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Rangel-Peláez, C.; Rodriguez-Martin, I.; Rosa-Baez, C.; Kerick, M.; Guillén-Del-Castillo, A.; Simeón-Aznar, C.P.; ... ; Australian Scleroderma Interest Grp ASIG

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Novel pleiotropic loci link vascular and immune pathways in systemic sclerosis and primary Raynaud's phenomenon

Carlos Rangel-Peláez[1], Inmaculada Rodriguez-Martin[1], Carlos Rosa-Baez[1], Martin Kerick[1], Alfredo Guillén-Del-Castillo[2], Carmen P. Simeón-Aznar[2], José L. Callejas[3], Oliver Distler[4], Susanna M. Proudman[5], Mandana Nikpour[6,7], Nicolas Hunzelmann[8], Gianluca Moroncini[9,10], Jeska K. de Vries-Bouwstra[11], Ariane L. Herrick[12], Yannick Allanore[13], Marta E. Alarcón-Riquelme[14], Lorenzo Beretta[15], Maureen D. Mayes[16], Christopher P. Denton[17], Shervin Assassi[16], Javier Martín[1,†], Marialbert Acosta-Herrera[1,†], Lourdes Ortiz-Fernández[1,†,*], and the International SSc Group, the PRECISESADS Clinical Consortium, and the Australian Scleroderma Interest Group (ASIG)[#]

[1]Institute of Parasitology and Biomedicine López-Neyra, CSIC, Granada, Spain
[2]Systemic Autoimmune Diseases Unit, Department of Internal Medicine, Hospital Universitari Vall d'Hebron, Barcelona, Spain
[3]Systemic Autoimmune Disease Unit, Hospital Clínico San Cecilio, Instituto de Investigación Biosanitaria Ibs.GRANADA, Granada, Spain
[4]Department of Rheumatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland
[5]Rheumatology Unit, Royal Adelaide Hospital and the University of Adelaide, Adelaide, South Australia, Australia
[6]Department of Medicine, University of Melbourne, Fitzroy, Victoria, Australia
[7]Faculty of Medicine and Health, The University of Sydney School of Public Health, Sydney, New South Wales, Australia
[8]Department of Dermatology and Venereology, University Hospital Cologne, Cologne, Germany
[9]Department of Clinical and Molecular Science, Marche Polytechnic University, Ancona, Italy
[10]Department of Internal Medicine, Marche University Hospital, Ancona, Italy
[11]The Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands
[12]Division of Musculoskeletal and Dermatological Sciences, The University of Manchester, Northern Care Alliance NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK
[13]Department of Rheumatology, Université Paris Cité UFR de Médecine, Paris, France
[14]Centre for Genomics and Oncological Research, Pfizer, University of Granada/Andalusian Regional Government, Spain, Granada
[15]Scleroderma Unit, Referral Center for Systemic Autoimmune Diseases, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy
[16]UT Health Houston, Division of Rheumatology, McGovern Medical School, Houston, TX, USA
[17]Centre for Rheumatology, Royal Free Hospital, UCL, London, UK
*Correspondence to: Lourdes Ortiz-Fernández, Institute of Parasitology and Biomedicine López-Neyra (IPBLN), Consejo Superior de Investigaciones Científicas (CSIC), Parque Tecnológico de Ciencias de la Salud, Avenida del Conocimiento, no 17, 18016, Armilla, Granada, Spain. E-mail: lourdes@ipb.csic.es
†Dr Martín, Dr Acosta-Herrera and Dr Ortiz-Fernández contributed equally to this work.
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Abstract

Objective: **Raynaud's phenomenon (RP) is the first noticeable symptom of systemic sclerosis (SSc), appearing even years before other signs. Vascular and immune pathways, hallmarks in SSc pathogenesis, are implicated in primary RP. Hence, we aimed to define the shared genetic architecture between these conditions to explore pathogenic mechanisms and whether pleiotropic loci could help identify primary RP patients at increased genetic risk of developing SSc.**

Methods: **We analysed genome-wide association study (GWAS) summary statistics for primary RP (4 986 cases and 850 981 controls) and SSc (10 654 cases and 18 043 controls). We performed a cross-trait meta-analysis (∼8.6M single nucleotide polymorphisms) to identify variants associated with both diseases. Functional annotation was used to prioritise potential causal genes. We also constructed a polygenic risk score (PRS) to assess clinical implications.**

Results: **Beyond the well-known HLA associations, we identified five additional pleiotropic loci, including *MEOX2* as a novel association for both traits with opposing effects, *ADRA2A* representing a novel genetic factor for SSc, and *IL12A*, *NFKB1***

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and *TNIP1* as novel loci for primary RP. Functional annotation highlighted vascular and inflammatory pathways. Finally, the PRS model shows modest discrimination (area under the curve = 0.57). However, it allows the identification of primary RP individuals at high genetic risk of developing SSc (75th percentile, relative risk =1.29 [95% CI 1.02, 1.62]; *P*-value= 3.58×10^{-2}).

***Conclusion:* This study reveals a genetic link between primary RP and SSc, identifying five novel pleiotropic loci and supporting the potential of genetic profiling for early risk assessment and personalised monitoring strategies.**

Keywords Raynaud's phenomenon, systemic sclerosis, GWAS, *MEOX2*, cross-trait, polygenic risk score

Rheumatology key messages

- We identified five pleiotropic loci including *MEOX2* as a novel genetic factor for both diseases.
- Shared loci highlight common vascular and inflammatory pathways in primary RP and SSc.
- The polygenic risk score model identified individuals with primary RP at high risk of developing SSc.

Introduction

Systemic sclerosis (SSc) is an immune-mediated inflammatory disease (IMID) that affects the connective tissue [1]. It is considered a rare disease (<500 cases per million) and remains a major therapeutic challenge despite the progress in understanding its pathogenesis, imposing a significant socioeconomic burden among those who suffer it [1–4]. Genome-wide association studies (GWAS) have improved our understanding of disease pathogenesis, and may also contribute to the development of genetic predictors for the disease [5]. In SSc, multiple loci associated with disease risk have been identified, such as key aspects of immune dysregulation and fibrosis, including those linked to vasculopathy [6].

