



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

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

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43 **Abstract**

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

51 **Methods:** We meta-analyzed ~6.5 million single nucleotide polymorphisms (SNPs) in
52 11,678 cases and 19,704 non-affected controls of European descent populations. The
53 functional roles of the associated variants were interrogated using publicly available
54 databases.

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

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

70

71 **Introduction**

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

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

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

102

103 **Subjects and Methods**

104 **Study population**

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

108

109 **Data quality control and imputation**

110 Unified quality control (QC) of the 18 case-control collections was conducted
111 separately, based on stringent criteria using PLINK v.1.07.[17] Given that related and/or
112 duplicated subjects may have been recruited for different studies, genome-wide
113 relatedness was assessed and one individual from each pair was removed. Samples with
114 <95% of successfully called genotypes were removed.

115 Further, single nucleotide polymorphisms (SNPs) with genotyping call rate
116 <98%, minor allele frequencies (MAF) <1% and deviating from Hardy-Weinberg
117 equilibrium (HWE) with a p -value <0.001 in the control group were removed. To
118 control for possible population stratification, we performed principal component (PC)
119 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 (R_{sq})
130 ≥ 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

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

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

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

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

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

166

167 **Results**

168 *Cross-phenotype meta-analysis and disease contribution*

169 Following sample QC and imputation, a total of 11,678 cases and 19,704 non-
170 overlapping controls were included in the genome-wide meta-analysis of 6,450,125
171 SNPs across the four diseases. The mean concordance rate among imputed and true
172 genotypes was 0.999 ± 0.0003 . The final λ showed minimal evidence of population
173 stratification in the meta-analysis ($\lambda=1.025$). Moreover, we calculated $\lambda_{1,000}$ with
174 consistent results ($\lambda_{1,000}=1.025$). Summary of sample/variant QC and QQ plots are
175 shown in Table S1 and Figure S1, respectively.

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

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

184

185 Among these 26 associations we found several key players in autoimmunity;
186 interestingly ten of these associations (38%) have never been reported before for SSc,
187 eight (31%) for SLE and RA, respectively, and 20 (77%) for IIM. Remarkably, five
188 SNPs have not been reported previously for any of the diseases under study and thus
189 constitute new shared risk *loci* in systemic seropositive rheumatic IMIDs (Table 1).

190 Amongst these five new associations we found the SNP rs744600 in the 3' region of the
191 NGFI-A binding protein 1 (*NABI*) (Odds ratio [OR] for the T allele 0.88, Confidence
192 Interval [CI]=0.85-0.92), p -value= 7.07×10^{-11}), and the intronic SNP rs13101828
193 mapping in the gene Diacylglycerol kinase theta (*DGKQ*) (OR for the G allele 1.11,

