Implication of \textit{IL-2/IL-21} region in systemic sclerosis genetic susceptibility

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\textbf{ABSTRACT}

\textbf{Objective} The interleukin 2 (\textit{IL-2}) and interleukin 21 (\textit{IL-21}) locus at chromosome 4q27 has been associated with several autoimmune diseases, and both genes are related to immune system functions. The aim of this study was to evaluate the role of the \textit{IL-2/IL-21} locus in systemic sclerosis (SSc).

\textbf{Patients and methods} The case control study included 4493 SSc Caucasian patients and 5856 healthy controls from eight Caucasian populations (Spain, Germany, The Netherlands, USA, Italy, Sweden, UK and Norway). Four single nucleotide polymorphisms (rs2069762, rs6822844, rs6835457 and rs907715) were genotyped using TaqMan allelic discrimination assays.

\textbf{Results} We observed evidence of association of the rs6822844 and rs907715 variants with global SSc (pc=6.6E-4 and pc=7.2E-3, respectively). Similar associations were observed for the rs6822844 polymorphism. Consistently, the rs2069762A-allele showed evidence of association with SSc and limited cutaneous SSc subtype (pc=1.7E-03 and pc=8E-4, respectively). Similar statistically significant associations were observed for the limited cutaneous form of the disease. The conditional regression analysis suggested that the most likely genetic variation responsible for the association was the rs6822844 polymorphism. Consistently, the rs2069762A:rs6822844T:rs6835457G:rs907715T allelic combination showed evidence of association with SSc and limited cutaneous SSc subtype (pc=1.7E-03 and pc=8E-4, respectively).

\textbf{Conclusions} These results suggested that the \textit{IL-2/IL-21} locus influences the genetic susceptibility to SSc. Moreover, this study provided further support for the \textit{IL-2/IL-21} locus as a common genetic factor in autoimmune diseases.

\textbf{INTRODUCTION}

Interleukin 2 (\textit{IL-2}) and interleukin 21 (\textit{IL-21}) are equally attractive biological candidates that may influence the pathogenesis of autoimmune diseases. Both are cytokines involved in the proliferation of T and B lymphocytes and different immunological activation pathways.\textsuperscript{1} Moreover, the \textit{IL-2} and \textit{IL-21} genes cover a region of approximately 200 kb that maps in the 4q27 locus. \textit{IL-2} has an important role in the maintenance of immune system homeostasis and self-tolerance. This cytokine has two paradoxical roles: promoting T cell proliferation and terminating T cell responses. Moreover, \textit{IL-2} facilitates the production of immunoglobulins through B cells and induces the differentiation and proliferation of natural killer cells.\textsuperscript{1,2} \textit{IL-21} is a potent immunomodulatory cytokine with pleiotropic effects on both innate and adaptive immune responses. These actions include the following positive effects: enhanced proliferation of lymphoid cells, increased cytotoxicity of CD8 T cells and natural killer cells, and differentiation of B cells into plasma cells. \textit{IL-21} is also produced by T helper 17 (Th17) cells and is a critical regulator of Th17 development.\textsuperscript{1,3} Genetic association studies have demonstrated that several \textit{IL-2/IL-21} polymorphisms influence the risk for autoimmune diseases (AIDs). The first evidence of this association was found in type 1 diabetes, Graves’ disease, coeliac diseases and rheumatoid arthritis.\textsuperscript{4-7} These results have been confirmed through replication studies in different populations and extended to other autoimmune diseases, such as inflammatory bowel diseases, giant cell arthritis, psoriasis and systemic lupus erythematosus (SLE).\textsuperscript{8-17} Systemic sclerosis (SSc) is a chronic fibrotic autoimmune disease in which patients are commonly classified into the following two major subgroups that are related to the specific autoantibodies against several nuclear and/or nucleolar antigens: (i) limited cutaneous SSc (lcSSc), which is related to the positive status of anticientromere autoantibodies (ACA) and (ii) diffuse cutaneous SSc (dcSSc), which is related to the positive status of antitopoisomerase
autoantibodies (ATA). More than 40 susceptibility loci to SSc have been identified during the last 10 years. Half of these variants need to be replicated in different populations and many of these variants are shared among different AIDs, especially SLE. In this regard, one single nucleotide polymorphism (SNP) of the IL-2 gene was proposed as risk factor to lcSSc subtype, but this association has not been confirmed by other studies. Moreover the IL-21 gene has been implicated as a potential driver of AIDs and recently a fine-mapping in SLE demonstrated that variants of the IL-2/IL-21 region are implicated in the genetic susceptibility to SLE. Thus, the aim of this study was to evaluate the influence of the IL-2/IL-21 region in SSc genetic susceptibility.