RP is a vascular disorder that causes sympathetic-mediated vasoconstriction in the extremities (primarily the digits, i.e. finger and toes) upon cold exposure, impairing thermoregulation and potentially disrupting nutrient blood flow [7]. In SSc, RP is classified as secondary RP and usually represents the initial clinical manifestation, emerging even years before any symptom [7, 8]. Notably, RP in SSc often presents in its severe form, exacerbating vascular and tissue complications [7]. Additionally, RP is significantly more prevalent in SSc patients (95%) than in the general population (5%) [7, 8]. RP can also occur in the absence of any underlying disease, where it is classified as primary RP. Recent GWAS have identified multiple loci associated with susceptibility to primary RP [9, 10], including *ADRA2A*, *IRX1* and the major histocompatibility complex (MHC) region. Notably, *ADRA2A* and *IRX1* play key roles in vascular function, while the MHC region is strongly implicated in autoimmune diseases such as SSc.

However, previous GWAS have been conducted independently for each condition, limiting the ability to detect shared genetic effects, particularly those with modest effect sizes acting across related phenotypes. In this context, cross-trait meta-analysis approaches are a powerful tool to systematically identify the common genetic component underlying correlated traits. Identifying shared genetic and molecular factors between primary RP and SSc could help predict which RP patients are at increased genetic risk of developing SSc and may provide insights into the pathogenic mechanisms involved, particularly those underlying differences in vascular severity. Thus, this study aimed to identify pleiotropic loci influencing both conditions through a cross-trait meta-analysis.

Methods

Primary RP cohorts

An overview of the primary RP cohorts included in this study is shown in Supplementary Table S1. Summary statistics for primary RP were retrieved from previously published GWAS conducted by Tervi *et al.* [9]. Specifically, we used the summary statistics from the meta-analysis of primary RP data from the FinnGen and UK Biobank, comprising 4 986 primary RP patients and 850 981 controls. Primary RP patients were defined following criteria established by Wigley and Flavahan [7] and all the secondary RP patients were removed from further analyses. Quality control procedures are described in detail in Supplementary Data S1.

SSc cohort

An overview of the SSc cohort included in this study is shown in Supplementary Table S1. The cohort comprised GWAS data from a previous study [6] and newly recruited participants, resulting in a total of 10 654 cases and 18 043 controls. All SSc patients fulfilled the 2013 American College of Rheumatology classification criteria, or the criteria proposed by LeRoy and Medsger for early SSc [11, 12]. In addition, patients were classified based on the extent of fibrosis as having limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc), as described in LeRoy *et al.* [13]. In lcSSc, fibrosis is limited to distal skin areas such as the hands and face, whereas in dcSSc, the fibrosis extends to the whole body and potentially affects internal organs and is usually associated with a worse prognosis. Patients lacking sufficient clinical data for subtype classification were excluded from these analyses. Moreover, the difference in sample size between lcSSc ($n = 6\,316$) and dcSSc ($n = 2\,936$) led to unequal statistical power across analyses, limiting the ability to detect statistically significant associations. Details regarding quality control procedures are provided in Supplementary Data S1. This study followed all relevant ethical regulations and was approved by the Ethics

Committee of the 'Consejo Superior de Investigaciones Científicas' (CSIC). Written informed consent was voluntarily provided by all participants, in line with the principles outlined in the Declaration of Helsinki.

Cross-trait meta-analysis

Cross-trait meta-analysis between primary RP and SSc was performed using METASOFT [14]. To assess population stratification, genomic inflation factors were calculated using METASOFT. Furthermore, residual confounding, including potential sample overlap, was calculated using LDSC genetic covariance [15]. Additionally, different meta-analyses were conducted for primary RP and SSc clinical subtypes: lcSSc and dcSSc. Cochran's Q test was performed to assess heterogeneity, applying a fixed-effect model to singlenucleotide polymorphisms (SNPs) showing no evidence of heterogeneity (Cochran's Q P-value > 0.05) and the random effect model (RE2) for SNPs exhibiting heterogeneity across datasets (Cochran's Q P-value < 0.05). Only non-HLA variants present in primary RP and SSc summary statistics were considered as the MHC region is highly complex and its genetic associations are well characterised. The criteria for defining shared genetic associations included three cutoffs [1]: a genome-wide significance threshold in the cross-trait meta-analysis (P-value $< 5 \times 10^{-8}$) [2], a nominal significance cutoff (P-value < 0.05) in each individual trait summary statistics, and [3] a lower P-value in the cross-trait meta-analysis compared with each specific trait summary statistics, ensuring that both diseases contribute to the observed association. Next, we used the COJO tool from GCTA to test for independent signals [16]. Additional details are included in Supplementary Data S1.

Functional annotation of shared genetic variants and gene prioritisation

Potential causal genes were prioritised using the SNP2GENE function from Functional Mapping and Annotation (FUMA) [17] based on variants identified in the cross-trait meta-analysis. Prioritisation included positional, quantitative trait loci (QTLs) and chromatin interaction mappings across relevant tissues for both diseases, including blood, immune cells, vascular, nervous and skin tissues. Additional methodological details are provided in Supplementary Table S2 and Supplementary Data S1.

Genetic risk prediction

To estimate the genetic predisposition of patients with primary RP to develop SSc, we conducted a polygenic risk score (PRS) based on the five shared lead variants identified in the cross-trait meta-analysis. PRS was calculated using the score function in PLINK, which sums the effect alleles weighted by the natural logarithm of the corresponding odds ratios. SNP selection was conducted following the predefined stringent criteria used to identify shared genetic associations in the cross-trait analysis. We applied this model to two UK Biobank cohorts: 708 individuals with primary RP and 213 SSc patients. Each participant was assigned a PRS based on the combination of alleles across the selected variants. PRS distributions were compared using a two-sample Student's t-test to assess discriminatory power, and model performance was evaluated via area under the curve (AUC) using the pROC package in R [18]. Additionally, we evaluated the ability of the PRS to identify individuals with primary RP at high genetic risk of developing SSc. For that, we categorised the individuals into two groups by applying a threshold at the 75th percentile of the PRS distribution. The statistical significance was tested using a chi-squared test.