194 95%CI: 1.07–1.16, p -value= 1.32×10^{-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= 1.42×10^{-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= 3.81×10^{-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= 3.36×10^{-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 ($p < 5 \times 10^{-8}$) 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	<i>IL12RB2</i>	Intronic	C	0.85 (0.79-0.91)	6.08×10^{-11}	1.02×10^{-02}	IIM, SLE, SSc
1	114303808	rs6679677	<i>PHTF1-RSBN1</i>	Intergenic	A	1.34 (1.21-1.49)	2.30×10^{-28}	2.14×10^{-04}	IIM, RA, SLE
1	114377568	rs2476601	<i>PTPN22</i>	Coding (missense)	G	0.75 (0.67-0.83)	1.74×10^{-28}	1.06×10^{-4}	IIM, RA, SLE
1	114433946	rs1217393	<i>AP4B1</i>	Intronic	A	0.89 (0.85-0.92)	5.21×10^{-09}	4.91×10^{-1}	IIM, RA, SLE, SSc
1	173337747	rs2422345	<i>TNFSF4-LOC100506023</i>	Intronic	A	1.11 (1.05-1.18)	2.55×10^{-08}	6.00×10^{-03}	IIM, SLE, SSc
1	183532580	rs17849502	<i>NCF2</i>	Coding (missense)	T	1.36 (1.16-1.59)	3.93×10^{-15}	2.84×10^{-04}	IIM, SLE
2	191564757	rs744600	<i>NAB1*</i>	3'Downstream	T	0.88 (0.85-0.92)	7.07×10^{-11}	7.60×10^{-1}	IIM, RA, SLE, SSc
2	191933283	rs13389408	<i>STAT4</i>	Intronic	C	1.27 (1.20-1.34)	3.10×10^{-17}	3.99×10^{-1}	IIM, SLE, SSc
2	191973034	rs10174238	<i>STAT4</i>	Intronic	A	0.73 (0.67-0.80)	2.76×10^{-42}	4.31×10^{-07}	IIM, SLE, SSc
3	58183636	rs35677470	<i>DNASE1L3</i>	Coding (missense)	A	1.22 (1.14-1.30)	4.96×10^{-09}	6.78×10^{-01}	IIM, SLE, SSc
3	160312921	rs112846137	<i>KPNA4-ARL14*</i>	Intergenic	T	1.27 (1.17-1.37)	1.42×10^{-08}	9.55×10^{-01}	IIM, RA, SLE, SSc
4	965720	rs13101828	<i>DGKQ*</i>	Intronic	G	1.11 (1.07-1.16)	1.32×10^{-08}	2.29×10^{-01}	IIM, RA, SLE, SSc
5	150438477	rs4958880	<i>TNIP1</i>	Intronic	A	1.16 (1.10-1.22)	1.45×10^{-11}	2.61×10^{-01}	IIM, RA, SLE, SSc
5	159887336	rs2431098	<i>PTTG1-MIR3142HG</i>	Intergenic	G	1.12 (1.05-1.20)	4.91×10^{-12}	1.42×10^{-01}	SLE, SSc
6	106569270	rs802791	<i>PRDM1-ATG5</i>	Intergenic	C	0.87 (0.83-0.92)	3.65×10^{-12}	1.13×10^{-01}	SLE, SSc
6	138243739	rs58721818	<i>TNFAIP3</i>	3'Downstream	T	1.64 (1.46-1.84)	4.64×10^{-23}	1.65×10^{-01}	IIM, SLE, SSc
7	73537902	rs193107685	<i>LIMK1*</i>	3'Downstream	C	1.52 (1.27-1.83)	3.21×10^{-09}	1.18×10^{-01}	RA, SLE, SSc
7	128589633	rs10954214	<i>IRF5</i>	3UTR	T	1.18 (1.13-1.23)	6.63×10^{-17}	3.64×10^{-01}	IIM, RA, SLE, SSc
7	128647942	rs13238352	<i>TNPO3</i>	Intronic	T	1.44 (1.30-1.60)	1.47×10^{-38}	2.12×10^{-01}	SLE, SSc
8	11341880	rs2736337	<i>FAM167A-BLK</i>	Intergenic	C	1.23 (1.17-1.30)	4.86×10^{-22}	1.29×10^{-01}	IIM, RA, SLE, SSc
11	633689	rs7929541	<i>SCT-DRD4</i>	Intergenic	G	0.89 (0.83-0.95)	2.14×10^{-10}	4.98×10^{-04}	IIM, RA, SLE, SSc

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

^aAccording to NCBI build GRCh37/hg19.

^bVariant localization based on the nearest gene.

^cFunctionality obtained from SNPnexus.²³

^dResults of meta-analysis either under a fixed effect if no heterogeneity was found based on Cochran's Q test (p -value \geq 0.05) or under a random effect if heterogeneity was found among studies.

^eDisease 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.