PATIENTS AND METHODS

Subjects

This case-control association study was comprised of 4493 SSc patients and 5896 controls of Caucasian ancestry. The discover cohort included the Spanish group, which consisted of 1176 SSc patients and 1721 healthy controls. The follow-up phase consisted of the following subjects: 609 SSc cases and 426 controls from Germany, 365 SSc cases and 754 controls from the Netherlands, 916 SSc cases and 884 controls from USA, 595 SSc cases and 1107 controls from Italy, 225 SSc cases and 273 controls from Sweden, 374 SSc cases and 456 controls from the UK and 102 SSc cases and 278 controls from Norway. There was an overlapping of 1726 SSc and 2578 controls with the previous GWAS in SSc. The patients fulfilled the 1980 American College of Rheumatology classification criteria for SSc or the criteria proposed for early SSc. In addition, the patients were classified as having lcSSc or dcSSc as described by LeRoy et al. The following clinical data were collected for the ascertainment of the clinical phenotype of the SSc patients: age, gender and presence of SSc-specific autoantibodies (Ab; ACA and ATA). The control population consisted of unrelated healthy individuals recruited in the same geographical regions as the SSc patients, and they were matched by age, sex and ethnicity with the SSc patient groups. The study was approved by local ethical committees from all the participating centres. Both patients and controls were included in the study after written informed consent was obtained.

SNP Selection and genotyping

Four SNPs of the IL-2/IL-21 region were selected for this study. The rs2069762 SNP was selected because it has been proposed to be a genetic factor of lcSSc subtype susceptibility by a study in a small Italian cohort. SSc and SLE share some immunogenetic pathways; thus, the rs6822844, rs6835457 and rs907715 polymorphisms were studied because they are the most associated variants in a recent fine-mapping of the region in SLE.

DNA from the patients and the controls were extracted from peripheral white blood cells following standard procedures. The samples were genotyped for the rs2069762, rs6822844, rs6835457 and rs907715 IL-2/IL-21 polymorphisms by using predesigned SNP genotyping assays from Applied Biosystems (Assay IDs: C__15859950_10, C__28983601_10, C__1597475_10 and C__8949748_10, respectively). TaqMan SNP genotyping was performed using a 7900HT Real-Time PCR system from Applied Biosystems following the manufacturer’s suggestions (Foster City, California, USA). In all the cohorts, the genotyping success rate was greater than 95%, and randomly selected samples were genotyped twice to verify the genotyping accuracy. Ninety-nine percent of the genotypes were identical.

RESULTS

The cases and controls of the eight Caucasian populations were in Hardy-Weinberg equilibrium at a 5% significance level. Additionally, the minor allelic frequencies of the four studied SNPs were similar to those reported by the HapMap project for the Utah residents with ancestry from northern and western Europe (CEU) population (http://hapmap.ncbi.nlm.nih.gov/). The LD structure of the eight cohorts is shown in the supplementary figure S1.

First, an association study was conducted in a Spanish case-control set, and a significant association was observed between the rs907715 SNPs minor allele and the global SSc (p=0.03, OR=0.85 95% CI 0.8 to 0.9) and the lcSSc subtype (p=0.04, OR=0.83 95% CI 0.7 to 0.9). A trend of association was observed between the minor allele of the rs822844 SNP and the global SSc (p=0.04, OR=0.84 95% CI 0.7 to 1) and lcSSc subtype (p=0.04, OR=0.79 95% CI 0.7 to 0.9). Also a trend of association was detected between the minor allele of rs6835457 and lcSSc subtype in this population (p=0.03, OR=0.87 95% CI 0.8 to 1). In contrast, no association was observed with the rs2069762 SNP (p=0.8 for both SSc and lcSSc) (see online supplementary tables S1–S3). Based on these observations, we decided to evaluate other Caucasian cohorts and to perform a meta-analysis.

