EXTENDED REPORT

Novel identification of the IRF7 region as an anticientromere autoantibody propensity locus in systemic sclerosis

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ABSTRACT

Objective Systemic sclerosis (SSc) and systemic lupus erythematosus (SLE) are related chronic autoimmune diseases of complex aetiology in which the interferon (IFN) pathway plays a key role. Recent studies have reported an association between IRF7 and SLE which confers a risk to autoantibody production. A study was undertaken to investigate whether the IRF7 genomic region is also involved in susceptibility to SSc and the main clinical features.

Methods Two case-control sets of Caucasian origin from the USA and Spain, comprising a total of 2316 cases of SSc and 2347 healthy controls, were included in the study. Five single nucleotide polymorphisms (SNPs) in the PHRF1-IRF7-CDHR5 locus were genotyped using TaqMan allelic discrimination technology. A meta-analysis was performed to test the overall effect of these genetic variants on SSc.

Results Four out of five analysed SNPs were significantly associated with the presence of anticientromere autoantibodies (ACA) in the patients with SSc in the combined analysis (rs1131665: \( P_{\text{FDR}} = 6.14 \times 10^{-4} \), OR = 0.98; rs4963128: \( P_{\text{FDR}} = 6.14 \times 10^{-4} \), OR = 0.79; rs1202966: \( P_{\text{FDR}} = 3.83 \times 10^{-3} \), OR = 0.82; and rs2246614: \( P_{\text{FDR}} = 3.83 \times 10^{-3} \), OR = 0.83). Significant p values were also obtained when the disease was tested globally; however, the statistical significance was lost when the ACA-positive patients were excluded from the study, suggesting that these associations rely on ACA positivity. Conditional logistic regression and allelic combination analyses suggested that the functional IRF7 SNP rs1131665 is the most likely causal variant.

Conclusions The results show that variation in the IRF7 genomic region is associated with the presence of ACA in patients with SSc, supporting other evidence that this locus represents a common risk factor for autoantibody production in autoimmune diseases.

INTRODUCTION

Systemic sclerosis (SSc) is a chronic fibrotic autoimmune disease in which autoantibodies against several nuclear and/or nucleolar antigens are commonly produced; however, each SSc-associated antibody specificity tends to be mutually exclusive in distinct clinical subsets of the disease. Thus, they are important diagnostic and prognostic markers in clinical practice. Although antinuclear autoantibodies are detected in different connective tissue autoimmune diseases, SSc shows its own particular autoantibody profile that tends not to overlap with that of other related diseases. In SSc the two major subclasses of specific autoantibodies are the anticientromere autoantibodies (ACA), which are related to limited skin involvement and an increased risk of pulmonary arterial hypertension, and the antitopoisomerase autoantibodies (ATA), which confer susceptibility to diffuse skin and pulmonary fibrosis with an increased mortality.1−3

SSc has a complex aetiology with multiple susceptibility genes interacting for the development of the disease in concert with epigenetic and environmental factors. It is likely that an imbalance between risk and protective loci is a key factor contributing to the predisposition and clinical phenotype of SSc.4 Recent candidate gene and genome-wide association studies (GWAS) have identified several markers that are clearly associated with SSc.5 Noteworthy are the associations reported for STAT4 and IRF5, since polymorphisms of these genes showed the strongest signals outside the HLA region in a recent GWAS of SSc.6 These two genes are representative regulators in the interferon (IFN) pathway, which comprise a large number of cytokines with different modulatory effects on innate and adaptive immunity. In this regard, type I IFNs were reported to have a central aetiopathogenic role in the development and progression of systemic lupus erythematosus (SLE).7 Interestingly, a type I IFN signature similar to that described in SLE has also been observed in microarray analyses of peripheral blood and skin cells of patients with SSc.8,9

Interferon regulatory factor 7 (IRF7) has recently been described as a susceptibility locus for SLE.10,11 This gene encodes a member of the IFN regulatory transcription factor family, which plays a key role in the IFN-inducible pathway by activating type I IFN genes in response to viral infection or DNA/RNA-containing immune complexes.12 Hence, tight regulation of IRF7 expression and activity is...
crucial for appropriate IFN-mediated physiological functions.\textsuperscript{14} Taking into account the genetic similarities between SSc and SLE\textsuperscript{4,9,15} we aimed to investigate whether variation within this genomic region is also involved in SSc susceptibility and/or its major clinical and autoantibody manifestations.

