Genome-wide meta-analysis reveals shared new *loci* in systemic seropositive rheumatic diseases

Marialbert Acosta-Herrera,[1†*] Martin Kerick,[1†] David González-Serna,[1] Myositis Genetics Consortium,[ϕ] Scleroderma Genetics Consortium,[ϕ] Cisca Wijmenga,[2] Andre Franke,[3] Peter K. Gregersen,[4] Leonid Padyukov,[5] Jane Worthington,[6] Timothy Vyse,[7-8] Marta E Alarcón-Riquelme,[9] Maureen D. Mayes,[10] Javier Martin.[1*]

[1] Institute of Parasitology and Biomedicine López-Neyra, IPBLN-CSIC, PTS Granada, Granada, Spain; [2]Department of Genetics, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands; [3]Institute of Clinical Molecular Biology, Christian-Albrechts-University of Kiel, Kiel, Germany; [4]Robert S. Boas Center for Genomics and Human Genetics, Feinstein Institute for Medical Research, Manhasset, NY, USA; [5]Rheumatology Unit, Department of Medicine, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden; [6]Manchester NIHR Biomedical Research Centre, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK; [7]Division of Genetics and Molecular Medicine, King's College London, London, UK; [8]Division of Immunology, Infection and Inflammatory Disease, King's College London, London, UK; [9]Centre for Genomics and Oncological Research (GENYO), Pfizer-University of Granada-Andalusian Regional Government, Granada, Spain; [10]The University of Texas Health Science Center–Houston, Houston, Texas, USA; [ϕ]Members of the Myositis Genetics Consortium (MYOGEN) and Scleroderma Genetics Consortium are listed in the supplemental note.

[†]These authors contributed equally to this work.

***Corresponding authors**

Marialbert Acosta-Herrera: Institute of Parasitology and Biomedicine López-Neyra, CSIC, Av. del Conocimiento 17. Armilla (Granada), Spain 18016. Phone: (+34) 958181621; Fax: (+34) 958181632; email: m.acostaherrera@ipb.csic.es

Javier Martín: Institute of Parasitology and Biomedicine López-Neyra, CSIC, Av. del Conocimiento 17. Armilla (Granada), Spain 18016. Phone: (+34) 958181669; Fax: (+34) 958181632; email: javiermartin@ipb.csic.es

Abstract

Objective: Immune-mediated inflammatory diseases (IMIDs) are heterogeneous and complex conditions with overlapping clinical symptoms and elevated familial aggregation, which suggests the existence of a shared genetic component. In order to identify this genetic background in a systematic fashion, we performed the first cross-disease genome-wide meta-analysis in systemic seropositive rheumatic diseases, namely: systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis and idiopathic inflammatory myopathies.

Methods: We meta-analyzed ~6.5 million single nucleotide polymorphisms (SNPs) in 11,678 cases and 19,704 non-affected controls of European descent populations. The functional roles of the associated variants were interrogated using publicly available databases.

Results: Our analysis revealed five shared genome-wide significant independent *loci* that had not been previously associated with these diseases: *NAB1*, *KPNA4-ARL14*, *DGQK*, *LIMK1*, and *PRR12*. All of these *loci* are related with immune processes such as interferon and epidermal growth factor signaling, response to methotrexate, cytoskeleton dynamics, and coagulation cascade. Remarkably, several of the associated *loci* are known key players in autoimmunity, which supports the validity of our results. All the associated variants showed significant functional enrichment in DNase hypersensitivity sites, chromatin states and histone marks in relevant immune cells, including shared expression quantitative trait *loci*. Additionally, our results were significantly enriched in drugs that are being tested for the treatment of the diseases under study.

Conclusions: We have identified shared new risk *loci* with functional value across diseases and pinpoint new potential candidate *loci* that could be further investigated. Our results highlight the potential of drug repositioning among related systemic seropositive rheumatic IMIDs.

Introduction

Autoimmunity occurs when the mechanisms related to immune self-tolerance fail, leading to an inappropriate destruction of normal tissue by the immune system. Genetic factors play an important role in the development of more than 80 immune-mediated inflammatory diseases (IMIDs) identified so far.[1] Comorbidity of these diseases, increased familial clustering, and shared risk variants have been widely documented.[2] However, to date, these shared *loci* have been identified by simple comparison between studies, and just recently they have been determined by rigorous and systematic analysis.[3] In this sense, combining genome-wide association studies (GWAS) across several diseases has proven to be a very useful tool for the identification of new genetic risk variants simultaneously associated with several IMIDs, and to expose shared pathways involved in the pathophysiology of these conditions.[4-7] To date, two large studies combining several diseases were recently published following this strategy. One of them was a meta-GWAS across 10 pediatric autoimmune diseases with shared population-based controls that revealed new candidate *loci* with immunoregulatory functions.[8] In the other study, the authors identified new shared associations by combining immunochip data across five chronic inflammatory diseases.[9]

Systemic seropositive rheumatologic IMIDs, such as systemic sclerosis (SSc), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and idiopathic inflammatory myopathies (IIM), are heterogeneous diseases of the connective tissue that share clinical and epidemiological manifestations, as well as life-threatening complications.[10] The common genetic component of these conditions has not been previously assessed systematically, although the overlap of associated genes is elevated when performing a pairwise comparison.[8] Autoantibody production is the main

feature of these diseases, comprising additionally a broad deregulation of the innate and adaptive immune response. However, the low prevalence of most of these diseases hinders the collection of large datasets that makes possible to attain sufficient statistical power. Therefore, our study aimed to combine previously published GWAS datasets – all from European descent populations– to identify shared genetic etiologies among systemic seropositive rheumatologic IMIDs in a systematic fashion.