Results

Genetic correlation

To evaluate the extent of the genetic overlap between primary RP and SSc, we conducted a pairwise genome-wide genetic correlation analysis. Remarkably, a statistically significant genetic correlation was observed between the two traits ($r_g = 0.315$ [0.105], P-value = 0.003), indicating a moderate genetic overlap. This supports the idea that a subset of individuals with primary RP may carry genetic susceptibility factors relevant to SSc, and highlights the utility of genetic profiling for early risk assessment (Supplementary Table S3).

Identification of shared loci

Three cross-trait meta-analyses were performed between primary RP and SSc, lcSSc and dcSSc, analysing >8.6 million variants (Supplementary Table S1). Genomic control analysis showed no evidence of substantial test statistic inflation (Supplementary Table S4). In addition, we estimated the genetic covariance intercept using LDSC. The intercept between primary RP and SSc was close to zero (intercept = 0.0064, SE = 0.0054), indicating negligible sample overlap. Consistent with this, the mean product of Z-scores was low (0.0348), supporting the independence of the datasets and suggesting that the observed associations are unlikely to be driven by overlapping individuals. As a result of the meta-analyses, 31 variants met the criteria in the primary RP-SSc meta-analysis, while three variants were identified in the primary RP-lcSSc meta-analysis and four in the primary RP-dcSSc meta-analysis (Supplementary Table S5). Following conditional analysis, five non-HLA loci were identified in primary RP-SSc meta-analysis: *IL12A*, *NFKB1*, *TNIP1*, *MEOX2* and *ADRA2A* (Fig. 1). Notably, *MEOX2* was newly associated with both SSc and primary RP and was the only locus where the effect differed by trait, acting as a risk factor for SSc but as a protective factor for primary RP. This trait-specific pattern likely reflects context-dependent regulation driven by differences in cell type, tissue environment or disease mechanisms. It is noteworthy that colocalization analysis revealed a high posterior probability (PP) for this locus (PP = 84.1%) indicating a shared causal variant between SSc and primary RP (Supplementary Table S6). Furthermore, *ADRA2A* emerged as a novel associated locus to SSc in both primary RP-SSc and primary RP-dcSSc meta-analyses, potentially representing a new candidate susceptibility locus contributing to vasculopathy in the disease. Additionally, *IL12A*, *NFKB1* and *TNIP1* were identified as novel loci associated with primary RP, highlighting the involvement of immune and inflammatory pathways in its pathogenesis. Finally, other non-HLA loci were identified such as *IL12A* in primary RP and lcSSc meta-analysis (Supplementary Fig. S1) and *LINC02572* in the

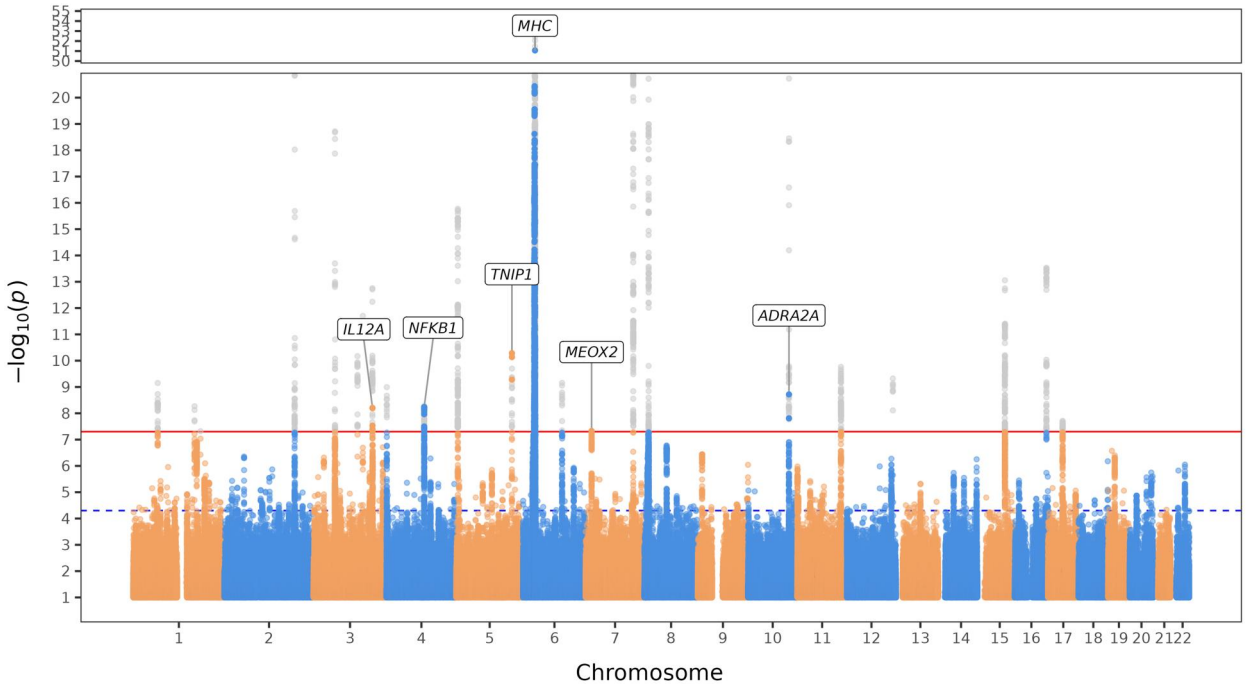

Figure 1 Manhattan plot for the cross-trait meta-analysis of primary RP and SSc. Chromosomes are displayed on the *x*-axis, while statistical significance is represented on the *y*-axis in $-\log_{10}$(*P*-value) format. The red line denotes the genome-wide significance threshold (*P*-value = 5×10^{-8}), and the blue dashed line marks the suggestive significance threshold (*P*-value= 5×10^{-6}). Variants shown in grey are significant but do not meet the predefined criteria (nominal significance in each trait and a lower *P*-value in the meta-analysis compared with each individual trait). Loci that meet these criteria are labelled. RP: Raynaud's phenomenon; SSc: systemic sclerosis