**METHODS**

**Study population**

Two independent Caucasian populations, a discovery cohort from the USA and a replication cohort from Spain, were analysed in this study, comprising a total of 2516 SSc cases and 2347 unrelated healthy individuals recruited in the same geographical areas and matched by age, sex and ethnicity. The US cohort was composed of 1282 cases of SSc and 875 controls. Samples from patients in the USA came from the Scleroderma Registry and DNA Repository, Genetics versus Environment in Scleroderma Outcomes Study (GENISOS) and the rheumatology divisional collection evaluated at the University of Texas Health Science Center at Houston. The Spanish cohort consisted of 1034 cases of SSc and 1472 controls from previously established collections with nationally representative recruitment. Clinical features of the patients from both cohorts are summarised in table 1.

All patients with SSc fulfilled the 1980 American College of Rheumatology classification criteria for this disease\textsuperscript{16} or had at least three of the five CREST (Calcinosis, Raynaud’s phenomenon, Esophageal dysmotility, Sclerodactyly, Telangiectasias) features.\textsuperscript{17} Case sets were further subdivided based on their skin involvement into limited cutaneous scleroderma (lcSSc) and diffuse cutaneous scleroderma (dcSSc) subgroups,\textsuperscript{18} and by autoantibody status according to the presence of ACA or ATA. ACAs were determined by their characteristic distinctive pattern on fusion against calf thymus extract (Inova Diagnostics, Davis, California, USA).

**SNP selection and genotyping**

Four single nucleotide polymorphisms (SNPs), rs12286521, rs4963128, rs702966 and rs2246614, which span a 48 kb genomic region including PHD and ring finger domains 1 (PHRF1, also known as KIAA1542), cadherin-related family member 5 (CDHR5) and IRF7 genes were selected to tag haplotype blocks present in the CEU HapMap reference dataset, as described previously.\textsuperscript{10} A fifth SNP within the IRF7 gene, rs1131665, was also included in the study because it produces a non-synonymous change in the DNA sequence (Q412R) and has recently been genotyped for the above PHRF1-IRF7-CDHR5 genetic variants using TaqMan 5’ allele discrimination assays (rs12286521, rs4963128, rs702966 and rs2246614 were predesigned assays with IDs: C_26650291_10, C_1611594_10, C_7470754_10 and C_16061601_10, and rs1131665 was designed as a custom assay) in a 7900HT Fast Real-Time PCR System (Applied Biosystems, Foster City, California, USA).

**Statistical analysis**

The statistical power of the combined analysis was >99% for all the SNPs to detect associations with OR=1.3 at the 5% significance level, according to Power Calculator for Genetic Studies 2006 software which uses the methods described by Skol et al.\textsuperscript{19}

All statistical analyses of the allele frequencies were carried out using the Linux software PLINK V.1.07 (http://pngu.mgh.harvard.edu/purcell/plink/).\textsuperscript{20} To test for association, 2 × 2 contingency tables and χ² and/or Fisher exact tests, when appropriate, were used to calculate p values. OR and 95% CIs were obtained according to the Woolf method. Mantel–Haenszel tests under fixed effects or random effects (DerSimonian–Laird), when necessary, were performed to submit the combined data to meta-analysis and the Breslow–Day method was used to estimate the homogeneity among the two cohorts. The Benjamini and Hochberg step-up false discovery rate (FDR) control correction\textsuperscript{21} for multiple testing was applied to the p values in the analyses of the discovery cohort and in the combined meta-analyses; p values <0.05 were considered statistically significant.

Dependency of association between each SNP and every studied genetic variant was determined by conditional logistic regression analysis as implemented in PLINK. We also analysed the different allelic combinations using PLINK and Haploview (V.4.2).\textsuperscript{22} Allelic combinations with a frequency <5% in control groups were excluded from the analysis. Meta-analyses of the different allelic combinations were performed using PLINK and StatsDirect V.2.6.6 (StatsDirect, Altrincham, UK).