209 *Associated loci and their functional enrichment on regulatory elements*

210 To assess whether the associated variants lie in coding and non-coding
211 regulatory and cell-type-specific elements of the genome, we performed an enrichment
212 analysis with GARFIELD.[39] The results obtained showed marked enrichment
213 patterns mainly in blood cells and skin cells, with 247 significant enrichments
214 ($p \leq 5 \times 10^{-05}$) (Figure S3 and Table S3). Table 2 summarizes the main enrichment results.
215 We found that the majority of associated variants were enriched in DNase I
216 hypersensitivity site (DHS) hotspots in blood, as depicted in Figure 2. This functional
217 category included a repertoire of cells from the immune system, such as B-lymphocytes
218 (Fold enrichment (FE)=11.68, empirical p (p_{emp}) $<1 \times 10^{-05}$), T-lymphocytes (FE=10.42,
219 $p_{emp}<1 \times 10^{-05}$), including T helper cells (FE=7.81, $p_{emp}<1 \times 10^{-05}$), T CD8+ (FE=7.61,
220 $p_{emp}<1 \times 10^{-05}$), natural killer cells (FE=11.36, $p_{emp}<1 \times 10^{-05}$), and monocytes
221 (FE=8.99, $p_{emp}<1 \times 10^{-05}$). In line with this enrichment, disease-associated SNPs were
222 enriched in enhancers (FE=14.99, $p_{emp}<1 \times 10^{-05}$), within TSS (FE=14.87,
223 $p_{emp}<1 \times 10^{-05}$), and on transcription factor binding sites (FE=12.20, $p_{emp}<1 \times 10^{-05}$) in
224 the B-lymphocyte cell line GM12878. Additionally, the highest enrichment was
225 observed in the histone modification H3K9ac (FE=14.02, $p_{emp}<1 \times 10^{-05}$), and
226 H3K27ac (FE=10.81, $p_{emp}<1 \times 10^{-05}$) in the B-lymphocyte cell line, which are
227 positively associated with gene activation. Although these modifications are increased
228 in the promoters of active genes, the latter has been shown to be associated with active
229 enhancers.[40] Moreover, enrichment was observed in H3K4me1,2,3 sites, which
230 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 ($p < 5 \times 10^{-8}$).

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	$<1 \times 10^{-5}$
		GM12878	TSS	12	10,182	33	416,420	14.87	$<1 \times 10^{-5}$
Footprints	Blood	GM06990	Footprints	8	3,153	33	416,420	32.02	$<1 \times 10^{-5}$
		GM12878	H3K9ac	21	18,903	33	416,420	14.02	$<1 \times 10^{-5}$
		GM12878	H3K27ac	22	25,674	33	416,420	10.81	$<1 \times 10^{-5}$
		GM12878	H2AFZ	22	25,824	33	416,420	10.75	$<1 \times 10^{-5}$
		GM12878	H3K4me3	17	25,365	33	416,420	8.46	$<1 \times 10^{-5}$
Histone modifications	Blood	GM12878	H3K4me2	23	34,807	33	416,420	8.34	5×10^{-5}
		GM12878	H3K4me1	25	39,871	33	416,420	7.91	$<1 \times 10^{-5}$
		GM12878	H3K79me2	16	25,683	33	416,420	7.86	$<1 \times 10^{-5}$
		GM06990	Hotspots	23	24,839	33	416,420	11.68	$<1 \times 10^{-5}$
Hotspots	Skin	NHEK	Hotspots	25	54,667	33	416,420	5.77	$<1 \times 10^{-5}$
		GM06990	Peaks	13	6,433	33	416,420	25.50	$<1 \times 10^{-5}$
Peaks	Blood	GM06990	Peaks	13	6,433	33	416,420	25.50	$<1 \times 10^{-5}$
TFBS	Blood	GM12878	TFBS	19	19,650	33	416,420	12.20	$<1 \times 10^{-5}$

^aFunctional categories from the Encode²⁸ and Roadmap Epigenomics.²⁹

^bNumber of LD-pruned annotated variants passing the meta-analysis threshold.

^cNumber of LD-pruned annotated variants in the reference dataset UK10K project.

^dNumber of LD-pruned variants passing the meta-analysis threshold.

^eNumber 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.