Table 1 Summary statistics for the meta-analysis of primary RP and SSc

rsID	Chr	BP (hg38)	EA	Gene	Cross-trait		SSc		Primary RP	
					OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
rs55669430	3	16 0189611	A	*IL12A*	1.27 (1.17, 1.37)	6.21×10^{-9}	1.40 (1.24, 1.57)	2.22×10^{-8}	1.15 (1.04, 1.28)	6.71×10^{-3}
rs230507	4	10 2559089	A	*NFKB1*	0.92 (0.89, 0.94)	5.74×10^{-9}	0.87 (0.84, 0.92)	7.13×10^{-9}	0.95 (0.92, 0.99)	1.74×10^{-2}
rs7708392	5	15 1077924	C	*TNIP1*	1.11 (1.08, 1.15)	5.16×10^{-11}	1.17 (1.11, 1.22)	5.59×10^{-11}	1.06 (1.01, 1.11)	1.38×10^{-2}
rs6971581	7	15 789995	T	*MEOX2*	0.99 (0.99, 1.00)	4.67×10^{-8}	1.12 (1.06, 1.19)	1.36×10^{-4}	0.88 (0.83, 0.93)	1.18×10^{-6}
rs61862976	10	11 1100974	T	*ADRA2A*	1.19 (1.13, 1.26)	1.92×10^{-9}	1.11 (1.01, 1.23)	3.30×10^{-2}	1.24 (1.15, 1.33)	4.46×10^{-9}

BP (hg38): base pair position (human genome build 38); Chr: chromosome; EA: effect allele; OR: odds ratio; RP: Raynaud's phenomenon; rsID: reference single nucleotide polymorphism identifier; SSc: systemic sclerosis.

primary RP and dcSSc meta-analysis (Supplementary Fig. S2). Table 1 summarizes the lead variant statistics from primary RP and SSc meta-analysis.

Functional annotation of pleiotropic loci

Notably, all significantly associated variants were located in non-coding regions of the genome. Thus, to prioritise potential causal genes, functional annotations of the lead SNPs and their proxies ($r^2 \geq 0.6$) were performed. Interestingly, the majority of the pleiotropic loci were associated with functional categories, including QTLs in relevant tissues or cell types, and chromatin interactions, suggesting that their contribution to disease may occur through alterations in regulatory mechanisms (Fig. 2).

In total, 17 potentially causal genes were prioritised (Fig. 2). Notably, our results indicate that the shared genetic variants may influence genes involved in vascular and immune pathways, both of which play key roles in the pathogenesis of primary RP and SSc. On the vascular side, variants on chromosome 7 act as expression QTLs (eQTLs) for *MEOX2* in tibial

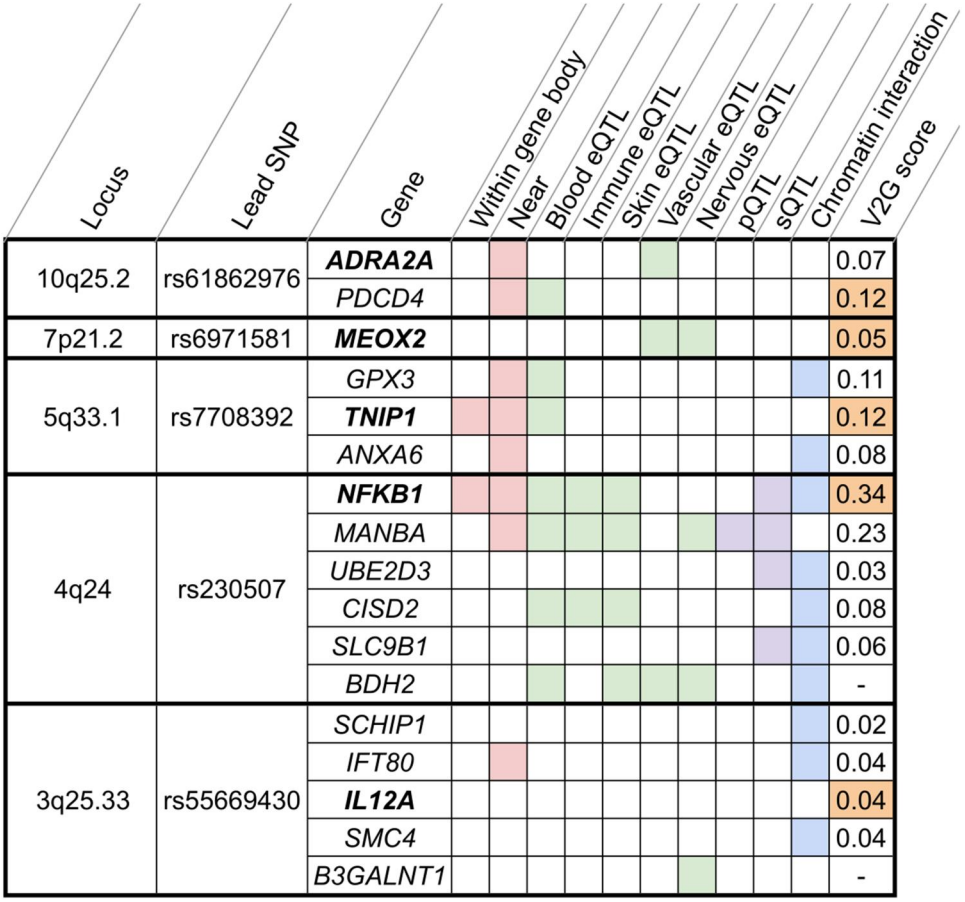

Figure 2 Functional annotation summary for all cross-trait meta-analyses. Colours indicate lead SNPs and/or proxies overlapping with the regulatory features analysed. Positional mapping: orange; eQTL effect: green; others QTL effects: purple; chromatin interaction: blue. eQTL: expression quantitative trait loci; pQTL: protein quantitative trait loci; SNP: single-nucleotide polymorphism; sQTL: splicing quantitative trait loci; V2G: variant to gene score from OpenTargets Genetics