Table 1 shows the meta-analysis results for the IL-2/IL-21 SNPs, the global SSc, the main SSc subtypes, the ACA and the ATA antibodies positive status. The combined analysis showed that the minor allele frequencies of the rs6822844 and rs907715 SNPs were significantly higher in controls than in SSc (p=0.06 OR=0.86 95% CI 0.79 to 0.95 and p=0.72E-3 OR=0.91 95% CI 0.85 to 0.96, respectively).
and lcSSc patients (p_c=0.01 OR=0.92 95% CI 0.85 to 1, respectively). The rs6835457 SNP also had a trend of association with global SSc and lcSSc (p_c=0.01 OR=0.87 95% CI 0.86 to 0.97 and p_value=0.03 0.86 to 0.97, respectively).

Table 1
Genotype and minor allele frequencies of meta-analysis of four IL-2/IL-21 SNPs located in SSc patients and healthy controls from European and US populations

<table>
<thead>
<tr>
<th>SNP</th>
<th>Genotype, N (%)</th>
<th>Allele test</th>
<th>MAF (%)</th>
<th>p value*</th>
<th>p_c†</th>
<th>OR (CI 95%)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1/2 Subgroup (N)</td>
<td>1/1</td>
<td>1/2</td>
<td>2/2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| rs2069762 | C/A Controls (n=5482) | 510 (9.30) | 2266 (41.34) | 2706 (49.36) | 29.97
|       | SSc (n=4281) | 429 (10.02) | 1778 (41.53) | 2074 (48.47) | 30.79
|       | lcSSc (n=2897) | 295 (10.18) | 1203 (42.05) | 730 (48.16) | 30.82
|       | ACA+ (n=1736) | 170 (9.79) | 730 (42.05) | 836 (48.16) | 29.87
|       | ATA+ (n=1031) | 94 (9.12) | 428 (41.51) | 509 (49.37) | 29.87
| rs6822844 | T/G Controls (n=5792) | 149 (2.57) | 1475 (25.47) | 4168 (71.96) | 15.31
|       | SSc (n=4407)** | 98 (2.25) | 996 (22.60) | 3313 (75.18) | 13.52
|       | lcSSc (n=2977)*** | 67 (2.25) | 659 (22.14) | 2251 (75.61) | 13.32
|       | ACA+ (n=1763) | 38 (2.16) | 395 (22.40) | 1330 (75.44) | 13.36
|       | ATA+ (n=1074) | 94 (9.12) | 428 (41.51) | 509 (49.37) | 29.87
| rs6835457 | G/A Controls (n=5720) | 668 (11.68) | 2507 (43.83) | 2545 (44.49) | 33.59
|       | SSc (n=4392)**** | 445 (10.13) | 1908 (43.44) | 2039 (46.42) | 31.85
|       | lcSSc (n=2965)***** | 312 (10.52) | 1255 (42.33) | 1398 (47.15) | 31.69
|       | ACA+ (n=1765) | 170 (9.79) | 730 (42.05) | 836 (48.16) | 29.87
|       | ATA+ (n=1074) | 29 (2.70) | 481 (45.21) | 788 (47.37) | 14.66
| rs907715 | T/C Controls (n=5644) | 670 (11.87) | 2491 (44.14) | 2543 (44.99) | 33.94
|       | SSc (n=4341)****** | 437 (10.07) | 1883 (43.38) | 2021 (46.56) | 31.76
|       | lcSSc (n=2929)******* | 307 (10.48) | 1236 (42.20) | 1386 (47.32) | 31.58
|       | ACA+ (n=1744) | 180 (10.32) | 754 (43.23) | 810 (46.44) | 31.95
|       | ATA+ (n=1056) | 109 (10.32) | 475 (45.21) | 472 (44.70) | 32.81

