Study of the common genetic background for rheumatoid arthritis and systemic lupus erythematosus

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ABSTRACT

Background Evidence is beginning to emerge that there may be susceptibility loci for rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) that are common to both diseases.

Objective To investigate single nucleotide polymorphisms that have been reported to be associated with SLE in a UK cohort of patients with RA and controls.

Methods 3962 patients with RA and 9275 controls were included in the study. Eleven SNPs mapping to confirmed SLE loci were investigated. These mapped to the *TNFSF4, BANK1, TNIP1, PTTG1, UHRF1BP1, ATG5, JAZF1, BLK, KIAA1542, ITGAM* and *UBE2L3* loci. Genotype frequencies were compared between patients with RA and controls using the trend test.

Results The SNPs mapping to the *BLK* and *UBE2L3* loci showed significant evidence for association with RA. Two other SNPs, mapping to *ATG5* and *KIAA1542*, showed nominal evidence for association with RA ($p=0.02$ and $p=0.02$, respectively) but these were not significant after applying a Bonferroni correction. Additionally, a significant global enrichment in carriage of SLE alleles in patients with RA compared with controls ($p=9.1\times10^{-7}$) was found. Meta-analysis of this and previous studies confirmed the association of the *BLK* and *UBE2L3* gene with RA at genome-wide significance levels ($p<5\times10^{-8}$). Together, the authors estimate that the SLE and RA overlapping loci, excluding *HLA-DRB1* alleles, identified so far explain ~5.8% of the genetic susceptibility to RA as a whole.

Conclusion The findings confirm the association of the *BLK* and *UBE2L3* loci with RA, thus adding to the list of loci showing overlap between RA and SLE.

INTRODUCTION

Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are both autoimmune rheumatological diseases thought to have a substantial genetic contribution to susceptibility.[1 2] Recent genome-wide association studies (GWAS) in both diseases have disclosed a number of genetic loci that that are commonly associated. Examples include the human leucocyte antigen (HLA) locus, the R620W (rs2476601) polymorphism within the *PTPN22* gene and association with the chromosome 6q23/*TNFAIP3* locus.[3 4] The high degree of familial aggregation that has been shown for RA and SLE further supports the presence of common genetic risk factors for both diseases.[5 6]

Recent GWAS in SLE have identified a number of novel associations, some of which have not been previously investigated in RA.[4 7–10] We have reported previously on the overlap between type 1 diabetes and RA susceptibility loci and there are now numerous examples of overlap between diverse autoimmune diseases.[11–14] We, therefore, hypothesised that the underlying autoimmunity of SLE and RA may be underpinned by additional overlap in the genetic susceptibility loci. The aim of this work was to investigate whether single nucleotide polymorphism (SNP) markers that had been reported to be associated with SLE were also associated with RA in a UK population of patients with RA and controls.

METHODS

Samples

Three thousand nine hundred and sixty-two patients with RA and 9275 controls were included in the study. The patients with RA were recruited as described previously[15] and all satisfied the 1987 American College of Rheumatology criteria for RA modified for genetic studies.[16 17] The clinical characteristics of the cohort have been described previously, but briefly, 71.8% were female, 72.1% were positive for rheumatoid factor and 69.7% positive for anticyclic citrullinated peptide (anti-CCP) antibodies. All samples were collected with ethical committee approval (MREC 99/8/84) and all individuals provided informed consent.

SNP selection and genotyping

A panel of 15 autosomal SNPs was selected for investigation from a recent large-scale replication study of SLE-associated loci,[10] and proxy SNPs were included where assays could not be designed for the original SNP tested.

Of the 21 SLE loci identified to date, we have previously reported association with *PTPN22*, *STAT4* and the 6q23/*TNFAIP3* locus.[15 18–20] The association of *HLA-DRB1* alleles with RA has been extensively studied in the past. Different SNPs mapping to the *FCGR2A* gene (rs12746613; $r^2=0.19$ with the SLE SNP rs1801274) and *PRDM1* (rs548234, $r^2=0.07$ with the SLE SNP rs2245214) have been reported to be associated with RA in meta-analysis including the samples tested in the current cohort.[21] SNPs mapping to the remaining 15 loci were selected for investigation. However, four SNPs mapping to *IRF5, IRAK1*, *PXK* and *IL10* either failed assay

Table 1 Association results for SLE risk variants genotyped in UK RA cases and controls

