A GWAS follow-up study reveals the association of the IL12RB2 gene with systemic sclerosis in Caucasian populations


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A single-nucleotide polymorphism (SNP) at the *IL12RB2* locus showed a suggestive association signal in a previously published genome-wide association study (GWAS) in systemic sclerosis (SSc). Aiming to reveal the possible implication of the *IL12RB2* gene in SSc, we conducted a follow-up study of this locus in different Caucasian cohorts. We analyzed 10 GWAS-genotyped SNPs in the *IL12RB2* region (2309 SSc patients and 5161 controls). We then selected three SNPs (rs3790567, rs3790566 and rs924080) based on their significance level in the GWAS, for follow-up in an independent European cohort comprising 3344 SSc and 3848 controls. The most-associated SNP (rs3790567) was further tested in an independent cohort comprising 597 SSc patients and 1139 controls from the USA. After conditional logistic regression analysis of the GWAS data, we selected rs3790567 [P\text{MH} = 1.92 \times 10^{-5} \text{ odds ratio (OR)} = 1.19] as the genetic variant with the firmest independent association observed in the analyzed GWAS peak of association. After the first follow-up phase, only the association of rs3790567 was consistent (P\text{MH} = 4.84 \times 10^{-3} \text{ OR} = 1.12). The second follow-up phase confirmed this finding (P_{X2} = 2.82 \times 10^{-4} \text{ OR} = 1.34). After performing overall pooled-analysis of all the cohorts included in the present study, the association found for the rs3790567 SNP in the *IL12RB2* gene region reached GWAS-level significant association (P_{MH} = 2.82 \times 10^{-9} \text{ OR} = 1.17). Our data clearly support the *IL12RB2* genetic association with SSc, and suggest a relevant role of the interleukin 12 signaling pathway in SSc pathogenesis.

**INTRODUCTION**

Systemic sclerosis or scleroderma (SSc) is a rare complex connective tissue disorder characterized by extensive fibrosis of multiple organs produced by vascular damage and autoimmune dysfunction (1,2). Patients are commonly classified into two major subgroups: the limited cutaneous SSc (lcSSc) and the diffuse cutaneous (dcSSc) form of the disease (3). Positive auto-antibody titers are a main feature of this disabling condition, especially anticientromere autoantibodies (ACA) and antitopoisomerase autoantibodies (ATA) (1,2). To date, a number of genes have been implicated in an increased susceptibility to SSc, confirming the genetic component of this complex disease (4,5). Some of these genes are shared with other related autoimmune diseases, supporting the idea of common pathogenic pathways underlying autoimmune imbalance (6,7).

Recently, our group published the first genome-wide association study (GWAS) conducted in Caucasian SSc patients (5). GWASs are often followed by follow-up studies focused on the regions where association peaks are observed, not only in the associations which reached the GWAS significance level, but also those which are below the GWAS level but might result in true association with the disease. In this line, a single-nucleotide polymorphism (SNP) at the *IL12RB2* locus showed a suggestive association signal in the previously mentioned GWAS [P\text{MH} = 1.92 \times 10^{-5} \text{ odds ratio (OR)} = 1.19 (1.10–1.29)] (5).

Noteworthy, interleukin 12 (IL-12) binding to its receptor powerfully induces IFNγ production and promotes Th helper differentiation in Th1 cells (8). In addition, several experimental and clinical studies have implicated IL-12 and IFNγ in the development of autoimmune inflammation (8,9). The IL-12 receptor (IL-12R) comprises two subunits, IL-12R β1 subunit (IL-12Rβ1) and IL-12R β2 subunit (IL-12Rβ2), which are both homologous to gp130 (a shared component of the receptors for several type I cytokines) (10). *IL12RB2* encodes IL-12Rβ2, which constitutes the transducing component of the receptor heterodimer and recruits different tyrosine kinases, signal transducers and activators of transcription (11–13). Interestingly, animal models lacking IL12Rβ2 signaling develop autoimmune events (14). Moreover, polymorphisms in the *IL12RB2* gene region and upstream this locus have been related to several human autoimmune disorders, such as psoriasis (PS) (15), primary biliary cirrhosis (PBC) (16), Behçet disease (17,18) and giant cell arteritis (GCA) (19).

