevalence of autoimmune diseases due to their younger age. Multiplex SSc families with more than one case of SSc were excluded from our study in order to avoid the potential confounding effect of the increased genetic load in these families. Furthermore, the characteristics of the 18 multiplex families in the Registry have been reported previously [16]. The control group in the Registry was made up of primarily unrelated friends and spouses of SSc patients. All enrolled study subjects provided written informed consent and the study was approved by the institutional review board of the University of Texas Health Science Center at Houston.

2.2. Case ascertainment and confirmation among FDRs of SSc probands

SSc probands and their enrolled FDR’s were asked to report on family history of autoimmune diseases using a standardized questionnaire eliciting a history of the following diagnoses: RA, thyroid disease, SLE, primary Sjögren’s syndrome, multiple sclerosis, Crohn’s disease, polymyositis, dermatomyositis, polymyalgia rheumatica, and PBC. The information on presence of autoimmune diseases in FDRs was obtained directly from the FDRs if they were enrolled in the Registry (n = 1009), otherwise it was based on SSc proband’s report. An attempt was made to contact all probands’ FDRs that had an autoimmune disease per self- or other report. All successfully contacted FDRs were interviewed to collect clinical information. Confirmation of the diseases was done by chart review or by interview soliciting typical disease features with aid of the Multiple Autoimmune Disease Genetics Consortium (MADGC) study questionnaires [10]. All interviews were conducted by one rheumatologist (R.K.A.). Most cases of hypothyroidism and RA were confirmed by telephone interview. Hypothyroidism was confirmed if the FDR was on supplemental thyroid hormone without history of malignancy or other thyroid surgery/ablation. RA was confirmed in most cases by presence of typical disease features in addition to medication regimen consisting of DMARDs. Medical records were requested from appropriate subspecialty clinics for all other diagnoses as well as questionable hypothyroidism and rheumatoid arthritis diagnoses.

Lifetime prevalence of autoimmune disease was defined as the occurrence of the disease at any time during the individual’s past. Singleton families were defined as those in which no autoimmune disease in the FDRs was reported. Multi-autoimmune families had one or more FDRs reportedly affected with autoimmune diseases.

2.3. Lifetime familial prevalence of autoimmune diseases in controls

Because family history of autoimmune diseases was not available for the control subjects in the Registry, other alternatives for valid comparison data were explored. After an extensive literature review, we identified a single study with appropriate comparison data from a similar population [17]. This study investigated the prevalence of autoimmune diseases in the FDR’s of probands with multiple sclerosis (MS) using a case-control method. Controls free from MS were selected by the probands from a choice of spouse, friend, partner, or care giver. The control probands received identical questionnaires regarding family history of autoimmune disease in their parents and siblings. The diseases overlapping with our questionnaire included: hypothyroidism, hyperthyroidism, SLE and RA. We used the reported prevalence of one or more cases of autoimmune disease among control families from this study as our standard for comparison to investigate the aggregation of these four autoimmune diseases in families of SSc probands.

2.4. Autoantibody testing

All available sera from SSc patients, FDRs, and control subjects in the Registry were investigated. We also included sera from offspring of SSc probands for this part of our study, because of our ability to appropriately adjust the final analyses for age and sex. Multiplex SSc families were again excluded because the data on prevalence of ANAs in this group has been previously reported [16]. Antinuclear antibodies (ANA) were determined using indirect immunofluorescence (IF) on HEP-2 cells (Antibodies Inc., Davis, CA). An ANA titer ≥1:80 was considered positive. IIF patterns were classified as speckled, centromere, nucleolar, homogenous and mitochondrial based on interpretation of a single investigator (F.C.A.) for all samples. Anti-centromere antibodies (ACA) were determined by their distinctive IIF pattern. The sera showing a positive mitochondrial pattern on IIF, underwent anti-mitochondrial M2 determination by ELISA (MBL IC, Woburn, MA). The sera from subjects with antinuclear antibodies were further tested for the presence of more specific antibodies. Autoantibodies to topoisoasmerase 1 (ATA), RNP, Ro, and La were determined by passive immunodiffusion against calf thymus extract using commercially available kits (Inova Diagnostics, San Diego, CA).