*All p values have been calculated for the allelic model.
**Breslow-Day p-value=0.29. Higgins’ test (I²)=17.3%. Random-effects model p-value=8.8E-04 pc=3.5E-3 Random-effects OR=0.86.
***Breslow-Day p-value=0.16. I²=33.9%. Random-effects model p-value=4.1E-03. Random-effects OR=0.86.
****Breslow-Day p-value=0.02. I²=48.6%. Random-effects model p-value=1. Random-effects OR estimate=0.93.
*****Breslow-Day p-value=0.06. I²=43.4%. Random-effects model p-value=0.11. Random-effects OR estimate=0.92.
******Breslow-Day p-value=0.09. I²=58%. Random-effects model p-value=0.08. Random-effects OR estimate=0.91.
*******Breslow-Day p-value=0.09. I²=43.7%. Random-effects model p-value=0.05. Random-effects OR estimate=0.91.
†If it is applicable, Bonferroni correction is shown.
‡OR for the minor allele.

ACA, anticentromere autoantibodies; ATA, antitopoisomerase autoantibodies; dcSSc, diffuse cutaneous SSc; NA, not applicable; SNP, single nucleotide polymorphisms; SSc, systemic sclerosis.

and lcSSc patients (p_c=0.01 OR=0.92 95% CI 0.85 to 1 and p_c=0.01 OR=0.92 95% CI 0.85 to 0.96, respectively). A trend of association was observed in the meta-analysis for the rs6822844 and rs6835457 variants and ACA positive status (p_value=0.01 OR=0.87 95% CI 0.78 to 0.97 and p_value=0.05 OR=0.92 95% CI 0.85 to 1, respectively). The rs6835457 SNP also had a trend of association with global SSc and lcSSc (p_value=0.01 OR=0.93 95% CI 0.87 to 0.98 and

Table 2
Conditional logistic regression analysis for the IL-2/IL-21 SNPs located in SSc considering the eight European and US populations as covariate

<table>
<thead>
<tr>
<th>Group of analysis</th>
<th>SNP</th>
<th>MAF Cases</th>
<th>MAF Controls</th>
<th>p value of each SNP conditioned by rs6822844</th>
<th>p value of rs6822844</th>
<th>r² with rs6822844</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSc</td>
<td>rs2069762</td>
<td>0.31</td>
<td>0.30</td>
<td>0.69</td>
<td>1.30E-03</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>rs6835457</td>
<td>0.32</td>
<td>0.34</td>
<td>0.43</td>
<td>0.024</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>rs907715</td>
<td>0.32</td>
<td>0.34</td>
<td>0.19</td>
<td>0.026</td>
<td>0.26</td>
</tr>
<tr>
<td>lcSSc</td>
<td>rs2069762</td>
<td>0.31</td>
<td>0.30</td>
<td>0.69</td>
<td>9.07E-04</td>
<td>– –</td>
</tr>
<tr>
<td></td>
<td>rs6835457</td>
<td>0.32</td>
<td>0.34</td>
<td>0.53</td>
<td>0.014</td>
<td>– –</td>
</tr>
<tr>
<td></td>
<td>rs907715</td>
<td>0.32</td>
<td>0.34</td>
<td>0.3</td>
<td>0.015</td>
<td>– –</td>
</tr>
<tr>
<td>ACA+</td>
<td>rs2069762</td>
<td>0.31</td>
<td>0.30</td>
<td>0.64</td>
<td>0.015</td>
<td>– –</td>
</tr>
<tr>
<td></td>
<td>rs6835457</td>
<td>0.32</td>
<td>0.34</td>
<td>0.81</td>
<td>0.061</td>
<td>– –</td>
</tr>
<tr>
<td></td>
<td>rs907715</td>
<td>0.32</td>
<td>0.34</td>
<td>0.56</td>
<td>0.063</td>
<td>– –</td>
</tr>
</tbody>
</table>

ACA, anticentromere autoantibodies; lcSSC, limited cutaneous SSc; MAF, minor allelic frequencies; SNP, single nucleotide polymorphisms; SSc, systemic sclerosis.