artery and tibial nerve. *MEOX2* encodes a transcription factor involved in endothelial cell differentiation and vascular remodelling [19, 20]. In addition, variants on chromosome 10 influence *ADRA2A* expression in vascular tissue (tibial artery). As *ADRA2A* encodes 2-adrenergic receptor, a key regulator of vasoconstriction [9], altered expression provides a mechanistic link to the exaggerated vascular response characteristic of RP. From an immunological perspective, variants on chromosome 5 are located within the gene body of *TNIP1* and also exhibit eQTL activity in blood. Considering that *TNIP1* negatively regulates nuclear factor κB (NF-κB) signalling, changes in its expression may point to systemic modulation of pro-inflammatory pathways. Moreover, according to the V2G score from OpenTargets, *NFKB1* showed the strongest functional association with the variants identified on chromosome 4. The variants map within the *NFKB1* gene body and act as eQTLs across multiple tissues, including blood, skin and immune cells, such as neutrophils, T cells and monocytes. They also function as splicing QTLs in fibroblasts and tibial artery tissue. This complex QTL pattern across tissues further suggests a broad and context-dependent immunomodulatory role for *NFKB1*, a central regulator of inflammatory responses. In addition to *NFKB1*, QTL effects were also observed for *MANBA* in the same tissues and cell types, including protein QTL (pQTL) associations in blood plasma. Finally, variants on chromosome 3 point to *IL12A*, a cytokine crucial for promoting T helper 1 cell-driven immune responses, which have been consistently implicated in SSc pathogenesis [6, 21]. Additionally, other potential candidate genes such as *SMC4* and *SCHIP1* could also be considered.

Genetic risk prediction

Remarkably, the PRS significantly distinguish individuals with primary RP from those with SSc (mean PRS primary RP: -3.51×10^{-3} *vs* mean PRS SSc: 7.01×10^{-5}; *P*-value two sample *t*-test = 7.52×10^{-3}). Although the model showed modest discriminative ability (AUC = 0.57; Supplementary Fig. S3), individuals in the top 25% PRS risk group within the primary RP cohort had a significantly higher likelihood of SSc comorbidity (*P*-value = 3.58×10^{-2}, chi-squared test), corresponding to a relative risk of 1.29 (95% CI: 1.02, 1.62).

Discussion

Our study reveals a significant genetic correlation between primary RP and SSc, providing new evidence of shared genetic risk

factors between these two conditions. This contrasts with the findings of Tervi *et al.* [9], where no statistically significant genetic correlation was detected between primary RP and RP in SSc (Supplementary Table S3). This discrepancy is likely attributed to the smaller sample size for SSc used in their study compared with the one reported in this analysis. Considering all of the above and the markedly higher prevalence of RP in patients with SSc compared with the general population, our study reinforces the hypothesis of a shared genetic predisposition, suggesting that primary RP may, in some cases, represent an early or partial expression of the genetic risk underlying SSc.

Through a cross-phenotype GWAS meta-analysis, we identified five significant non-HLA loci representing new associations with one or both traits: *MEOX2*, *NFKB1*, *TNIP1*, *IL12A* and *ADRA2A*. Particularly, *NFKB1*, *TNIP1* and *IL12A* were newly associated with primary RP, *ADRA2A* with SSc, and *MEOX2* with both conditions. Notably, the identified loci intersect known vascular and immune pathways in SSc and offer potential mechanistic links with primary RP.

Interestingly, our results revealed *MEOX2* as a novel locus associated with both primary RP and SSc showing opposite effects and evidence of a shared causal variant (Fig. 1, Table 1 and Supplementary Table S6). It is worth noting that cross-trait meta-analyses of IMIDs occasionally reveal single genetic alterations that can increase risk for one disease while being neutral or protective in another [22]. MEOX2 is a mesodermal transcription factor that plays a critical role in vascular homeostasis by inducing cycle arrest, and acting as a negative regulator of angiogenesis, primarily through the inhibition of NF-κB in vascular endothelial cells [19, 20]. Remarkably, functional annotation showed that the associated genetic variants act as eQTLs in the tibial artery, supporting a regulatory role for *MEOX2* in vascular function. In that sense, the effect allele correlates with a decreased *MEOX2* expression in endothelial cells. Given that *MEOX2* has been linked to inhibited angiogenesis [19, 20], reduced *MEOX2* expression could be beneficial in primary RP by promoting angiogenesis and microvascular perfusion, while the same molecular shift may become pathogenic once systemic immune activation and other complementary processes characteristic of SSc emerge. Notably, *MEOX2* suppresses NF-κB signalling, thereby exacerbating inflammation and fibrosis, hallmarks of SSc pathogenesis [23]. Taken together, the antagonistic effects observed at *MEOX2* variants may provide insight into the transition from isolated vasospasm to immune-mediated vasculopathy. Noticeably, a study in synovial tissues from rheumatoid arthritis has highlighted the role of *MEOX2* in the disease as a novel transcriptional regulator in its pathogenesis [24].