2.5. Statistical analysis

The analysis of categorical values was conducted by chi-square test, and odds ratios and corresponding 95% confidence intervals (CI) were computed. Continuous variables were analyzed by t-test. Logistic regression analyses were used to adjust for the effect of multiple independent variables. Two-sided p-values less than 0.05 were considered significant. The analyses were performed utilizing...
the SAS 9.1.3 (SAS Institute Inc., Cary, NC) and NCSS 2007 (NCSS, Kaysville, UT) statistical programs.

3. Results

3.1. Demographic characteristics of SSC probands and their families

Of the 1071 SSC probands, 614 (57.3%) had limited and 961 (89.7%) were female. The mean age of the SSC probands was 58.1 ± 13.8 (±SD) years. The majority of probands (76.7%, n = 821) were Caucasians, whereas the remainder of patients were 10.7% (n = 115) Hispanic, 8.8% (n = 94) African American, and 3.8% (n = 41) other. A total of 4612 FDR’s were investigated. As expected, the FDR cohort had an approximately equal proportion of females to males and had an ethnic composition similar to the SSC probands. The average age of the FDR cohort was 65.9 years, which is higher than the index cases because of inclusion of parents. A total of unique 497 FDRs (10.8%) with one or more autoimmune diseases of interest were reported within 393 multi-autoimmune families. A total of 67 of the 497 FDRs were reported to have more than one autoimmune disease. These most commonly included: rheumatoid arthritis, hypothyroidism, and SLE. The demographic information of index cases and FDR’s are shown in Table 1. The average sibship size per family was 3.3; the proportion of sisters was 50.6% (n = 1249). The details of family relationship are shown in Table 2.

3.2. Autoimmune disease confirmation

We were able to contact 302 of the 497 FDRs with reported autoimmune disease (61%) over a period of 5 months. Reasons for being unable to contact the remainder of the FDRs included: having incorrect/disconnected telephone numbers, not receiving permission from the SSC probands to contact the family members, inability to reach FDR by telephone after leaving at least two messages with call back instructions, or finding that the FDR was deceased.

A report of autoimmune disease in an FDR was defined as verified if the FDR was successfully contacted and the appropriate medical information was received. Furthermore, a subset of the verified reports was defined as confirmed if the reported diagnosis of an autoimmune disease was corroborated. Of the 302 successfully contacted FDR’s, 253 reports could be verified with the evidence available and the accuracy of the diagnosis was confirmed in 189 subjects. Rheumatoid arthritis and hypothyroidism were the most commonly reported diseases in the FDR cohort (Table 3). Half of the reported rheumatoid arthritis and SLE diagnoses were inaccurate, resulting in an estimated prevalence rate of 1.5% and 0.4% for these two diseases. Reports of hypothyroidism and hyperthyroidism were more often accurate (88% and 74%, respectively). Therefore, among the confirmed cases, hypothyroidism was the most common autoimmune disease. The estimated prevalence rate for hypothyroidism and hyperthyroidism were 4% and 1.3%, respectively. The confirmation rate for Crohn’s disease, multiple sclerosis, and PBC was 100%. The lowest confirmation rate was for polymyalgia rheumatica at 25%; in the remainder of cases, the diagnosis of fibromyalgia was confused with this condition (Table 4 and Table 5).

3.3. Comparative analysis

In the study by Bradley et al., 44 of 375 (11.7%) of control families had one or more FDRs with one or more autoimmune diseases [17]. The corresponding familial prevalence of the specific diseases, RA, hypothyroidism, hyperthyroidism, SLE in the FDRs of control group was reported as 7.2%, 4.3%, 1.6%, and 0%, respectively.

Adjusting for age and family size differences, the corresponding familial prevalence of RA, hypothyroidism, hyperthyroidism, and SLE in the families of our SSC probands was 7.0% (OR = 0.97, 95% CI = 0.61–1.59, p = 0.90), 10% (OR = 2.51, 95% CI = 1.46–4.62, p < 0.001), 4.2% (OR = 2.76, 95% CI = 1.16–7.97, p = 0.016) and 2.2% (OR = 16.98, 95% CI = 1.02–227.82, p = 0.004), respectively. Of the four most common autoimmune diseases among families of our SSC probands, only the prevalence of RA was not significantly increased compared to the control families of Bradley et al. (Table 4).