Subjects and Methods

Study population

A total of 12,132 affected subjects with four systemic seropositive rheumatic IMIDs (SSc, SLE, IIM, and RA) and 23,260 controls were included in this study from previously published GWAS [11-16] (Table S1).

Data quality control and imputation

Unified quality control (QC) of the 18 case-control collections was conducted separately, based on stringent criteria using PLINK v.1.07.[17] Given that related and/or duplicated subjects may have been recruited for different studies, genome-wide relatedness was assessed and one individual from each pair was removed. Samples with <95% of successfully called genotypes were removed.

Further, single nucleotide polymorphisms (SNPs) with genotyping call rate <98%, minor allele frequencies (MAF) <1% and deviating from Hardy-Weinberg equilibrium (HWE) with a p-value <0.001 in the control group were removed. To control for possible population stratification, we performed principal component (PC) analysis using GCTA64 and R-base software under GNU Public license v.2.

120 Imputation of autosomal SNPs was conducted in the Michigan Imputation
121 Server using Minimac3.[18] The software SHAPEIT[19] was used for haplotype
122 reconstruction and the Haplotype Reference Consortium r1.1 was used as the reference
123 population.[20]
124
125 **Statistical analyses**
126 *Disease-specific association testing:* Association testing for allele dosages was
127 performed by logistic Wald test using EPACTS software,[21] adjusting by the first two
128 or five PCs as appropriate to control for the genomic inflation factor in European
129 population ($\lambda<1.05$) (Table S1). SNPs with a MAF $\geq$1% and squared correlation (Rsq)
130 $\geq$0.3 were maintained in the analyses as suggested by the imputation software.
131 Additionally, we calculated a concordance rate by comparing imputed and true
132 genotypes.
133 *Cross-phenotype meta-analysis:* to identify shared *loci*, the summary-level statistics
134 were meta-analyzed using METASOFT.[22] A fixed-effects model was applied for
135 those SNPs without evidence of heterogeneity (Cochran's Q test *p*-value $Q > 0.05$), and
136 random-effects model was applied for SNPs displaying heterogeneity of effects between
137 studies ($Q \leq 0.05$). Genome-wide significance was established at a *p*-value $\leq 5 \times 10^{-08}$.
138 SNP independence was assessed with the software GCTA-COJO (Table S2).[23, 24] To
139 annotate the independent signals SNPnexus[25] was used to the build37 genomic
140 coordinates.
141 *Model search to identify the diseases contributing to the association:* to identify the
142 diseases most likely contributing to the association signals, we performed an exhaustive
143 disease-subtype model search with the R statistical package ASSET.[24] The

contribution of a disease was considered if at least two independent case-control collections from the same disease were grouped with consistent effects.

Novelty of the variants: Our independent SNP associations were classified into "known" or "new" associations based on the information retrieved from the NHGRI-EBI GWAS catalog and the Phenopedia and Genopedia from HuGE Navigator.[26]

Functional enrichment analysis: in order to systematically characterize the functional, cellular and regulatory contribution of the associated variants, a non-parametric enrichment analysis implemented in GARFIELD was performed.[27] Furthermore, the online tools HaploReg v.4.1[28] and the Genotype-Tissue Expression project (GTEx)[29] were queried to determine whether any of the lead associated variants was an expression quantitative trait locus (eQTL). The online tool Capture HiC plotter was used to assess physical interactions between restriction fragments containing the variants and the promoter of genes in the three-dimensional nuclear space.[30]

Drug Target Enrichment Analysis: the target genes of the eQTLs were used to model a protein-protein interaction (PPI) network using String v10.[31] These protein products were then used to query the OpenTargets Platform[32] for drug targets. Moreover, this platform was used to search for drugs indicated or in different phases of drug development for the treatment of SSc, SLE, IIM and RA. The Fisher's exact test was used to calculate if the results of the meta-analysis were significantly enriched in pharmacologically active drug targets.

Additional details of the Methods section are available in the online supplementary methods.

Results

Cross-phenotype meta-analysis and disease contribution

Following sample QC and imputation, a total of 11,678 cases and 19,704 non-overlapping controls were included in the genome-wide meta-analysis of 6,450,125 SNPs across the four diseases. The mean concordance rate among imputed and true genotypes was 0.999±0.0003. The final λ showed minimal evidence of population stratification in the meta-abalysis (λ=1.025). Moreover, we calculated λ1,000 with consistent results (λ1,000=1.025). Summary of sample/variant QC and QQ plots are shown in Table S1 and Figure S1, respectively.

The global meta-analysis revealed 42 non-hla significantly associated *loci*. Subsequent conditional analyses showed that 27 SNPs were independent (Figure 1 and Figure S2). Sixteen variants were meta-analyzed under a fixed effects model, whereas eleven with random effects based on study heterogeneity.

To comprehensively explore the combinations of diseases contributing to the associations we applied a subset-based meta-analysis implemented in ASSET.[24] Our model search yielded 26 SNPs associated with at least two IMIDs (Table 1). All of these variants were imputed in at least one dataset.