Additionally, our study also identified *NFKB1* as a novel association for primary RP (Fig. 1 and Table 1). *NFKB1* encodes nuclear factor κB subunit 1, which undergoes protein processing to generate the key regulatory complex NF-κB. Functional annotation showed variants at this locus associated with differential *NFKB1* expression in immune cells and fibroblasts among other cell types. This complex cell-type-specific QTL profile suggests that *NFKB1* regulation in primary RP and SSc does not follow a uniform pattern but instead reflects a broader immunomodulatory role. Remarkably, *NFKB1* likely affects both vascular and immune pathways, contributing to a subtle interplay between angiogenesis, inflammation and fibrosis. Thus, dysregulated NF-κB signalling cascade, long recognised in SSc [23], might be involved in primary RP pathogenesis. Moreover, our study also highlights *MANBA* as a potential candidate gene that harbours significant QTLs in blood, immune cells, fibroblasts and the nervous system, including a pQTL in blood plasma (Fig. 2). This gene has been previously linked to IMIDs in European populations, including systemic lupus erythematosus (SLE) and primary sclerosing cholangitis [25, 26]. *MANBA* encodes β-mannosidase, a lysosomal enzyme essential for the autophagy process, which has been reported in conjunction with NF-κB in primary biliary cholangitis, an autoimmune digestive disorder genetically correlated with SSc [27, 28]. Although *MANBA* has not been previously associated with SSc, autophagy-related loci such as *ATG5* and *RAB2A* have already been identified, supporting a role for this mechanism in SSc pathogenesis [6, 29]. In this context, *MANBA* could represent a novel autophagy-related candidate gene contributing to SSc and primary RP susceptibility.

In addition to previously identified loci, our meta-analysis also reveals *TNIP1* and *IL12A* as novel risk genes implicated in the pathogenesis of primary RP (Table 1). *TNIP1*, which encodes TNFAIP3-interacting protein 1, is a well-known negative regulator of the NF-κB signalling pathway. This gene has been previously associated with impaired regulation of innate immune signalling and vascular inflammation in SSc [29]. Thereby, these findings suggest that dysregulated *TNIP1*-mediated NF-κB control may also contribute to the pathogenesis of primary RP. Dysregulated IL-12 signalling has been implicated in the imbalance between T helper 1 and T helper 2 cells and has been associated with SSc [6, 21]. Moreover, altered IL-12 regulation has also been reported in other IMIDs such as SLE [30]. Given its role, IL-12 signalling could contribute to primary RP pathogenesis by driving immune activation and inflammation [23, 31].

Our study identified *ADRA2A* as a novel risk locus for SSc. Variants annotated to *ADRA2A* are eQTLs in the tibial artery, where the effect allele showed an increased gene expression. These findings align with previous results from Tervi and colleagues [9], who proposed the *ADRA2A* role in primary RP. *ADRA2A* encodes the α2-adrenergic receptor, which, when overexpressed in smooth muscle cells under cold conditions, leads to enhanced adrenergic signalling and excessive vascular contraction. In SSc, this mechanism may contribute not only to thermoregulatory dysfunction, but also to the impaired nutritional blood flow commonly seen in SSc patients with RP, alongside the broader vascular abnormalities characteristic of the disease. Notably, in the primary RP-dcSSc meta-analysis, *ADRA2A*-associated variants exhibit a stronger effect compared with SSc meta-analysis (Table 1 and Supplementary Table S5), suggesting a possible role of *ADRA2A* in vascular pathogenesis in dcSSc, where *ADRA2A* may contribute more significantly. This finding is consistent with the observation that *ADRA2A* was not identified in the primary RP-lcSSc meta-analysis. Finally, *ADRA2A* was not identified in the secondary RP GWAS conducted by Tervi *et al.* [9], which may indicate that this locus is specifically relevant in SSc rather than other IMIDs that also manifest RP. Therefore, this locus integrates directly into SSc vasculopathy, in which excessive vasoconstriction and reduced perfusion are drivers of tissue inflammation and endothelial cell injury [23].

The identification of shared genetic variants between primary RP and SSc enabled the development of a PRS. Our PRS model shows lower discriminative ability than those reported in other IMIDs [5, 32–33], likely due to the reduced number of SNPs used to construct the PRS. However, because SNP selection was derived from the cross-trait meta-analysis between primary RP and SSc, our PRS was specifically developed for primary RP patients rather than for the general population; therefore, direct comparisons of PRS are not entirely suitable. Additionally, as in Bossini-Castillo *et al.* [5], integrating key clinical predictors would improve the PRS predictive power, particularly when including nailfold capillaroscopy patterns, antinuclear antibodies positivity or puffy fingers, which have been shown to be associated with increased risk of SSc among patients with RP [34]. Despite these limitations, individuals within the top 25% of the PRS distribution exhibited a significantly higher SSc associated genetic load, corresponding to an increased relative risk (RR = 1.29). This suggests that patients initially classified as having primary RP who present a high PRS could potentially be identified early as at elevated risk and prioritised for closer monitoring. These findings represent a first step toward integrating genomic data into personalised monitoring strategies for patients with primary RP. Future research using larger cohorts and integrating clinical markers of early SSc may improve the predictive power of this PRS and support its applicability in clinical practice.

We acknowledge several limitations of this study. While we demonstrate a shared genetic component between primary RP and SSc, some individuals classified as having primary RP may later develop SSc or other IMIDs. This potential phenotype misclassification could not be resolved using externally derived summary statistics. Nevertheless, the consistency of the signal across analyses and the well powered study suggests that the genetic overlap is not solely driven by random error, thereby enhancing the reliability of our findings. Moreover, we acknowledge that the PRS was not externally validated or calibrated, as no independent cohort was available. Additionally, our results are based on European-ancestry populations, limiting their transferability to other ethnic groups. Future studies in more diverse populations are necessary to determine whether the identified loci exert similar effects across different genetic backgrounds.

In conclusion, we identified five non-HLA pleiotropic loci, highlighting *MEOX2* as a novel gene associated with both traits. Notably, *MEOX2* showed an antagonistic effect, being protective in primary RP while conferring increasing risk in SSc. Although our PRS model is still far from clinical implementation, the results are promising and underscore the potential of genetic profiling to support early evaluation and tailored monitoring strategies for individuals with primary RP with high genetic risk of SSc development.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The summary statistics data for the three cross-trait meta-analyses are publicly available at https://zenodo.org/records/17569145.