3.4. Comparison of SSC probands stratified according to family type

SSC probands with limited disease type (p = 0.041; OR: 1.31; CI: 1.01–1.69) and ACA antibodies (p = 0.022; OR: 1.39; CI: 1.05–1.84) belonged more frequently to multi-autoimmune families. On the other hand, SSC probands with ATA reported fewer cases of autoimmune disease in their families (p = 0.021; OR: 0.688; CI: 0.498–0.949). Even after adjustment for the proband’s age, the lifetime prevalence of autoimmune disease among FDRs was higher when probands had limited disease (p = 0.034) or ACA antibodies (p = 0.012) and lower when probands had ATA antibodies (p = 0.014). The prevalence of ANA and anti-RNP antibodies and age at enrollment did not differ among SSC probands from singleton and multi-autoimmune families (p = 0.13, p = 0.689 and p = 0.09, respectively).

3.5. Frequency of autoantibodies among patients, FDRs, spouses and controls

Serum samples were available on 1058 patients with SSC, 1005 FDR, 644 controls (including 186 spouses). The FDR cohort with an available serum sample consisted of 368 parents (36.6%), 408 siblings (40.6%) and 229 children (22.8%) of enrolled SSC probands. The mean age at enrollment was 53.2 ± 18 (±SD) in the FDR group whereas the mean age in the control group (including spouses) and spouse only group was 48.7 ± 15.2 and 56 ± 12.7. In the FDR group, 628 (62.5%) participants were female whereas 344 (53.4%) and 32 (17.2%) participants were female in the overall control and spousal groups, respectively. As shown in Table 5, ANAs were present in 91.4% of cases and 14.2% of FDRs whereas 10.6% of controls and 8.6% of spouses had positive ANAs. The most common pattern in both the FDR and control cohorts was diffuse speckled. Of the sampled FDRs, 2 (0.2%) had ACA, with none having ATA. Neither of these two antibodies was present in the overall control or spousal groups. A total of 33 FDRs with a positive ANA had an autoimmune disease.
Table 3
Reported, verified and confirmed cases among FDRs.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Reported cases in FDRs (% = 497)</th>
<th>Verified cases (%#)</th>
<th>False report (%)</th>
<th>Confirmed verified cases (%)</th>
<th>Estimated prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>147 (29.6)</td>
<td>59 (40.1)</td>
<td>30 (50.8)</td>
<td>29 (49.2)</td>
<td>1.5</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>213 (42.9)</td>
<td>110 (51.6)</td>
<td>15 (13.6)</td>
<td>95 (86.4)</td>
<td>4</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>80 (16.1)</td>
<td>35 (43.8)</td>
<td>8 (22.8)</td>
<td>27 (77.2)</td>
<td>1.3</td>
</tr>
<tr>
<td>SLE</td>
<td>41 (8.2)</td>
<td>12 (29.2)</td>
<td>6 (50.0)</td>
<td>6 (50.0)</td>
<td>0.4</td>
</tr>
<tr>
<td>Primary Sjögren’s</td>
<td>22 (4.4)</td>
<td>12 (54.5)</td>
<td>3 (33.3)</td>
<td>9 (66.7)</td>
<td>0.3</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>16 (3.2)</td>
<td>6 (37.5)</td>
<td>0 (0)</td>
<td>6 (100)</td>
<td>0.3</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>11 (2.2)</td>
<td>5 (45.5)</td>
<td>0 (0)</td>
<td>5 (100)</td>
<td>0.2</td>
</tr>
<tr>
<td>PM/DM</td>
<td>8 (1.6)</td>
<td>6 (75.0)</td>
<td>1 (16.6)</td>
<td>5 (63.4)</td>
<td>0.1</td>
</tr>
<tr>
<td>PMRA</td>
<td>13 (2.6)</td>
<td>4 (30.8)</td>
<td>3 (75.0)</td>
<td>1 (25.0)</td>
<td>0.1</td>
</tr>
<tr>
<td>PBC</td>
<td>16 (3.2)</td>
<td>7 (43.8)</td>
<td>0 (0)</td>
<td>7 (100)</td>
<td>0.3</td>
</tr>
<tr>
<td>Overall</td>
<td>567</td>
<td>257 (45.3)</td>
<td>73 (28.4)</td>
<td>184 (71.6)</td>
<td></td>
</tr>
</tbody>
</table>

*567 autoimmune diseases were reported in 497 FDRs.
†The estimated prevalence was calculated based on the percentage of confirmed cases applied to the total number of reported disease entities for a given disease.
§Polyomysitis (PM) and dermatomyositis (DM).
ΔPolyangiitis rheumatica.