Hence, with the aim of investigating the possible role of the *IL12RB2* gene in SSc, we conducted a GWAS follow-up study in different European and US Caucasian cohorts.

**RESULTS**

*IL12RB2* region analysis in the GWAS set

Ten SNPs in the *IL12RB2* region were included in the initial GWAS analysis set, six of them were found to be significantly associated with SSc, but only four remained significant after GC correction (Table 1). However, conditioned logistic regression revealed that among the initially observed associations, only the rs3790567 association was independent from the others (Table 1). HapMap linkage disequilibrium patterns defined rs3790566 (not included in the GWAS phase) as the unique tag-SNP for rs3790567. Hence, both the most-associated SNP (rs3790567) and this tag-SNP (rs3790566) were selected for replication.

Despite the loss of the observed association after correction for multiple testing (Table 1), we also included rs924080 in the first follow-up phase. This genetic variant was located in the intergenic region between *IL12RB2* and *IL23R*, and it was the last GWAS SNP contained in the *IL23R* haplotype block (Fig. 1). In addition, this polymorphism mapped in a recombination hotspot identified in the HapMap Project (Phase II, Caucasian and Asian populations; http://www.hapmap.org) and previous reports (17).

**European follow-up phase**

Table 2 shows the pooled analysis of seven independent white European cohorts of the three SNPs analyzed in the first follow-up phase. No evidence of association was observed...
for rs924080. Despite an initial association of rs3790566 and rs3790567, after performing Bonferroni multiple test correction only the association of rs3790567 remained significant (Table 2). The pooled analysis of this genetic variant in the GWAS cohort and the independent follow-up set reached a notable statistically significant association \( P_{\text{MH}} = 5.19 \times 10^{-7} \) (OR = 1.16 (1.09–1.22), Table 3).

The subgroup and autoantibody titer stratified pooled analyses comprising the GWAS and the European follow-up cohorts showed firm statistically significant risk association signals in all the subgroups of the disease considered (Supplementary Material, Tables S1–S2).

### US follow-up phase

In order to confirm the rs3790567 signal, an independent US cohort was included (597 SSc and 1139 controls). Case–control frequency analysis revealed another strong association \( P_{\text{GC}} = 2.82 \times 10^{-4} \) OR = 1.34 (1.14–1.57), Table 3). After stratification, only lcSSc subgroup reached statistical significance, probably due to a lack of power since the other subgroups are relatively smaller (Supplementary Material, Tables S1–S2).

The overall pooled analysis of rs3790567 comprising the GWAS set and the both the European and the US follow-up sets reached GWAS-level statistically significant association in the whole set of SSc patients \( P_{\text{MH}} = 2.82 \times 10^{-4} \) OR = 1.17 (1.11–1.24)) and remained significant after stratification in all the subgroups (Table 3 and Supplementary Material, Tables S1–S2). Hence, we suggest that the association found in rs3790567 most likely belonged to the whole SSc set of patients rather than any of its subgroups. The rs3790567 individual population allele distributions and association tests are shown in Supplementary Material, Tables S3–S5.

### IL23R locus dependence analysis

Aiming to further confirm the independence of the reported IL12RB2 signal from the IL23R locus, we analyzed the association of the SNPs in the IL23R region which were included in the GWAS initial phase and their effect on the IL12RB2 rs3790567 association. The IL23R region comprised 27 SNPs and only 4 of them showed some marginal association with SSc, considering uncorrected \( P \)-values (Supplementary Material, Table S7). Nevertheless, the association observed in rs3790567 was found independent of these weak signals (Supplementary Material, Table S7).