Contribution statement

C.R.-P.: data curation, formal analysis, methodology, visualization, writing—original draft, writing–review & editing. I.R.-M.: data curation, writing—review & editing. C.R.-B.: data curation, writing—review & editing. M.K.: data curation, writing—review & editing. A.G.-C., C.P.S.-A., J.L.C., O.D., S.M.P., M.N., N.H., G.M., J. K.V.-B., A.L.H., Y.A., M.A.-R., L.B., M.D.M., C.P.D., S.A.: resources, writing—review & editing. J.M.: conceptualization, methodology, supervision, funding acquisition, resources, writing—original draft, writing—review & editing. M.A.-H., L.O.-F.: conceptualization, methodology, supervision, writing—original draft, writing—review & editing.

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Members of the consortia

International SSc group

P. Carreira, Department of Rheumatology, 12 de Octubre University Hospital, Madrid, Spain; I. Castellvi, Department of

Rheumatology, Santa Creu i Sant Pau University Hospital, Barcelona, Spain, R. Ríos, Department of Internal Medicine, San Cecilio Clinic University Hospital, Granada, Spain; N. Ortego-Centeno, Department of Medicine, University of Granada, Granada, Spain; R. García Portales, Department of Rheumatology, Virgen de la Victoria Hospital, Málaga, Spain; A. Fernández-Nebro, Department of Rheumatology, Carlos Haya Hospital, Málaga, Spain; F. J. García-Hernández, Department of Internal Medicine, Virgen del Rocío Hospital, Sevilla, Spain; M. A. Aguirre, Department of Rheumatology, Reina Sofía/IMIBIC Hospital, Córdoba, Spain; B. Fernández-Gutiérrez, Department of Rheumatology, San Carlos Clinic Hospital, Madrid, Spain; L. Rodríguez-Rodríguez, Department of Rheumatology, San Carlos Clinic Hospital, Madrid, Spain; P. García de la Peña, Department of Rheumatology, Madrid Norte Sanchinarro Hospital, Madrid, Spain; E. Vicente, Department of Rheumatology, La Princesa Hospital, Madrid, Spain; J. L. Andreu, Department of Rheumatology, Puerta de Hierro Hospital-Majadahonda, Madrid, Spain; M. Fernández de Castro, Department of Rheumatology, Puerta de Hierro Hospital-Majadahonda, Madrid, Spain; F. J. López-Longo, Department of Rheumatology, Gregorio Marañón University Hospital, Madrid, Spain; V. Fonollosa, Department of Internal Medicine, Valle de Hebrón Hospital, Barcelona, Spain; A. Guillén, Department of Internal Medicine, Valle de Hebrón Hospital, Barcelona, Spain; G. Espinosa, Department of Internal Medicine, Clinic Hospital, Barcelona, Spain; C. Tolosa, Department of Internal Medicine, Parc Tauli Hospital, Sabadell, Spain; A. Pros, Department of Rheumatology, Hospital Del Mar, Barcelona, Spain; E. Beltrán, Department of Rheumatology, Hospital Del Mar, Barcelona, Spain; M. Rodríguez Carballeira, Department of Internal Medicine, Hospital Universitari Mútua Terrasa, Barcelona, Spain; F. J. Narváez, Department of Rheumatology, Bellvitge University Hospital, Barcelona, Spain; M. Rubio Rivas, Department of Internal Medicine, Bellvitge University Hospital, Barcelona, Spain; V. Ortiz-Santamaría, Department of Rheumatology, Granollers Hospital, Granollers, Spain; A. B. Madroñero, Department of Internal Medicine, Hospital General San Jorge, Huesca, Spain; M. A. González-Gay, Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, IDIVAL, University of Cantabria, Santander, Spain; B. Díaz, Department of Internal Medicine, Hospital Central de Asturias, Oviedo, Spain; L. Trapiella, Department of Internal Medicine, Hospital Central de Asturias, Oviedo, Spain; M. V. Egurbide, Department of Internal Medicine, Hospital Universitario Cruces, Barakaldo, Spain; P. Fanlo-Mateo, Department of Internal Medicine, Hospital Virgen del Camino, Pamplona, Spain; L. Saez-Comet, Department of Internal Medicine, Hospital Universitario Miguel Servet, Zaragoza, Spain; F. Díaz, Department of Rheumatology, Hospital Universitario de Canarias, Tenerife, Spain; J. A. Roman-Ivorra, Department of Rheumatology, Hospital Universitari i Politecnic La Fe, Valencia, Spain; J. J. Alegre Sancho, Department of Rheumatology, Hospital Universitari Doctor Peset, Valencia, Spain; M. Freire, Department of Internal Medicine, Thrombosis and Vasculitis Unit, Complexo Hospitalario Universitario de Vigo, Vigo, Spain; F. J. Blanco Garcia, Department of Rheumatology, INIBIC-Hospital Universitario A Coruña, La Coruña, Spain; N. Oreiro, Department of Rheumatology, INIBIC-Hospital Universitario A Coruña, La Coruña, Spain; T. Witte, Department of Clinical Immunology, Hannover Medical School, Hannover, Germany; A. Kreuter, Department of Dermatology, Josefs-Hospital, Ruhr University Bochum, Bochum, Germany; G. Riemekasten, Clinic of Rheumatology, University of Lübeck, Lübeck, Germany; P. Airo, Service of Rheumatology and Clinic Immunology Spedali Civili, Brescia, Italy; C. Magro, Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands; A. E. Voskuyl, Department of Rheumatology, VU University Medical Center, Amsterdam, The Netherlands; M. C. Vonk, Department of Rheumatology, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands; R. Hesselstrand, Department of Rheumatology, Lund University, Lund, Sweden; A. Nordin, Division of Rheumatology, Department of Medicine, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden; C. Lunardi, Department of Medicine, Università degli Studi di Verona, Verona, Italy; G. Moroncini, Department of Clinical and Molecular Science, Università Politecnica delle Marche and Ospedali Riuniti, Ancona, Italy; A. Gabrielli, Istituto di Clinica Medica Generale, 2 Ematologia ed Immunologia Clinica, Università Politecnica delle Marche, Ancona, Italy; A. Hoffmann-Vold, Department of Rheumatology, Oslo University Hospital, Oslo, Norway; J. H. W. Distler, Department of Internal Medicine 3, Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany; L. Padyukov, Division of Rheumatology, Department of Medicine, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden; B. P. C. Koeleman, University Medical Center Utrecht, Utrecht, The Netherlands; T. R. D. J. Radstake, University Medical Center Utrecht, Utrecht, The Netherlands; G. Orozco, Centre for Genetics and Genomics Versus Arthritis, Division of Musculoskeletal and Dermatological Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester; A. Barton, Centre for Genetics and Genomics Versus Arthritis, Division of Musculoskeletal and Dermatological Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester; C. Fonseca, Center for Rheumatology, Royal Free and University College Medical School, London, UK.