ANA positivity was not more prevalent in the overall FDR group when compared to controls (p = 0.124, OR = 1.28; 95% CI = 0.93–1.75) after adjustment for age and sex. Furthermore, the frequency of ANAs was not significantly higher in FDRs of SSc patients in comparison to non-spousal controls (p = 0.17, OR = 0.79, 95% CI 0.55–1.11). In a similar analysis, ANA positivity in the spousal controls also did not differ significantly from the rest of the control group (p = 0.477, OR = 1.29, 95% CI 0.64–2.59). The results of these comparisons are shown in Table 6.

Anti-mitochondrial antibodies were seen in 14 FDRs (1.4%). After adjustment for age and sex, the frequency of anti-mitochondrial antibodies in FDRs did not differ significantly from controls (p = 0.091, OR = 5.89, 95% CI = 0.75–46.2), though results indicated a trend for a higher frequency in this population. We also retested the sera that showed an anti-mitochondrial pattern by IFI using a M2 ELISA. The presence of anti-mitochondrial antibodies was confirmed by ELISA in 11 FDRs and one control subject. Only one of the FDRs with anti-mitochondrial antibodies was reported to have PBC at the time of enrollment. The rest of the individuals were contacted to see if PBC had developed after enrollment. None of the successfully contacted FDRs (n = 7) had developed PBC in the interim.

4. Discussion

The current study investigated the prevalence of autoimmune diseases in FDRs of a large sample of SSc patients. Compared with the prevalence in controls families (17), SLE, hypothyroidism and hyperthyroidism were significantly increased in our families with SSc. We attempted to confirm all the reported autoimmune diseases. Furthermore, we investigated the presence of ANA and more specific autoantibodies in FDRs and spouses of patients with SSc in addition to unrelated controls.

We report the novel finding that proband’s SSc subtype appeared to modify the degree of familial autoimmunity. SSc patients with ACA and limited disease type showed a positive association with familial autoimmunity while SSc patients with ATA have a negative association with this phenomenon. The usually non-overlapping SSc related autoantibodies such as ACA and ATA are associated with different clinical manifestations of disease [18]. Our group has previously shown that SSc-affected members of multiplex families tend to share a similar autoantibody profile [16]. Furthermore, previous HLA studies have demonstrated that the major histocompatibility genes exert their influence primarily on autoantibody expression in SSc [19,20]. The DPB1*1301 allele is a strong susceptibility gene for ATA positive SSc while ACA is best explainable by DQB1*0501 and DQB1*26 epi alleles. Moreover, ACA positive SSc patients have more often concomitantly PBC and/or Sjögren syndrome than other subtypes of SSc [21,22]. Our results along with the above mentioned findings indicate that serological subtypes of SSc have different genetic backgrounds and carry a varying degree of genetic risk for familial autoimmunity.

We utilized control families from the study by Broadley et al. as they provided the only appropriate standard for comparison available in the literature [17]. Our study population differed from the utilized control group in geographic location, and to some extent in genetic background. Furthermore, different questionnaires and verification processes were used. Despite these shortcomings, we think it is more accurate to utilize the data from the above mentioned control group than general population point prevalence data. Numerous other studies of the familial aggregation of diseases have made comparisons with general population point prevalence rates available in the literature. Point prevalence is the frequency of disease in a population at a single point in time. However, an obtained family history is more reflective of the lifetime cumulative

Table 5
Results of autoantibodies in SSc patients, their FDRs and controls.