Among these 26 associations we found several key players in autoimmunity; interestingly ten of these associations (38%) have never been reported before for SSc, eight (31%) for SLE and RA, respectively, and 20 (77%) for IIM. Remarkably, five SNPs have not been reported previously for any of the diseases under study and thus constitute new shared risk *loci* in systemic seropositive rheumatic IMIDs (Table 1). Amongst these five new associations we found the SNP rs744600 in the 3' region of the NGFI-A binding protein 1 (*NAB1*) (Odds ratio [OR] for the T allele 0.88, Confidence Interval [CI]=0.85-0.92), *p*-value=7.07×10^{-11}), and the intronic SNP rs13101828 mapping in the gene Diacylglycerol kinase theta (*DGKQ*) (OR for the G allele 1.11,

194 95%CI: 1.07–1.16, *p*-value=1.32x10^{-08}). Of note, both genes have been previously
195 associated with a chronic autoimmune liver disease.[33, 34] The intergenic SNP
196 rs112846137, maps between the genes Karyopherin subunit alpha 4 (*KPNA4*) and the
197 ADP ribosylation factor like GTPase 14 (*ARL14*) (OR for the T allele 1.29, 95%CI:
198 1.07–1.56, *p*-value=1.42x10^{-08}). Interestingly, the gene *ARL14* showed a suggestive
199 association in a pharmacogenomic GWAS of response to methotrexate in RA
200 patients.[35] In addition, we observe the associated SNP rs193107685 located in the 3'
201 region of the LIM domain kinase 1 *(LIMK1*) gene (OR for the C allele 1.52, 95%CI:
202 1.27–1.83, *p*-value=3.81x10^{-09}). The protein encoded by this gene regulates actin
203 polymerization, a critical process in the activation of T cells.[36] Finally, the SNP
204 rs76246107 is located in an intron of the gene Proline rich 12 (*PRR12*) (OR for the G
205 allele 1.28, 95%CI: 1.14–1.43, *p*-value=3.36x10^{-08}), which was associated with
206 fibrinogen concentration,[37] and is an active regulator of the inflammatory
207 response.[38]

Table 1. Twenty-six independent variants associated at a genome-wide significance level (p <5x10^{-8}) in the meta-analysis.

Chr	Position[a]	SNP	Gene[b]	Functionality[c]	Effect Allele	OR (CI 95%)	Meta-Analysis p-value[d]	Cochran's p-value	Contributing Disease[e]
1	67802371	rs6659932	*IL12RB2*	Intronic	C	0.85 (079-0.91)	6.08x10^{-11}	1.02x10^{-02}	**IIM, SLE**, SSc
1	114303808	rs6679677	*PHTF1-RSBN1*	Intergenic	A	1.34 (1.21-1.49)	2.30x10^{-28}	2.14x10^{-04}	**IIM, RA**, SLE
1	114377568	rs2476601	*PTPN22*	Coding (missense)	G	0.75 (0.67-0.83)	1.74x10^{-28}	1.06x10^{-4}	IIM, RA, SLE
1	114433946	rs1217393	*AP4B1*	Intronic	A	0.89 (0.85-0.92)	5.21x10^{-09}	4.91x10^{-1}	**IIM, RA**, SLE, **SSc**
1	173337747	rs2422345	*TNFSF4-LOC100506023*	Intronic	A	1.11 (1.05-1.18)	2.55x10^{-08}	6.00x10^{-03}	**IIM**, SLE, **SSc**
1	183532580	rs17849502	*NCF2*	Coding (missense)	T	1.36 (1.16-1.59)	3.93x10^{-15}	2.84x10^{-04}	**IIM**, SLE
2	191564757	rs744600	*NAB1**	3'Downstream	T	0.88 (0.85-0.92)	7.07x10^{-11}	7.60x10^{-1}	**IIM, RA, SLE, SSc**
2	191933283	rs13389408	*STAT4*	Intronic	C	1.27 (1.20-1.34)	3.10x10^{-17}	3.99x10^{-1}	**IIM**, SLE, SSc
2	191973034	rs10174238	*STAT4*	Intronic	A	0.73 (0.67-0.80)	2.76x10^{-42}	4.31x10^{-07}	**IIM**, SLE, SSc
3	58183636	rs35677470	*DNASE1L3*	Coding (missense)	A	1.22 (1.14-1.30)	4.96x10^{-09}	6.78x10^{-01}	**IIM**, SLE, SSc
3	160312921	rs112846137	*KPNA4-ARL14**	Intergenic	T	1.27 (1.17-1.37)	1.42x10^{-08}	9.55x10^{-01}	**IIM, RA, SLE, SSc**
4	965720	rs13101828	*DGKQ**	Intronic	G	1.11 (1.07-1.16)	1.32x10^{-08}	2.29x10^{-01}	**IIM, RA, SLE, SSc**
5	150438477	rs4958880	*TNIP1*	Intronic	A	1.16 (1.10-1.22)	1.45x10^{-11}	2.61x10^{-01}	**IIM, RA**, SLE, SSc
5	159887336	rs2431098	*PTTG1-MIR3142HG*	Intergenic	G	1.12 (1.05-1.20)	4.91x10^{-12}	1.42x10^{-01}	SLE, **SSc**
6	106569270	rs802791	*PRDM1-ATG5*	Intergenic	C	0.87 (0.83-0.92)	3.65x10^{-12}	1.13x10^{-01}	SLE, SSc
6	138243739	rs58721818	*TNFAIP3*	3'Downstream	T	1.64 (1.46-1.84)	4.64x10^{-23}	1.65x10^{-01}	**IIM**, SLE, SSc
7	73537902	rs193107685	*LIMK1**	3'Downstream	C	1.52 (1.27-1.83)	3.21x10^{-09}	1.18x10^{-01}	**RA, SLE, SSc**
7	128589633	rs10954214	*IRF5*	3UTR	T	1.18 (1.13-1.23)	6.63x10^{-17}	3.64x10^{-01}	**IIM,** RA, SLE, SSc
7	128647942	rs13238352	*TNPO3*	Intronic	T	1.44 (1.30-1.60)	1.47x10^{-38}	2.12x10^{-01}	SLE, SSc
8	11341880	rs2736337	*FAM167A-BLK*	Intergenic	C	1.23 (1.17-1.30)	4.86x10^{-22}	1.29x10^{-01}	**IIM,** RA, SLE, SSc
11	633689	rs7929541	*SCT-DRD4*	Intergenic	G	0.89 (0.83-0.95)	2.14x10^{-10}	4.98x10^{-04}	**IIM, RA**, SLE, **SSc**