Chr	Locus	SNP	Major allele/ minor allele	MAF cases	MAF controls	HWE controls	Trend test p value	Corrected p value	Allelic OR (95% CI)
1	*TNFSF4*	rs10489265	T/G	0.25	0.24	0.56	0.11		1.05 (0.99 to 1.12)
4	*BANK1*	rs10516487	C/T	0.31	0.31	0.66	0.52		0.98 (0.93 to 1.04)
5	*TNIP1*	rs10036748	C/T	0.24	0.24	0.21	0.46		1.02 (0.96 to 1.09)
5	*PTTG1*	rs2431697	T/C	0.42	0.43	0.62	0.06		0.95 (0.90 to 1.00)
6	*UHRF1BP1*	rs11755393	A/G	0.34	0.34	0.41	0.79		1.01 (0.95 to 1.07)
6	*ATG5*	rs6568431	C/A	0.41	0.39	0.27	0.02	0.22	1.07 (1.01 to 1.13)
7	*JAZF1*	rs864745	G/A	0.49	0.49	0.98	0.20		1.03 (0.98 to 1.08)
8	*BLK*	rs2736340	C/T	0.26	0.24	0.95	3.0×10^{-4}	3.3×10^{-3}	1.11 (1.05 to 1.17)
11	*KIAA1542*	rs4963128	G/A	0.32	0.34	0.96	0.02	0.22	0.93 (0.88 to 0.99)
16	*ITGAM*	rs9888739	C/T	0.10	0.11	0.42	0.16		0.94 (0.85 to 1.03)
22	*UBE2L3*	rs5754217	G/T	0.21	0.19	0.37	2.4×10^{-3}	0.026	1.11 (1.04 to 1.19)

Linkage disequilibrium between the genotyped and reported variant (in brackets), when different: *TNFSF4* (rs2205960): $r^2=0.95$; *TNIP1* (rs7708392): $r^2=0.90$; *PTTG1* (rs2431099): $r^2=0.60$; *JAZF1* (rs849142): $r^2=1$; *ITGAM* (rs11860650): $r^2=0.92$.
Chr, chromosome; CI, confidence interval; HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency; OR, odds ratio; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SNP, single nucleotide polymorphism.

design or failed genotyping, resulting in 11 SNP markers being available for analysis (rs10489265 in *TNFSF4,* rs10516487 in *BANK1,* rs10036748 in *TNIP1,* rs2431697 in *PTTG1,* rs11755393 in *UHRF1BP1,* rs6568431 in *ATG5,* rs864745 in *JAZF1,* rs2736340 in *BLK,* rs4963128 in *KIAA1542,* rs9888739 in *ITGAM* and rs5754217 in *UBE2L3*).

Genotyping was undertaken using a Sequenom platform with iPlex chemistry according to manufacturer's instructions (http://www.sequenom.com). Quality control analysis was undertaken such that only SNPs and samples that passed a 90% quality control threshold were subject to further statistical analysis. Control allele frequencies were tested to ensure that they conformed to Hardy–Weinberg expectations, and SNPs that deviated significantly from this were removed from further analysis.

Analysis

First, genotype frequencies were compared between RA cases and controls using the χ^2 trend test implemented in PLINK software[22] to determine whether individual SLE susceptibility loci were also associated with RA. Where data were available for SLE variants in independent RA samples, data from this study were added to the data already available and reanalysed to determine the best estimate of the effect size. p Values <0.0045 were regarded as significant after correcting for multiple testing (11 tests) applying the Bonferroni correction.

Second, pathway analysis was carried out using Ingenuity Pathway Analysis 8.6 (Ingenuity Systems, http://www.ingenuity.com) in order to explore whether SNPs uniquely associated with either RA or SLE identified characteristic pathways. Bioinformatic analysis, using the Ingenuity Pathways Analysis library, identified the pathways that were most supported by the dataset. Molecules from the dataset that were associated with a canonical pathway in Ingenuity's knowledge base were considered for the analysis. Fisher's exact test was used to calculate a p value determining the probability that the association between the genes in the dataset and the canonical pathway is explained by chance alone.

Third, analysis of carriage of SLE alleles in patients with RA was carried out using STATA version 9.2 to determine if there is an overall enrichment of SLE susceptibility variants in RA cases. A SLE loci carriage score was calculated by summing the number of SLE risk (coded as 1) and protection (coded as −1) alleles carried by each individual, and differences in the mean score between RA cases and controls was tested using the Wilcoxon rank-sum test.