**RESULTS**

In all cohorts the genotyping success rate was >95% and there was no significant departure from Hardy–Weinberg equilibrium at the 5% significance level. In addition, control allelic frequencies of rs4963128, rs702966, rs1131665 and rs12286521 were similar to those reported for the CEU population in the HapMap project (http://hapmap.ncbi.nlm.nih.gov/). The genetic variant rs1131665 was not genotyped in HapMap; however, the minor allele frequency that we have observed for this SNP in the control population is in agreement with previous published data.\textsuperscript{11}

**Independent analyses**

We first investigated whether these five representative polymorphisms within the genomic region around the IRF7 locus were associated with SSc and clinical/autoantibody phenotypes in a large Caucasian US cohort (see table S1 in online supplement). This preliminary analysis showed significant differences in allele frequencies between the ACA-positive subgroup and the control set for rs1131665 (pFDR=3.09 × 10⁻³, OR=0.70, CI 95% 0.57 to 0.87), rs702966 (pFDR=3.09 × 10⁻³, OR=0.71, CI 95% 0.58 to 0.83), rs4963128 (pFDR=0.028, OR=0.79, CI 95% 0.65 to 0.96) and rs2246614 (pFDR=0.046, OR=0.82, CI 95% 0.68 to 0.99). To further explore the possible involvement of the IRF7 region in ACA susceptibility, a second large and well-defined Caucasian cohort from Spain was genotyped (see table S2 in online supplement). Three of

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**Table 1** Main clinical features of patients with systemic sclerosis (SSc) included in the study

<table>
<thead>
<tr>
<th>Feature</th>
<th>Spain, n (%)</th>
<th>USA, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>923 (88.99)</td>
<td>1137 (88.69)</td>
</tr>
<tr>
<td>Men</td>
<td>114 (11.01)</td>
<td>145 (11.31)</td>
</tr>
<tr>
<td>lcSSc</td>
<td>710 (68.67)</td>
<td>789 (61.54)</td>
</tr>
<tr>
<td>dcSSc</td>
<td>324 (31.33)</td>
<td>493 (38.46)</td>
</tr>
<tr>
<td>ACA+</td>
<td>478 (46.23)</td>
<td>357 (27.85)</td>
</tr>
<tr>
<td>ACA−</td>
<td>528 (51.06)</td>
<td>778 (60.69)</td>
</tr>
<tr>
<td>ATA+</td>
<td>228 (21.86)</td>
<td>205 (15.99)</td>
</tr>
<tr>
<td>ATA−</td>
<td>757 (73.21)</td>
<td>928 (72.39)</td>
</tr>
</tbody>
</table>

Data are referred to the total analysed individuals.

ACA, anticientromere antibodies; ATA, antitopoisomerase antibodies; dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis.
Meta-analysis

Since no heterogeneity of the ORs among the US and Spanish populations was observed, a combined meta-analysis was performed to increase the statistical power and hence to obtain more accurate estimates of susceptibility (table 2). The Mantel–Haenszel test under an allelic model revealed strong association signals in the ACA analysis for rs1131665 ($p_{FDR}=6.14 \times 10^{-3}$, OR=0.90, CI 95% 0.76 to 1.06). Since no heterogeneity of the ORs among the US and Spanish populations was observed, a combined meta-analysis was performed to increase the statistical power and hence to obtain more accurate estimates of susceptibility (table 2). The Mantel–Haenszel test under an allelic model revealed strong association signals in the ACA analysis for rs1131665 ($p_{FDR}=6.14 \times 10^{-3}$, OR=0.90, CI 95% 0.76 to 1.06).

Table 2 Genotype and minor allele frequencies of SNPs located around the IRF7 locus in Caucasian patients with systemic sclerosis (SSc) and healthy controls from Spain and the USA

<table>
<thead>
<tr>
<th>SNP</th>
<th>Genotype, N (%)</th>
<th>M–H allele test</th>
<th>p Value*</th>
<th>pFDR†</th>
<th>OR (CI 95%)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1131665</td>
<td>G/A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>(n=2260)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/1</td>
<td>165 (7.30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/2</td>
<td>1156 (51.15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAF (%)</td>
<td>0.713</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs2246614</td>
<td>C/G</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>(n=2258)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/1</td>
<td>164 (7.26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/2</td>
<td>1174 (51.98)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAF (%)</td>
<td>0.713</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*All p values have been calculated for the allelic model.
†Benjamini and Hochberg (1995) step-up FDR control.
‡OR for the minor allele.

ACA, anticitrulline antibodies; ATa, anti-topoisomerase antibodies; dcSSc, diffuse cutaneous systemic sclerosis; FDR, false discovery rate; lcSSc, limited cutaneous systemic sclerosis; MAF, minor allele frequency; M–H, Mantel–Haenszel test under fixed effect; SNP, single nucleotide polymorphism; SSc, systemic sclerosis.
rs2246614 is indeed carried out to investigate whether genetic variants, which have been correlated with increased disease activity and specific autoantibody profiles in patients with SLE. Recent studies have also shown a dysregulation of the type I IFN pathways in patients with SSc compared with healthy controls. In this regard, it is likely that type I IFN molecules increase the inflammatory potential of dermal fibroblasts through the upregulation of Toll-like receptors. In addition, several genetic variants in the IFN pathway, including polymorphisms within IRF5 and STAT4 loci, have been reported to be associated with both SLE and SSc susceptibility. Hence, it is likely that the presence of a type I IFN signature is also of special relevance in the pathophysiology of SSc.