12	112871372	rs11066301	*PTPN11*	Intronic	T	1.11 (1.07-1.15)	$4.20x10^{-08}$	$5.86x10^{-01}$	**IIM, SLE, SSc**
16	85994484	rs35929052	*IRF8*	Intergenic	T	0.83 (0.78-0.88)	$1.71x10^{-09}$	$4.69x10^{-01}$	**IIM**, SLE, SSc
19	10462513	rs11085725	*TYK2*	Intronic	A	0.88 (0.83-0.92)	$2.65x10^{-10}$	$1.86x10^{-01}$	**IIM**, SLE, SSc
19	50121274	rs76246107	*PRR12**	Intronic	G	1.28 (1.14-1.43)	$3.36x10^{-08}$	$1.50x10^{-02}$	**IIM, SLE, SSc**
22	21985094	rs5754467	*YDJC*	5'Upstream	G	1.20 (1.13-1.27)	$1.24x10^{-13}$	$8.59x10^{-02}$	**IIM**, RA, SLE, **SSc**

[a]According to NCBI build GRCh37/hg19.

[b]Variant localization based on the nearest gene.

[c]Functionality obtained from SNPnexus.[23]

[d]Results of meta-analysis either under a fixed effect if no heterogeneity was found based on Cochran's Q test (p-value≥0.05) or under a random effect if heterogeneity was found among studies.

[e]Disease contributing to the association observed by the subset meta-analysis method with ASSET.[25] The diseases for which this locus has never been reported before at genome-wide significance level are shown in boldface.

*Denotes novel *loci* in the study.

Chr: chromosome; OR: odds ratio; CI: confidence interval; IIM: idiopathic inflammatory myopathy; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SSc: systemic sclerosis.

All the variants in the table were imputed in at least one of the 18 case-control collections.

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Associated loci and their functional enrichment on regulatory elements

To assess whether the associated variants lie in coding and non-coding regulatory and cell-type-specific elements of the genome, we performed an enrichment analysis with GARFIELD.[39] The results obtained showed marked enrichment patterns mainly in blood cells and skin cells, with 247 significant enrichments ($p \leq 5 \times 10^{-05}$) (Figure S3 and Table S3). Table 2 summarizes the main enrichment results. We found that the majority of associated variants were enriched in DNase I hypersensitivity site (DHS) hotspots in blood, as depicted in Figure 2. This functional category included a repertoire of cells from the immune system, such as B-lymphocytes (Fold enrichment (FE)=11.68, empirical *p* (*pemp*)$<1 \times 10^{-05}$), T-lymphocytes (FE=10.42, *p*emp$<1 \times 10^{-05}$), including T helper cells (FE=7.81, *p*emp$<1 \times 10^{-05}$), T CD8+ (FE=7.61, *p*emp$<1 \times 10^{-05}$), natural killer cells (FE=11.36, *p*emp$<1 \times 10^{-05}$), and monocytes (FE=8.99, *p*emp$<1 \times 10^{-05}$). In line with this enrichment, disease-associated SNPs were enriched in enhancers (FE=14.99, *p*emp$<1 \times 10^{-05}$), within TSS (FE=14.87, *p*emp$<1 \times 10^{-05}$), and on transcription factor binding sites (FE=12.20, *p*emp$<1 \times 10^{-05}$) in the B-lymphocyte cell line GM12878. Additionally, the highest enrichment was observed in the histone modification H3K9ac (FE=14.02, *p*emp$<1 \times 10^{-05}$), and H3K27ac (FE=10.81, *p*emp$<1 \times 10^{-05}$) in the B-lymphocyte cell line, which are positively associated with gene activation. Although these modifications are increased in the promoters of active genes, the latter has been shown to be associated with active enhancers.[40] Moreover, enrichment was observed in H3K4me1,2,3 sites, which usually surround TSS and are also positively correlated with gene expression.[40]

Table 2. Summary of the most enriched functional annotations for the SNPs associated in the meta-analysis at a genome-wide significance threshold (p <5x10^{-8}).