Finally, in order to explore how much of the genetic susceptibility to RA could be accounted for by variants identified to date, the sibling recurrence risk ratio (λs) was calculated using the formula:

$$\lambda s = \left(1 + \frac{pq(\gamma-1)^2}{2(p+\gamma q)^2}\right)^2$$

where q is the risk allele frequency, $p=1-q$ and γ is the genotype relative risk under the additive model.

RESULTS

For the *BANK1*, *JAZF1* and *BLK* SNPs, data were available from a previous GWAS in a UK population including 2000 RA cases and 3000 controls.[23] In addition, part of the cohort used in our study had been previously genotyped for *UBE2L3*.[24] Therefore, non-overlapping samples from these studies were added to the current cohort for the analysis of the three markers. Control allele frequencies for all SNPs tested conformed to Hardy–Weinberg expectations (table 1). Four SNPs, rs6568431 mapping to the *ATG5* locus, rs2736340 close to *BLK*, rs4963128 mapping to the *KIAA1542* locus and rs5754217 in *UBE2L3* showed nominal evidence for association (p<0.05). After applying a Bonferroni correction for the number of SNPs tested, only the SNPs mapping to *BLK* and *UBE2L3* retained statistically significant evidence for association. It should be noted that control allele frequencies were similar and the direction of association was the same at all four loci with that observed in the SLE studies, although effect sizes were smaller. Therefore, although non-significant after applying a Bonferroni correction, *ATG5* and *KIAA1542* remain interesting candidates for further investigation. Repeating the association analysis in the anti-CCP positive and negative subgroups of RA cases did not substantially alter the observed effect sizes (data not shown). A test of heterogeneity of odds ratios (ORs) showed that the effect sizes were similar among all RA, anti-CCP positive RA and anti-CCP negative RA subgroups for all analysed SNPs (p>0.05).

A meta-analysis including our UK cohort and the US cohort in which association of *BLK* with RA was described for the first time showed a strong association between the rs2736340 SNP in the *BLK* locus and RA ($p=5.6\times10^{-11}$, OR=1.14 95% CI 1.10 to 1.19). We also performed a pooled analysis for *UBE2L3*, expanding the validation cohort from the meta-analysis of Stahl *et al*[24] with the UK non-overlapping samples genotyped in our study,

and including data from GWAS. In this expanded analysis, the rs5754217 at the *UBE2L3* locus now reaches genome-wide significance ($p=2.3\times10^{-10}$, OR=1.14 95% CI 1.09 to 1.19).

We next performed a pathway analysis including the loci that have shown evidence of association with both SLE and RA (*HLA-DRB1*, *PTPN22*, *STAT4, TNFAIP3, FCGR2A, PRDM1, IRF5, PXK, BLK* and *UBE2L2*). All the over-represented pathways are involved in the immune response, such as dendritic cell maturation, T helper (Th) cell differentiation or CTLA4 signalling in cytotoxic T lymphocytes (table 2). As is the case in the overlapping loci, genes exclusively associated with RA (*AFF3, ANKRD55/IL6ST, C5orf13, CCL21, CCR6, CD2/CD58, CD28, CD40, CTLA4, IL2/IL21, IL2RA, IL2RB, KIF5A, PRKCQ, PTPRC, RBPJ, REL, SPRED2, TAGAP, TRAF1/C5* and *TRAF6*) are part of immune response pathways, with pathways related to Th cell activation being most over-represented. However, when analysing genes associated only with SLE (*ATG5, BANK1, ITGAM, JAZF1, PHRF1, PTTG1, TNFSF4, TNIP1* and *UHRF1BP1*), a different pattern emerged. Four significantly over-represented pathways were identified but each included only one gene and only one of them was immune response related (table 2).

The number of SLE-associated SNPs showing at least nominal evidence for association with RA was higher than would be expected by chance alone. We explored, therefore, the extent of the total burden of SLE susceptibility alleles in RA. For this analysis we included previously generated genotype data for the markers: rs7574865 in *STAT4*, rs2476601 in *PTPN22* and rs5029937 in *TNFAIP3*; and from this study: rs10489265 in *TNFSF4,* rs10516487 in *BANK1,* rs10036748 in *TNIP1*, rs2431697 in *PTTG1*, rs11755393 in *UHRF1BP1,* rs6568431 in *ATG5,* rs864745 in *JAZF1,* rs2736340 in *BLK,* rs4963128 in *KIAA1542,* rs9888739 in *ITGAM* and rs5754217 in *UBEL2L3*. We found that the mean number of SLE risk alleles carried by patients with RA was significantly higher than that found in controls (2.9 vs 2.5, $p=9.1\times10^{-7}$).