### DISCUSSION

Our data clearly support an association of IL12RB2 rs3790567 with SSc. The risk effect of the IL12RB2 rs3790567 minor allele is consistent in all the analyzed cohorts with the exception of the Italian population. In contrast to other cohorts, the minor allele rs3790567*A is over-represented in controls compared with SSc patients in the Italian sample set. The Italian control group showed the highest minor allele frequency among all the included populations, and the linkage disequilibrium between rs3790567 and rs3790566 in the Italian cohort was considerably lower \( r^2 = 0.70 \) than in the other European populations \( r^2 > 0.90 \). In addition, this over-representation of the rs3790567*A minor allele is also observed in the TSI (Tuscan in Italy) population in the HapMap Project (Phase III) (MAF_{TSI} = 0.30) when compared with the CEU population (MAF_{CEU} = 0.26). However, the linkage disequilibrium observed between rs3790567 and rs3790566 in the Hapmap TSI population compared with the CEU population decreased very slightly \( r^2_{TSI} = 0.97, r^2_{CEU} = 1 \). Hence, it is likely that the observed discrepancies in the Italian subset were due to ethnic differences in linkage disequilibrium patterns. Supporting this notion, BD test revealed significant heterogeneity in the lcSSc overall pooled analysis caused by the Italian patients (\( P_{\text{BD}} \) with the Italian population = 0.04; \( P_{\text{BD}} \) without the Italian population = 0.45). Although cases and controls were geographically matched, the potential effect of population substructure in the replication cohorts could not be controlled by deriving principal components on a population-specific basis, as it was performed for the GWAS cohorts, due to the lack of high-throughput genotype information for these individuals. Considering the reported heterogeneous genetic background for Italian populations (20), the influence of this factor on the deviation observed in our Italian subset cannot be ignored.
As stated above, different IL12RB2 genetics variants have been associated with multiple autoimmune disorders (15–19). However, the fact that the same IL12RB2 variant, rs3790567, has been associated with increased susceptibility to both PBC and GCA (16,19), together with the lack of association in our data of a nearby highly linked variant (rs3790566), suggest that rs3790567 intronic SNP may be tagging a functional variant or even has a yet unknown functional implication itself.

The IL12RB2 gene maps close to the IL-23R coding gene (IL23R), which are located <50 kb from each other. IL-23R binds IL-12Rβ1 chain constituting the heterodimeric receptor for IL-23 (21). Although IL23R polymorphisms have been associated with different autoimmune diseases (22–28), its implication in SSc is not clear (29–31). In this report, conditional regression analyses showed that the association of IL12RB2 rs3790567 with SSc is independent from all the studied IL23R genetic polymorphisms, even from IL23R rs11209026 (Arg281Gln) missense variant. Hence, we suggest that the reported association of the IL12RB2 gene with SSc susceptibility does not rely on the IL23R locus. Nevertheless, further studies will be necessary to investigate the possible effect of IL12RB2 genetic variants on IL23R gene expression.

IL-12 levels are increased in the serum of SSc patients as well as in the alveolar lavage fluid (BAL-f) from patients with SSc-associated interstitial lung disease (ILD) (32,33). Although IL-12 classical implication in immune imbalance

### Table 2. Genotype and allele distribution of IL12RB2 genetic variants in the European SSc patients and controls follow-up study (3344 SSc/3848 controls)