Conditional haplotype-based association analysis of four IL-2/IL-21 SNPs located according to diseases, lcSSc diseases subtype and ACA status and considering the eight European and US populations as covariates

<table>
<thead>
<tr>
<th>Allelic combination†</th>
<th>Controls</th>
<th>SSc (OR [CI 95%])</th>
<th>P*</th>
<th>Pct</th>
<th>lcSSc (OR [CI 95%])</th>
<th>P*</th>
<th>Pct</th>
<th>ACA+ (OR [CI 95%])</th>
<th>P*</th>
<th>Pct</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGGT</td>
<td>0.182</td>
<td>0.181</td>
<td>-ref-</td>
<td>-**</td>
<td>0.181</td>
<td>-ref-</td>
<td>-**</td>
<td>0.183</td>
<td>-ref-</td>
<td>-****</td>
</tr>
<tr>
<td>ATGT</td>
<td>0.152</td>
<td>0.133</td>
<td>0.89 (0.81 to 0.98)</td>
<td>4.12E-04</td>
<td>1.65E-03</td>
<td>0.131</td>
<td>0.86 (0.77 to 0.96)</td>
<td>2.01E-04</td>
<td>8.04E-04</td>
<td>0.132</td>
</tr>
<tr>
<td>GCAG</td>
<td>0.298</td>
<td>0.306</td>
<td>1.04 (0.96 to 1.12)</td>
<td>0.18</td>
<td>NA</td>
<td>0.308</td>
<td>1.03 (0.94 to 1.13)</td>
<td>0.2</td>
<td>NA</td>
<td>0.308</td>
</tr>
<tr>
<td>AGAC</td>
<td>0.369</td>
<td>0.379</td>
<td>1.04 (0.96 to 1.13)</td>
<td>0.1</td>
<td>NA</td>
<td>0.38</td>
<td>1.03 (0.94 to 1.13)</td>
<td>0.2</td>
<td>NA</td>
<td>0.377</td>
</tr>
</tbody>
</table>

†The order of the SNPs is rs2069762, rs6822844, rs6835457, rs907715.

1p_{value} of the likelihood ratio test. Based on WHAP method.

**Omnibus test X^2 = 14.5 (df = 3); p-value = 2.35E-03; P_{c} = 9.4E-03.

***Omnibus test X^2 = 14.5 (df = 3); p-value = 2.2E-03; P_{c} = 9.2E-03.

****Omnibus test X^2 = 8.92 (df = 3); p-value = 0.03; P_{c} = 0.12.

ACA, antcenromere autoantibodies; lcSSc, limited cutaneous SSc; SNP, single nucleotide polymorphisms; SSc, systemic sclerosis.
significant association for rs2069762 might stem from type 1 statistical error. This fact together with the location of the associated SNP suggests a highlighted role of the IL-21 cytokine. By examining the expression and regulation of IL-21 and the IL-21 receptor (IL-21R) in patients with SSc, a previous study demonstrated an upregulation of IL-21R in epidermis samples. However, a recent study has demonstrated that the scleroderma burden in allogeneic haemopoietic stem cell transplantations is driven by Th17 induction via IL-21 and IL-23 signalling. Together, these results suggest that IL-21/IL-21R signalling has a pathogenic function in SSc.

The role of IL-2 and IL-21 in the immune system makes these genes plausible candidates for the genetic component of autoimmune diseases. The rs682284 polymorphism confers the best association signal for SSc. It is a susceptibility region (rs13132245, rs13122573, rs4459999, rs15151961, rs13140464, rs6814280 and rs2069778), but clear evidence that connects any of these variants with the rs6822844 signalling has a pathogenic function in SSc. To conclude, consistent with previous studies on autoimmune diseases, the IL-2/IL-21 region is a susceptibility genetic factor for SSc and its lcSSc subtype. The rs682284 polymorphism confers the best association signal for SSc. It is also worth mentioning that this study shows the importance of the study of different populations and broad collaboration to find the missing heritability for relatively rare diseases like SSc.

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Contributors All the authors listed participated in all or at least one of these activities: Conception and design, acquisition of data or analysis and interpretation of data. Drafting the article or revising it critically for important intellectual content. Final approval of the version published.

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Basic and translational research

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