Finally, we calculated the sibling recurrence risk ratio (λs) for the confirmed RA and SLE overlapping loci (*PTPN22*, *STAT4, TNFAIP3, FCGR2A, PRDM1, IRF5, PXK, BLK* and *UBE2L2*). We estimate that, after excluding *HLA-DRB1* alleles, these explain 5.8% of the genetic susceptibility to RA as a whole, while all the non-HLA confirmed RA loci identified to date[24] are able to explain 10.7%.

DISCUSSION

The findings confirm the association of the *BLK* and *UBE2L3* loci with RA thus adding to the list of loci showing overlap between RA and SLE, which currently include *HLA-DRB1*, *PTPN22*, *STAT4, TNFAIP3, FCGR2A, PRDM1, IRF5* and *PXK*. In addition, two loci, *ATG5* and *KIAA1542*, showed nominal association with RA and the associated allele was the same as that previously reported for SLE, although the associations did not remain statistically significant after Bonferroni correction was applied. However, the effect sizes conferred by *BLK*, *ATG5* and *KIAA1542* were significantly higher for SLE than for RA (test of heterogeneity of ORs p values=1×10^{-6}, 3×10^{-3} and 4×10^{-3}, respectively).

The finding of an association with *BLK* confirms a study in a US population where this locus was also associated with RA.[25] Interestingly, the *BLK* locus has also shown association with RA in a Japanese population.[26] *BLK* encodes a tyrosine kinase that is involved in the regulation of B-cell activation.[27] B cells have a key role in the pathogenesis of both RA and SLE through the production of autoantibodies, antigen presentation to T cells and cytokine production, and B-cell depletion has proved successful in the treatment of these diseases.[28] *UBE2L3* encodes an ubiquitin-conjugating enzyme involved in the regulation of interferon and TLR7/9 signalling pathways.[4] Furthermore, this locus has been shown to be associated with coeliac disease.[29] Therefore, *BLK* and *UBE2L3* are promising candidate genes for both RA and SLE.

The lack of association in our population between RA and markers mapping to *ITGAM* and *BANK1* is in accordance with a previous study in a Spanish population.[30] However, the Spanish study failed to detect association with *BLK*, probably owing to lack of power to detect modest effect sizes. In this regard, our study had >95% power to detect an association with similar effect sizes as those previously reported for SLE at the 5% significance level for all the loci tested.

All the shared SLE–RA loci and RA-only loci are involved in important pathways for autoimmunity and inflammation. On the other hand, the burden of immune pathways seems to be lower for genes associated with SLE only. However, pathway analysis results should be considered with caution since, for most of the disease-associated loci, the true causal variant and therefore the gene responsible for the association has not yet been identified. In addition, the exact role of several associated genes has not been elucidated and our knowledge of the relationships between molecules is limited.

The degree of genetic overlap between RA and SLE is substantial, but it is difficult to assess and likely to be an underestimate, based on several factors. First, we have only analysed associated loci at genome-wide significance levels; however, additional SLE loci not yet satisfying this criterion have been identified and there are probably more to be discovered. Second, large sample sizes were included in the studies undertaken in SLE leading to the identification of variants with small effects, for which studies in RA may be underpowered to detect. Third, as only the SNP identified in the primary study is tested in the other diseases, it may be that a different variant in the same gene/region is responsible for risk in the second disease.

There are already examples of loci common to two or more autoimmune diseases for which the associated SNP and/or allele is not the same in each disease. For example, the SNPs at the *TNFAIP3* region, associated with RA, SLE, type 1 diabetes, are different from those associated with coeliac disease and psoriasis.[20 31–36] Another example is the R620W variant of the *PTPN22* gene, which has been widely associated with many autoimmune diseases but not psoriasis,[37 38] for which evidence of association of two different *PTPN22* SNPs (rs1217414 and rs3789604) has been found and this has been independently replicated.[39 40] In addition, with regard to the *JAZF1* locus, the variant associated with prostate cancer[41] differs from that associated with SLE,[10] type 2 diabetes[42] and height variation.[43] For these reasons, the actual overlap between the two diseases may be higher than estimated in this study.