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Cases (n = 1058) (%)</th>
<th>FDRs (n = 1005)*</th>
<th>Controls (n = 644)*</th>
<th>Spouses (n = 186)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>967 (91.4)</td>
<td>143 (14.2)</td>
<td>68 (10.6)</td>
<td>16 (8.6)</td>
</tr>
<tr>
<td>Diffuse speckled (%)</td>
<td>522 (49.3)</td>
<td>122 (12.1)</td>
<td>54 (8.3)</td>
<td>12 (6.4)</td>
</tr>
<tr>
<td>Nucleolar (%)</td>
<td>291 (27.5)</td>
<td>20 (1.9)</td>
<td>9 (1.4)</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Centromere (%)</td>
<td>286 (27.0)</td>
<td>6 (0.6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cytoplasmic (%)</td>
<td>117 (11.0)</td>
<td>30 (2.9)</td>
<td>5 (0.7)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Anti-mitochondrial (%)</td>
<td>29 (2.7)</td>
<td>14 (1.4)</td>
<td>1 (0.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Anti-Ro (%)</td>
<td>46 (4.3)</td>
<td>4 (0.4)</td>
<td>2 (0.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Anti-La (%)</td>
<td>11 (1.0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Anti-RNP (%)</td>
<td>193 (18.2)</td>
<td>4 (0.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Anti-Topo-1 (%)</td>
<td>216 (20.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Controls include both spousal and non-spousal controls.
risk, or more accurately, the “lifetime prevalence” of the disease among relatives. A point prevalence can be lower than the lifetime prevalence of a given disease by several orders of magnitude [23].

In our comparative analysis, the most striking increase in familial prevalence was for SLE. Much data exist regarding similarities of SLE and SSc from both a genetic and immunologic perspective. The observation of familial occurrence of SSc and SLE was initially made by Arnett et al. describing eight families with cases of both SSc and SLE. None of the cases shared residence, and full family histories were obtained. ANA positivity is a hallmark of both SSc and SLE. Similar disease manifestations may also be present. An interferon gene expression signature also has been reported in both diseases [25,26]. Moreover, several overlapping susceptibility genes such as PTPN22 [6,7], IRF5 [27,28], STAT4 [12,13], C8orf13-BLK [29–31] have been identified in SSc and SLE. The findings of this study further support that similar genetic backgrounds contribute to the development of SSc and SLE. It is also possible that SSc and SLE share common environmental factors leading to the disease. However, there is a relative paucity of large scale case-control or cohort studies that investigate the predisposing environmental factors in SLE and SSc (reviewed in ref. [32]). Occupational exposure to silica has been implicated in the development of both SLE [33] and SSc (reviewed in ref. [34]). However, almost all reported cases have been male. Silica exposure does not seem to play an important role in development of SSc in female patients [35]. Furthermore, silica exposure does not explain most male SSc cases [36]. Further large case-control studies are needed to explore the possibility of common environmental triggers predisposing to autoimmune diseases that show polyautoimmunity and/or familial autoimmunity.

Disease confirmation was a major part of this study. Hypothyroidism was the most prevalent autoimmune disease among FDRs of SSc probands after case verification. This is likely in part due to the high population prevalence of hypothyroidism in the general population [37]. We did not determine thyroid related autoantibodies in our study. However, the most common cause of hypothyroidism in iodine sufficient areas like USA is by far Hashimoto’s thyroiditis [38]. Therefore, the assumption was made that FDRs on supplemental thyroid hormone without history of malignancy or thyroid surgery/ablation had Hashimoto’s thyroiditis. While RA was the most frequently reported disease among FDRs, it became the second most prevalent autoimmune disease after the verification process was completed. RA was found to be incorrectly reported approximately 50% of the time, and was often confused with osteoarthritis on the questionnaire (as it was in Broadley et al. [17]). We targeted all FDRs with a reported autoimmune disease according to a standard protocol in order to ensure that data for disease verification are missing at random. Nevertheless, it is possible that there are systematic differences between the FDRs with and without sufficient medical data for disease verification. We were able to obtain sufficient medical data in a relatively large portion of reported diagnoses (51.7%) and confirm the reported diseases in 71.6% of FDRs with sufficient medical data. Our verification and confirmation rates are consistent with a study by Cooper et al. that investigated the prevalence and accuracy of self-reported history of autoimmune diseases in FDRs of SLE patients in a Canadian cohort [39]. In this study, sufficient medical records for verification of reported autoimmune diseases were obtained in 44% of the diagnoses. Excluding those whose medical records were not available, the confirmation rate was 76% [39]. Furthermore, Cooper et al. reported that the diagnosis of rheumatoid arthritis was confirmed in 48% of the cases, consistent with our confirmation rate of 50% for this disease.