231 *Expression quantitative trait loci (eQTL) and associated variants*

232 *In silico* analysis of eQTLs revealed the role of 16 of the lead SNPs as eQTLs in
233 whole blood, lymphoblastoid cell lines, transformed lymphocytes, skeletal muscle and
234 transformed fibroblasts derived from European individuals from HaploReg v.4.1[28]
235 (Table 3 and Table S4). Focusing on new associated variants, the SNP rs744600
236 modifies *NABI* gene expression in lymphoblastoid cell lines ($p=1.30 \times 10^{-34}$), whereas
237 the T allele increases *HIBCH* expression in skeletal muscles ($p=8.09 \times 10^{-07}$). The G
238 allele of rs13101828 increases *DGKQ* expression in whole blood ($p=3.29 \times 10^{-45}$),
239 lymphocytes ($p=5.23 \times 10^{-19}$), fibroblasts ($p=4.44 \times 10^{-06}$), lung cells ($p=8.42 \times 10^{-28}$) and
240 several other tissues. The A allele of rs76246107 can reduce *ALDH16A1* expression in
241 lung cells ($p=6.45 \times 10^{-06}$), and the protein encoded by this gene is involved in
242 oxidoreductase activity. Reassuringly, 14 of the 16 (87%) reported eQTLs showed a
243 physical interaction between the SNP and the promoter of 15 of the genes affected by
244 the eQTLs (Table 3), as suggested by Capture HiC (C-HiC) data (Table S5). These
245 independent evidences propose a mechanistic approach to understand the modulation of
246 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	<i>p</i> -value
rs6659932*	C	GTEEx2015_v6	<i>IL12RB2</i>	Whole blood	3.72x10 ⁻¹¹
rs6679677*	A	Westra 2013	<i>PTPN22</i>	Whole blood	4.84x10 ⁻¹⁰
rs2476601*	G	Westra2013	<i>PTPN22</i>	Whole blood	3.36x10 ⁻¹⁰
		GTEEx2015_v6	<i>AP4B1</i>	Skeletal muscle	5.45x10 ⁻⁰⁷
		GTEEx2015_v6	<i>HIPK1</i>	Whole blood	7.71x10 ⁻⁰⁹
rs1217393*	A	Westra 2013	<i>PHTF1</i>	Whole blood	9.56x10 ⁻⁰⁵
		Westra 2013	<i>PTPN22</i>	Whole blood	2.67x10 ⁻¹⁰
		Westra 2013	<i>RSBN1</i>	Whole blood	1.41x10 ⁻¹⁰
rs744600*	T	GTEEx2015_v6	<i>HIBCH</i>	Skeletal muscle	8.09x10 ⁻⁰⁷
		Lappalainen2013	<i>NAB1</i>	Lymphoblastoid cell line	1.30x10 ⁻³⁴
		GTEEx2015_v6		Skeletal muscle	3.42x10 ⁻⁰⁹
rs13389408	C	Westra 2013	<i>GLS</i>	Whole blood	2.98x10 ⁻⁰⁷
rs35677470*	A	GTEEx2015_v6	<i>PXK</i>	Skeletal muscle	7.08x10 ⁻⁰⁶
				Whole blood	9.28x10 ⁻⁴⁵
				Transformed lymphocytes	1.21x10 ⁻²³
rs13101828	G	GTEEx2015_v6	<i>DGKQ</i>	Transformed fibroblasts	9.78x10 ⁻⁰⁷
				Lung	8.42x10 ⁻²⁸
rs4958880*	A	Westra 2013	<i>TNIP1</i>	Whole blood	1.09x10 ⁻⁰³
		GTEEx2015_v6		Whole blood	2.56x10 ⁻¹⁶
rs10954214*	T	Lappalainen2013	<i>IRF5</i>	Lymphoblastoid cell line	7.54x10 ⁻³¹
rs13238352*	T	Lappalainen2013	<i>IRF5</i>	Lymphoblastoid cell line	2.88x10 ⁻¹³
			<i>FAM167A</i>	Whole blood	2.90x10 ⁻²⁶
			<i>FAM167A</i>	Transformed fibroblasts	1.90x10 ⁻¹⁸
rs2736337*	C	GTEEx2015_v6	<i>FAM167A</i>	Transformed lymphocytes	2.10x10 ⁻¹⁵
			<i>BLK</i>	Whole blood	5.30x10 ⁻¹³