A high degree of overlap between SLE and RA susceptibility loci might be expected as the two diseases show some clinical overlap in joint involvement, autoantibody production, systemic features and response to treatments such as B-cell depletion (rituximab). Indeed, there was a proposal put forward for an overlap syndrome of 'rhupus' as some patients develop features of both diseases.[44] For example, the frequency of antinuclear antibody, the hallmark of SLE, is higher in patients with RA than the general population.[45] Unfortunately, antinuclear

Table 2 Over-represented ($p<0.05$) canonical pathways in which RA and SLE overlapping loci, RA only loci and SLE only loci are involved

Canonical pathway	Type of pathway	p Value	Genes in pathway
SLE/RA overlap			
Dendritic cell maturation	Cellular immune response, cytokine signalling, pathogen-influenced signalling	1.4×10^{-4}	*STAT4, FCGR2A, HLA-DRB1*
T helper cell differentiation	Cellular immune response, cytokine signalling	9.8×10^{-4}	*STAT4, HLA-DRB1*
CTLA4 signalling in cytotoxic T lymphocytes	Cellular immune response	1.8×10^{-3}	*HLA-DRB1, PTPN22*
Role of NFAT in regulation of the immune response	Cellular immune response, humoral immune response, intracellular and second messenger signalling	6.2×10^{-3}	*FCGR2A, HLA-DRB1*
TNFR2 signalling	Apoptosis, cytokine signalling	0.02	*TNFAIP3*
B-cell development	Cellular growth, proliferation and development, humoral immune response	0.02	*HLA-DRB1*
Antigen presentation pathway	Cellular immune response, humoral immune response	0.03	*HLA-DRB1*
Allograft rejection signalling	Cellular immune response, disease specific pathway	0.03	*HLA-DRB1*
Autoimmune thyroid disease signalling	Cellular immune response, disease specific pathway, humoral immune response	0.03	*HLA-DRB1*
Graft-versus-host disease signalling	Cellular immune response, disease specific pathway	0.03	*HLA-DRB1*
TNFR1 signalling	Apoptosis, cytokine signalling	0.03	*TNFAIP3*
Nur77 signalling in T lymphocytes	Apoptosis, cellular immune response, Nuclear receptor signalling	0.04	*HLA-DRB1*
Calcium-induced T lymphocyte apoptosis	Apoptosis, cellular immune response	0.04	*HLA-DRB1*
CD40 signalling	Cellular immune response, humoral immune response	0.04	*TNFAIP3*
IL-10 signalling	Cellular immune response, cytokine signalling	0.04	*FCGR2A*
JAK/Stat signalling	Apoptosis, cellular growth, proliferation and development, intracellular and second messenger signalling	0.04	*STAT4*
RA only			
iCOS-iCOSL signalling in T helper cells	Cellular immune response	9.8×10^{-9}	*PTPRC, CD28, PRKCQ, CD40, IL2RA, IL2RB*
T helper cell differentiation	Cellular immune response, cytokine signalling	5.2×10^{-8}	*IL21, IL6ST, CD28, CD40, IL2RA*
Altered T-cell and B-cell signalling in RA	Cellular immune response, disease-specific pathways	6.6×10^{-6}	*IL21, CD28, CD40, CCL21*
T-cell receptor signalling	Cellular immune response	1.3×10^{-5}	*PTPRC, CD28, PRKCQ, CTLA4*
IL-12 signalling and production in macrophages	Cellular immune response, cytokine signalling	2.0×10^{-5}	*TRAF6, PRKCQ, CD40, REL*
CD28 signalling in T helper cells	Cellular immune response	2.7×10^{-5}	*PTPRC, CD28, PRKCQ, CTLA4*
CD40 signalling	Cellular immune response, humoral immune response	1.0×10^{-4}	*TRAF6, CD40, TRAF1*
Cross-talk between dendritic cells and natural killer cells	Cellular immune response	3.7×10^{-4}	*CD28, CD40, IL2RB*
B cell development	Cellular growth, proliferation and development, humoral immune response	9.3×10^{-4}	*PTPRC, CD40*
Systemic lupus erythematosus signalling	Disease-specific pathways	1.0×10^{-3}	*PTPRC, CD28, CD40*
Role of macrophages, fibroblasts and endothelial cells in rheumatoid arthritis	Disease-specific pathways	1.2×10^{-3}	*TRAF6, IL6ST, PRKCQ, TRAF1*