Despite the fact that no functional or mechanistic data have been obtained, which is certainly an important limitation of this study, our results clearly indicate that the IRF7 genomic region is a susceptibility locus for SSc and may confer disease risk through a role in ACA production. This is supported by the fact that the statistical significance observed when the global disease and the limited/diffuse subsets were tested was lost when the ACA-positive patients were removed from the analyses. Four of the five polymorphisms analysed showed strong evidence of association with ACA production. In relation to rs2246614, this genetic variant is specifically located within the IRF7 adjacent gene CDHR5, a novel mucin-like gene member of the cadherin superfamily whose specific function has not yet been determined. Interestingly, rs2246614 corresponds to a non-synonymous modification (R357S), although its possible functional implication is still unknown. Our logistic regression data indicate that this SNP may be tagged by rs1131665 and/or rs702966. However, since the remaining p values of the latter data indicate that this SNP may be tagged by rs1131665 and/or rs702966, further studies should be carried out to investigate whether CDHR5 rs2246614 is indeed involved in SSc susceptibility or simply reflects association signals within IRF7. In relation to the analysed IRF7-PHRF1 genetic variants, rs4963128 and rs702966 were highly associated with the presence of ACA in our study. Interestingly, GWAS data showed a strong association between rs4963128 and SLE, and subsequent studies suggested that this association is probably specific for autoantibody production. On the other hand, the

### Table 3

Conditional logistic regression analysis for the PHRF1-IRF7-CDHR5 SNPs in ACA data considering the two populations as covariate

<table>
<thead>
<tr>
<th>SNP</th>
<th>MAF (cases)</th>
<th>MAF (controls)</th>
<th>p Value: add to rs1131665</th>
<th>rs1131665 p value: add to SNP</th>
<th>OR (95% CI)</th>
<th>USA</th>
<th>Spain</th>
<th>p MH</th>
<th>USA</th>
<th>Spain</th>
<th>p MH</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1131665</td>
<td>0.23</td>
<td>0.28</td>
<td>NA</td>
<td>NA</td>
<td>1.29</td>
<td>0.2595</td>
<td>0.2427</td>
<td>0.62</td>
<td>0.2427</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>rs4963128</td>
<td>0.28</td>
<td>0.33</td>
<td>0.2427</td>
<td>0.2595</td>
<td>0.62</td>
<td>0.70</td>
<td>0.4099</td>
<td>0.2185</td>
<td>0.66</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>rs702966</td>
<td>0.24</td>
<td>0.28</td>
<td>0.5861</td>
<td>0.2446</td>
<td>0.93</td>
<td>0.97</td>
<td>0.0499</td>
<td>0.2185</td>
<td>0.66</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>rs2246614</td>
<td>0.31</td>
<td>0.34</td>
<td>0.2980</td>
<td>0.0283</td>
<td>0.33</td>
<td>0.41</td>
<td>0.4222</td>
<td>0.0283</td>
<td>0.41</td>
<td>0.39</td>
<td></td>
</tr>
</tbody>
</table>

(see table S3 in online supplement) showed statistically significant differences for rs1131665 (pFDR=0.015, OR=0.80, CI 95% 0.69 to 0.93), rs4963128 (pFDR=0.005, OR=0.05, CI 95% 0.74 to 0.98) and rs702966 (pFDR=0.029, OR=0.83, CI 95% 0.72 to 0.96), which strengthens the consistency of our results.

### Table 4

Pooled analysis of rs4963128–rs1131665 allelic combinations according to disease and ACA status