<table>
<thead>
<tr>
<th>SNP</th>
<th>1/2</th>
<th>CTRL 1/1 (n)</th>
<th>CTRL 1/2 (n)</th>
<th>CTRL 2/2 (n)</th>
<th>SSc 1/1 (n)</th>
<th>SSc 1/2 (n)</th>
<th>SSc 2/2 (n)</th>
<th>MAF</th>
<th>P_MH</th>
<th>OR</th>
<th>95% CI</th>
<th>P_BD</th>
<th>95% CI</th>
<th>P_BD</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs924080</td>
<td>C/T</td>
<td>0.22 (827)</td>
<td>0.48 (1807)</td>
<td>0.29 (1094)</td>
<td>0.46</td>
<td>0.22 (687)</td>
<td>0.49 (1545)</td>
<td>0.30 (934)</td>
<td>0.46</td>
<td>0.96</td>
<td>1.00</td>
<td>0.93–1.07</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>rs3790566</td>
<td>T/C</td>
<td>0.08 (280)</td>
<td>0.37 (1334)</td>
<td>0.55 (1978)</td>
<td>0.26</td>
<td>0.09 (273)</td>
<td>0.39 (1196)</td>
<td>0.52 (1617)</td>
<td>0.28</td>
<td>3.35 × 10^{-2}</td>
<td>1.09</td>
<td>1.01–1.18</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>rs3790567</td>
<td>A/G</td>
<td>0.08 (241)</td>
<td>0.37 (1169)</td>
<td>0.56 (1773)</td>
<td>0.26</td>
<td>0.09 (282)</td>
<td>0.38 (1187)</td>
<td>0.52 (1616)</td>
<td>0.28</td>
<td>4.84 × 10^{-3}</td>
<td>1.12</td>
<td>1.04–1.22</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

SSc, systemic sclerosis patients; CTRL, healthy controls; 1/2, minor allele/major allele; MAF, minor allele frequency; P_MH, allelic Mantel–Haenszel fixed effects model P-value; OR, odds ratio; 95% CI, 95% confidence interval; P_BD, Breslow–Day test P-value; NS, not statistically significant.

Figure 1. GWAS phase of the IL12RB2 region. Regional association plot, recombination rate, linkage disequilibrium pattern and pairwise r² of the SNPs with rs3790567.

Table 2.
has been mainly related to a pro-inflammatory cell-mediated immunity and Th1 response (9) and increased levels of IL-12 correlate with renal vascular damage (32), the role of IL-12 in SSc pathogenesis should be considered cautiously. Indeed, SSc patients and especially those with ILD have a Th2-polarized response (34). Additionally, it has been suggested that IL-12 drives a drift from a Th2 to Th1 response which improves skin score in SSc patients (35). Moreover, IL-12 is known to have anti-fibrotic effects in fibroblasts (36), and the administration of IL-12 coding plasmid to the tight skin SSc mouse model prevents collagen accumulation in the skin (37). On the other hand, the implication IL-12Rβ2 in autoimmune events seems to be complex as well. For instance, IL12rb2 knock-out mice do not display IL-12-mediated NK cytotoxicity (38) and the IL-12/IL-12Rβ2 axis is known to be critical for the generation of Th1 autoreactive cells (39), but, despite this, these mice develop spontaneous autoimmune pathology (immune-complex glomerulonephritis) and B-cell tumors by a strong IL-6 up-regulation (14,40). In addition, IL-12R signals predominantly through the STAT pathway, especially STAT4 (37,40). In this regard, it should be noted that polymorphisms in the STAT4 gene are well-established risk factors for SSc (4). Hence, it is likely that genetically predisposed individuals may present subtle differences in IL-12 signaling pathway regulation that could influence the prognosis of SSc.

To date, only a few SSc-related loci have reached a GWAS-level significance (i.e., P-value < 5.00 × 10^-8), both in the previously mentioned GWAS and recent studies: the HLA region, STAT4, TNPO3-IRF5, CD247, PSORS1C1, TNPI1 and IRF8 (5,41,42). Hence, we consider that the reported GWAS-level significant association may firmly contribute to the genetic knowledge of the disease.

In conclusion, we report for the first time the association of an IL12RB2 genetic variant with SSc. Our data together with previous reports identify IL12RB2 as a common genetic risk factor for autoimmunity.