NF- B signalling	Cellular immune response, cytokine signalling, humoral immune response, organismal growth and development	1.3×10^{-3}	*TRAF6, PRKCQ, CD40*
April -mediated signalling	Apoptosis	1.5×10^{-3}	*TRAF6, TRAF1*
Dendritic cell maturation	Cellular immune response, cytokine signalling, pathogen-influenced signalling	1.6×10^{-3}	*TRAF6, CD40, CD58*
B-cell activating factor signalling	Cellular growth, proliferation and development, humoral immune response	1.7×10^{-3}	*TRAF6, TRAF1*
Allograft rejection signalling	Cellular immune response, disease-specific pathways	1.8×10^{-3}	*CD28, CD40*
Autoimmune thyroid disease signalling	Cellular immune response, disease-specific pathways, humoral immune response	1.9×10^{-3}	*CD28, CD40*
Primary immunodeficiency signalling	Cellular immune response, disease-specific pathways, humoral immune response	2.3×10^{-3}	*PTPRC, CD40*
IL-2 signalling	Cellular immune response, cytokine signalling	3.1×10^{-3}	*IL2RA, IL2RB*
Lymphotoxin receptor signalling	Apoptosis	3.2×10^{-3}	*TRAF6, TRAF1*
Activation of IRF by cytosolic pattern recognition receptors	Cellular immune response	4.1×10^{-3}	*TRAF6, CD40*
Small cell lung cancer signalling	Cancer, disease-specific pathways	5.5×10^{-3}	*TRAF6, TRAF1*
Communication between innate and adaptive immune cells	Cellular immune response	5.8×10^{-3}	*CD28, CD40*
IL-6 signalling	Cellular immune response, cytokine signalling	8.1×10^{-3}	*TRAF6, IL6ST*
CTLA4 aignalling in cytotoxic T lymphocytes	Cellular immune response	8.7×10^{-3}	*CD28, CTLA4*
Type I diabetes mellitus signalling	Apoptosis, disease-specific pathways,	0.01	*TRAF6, CD28*
PKC signalling in T lymphocytes	Cellular immune response	0.01	*CD28, PRKCQ*
Hepatic fibrosis/hepatic stellate cell activation	Disease-specific pathways	0.02	*CD40, CCL21*
Hepatic cholestasis	Disease-specific pathways	0.02	*TRAF6, PRKCQ*
B cell receptor signalling	Humoral immune response	0.02	*PTPRC, PRKCQ*
IL-8 signalling	Cellular immune response, cytokine signalling	0.03	*TRAF6, PRKCQ*
Acute phase response signalling	Cytokine signalling	0.03	*TRAF6, IL6ST*
Role of NFAT in regulation of the immune response	Cellular immune response, humoral immune response, intracellular and second messenger signalling	0.03	*CD28, PRKCQ*
Role of NFAT in cardiac hypertrophy	Cardiovascular signalling, disease-specific pathways	0.03	*IL6ST, PRKCQ*

Continued

Table 2 Continued

Canonical pathway	Type of pathway	p Value	Genes in pathway
TNFR2 signalling	Apoptosis, cytokine signalling	0.04	*TRAF1*
4-1BB signalling in T lymphocytes	Cellular immune response	0.04	*TRAF1*
SLE only			
Mitotic roles of polo-like kinase	Cell cycle regulation	0.035	*PTTG1*
Angiopoietin signalling	Cardiovascular signalling, cellular growth, proliferation and development, growth factor signalling	0.041	*TNIP1*
Ubiquinone biosynthesis	Metabolism of cofactors and vitamins	0.045	*UHRF1BP1*
Caveolar-mediated endocytosis signalling	Cellular immune response, organismal growth and development, pathogen-influenced signalling	0.046	*ITGAM*

NFAT, nuclear factor of activated T cells; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

antibody data were not available for the RA samples tested here so we were not able to explore whether the associations seen were greater in the antinuclear antibody-positive subgroup.

In conclusion, this study has shown that a high degree of overlap exists between RA and SLE and raises the possibility that shared phenotypic characteristics may be a result of shared genetic susceptibility loci implicated in overlapping inflammatory pathways.

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