Category[a]	Tissue	Cell types	Type	NAnnotThesh[b]	NAnnot[c]	NThresh[d]	N (LD-pruned variants)[e]	Fold Enrichment	Empirical p-value
Chromatin_States	Blood	GM12878	Enhancer	13	10,944	33	416,420	14.99	<1x10^{-5}
		GM12878	TSS	12	10,182	33	416,420	14.87	<1x10^{-5}
Footprints	Blood	GM06990	Footprints	8	3,153	33	416,420	32.02	<1x10^{-5}
Histone modifications	Blood	GM12878	H3K9ac	21	18,903	33	416,420	14.02	<1x10^{-5}
		GM12878	H3K27ac	22	25,674	33	416,420	10.81	<1x10^{-5}
		GM12878	H2AFZ	22	25,824	33	416,420	10.75	<1x10^{-5}
		GM12878	H3K4me3	17	25,365	33	416,420	8.46	<1x10^{-5}
		GM12878	H3K4me2	23	34,807	33	416,420	8.34	5x10^{-5}
		GM12878	H3K4me1	25	39,871	33	416,420	7.91	<1x10^{-5}
		GM12878	H3K79me2	16	25,683	33	416,420	7.86	<1x10^{-5}
Hotspots	Blood	GM06990	Hotspots	23	24,839	33	416,420	11.68	<1x10^{-5}
	Skin	NHEK	Hotspots	25	54,667	33	416,420	5.77	<1x10^{-5}
Peaks	Blood	GM06990	Peaks	13	6,433	33	416,420	25.50	<1x10^{-5}
TFBS	Blood	GM12878	TFBS	19	19,650	33	416,420	12.20	<1x10^{-5}

[a]Functional categories from the Encode[28] and Roadmap Epigenomics.[29]

[b]Number of LD-pruned annotated variants passing the meta-analysis threshold.

[c]Number of LD-pruned annotated variants in the reference dataset UK10K project.

[d]Number of LD-pruned variants passing the meta-analysis threshold.

[e]Number of LD-pruned variants in the reference dataset UK10K project.

GM12878: B-Lymphocyte; GM06990: B-lymphocyte, lymphoblastoid; NHEK: Normal Human Epidermal Keratinocytes; LD: Linkage disequilibrium; TSS: Transcription Start Site; TFBS: Transcription Factor Binding Sites.

Expression quantitative trait loci (eQTL) and associated variants

In silico analysis of eQTLs revealed the role of 16 of the lead SNPs as eQTLs in whole blood, lymphoblastoid cell lines, transformed lymphocytes, skeletal muscle and transformed fibroblasts derived from European individuals from HaploReg v.4.1[28] (Table 3 and Table S4). Focusing on new associated variants, the SNP rs744600 modifies *NAB1* gene expression in lymphoblastoid cell lines (p=1.30x10^{-34}), whereas the T allele increases *HIBCH* expression in skeletal muscles (p=8.09x10^{-07}). The G allele of rs13101828 increases *DGKQ* expression in whole blood (p=3.29x10^{-45}), lymphocytes (p=5.23x10^{-19}), fibroblasts (p=4.44x10^{-06}), lung cells (p=8.42x10^{-28}) and several other tissues. The A allele of rs76246107 can reduce *ALDH16A1* expression in lung cells (p=6.45x10^{-06}), and the protein encoded by this gene is involved in oxidoreductase activity. Reassuringly, 14 of the 16 (87%) reported eQTLs showed a physical interaction between the SNP and the promoter of 15 of the genes affected by the eQTLs (Table 3), as suggested by Capture HiC (C-HiC) data (Table S5). These independent evidences propose a mechanistic approach to understand the modulation of gene expression.

Table 3. Summary of the eQTL results in European samples for the SNPs independently associated in the meta-analysis.

SNP	Allele	Source	Gene	Tissue	*p*-value
rs6659932*	C	GTEx2015_v6	*IL12RB2*	Whole blood	$3.72x10^{-11}$
rs6679677*	A	Westra 2013	*PTPN22*	Whole blood	$4.84x10^{-10}$
rs2476601*	G	Westra2013	*PTPN22*	Whole blood	$3.36x10^{-10}$
rs1217393*	A	GTEx2015_v6	*AP4B1*	Skeletal muscle	$5.45x10^{-07}$
		GTEx2015_v6	*HIPK1*	Whole blood	$7.71x10^{-09}$
		Westra 2013	*PHTF1*	Whole blood	$9.56x10^{-05}$
		Westra 2013	*PTPN22*	Whole blood	$2.67x10^{-10}$
		Westra 2013	*RSBN1*	Whole blood	$1.41x10^{-10}$
rs744600*	T	GTEx2015_v6	*HIBCH*	Skeletal muscle	$8.09x10^{-07}$
		Lappalainen2013	*NAB1*	Lymphoblastoid cell line	$1.30x10^{-34}$
rs13389408	C	GTEx2015_v6	*GLS*	Skeletal muscle	$3.42x10^{-09}$
		Westra 2013		Whole blood	$2.98x10^{-07}$
rs35677470*	A	GTEx2015_v6	*PXK*	Skeletal muscle	$7.08x10^{-06}$
rs13101828	G	GTEx2015_v6	*DGKQ*	Whole blood	$9.28x10^{-45}$
				Transformed lymphocytes	$1.21x10^{-23}$
				Transformed fibroblasts	$9.78x10^{-07}$
				Lung	$8.42x10^{-28}$
rs4958880*	A	Westra 2013	*TNIP1*	Whole blood	$1.09x10^{-03}$
rs10954214*	T	GTEx2015_v6	*IRF5*	Whole blood	$2.56x10^{-16}$
		Lappalainen2013		Lymphoblastoid cell line	$7.54x10^{-31}$
rs13238352*	T	Lappalainen2013	*IRF5*	Lymphoblastoid cell line	$2.88x10^{-13}$
rs2736337*	C	GTEx2015_v6	*FAM167A*	Whole blood	$2.90x10^{-26}$
			FAM167A	Transformed fibroblasts	$1.90x10^{-18}$
			FAM167A	Transformed lymphocytes	$2.10x10^{-15}$
			BLK	Whole blood	$5.30x10^{-13}$

rs2736337*	C	GTEx2015_v6	*BLK*	Transformed fibroblasts	$1.30x10^{-11}$
			BLK	Transformed lymphocytes	$3.30x10^{-06}$
rs7929541*	C	GTEx2015_v6	*TMEM80*	Transformed fibroblasts	$1.22x10^{-11}$
rs11085725*	T	GTEx2015_v6	*TYK2*	Whole blood	$2.30x10^{-06}$
			TMED1	Whole blood	$8.80x10^{-06}$
rs76246107*	A	GTEx2015_v6	*ALDH16A1*	Lung	$6.45x10^{-06}$
rs5754467*	G	GTEx2015_v6	*UBE2L3*	Whole blood	$4.68x10^{-06}$