**MATERIALS AND METHODS**

**Subjects**

The GWAS cohort was comprised of 2309 SSc patients and 5161 controls of Caucasian ancestry from Spain, Germany, the Netherlands and USA from a previously published study (5). The first follow-up phase consisted of 3085 SSc patients and 3183 controls from seven European Caucasian cohorts (Spain, Germany, The Netherlands, Italy, Sweden, UK and Norway). The second follow-up step comprised 1736 additional USA Caucasian individuals (597 SSc and 1139 controls). All the patients fulfilled the 1980 American College of Rheumatology (ACR) classification criteria for SSc (43) or the criteria proposed for early-SSc (44). In addition, patients were classified as having lcSSc or dcSSc as described in LeRoy et al. (3).

The following clinical data were collected for the ascertainment of the clinical phenotype of SSc patients: age, gender and presence of SSc-specific autoantibodies (Ab) ATA and ACA (Supplementary Material, Table S6). The control population consisted of unrelated healthy individuals recruited in the same geographical regions as SSc patients and matched by age, sex and ethnicity with the SSc patients groups.

The study was approved by local ethical committees from all the participating centers. Both patients and controls were included in the study after written informed consent. DNA from patients and controls were obtained using standard methods.

**SNP selection**

In the screening GWAS phase, we included a 116 kb region spanning the IL12RB2 region and ~13 kb upstream and downstream from this locus, from base pair 67 530 000 to 67 646 000 in chromosome 1, in the GWAS cohorts. After QC filtering as described in Radstake et al. (5), genotyping data for 10 SNPs over this region on chromosome 1 were available. The same procedure was applied for the analysis of the IL23R region, which comprised 163 kb and 27 SNPs.

TagMan SNP genotyping of the follow-up cohorts was performed in a 7900HT Real-Time Polymerase Chain Reaction (PCR) System from Applied Biosystems following the manufacturer’s suggestions (Foster City, CA, USA).

**Statistical analysis**

Significance was calculated using 2 × 2 contingency tables and Fisher’s exact test or χ² when necessary, to obtain P-values, OR and 95% confidence intervals using PLINK.
(v1.07) software (http://pngu.mgh.harvard.edu/purcell/plink/). P-values below 0.05 were considered statistically significant. Bonferroni correction and GC as described in Radstake et al. (5) were applied. The Hardy–Weinberg equilibrium (HWE) was tested for all the SNPs comparing the observed genotype distribution in controls with the expected genotype distribution under HWE by means of Fisher’s exact test or $\chi^2$ when necessary as described in Radstake et al. (5). The logistic regression and conditioned logistic regression analyses (considering the different cohorts as covariables) were performed using PLINK software. Linkage disequilibrium patterns across the region in the HapMap Project Phase I and II (CEU population) defined the haplotype-tagging SNPs using Haplovew (v.4.2) software (http://www.broadinstitute.org/haplovew/haplovew). The SNPs included in the GWAS phase were forced-included in the list of SNPs. Over this region on chromosome 1, the recombination rate was estimated from HapMap public database using LocusZoom (v.1.1) software (http://csg.sph.umich.edu/locuszoom/) (45). SNP & Variation Suite Version 7.5.1 (Golden Helix Inc.) and LocusZoom software were used for the composition of Figure 1. Cochran–Mantel–Haenszel meta-analysis was performed to control for the differences among populations as implemented in PLINK software. In addition, the Breslow–Day test (BD test) was performed as implemented in PLINK in each meta-analysis to assess the homogeneity of the association among populations. The power of the whole set of SSc patients and controls reached 100%. Power was calculated using the software Power Calculator for Genetic Studies 2006 (46) and assuming an additive model ($P$-value = 0.01 OR = 1.20). The genotyping success call rate in the GWAS cohort was of 99.8%, while in the replication set was over 95%.

SUPPLEMENTARY MATERIAL

Supplementary Material is available at HMG online.

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Conflict of Interest statement. None declared.

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APPENDIX

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