rs2736337*	C	GTEEx2015_v6	<i>BLK</i>	Transformed fibroblasts	1.30x10 ⁻¹¹
			<i>BLK</i>	Transformed lymphocytes	3.30x10 ⁻⁰⁶
rs7929541*	C	GTEEx2015_v6	<i>TMEM80</i>	Transformed fibroblasts	1.22x10 ⁻¹¹
rs11085725*	T	GTEEx2015_v6	<i>TYK2</i>	Whole blood	2.30x10 ⁻⁰⁶
			<i>TMED1</i>	Whole blood	8.80x10 ⁻⁰⁶
rs76246107*	A	GTEEx2015_v6	<i>ALDH16A1</i>	Lung	6.45x10 ⁻⁰⁶
rs5754467*	G	GTEEx2015_v6	<i>UBE2L3</i>	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.

247 *Drug target enrichment analysis*

248 Genetic associations have the potential to improve the rates of success in the
249 development of new therapies.[41] We assessed if the protein-products from disease
250 associated eQTLs and their direct protein-protein interaction (PPI) partners were
251 enriched with pharmacologically active targets (Table S6 and Table S7). We identified
252 as eQTLs and PPIs 608 proteins for SSc, 630 for SLE, 632 for IIM, and 413 for RA,
253 based on data on drugs at any stage of development collected from the Open Targets
254 Platform (Table S8).[32] Using this information, we found for SSc that 23 out of 73
255 (32%) proteins are targeted by drugs being studied for the disease (OR=16.80, p -
256 value= 1.41×10^{-18}). Similarly, 7 out of 25 (28%) proteins related to IIM and 13 out of
257 146 (9%) proteins related to SLE are addressed by drugs in consideration for IIM and
258 SLE (OR=13.40, p -value= 4.62×10^{-06} , OR=3.38, p -value= 2.85×10^{-04} , respectively)
259 (Table S9).

260

261 **Discussion**

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

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

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

321 anti-rheumatic drugs. As *TYK2* is associated with SSc, SLE and IIM, it is a good
322 candidate for therapy repositioning in these diseases. As a proof of concept, Tofacitinib
323 is currently on trial for SLE (clinical trial identifier NCT02535689), SSc
324 (NCT03274076) and Dermatomyositis (NCT03002649). Overall, we found that five of
325 the *loci* identified in our meta-analysis interact with 17 genes that are considered drug
326 targets, six of which are used for the treatment of these diseases (Table 4). Another
327 interesting candidate for drug repurposing is Imatinib, a kinase inhibitor that targets
328 ABL1, which interacts with the gene product of BLK, a known locus associated with
329 SSc and RA (Table 4). Imatinib is currently being tested for SSc (NCT00555581) and
330 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	--
			Nintedanib	PDGFRB	SSc
			Dasatinib	BLK	--
rs2736337	FAM167A-BLK	IIM, RA, SLE, SSc	Imatinib	ABL1	--
			Osimertinib	EGFR	--
			Vandetanib	EPHA1	--
			Fingolimod	S1PR1	--
			Bosutinib	SRC	--
			Tofacitinib	JAK kinases	RA
			Tocilizumab	IL6R	RA
rs11085725	TYK2	IIM, SLE, SSc	Interferon Apha-2B	IFNAR1	--
			Idelalisib	PIK3CD	--
			Ruxolitinib	JAK1	--

^aBased 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.

^bDrugs from the OpenTarget platform with their corresponding target.

^cCurrent 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.

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

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

351

352 **Competing interests**

353 The authors declare no competing interests.

354

355 **Contributorship**

356 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.
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390

391 **Ethical approval information**

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

394

395 **Data availability**

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

398

399 **Key messages**

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

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

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

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

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

413

414

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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 $-\log_{10}$ 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= 5×10^{-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

590 **Supplementary Figures**

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

595

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

600

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

604

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