New associated SNPs found in our meta-analysis are shown in boldface: rs744600 and rs13101828 associated with Systemic Sclerosis, Systemic Lupus Erythematosus, Rheumatoid Arthritis and idiopathic inflammatory myopathy; rs76246107 associated with Systemic Sclerosis, Systemic Lupus Erythematosus and idiopathic inflammatory myopathy. *Designates those SNPs where a physical interaction has been observed in Promoter Capture HiC data in relevant immune cells.

Drug target enrichment analysis

Genetic associations have the potential to improve the rates of success in the development of new therapies.[41] We assessed if the protein-products from disease associated eQTLs and their direct protein-protein interaction (PPI) partners were enriched with pharmacologically active targets (Table S6 and Table S7). We identified as eQTLs and PPIs 608 proteins for SSc, 630 for SLE, 632 for IIM, and 413 for RA, based on data on drugs at any stage of development collected from the Open Targets Platform (Table S8).[32] Using this information, we found for SSc that 23 out of 73 (32%) proteins are targeted by drugs being studied for the disease (OR=16.80, *p*-value=1.41×10^{-18}). Similarly, 7 out of 25 (28%) proteins related to IIM and 13 out of 146 (9%) proteins related to SLE are addressed by drugs in consideration for IIM and SLE (OR=13.40, *p*-value=4.62×10^{-06}, OR=3.38, *p*-value=2.85×10^{-04}, respectively) (Table S9).

Discussion

In the present study we identified five unreported shared *loci* associated with systemic seropositive rheumatic IMIDs. This is the first large-scale meta-analysis, including more than 11,000 cases and 19,000 non-overlapping controls aiming to improve our knowledge regarding the genetic resemblances among these conditions.

Our results show that 85% of the associated variants were shared by at least three diseases. Interestingly, for several known RA susceptibility *loci* the contribution of RA was limited. In this case, most of the associated variants were independent to the ones previously reported. Among the new associated SNPs, the signals mapping to *NAB1*, *DGKQ* and *KPNA4-ARL14* were associated to all of the diseases under study. NAB proteins are known to interact with early growth response (EGR) family members

and act as corepressors induced by type I interferons (IFN).[42] The 'IFN signature'– has been previously described in these diseases.[43-46] Interestingly, two IFN regulatory factors –*IRF5* and *IRF8*– previously associated to the conditions under study, were associated in the meta-analysis. Additionally, the associated SNP is an eQTL in lymphoblastoid cell line, which evidences its role in disease pathogenesis. The DGKQ protein mediates cell signal transduction and can indirectly enhance the epidermal growth factor receptor (EGFR) signaling activity.[47] This pathway regulates cell proliferation and migration, and its expression is augmented in the vasculature of SSc patients with pulmonary involvement.[48] Moreover, the risk allele was associated with an increased expression of the gene in lymphocytes, fibroblasts and lung. In the same line, this gene was associated with Sjögren's syndrome, a related connective tissue disease.[49] The protein encoded by the gene *ARL14* is a GTPase involved in the recruitment of MHC class II containing vesicles and control the movement of dendritic cells (DCs) along the actin cytoskeleton.[50] The protein LIMK1 regulates many actin-dependent processes, including the assembly of the immune synapse between T cells and antigen presenting cells, an expected biological process involved in seropositive IMIDs. Remarkably, rs193107685 and rs112846137 interact physically with the promoters of the genes *LIMK1* and *ARL14*, respectively, in DCs (Figure S4). The gene *PRR12* has been previously associated with fibrinogen concentrations.[37] Fibrinogen is considered a high-risk marker for vascular inflammatory diseases and is considered an accurate predictor of cardiovascular diseases.[38, 51] Moreover, this molecule is an active player in the coagulation cascade, responsible for the spontaneous formation of fibrin fibrils. Cardiovascular events and fibrosis are the most life-threatening complications described in SSc, IIM, and SLE.[52-54]

296 The associated SNPs are highly enriched in functional categories in B and T
297 cells, natural killer and monocytes, highlighting the relevance of these cells in systemic
298 seropositive rheumatic IMIDs. Beyond whole blood, the skin is the other tissue with
299 significant functional categories, which is not surprising given the nature of these
300 connective tissue diseases. Moreover, epithelial cells could transdifferentiate into
301 mesenchymal cells and eventually contribute in fibrotic processes.[55] Moreover, SSc
302 patients are usually stratified according to the extent of skin involvement.[43] On the
303 other hand, the histone modifications observed are consistent with the ones reported in
304 previous studies, where histone hyperacetilation have been described in synovial tissues
305 in RA, in B cells in SSc, and in CD4+ T cells in SLE.[40] Finally, the independent
306 associated SNPs have significant eQTLs in relevant tissues (Table 3) and *in silico* data
307 from promoter capture HiC experiments showed the potential mechanisms in which
308 most eQTLs modulate gene expression. Interestingly, all new associated SNPs interact
309 with the promoters of surrounding genes, suggesting them as putative candidates with a
310 role in the pathophysiology of these conditions (Figure S4 and Table S5).