PRECISESADS clinical consortium

Barbara Vigone[1], Jacques-Olivier Pers[2], Alain Saraux[2], Valérie Devauchelle-Pensec[2], Divi Cornec[2], Sandrine Jousse-Joulin[2], Bernard Lauwerys[3], Julie Ducreux[3], Anne-Lise Maudoux[3], Carlos Vasconcelos[4], Ana Tavares[4], Esmeralda Neves[4], Raquel Faria[4], Mariana Brandão[4], Ana Campar[4], António Marinho[4], Fátima Farinha[4], Miguel Angel Gonzalez-Gay Mantecón[5], Ricardo Blanco Alonso[5], Alfonso Corrales Martínez[5], Ricard Cervera[6], Ignasi Rodríguez-Pintó[6], Gerard Espinosa[6], Rik Lories[7], Ellen De Langhe[7], Nicolas Hunzelmann[8], Doreen Belz[8], Torsten Witte[9], Niklas Baerlecken[9], Georg Stummvoll[10], Michael Zauner[10], Michaela Lehner[10], Eduardo Collantes[11], Rafaela Ortega-Castro[11], M Angeles Aguirre-Zamorano[11], Alejandro Escudero-Contreras[11], M Carmen Castro-Villegas[11], Norberto Ortego[12], María Concepción Fernández Roldán[12], Enrique Raya[13], Inmaculada Jiménez Moleón[13], Enrique de Ramon[14], Isabel Díaz Quintero[14], Pier Luigi Meroni[15], Maria Gerosa[15], Tommaso Schioppo[15], Carolina Artusi[15], Carlo Chizzolini[16], Aleksandra Zuber[16], Donatienne Wynar[16], Laszló Kovács[17], Attila Balog[17],

Magdolna Deák[17], Márta Bocskai[17], Sonja Dulic[17], Gabriella Kádár[17], Falk Hiepe[18], Velia Gerl[18], Silvia Thiel[18], Manuel Rodriguez Maresca[19], Antonio López-Berrio[19], Rocío Aguilar-Quesada[19], Héctor Navarro-Linares[19]

Affiliations

1) Referral Center for Systemic Autoimmune Diseases, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Italy
2) Centre Hospitalier Universitaire de Brest, Hospital de la Cavale Blanche, Brest, France
3) Pôle de pathologies rhumatismales systémiques et inflammatoires, Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain, Brussels, Belgium
4) Centro Hospitalar do Porto, Portugal
5) Servicio Cantabro de Salud, Hospital Universitario Marqués de Valdecilla, Santander, Spain
6) Hospital Clinic I Provicia, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain
7) Katholieke Universiteit Leuven, Belgium
8) Klinikum der Universitaet zu Koeln, Cologne, Germany
9) Medizinische Hochschule Hannover, Germany
10) Medical University Vienna, Vienna, Austria
11) Servicio Andaluz de Salud, Hospital Universitario Reina Sofía Córdoba, Spain
12) Servicio Andaluz de Salud, Complejo hospitalario Universitario de Granada (Hospital Universitario San Cecilio), Spain
13) Servicio Andaluz de Salud, Complejo hospitalario Universitario de Granada (Hospital Virgen de las Nieves), Spain
14) Servicio Andaluz de Salud, Hospital Regional Universitario de Málaga, Spain
15) Università degli studi di Milano, Milan, Italy
16) Hospitaux Universitaires de Genève, Switzerland
17) University of Szeged, Szeged, Hungary
18) Charite, Berlin, Germany
19) Andalusian Public Health System Biobank, Granada, Spain

Australian Scleroderma Interest Group (ASIG)

A. Apostolopoulos, Department of Rheumatology, Monash Medical Centre, Melbourne, Victoria, Australia; Department of Medicine, Monash University, Melbourne, Australia; N. Ferdowsi, Department of Rheumatology, St Vincent's Hospital, Melbourne, Victoria, Australia; D. Hansen, Department of Rheumatology, St Vincent's Hospital, Melbourne, Victoria, Australia; L.V. Host, Fiona Stanley Hospital, Perth, Western Australia, Australia; G. Major, Department of Rheumatology, John Hunter Hospital, New Lambton Heights, New South Wales, Australia; Faculty of Medicine, University of Newcastle, Callaghan NSW Australia; G.-S. Ngian, Department of Rheumatology, Monash Medical Centre, Melbourne, Victoria, Australia; Department of Medicine, Monash University, Melbourne, Australia; A. Quinlivan; Department of Rheumatology, St Vincent's Hospital, Melbourne, Victoria, Australia; Department of Medicine, The University of Melbourne, Australia; L. Ross, Department of Rheumatology, St Vincent's Hospital, Melbourne, Victoria, Australia; Department of Medicine, The University of Melbourne, Australia; J. Sahhar, Department of Rheumatology, Monash Medical Centre, Melbourne, Victoria, Australia; Department of Medicine, Monash University, Melbourne, Australia; W. Stevens; Department of Rheumatology, St Vincent's Hospital, Melbourne, Victoria, Australia; M, Tabesh; Department of Rheumatology, St Vincent's Hospital, Melbourne, Victoria, Australia; J. Walker, Rheumatology unit, Royal Adelaide Hospital, Adelaide, SA, Australia; Flinders Medical Centre, SA, Australia; Flinders University, Adelaide, SA, Australia.

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rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis 2013;72:1747–55.
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