Maddison et al. investigated ANAs in 65 families of SSc patients. Of the enrolled 217 first degree relatives (FDRs), 58 (27%) had a positive ANA (42 speckled, 13 nucleolar, one centromere, two homogenous). Family members tended to share ANA patterns. ANA positivity was detected in nine out of 38 enrolled spouses (24%), and these all had a speckled pattern. ANA positivity also was found in 8% of a randomly selected cohort of blood donor controls for which age and sex were not available. The authors concluded that genetic and environmental factors predispose to the development of SSc and to a high prevalence of autoantibodies in FDRs and spouses of SSc probands [2]. Barnett et al. reported ANA data in 58 SSc patients, 74 FDRs, 30 spouses, and 66 controls broadly matched to the patients, their spouses, and about half of the relatives (siblings and parents) by age. They found 95% of patients, 18% of controls, 3% of spouses, and 7% of FDRs had a positive ANA; 64% of SSc patients had more specific antibodies compared to 0% in the other groups. ANA at a titer of >160 was considered positive. The authors concluded that no genetic or environmental factors contribute to the presence of ANAs in SSc. We did not detect any significant difference in the ANA positivity among FDRs of SSc patients in comparison to controls after adjustment for disparities in sex and gender. This adjustment was not done in previous studies investigating rates of ANA positivity in SSc families (2–3). Omitting this correction can lead to spurious associations because ANA positivity can be significantly influenced by age and gender [40]. Contrary to a previously published report (2), ANA positivity was also not seen at a higher frequency in spouses of SSc patients. This finding argues against an environmental trigger leading to ANA positivity among SSc patients and their spouses.

In summary, SSc patients with ACA and limited disease type are more likely to have another family member with an autoimmune disease. Hypothyroidism and rheumatoid arthritis are the most commonly present autoimmune diseases in the FDRs of SSc patients. Furthermore, SLE is particularly more prevalent in the families of SSc probands than control families. Our study implies varying risk for familial autoimmunity among subtypes of SSc. Furthermore, our results along with reports of common susceptibility genes [6,7,12,13,27–31] support a shared genetic and potentially environmental background predisposing to SSc and SLE.

Acknowledgements

The authors thank Mr. Julio Charles, Ms. Yasamin Salehi and Mr. William Babu for conducting the laboratory studies.

References


Table 6

<table>
<thead>
<tr>
<th>Comparison group</th>
<th>Number with positive ANA</th>
<th>Raw p-value</th>
<th>Adjusted p-value*</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All FDRs vs. controls</td>
<td>143 vs. 68</td>
<td>0.030</td>
<td>0.124</td>
<td>0.93–1.75</td>
</tr>
<tr>
<td></td>
<td>(14.2% vs. 10.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All FDRs vs. non-spousal controls</td>
<td>143 vs. 52</td>
<td>0.133</td>
<td>0.174</td>
<td>0.55–1.11</td>
</tr>
<tr>
<td></td>
<td>(14.2% vs. 11.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spousal vs. non-spousal controls</td>
<td>16 vs. 52</td>
<td>0.303</td>
<td>0.477</td>
<td>0.64–2.59</td>
</tr>
<tr>
<td></td>
<td>(8.6% vs. 11.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age and sex.

Please cite this article in press as: Arora-Singh RK, et al., Autoimmune diseases and autoantibodies in the first degree relatives of patients with systemic sclerosis, Journal of Autoimmunity (2010), doi:10.1016/j.jaut.2010.02.001


Rogers PM, Tulenbridge WM. Epidemiology and prevention of clinical and subclinical hypothyroidism. Thyroid 2002;12:839–47.


Vanderpump MP, Tulenbridge WM. Epidemiology and prevention of clinical and subclinical hypothyroidism. Thyroid 2002;12:839–47.