311 The prevalence of SSc, SLE, and IIM is low and there are no specific treatments
312 for these diseases in comparison with RA; therefore, given our current knowledge on
313 the use of genetic findings in drug target validation and drug repurposing, we evaluated
314 if drugs currently indicated for RA had the potential to be used in any of the other
315 IMIDs under study. Our meta-analysis revealed that ten *loci* overlap with known RA
316 risk genes. For instance, the gene-product of *TYK2* is targeted directly by Tofacitinib,
317 which inhibits janus kinases (https://www.drugbank.ca/drugs/DB08895) or indirectly
318 through the interleukin 6 (IL-6) family signaling pathway by targeting the IL6 receptor
319 with Tocilizumab (https://www.drugbank.ca/drugs/DB06273). Both drugs are currently
320 indicated for moderate to severe RA patients who respond poorly to disease-modifying

anti-rheumatic drugs. As *TYK2* is associated with SSc, SLE and IIM, it is a good candidate for therapy repositioning in these diseases. As a proof of concept, Tofacitinib is currently on trial for SLE (clinical trial identifier NCT02535689), SSc (NCT03274076) and Dermatomyositis (NCT03002649). Overall, we found that five of the *loci* identified in our meta-analysis interact with 17 genes that are considered drug targets, six of which are used for the treatment of these diseases (Table 4). Another interesting candidate for drug repurposing is Imatinib, a kinase inhibitor that targets ABL1, which interacts with the gene product of BLK, a known locus associated with SSc and RA (Table 4). Imatinib is currently being tested for SSc (NCT00555581) and RA (NCT00154336).

Table 4. Summary of the plausible target gene products with drug indications in systemic IMIDs.

Associated SNP	Gene product	Association results[a]	Drugs[b]	Targets	Disease indication[c]
rs6659932	IL12RB2	**IIM, SLE**, SSc	Canakinumab	IL1B	RA
			Anakinra	IL1R1	RA
			Tofacitinib	JAK kinases	RA
rs13389408	GLS	**IIM**, SLE, SSc	Azathioprine	PPAT	RA, SLE
rs13101828	DGKQ	**IIM, RA, SLE, SSc**	Orlistat	LIPF	--
rs2736337	FAM167A-BLK	**IIM**, RA, SLE, SSc	Nintedanib	PDGFRB	SSc
			Dasatinib	BLK	--
			Imatinib	ABL1	--
			Osimertinib	EGFR	--
			Vandetanib	EPHA1	--
			Fingolimod	S1PR1	--
			Bosutinib	SRC	--
rs11085725	TYK2	**IIM**, SLE, SSc	Tofacitinib	JAK kinases	RA
			Tocilizumab	IL6R	RA
			Interferon Apha-2B	IFNAR1	--
			Idelalisib	PIK3CD	--
			Ruxolitinib	JAK1	--

[a]Based on our meta-analysis, diseases contributing to the observed association. The diseases where the association of this variant has never been reported before at genome-wide significance level are shown in boldface.
[b]Drugs from the OpenTarget platform with their corresponding target.
[c]Current indication of the reported drug. Non-immune mediated diseases were omitted.
SSc: Systemic sclerosis; IIM: Idiopathic inflammatory myopathy; SLE: Systemic lupus erythematosus; RA: Rheumatoid arthritis.

As compared to previous cross-phenotype studies of autoimmune diseases, our study has the strength of analyzing systemic seropositive rheumatic diseases, which is a consistent clinical phenotype than in the diseases investigated previously, where mixed seropositive and seronegative diseases were analyzed, and combining systemic and organ-specific diseases.[8, 9] The study of a more homogenous phenotype allowed us to determine that the type I IFN signaling pathway and its regulation play a more prominent role in these conditions than in others, based on the associations observed in *NAB1*, *TYK2*, *PTPN11*, *IRF5*, and *IRF8*. Additionally, we performed a genome-wide scan to identify shared genetic etiologies, as opposed to the study performed by Ellinghaus *et al.* whose analyses were limited to the 186 autoimmune disease-associated *loci* implemented in the Immunochip platform. The study performed by Li *et al.* –which was also a meta-analysis of GWAS data– was focused on pediatric autoimmune diseases, whereas our study was on a new combination of diseases in adult population.

In summary, this is the first study to investigate shared common genetic variation in four systemic seropositive rheumatic IMIDs in adults. We identified 26 genome-wide significant independent *loci* associated with at least two diseases, of which five *loci* had not been reported before. The shared risk variants and their likely target genes are functionally enriched in relevant immune cells and significantly enriched in drug targets, indicating that it may assist drug repositioning among genetically related diseases based on genomics data.

Competing interests

The authors declare no competing interests.