<table>
<thead>
<tr>
<th>Allelic combination</th>
<th>Controls, n (%)</th>
<th>SSc, n (%)</th>
<th>OR (95% CI)</th>
<th>P BD</th>
<th>ACA+, n (%)</th>
<th>OR (95% CI)</th>
<th>P BD</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA</td>
<td>2920 (65.53)</td>
<td>3048 (68.19)</td>
<td>4.63E-03</td>
<td>1.14 (1.04 to 1.25)</td>
<td>0.72</td>
<td>1151 (70.70)</td>
<td>2.02E-04</td>
</tr>
<tr>
<td>AG</td>
<td>1180 (26.48)</td>
<td>1077 (24.09)</td>
<td>0.015</td>
<td>0.89 (0.80 to 0.98)</td>
<td>0.64</td>
<td>362 (22.24)</td>
<td>8.43E-04</td>
</tr>
<tr>
<td>AA</td>
<td>294 (6.60)</td>
<td>283 (6.33)</td>
<td>0.321</td>
<td>0.91 (0.77 to 1.08)</td>
<td>0.12</td>
<td>98 (6.02)</td>
<td>0.447</td>
</tr>
<tr>
<td>GG</td>
<td>62 (1.40)</td>
<td>62 (1.39)</td>
<td>0.962</td>
<td>0.98 (0.68 to 1.40)</td>
<td>0.99</td>
<td>17 (1.04)</td>
<td>0.559*</td>
</tr>
</tbody>
</table>


As none of the remaining allelic combinations between the four two most associated SNPs, rs4963128 and rs1131665 (table 4), as none of the remaining allelic combinations between the four associated SNPs increased their statistical significance (see table S4 in online supplement). However, the strength of the ACA association observed in the allelic combinations was not higher than that observed for rs4963128 and rs1131665 in the independent analysis (table 2).

### DISCUSSION

IRF7 has been shown to be a master factor in the transcriptional activation of type I IFN genes which encode proteins that are key regulators of the immune system. Upregulated expression levels of type I IFN-inducible genes in peripheral blood cells


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3'-untranslated region PHRF1 SNP rs702966 was also found to be associated with the presence of anti-double-stranded DNA (anti-dsDNA) antibodies in patients with SLE. Owing to the LD structure of the PHRF1-IRF7 genomic region, the associations of both SNPs—which are located 23 kb and 0.6 kb telomeric to IRF7, respectively—have been proposed to be representative of the SLE association signals within the IRF7 gene. Moreover, autoantibody-positive SLE patients carrying rs4963128 and/or rs702966 risk genotypes exhibited increased serum levels of IFNα,10 thus suggesting that these polymorphisms may be tagged by a causal IRF7 SNP. Supporting this notion, the analysis of the LD structure of our cohorts showed that rs1131665 is in strong LD with rs4963128 and in nearly complete LD with rs702966. This strong correlation between the alleles of these SNPs made it impossible to discern the true susceptibility variant. Nevertheless, we speculate that the best candidate should be rs1131665, since it produces a non-synonymous change (Q412R) located in exon 5 of the IRF7 gene. It has been reported that the risk allele of this SNP leads to increased activation of IRF7 in vitro, correlated with SLE susceptibility in populations of different ethnicity. This functional IRF7 variant showed the highest association signal with ACA production in our meta-analysis, and the genetic combinations that were associated with ACA susceptibility did not reach higher statistical significance than that observed in the independent analysis of rs1131665. The LD pattern of rs1131665 is not yet clear because it was not genotyped in the reference population of the HapMap project. However, since this IRF7 variant has been shown to have functional consequences in the downstream interferon pathway, it may represent the causal SNP of this association. In any case, this genomic region should be analysed in more detail to determine definitively whether rs1131665 is the tagger SNP or whether there are other independent signals.

In summary, together with previous findings, our results strongly suggest that the IRF7 genomic region plays an important role in ACA production among patients with SSc. The fact that this same locus is also associated with a specific autoantibody profile in SLE indicates that common immunological pathways may underlie both diseases. Supporting this idea, previous studies have reported that SLE showed the strongest familial accumulation in patients with SSc and that ACA positivity was associated with polyautoimmunity in SSc families. However, the main limitation of this study is the lack of functional data that would be essential for a better understanding of how IRF7 leads to a specific autoantibody profile in autoimmunity. More comprehensive studies therefore need to be performed to elucidate the causal polymorphism(s) of this association and to identify the molecular mechanisms involved in the production of autoantibodies, with the aim of developing more effective therapeutic strategies in autoimmune diseases.

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Competing interests None.

Ethics approval Ethical approval was obtained from the Committee for the Protection of Human Subjects of the University of Texas Health Science Center at Houston (USA) and the Instituto de Parasitología y Biomedicina López-Neyra, Consejo Superior de Investigaciones Científicas (Granada, Spain) and informed written consent was obtained from all participants in accordance with the tenets of the Declaration of Helsinki.

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- \textit{Systemic lupus erythematosus} (389 articles)
- \textit{Genetics} (607 articles)

\textbf{Notes}

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