Contributorship

Data providers: F.W.M., W.C., T.P.O, R.G.C., J.V., L.G.R., K.D., L.R.W., I.E.L., L. M.P., A.M.R., S.R.Y., A.S.O., T.R.R., D.A.I., H.C., W.E.R.O., P.S., B.P, A.L., J.A.L., C.I.A., C.D., D.H.J., P.P., H.V., on behalf of the Myositis Genetics Consortium; O.G., B.R., J.E.M., B.Z.A., R.P.M., M.J.C., M.C.V., A.E.V., A.J.S., J.C.B, P.L.C.M.R., R.S., A.I., R.A.O., G.R., N.H., C.P.S., N.O.C., M.A.G.G, M.G.E., P.A., J.V.L., A.H., R.H., V.S., F.D.K., F.H., M.M.C., R.M., P.S., R.W., A.K., H.K., E.D.B, T.W., L.K., L.B., R.S., B.A.L., A.M.H.V., P.C., J.V., M.H., A.T.L., J.Y., Y.H., S.F.W., F.M.W., L.H., J.L.N., S.K.A, S.A., P.G., F.K.T., B.P.C.K., F.C.A, on behalf of the Scleroderma Genetics Consortium; QC and imputation in the contributing studies: M.A.H., M.K., D.G.S.; Functional and drug enrichment analysis: M.A.H., M.K.; Meta-analysis, tables and figures: M.A.H., M.K., D.G.S.; Drafting and approved version of the manuscript: M.A.H., M.K., D.G.S., C.W., A.F., P.K.G., L.P., J.W., T.V., M.E.A.R., M.D.M., J.M., F.W.M., W.C., T.P.O, R.G.C., J.V., L.G.R., K.D., L.R.W., I.E.L., L. M.P., A.M.R., S.R.Y., A.S.O., T.R.R., D.A.I., H.C., W.E.R.O., P.S., B.P, A.L., J.A.L., C.I.A., C.D., D.H.J., P.P., H.V.; Study design and management: M.A.H., M.K., J.M.

Acknowledgements

We would like to thank Sofia Vargas, Sonia García, and Gema Robledo for their excellent technical assistance, as well as Dr. Carlos Flores, Dr. Maria Pino-Yanes, Dr. Elaine Remmers and Dr. Doug Bell for their outstanding advice. Additionally, we

would like to thank all the patients and healthy controls for their essential collaboration and the MYOGEN consortium for the provision of data. The results reported in this study were presented in the Genomics of Common Diseases 2017 conference and in EULAR 2018 (Acosta-Herrera M, Kerick M, González-Serna D *et al.* Ann Rheum Dis 2018; 77 Supp 2).

Funding

Funded by EU/EFPIA Innovative Medicines Initiative Joint Undertaking PRECISESADS (115565), The Spanish Ministry of Economy Industry and Competitiveness (SAF2015-66761-P), The Regional Ministry of Innovation, Science and Technologies of the Andalusian Regional Government (P12-BIO-1395), and Juan de la Cierva fellowship (FJCI-2015-24028). This research was supported in part by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences.

Ethical approval information

This study was conducted using available data included in previously published GWAS (Supplementary references 1-6).

Data availability

Summary statistics of the global meta-analysis generated and analyzed in the current study are available from the corresponding author on reasonable request.

Key messages

- Systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis and idiopathic inflammatory myopathies are systemic seropositive rheumatic diseases that share symptoms, progressions, environmental risk factors, high rates of familial aggregation, and susceptibility genes, pointing to a shared genetic architecture.

- The assessment of a shared genetic component among these conditions has not been performed before in a systematic fashion.

- We have identified five new shared *loci* among systemic seropositive rheumatic immune-mediated inflammatory diseases. The rest of the observed associations constitute firm susceptibility genes in autoimmunity, providing validity to our findings.

- The associated variants are enriched in marks related to gene activation in immune cells and constitute shared expression quantitative trait *loci*.

- For most of these diseases there are no specific treatments, therefore, therapy repositioning could be possible among genetically related conditions.

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572

573 ## Figure Titles and Legends

574

575 **Figure 1. Meta-analysis results for the four systemic immune-mediated**
576 **inflammatory diseases (IMIDs).** The Manhattan plot displays the -log10 transformed
577 *p*-values (*y-axis*) by position on each chromosome (*x-axis*). The red line depicts the
578 genome-wide significance threshold (*p*-value=$5x10^{-8}$). A total of 26 SNPs were
579 independently associated with at least two systemic IMIDs. Most of the signals map to
580 known susceptibility *loci* in autoimmunity (e.g. *PTPN22, STAT4, TNPO3, FAM167A-*
581 *BLK*) and five *loci* have never been reported before.

582

583 **Figure 2. GARFIELD functional enrichment analyses in DHS hotspots**. The wheel
584 plot shows functional enrichment in systemic IMIDs within DHS hotspot regions in
585 ENCODE and Roadmap Epigenomics. The radial axis depicts the fold enrichment (FE)
586 calculated at different meta-analysis *p*-value thresholds. The font size is proportional to
587 the number of cell types from the tissue, mainly enriched in blood cell types including a
588 repertoire of immune cell lines.

589

Supplementary Figures

Figure S1. Distribution of the observed and expected association *p*-values in each individual study that contributed to the meta-analysis. Quantile-Quantile (QQ) plots from: A) Systemic sclerosis case-control collections. B) Systemic Lupus Erythematosus. C) Rheumatoid Arthritis and D) Idiopathic Inflammatory Myopathies.

Figure S2. Non-Conditioned and conditioned analysis on the top associated variants from the meta-analysis. In panels where significant variants remained after conditioning, there are several independent variants in the region. In panels E, P, and Y the remaining independent variants were not significant in the meta-analysis.

Figure S3. Wheel plots from the functional enrichment analysis with GARFIELD at different thresholds of p-values from the meta-analysis. Functional categories from the ENCODE project and Roadmap Epigenomics.

Figure S4. Circular view of the interactions from the new shared risk SNPs with genes nearby obtained from Promoter Capture HiC data in relevant immune cell types. Interactions are displayed as connecting lines depending on the confidence of the interaction. Grey lines are below threshold in the tissue. Only genes with maximum interaction score are reported.