

Baricitinib-associated changes in global gene expression during a 24-week phase II clinical systemic lupus erythematosus trial implicates a mechanism of action through multiple immune-related pathways

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ABSTRACT

Objective To characterise the molecular pathways impacted by the pharmacologic effects of the Janus kinase (JAK) 1 and JAK2 inhibitor baricitinib in SLE.

Methods In a phase II, 24-week, randomised, placebo-controlled, double-blind study (JAHH), RNA was isolated from whole blood in 274 patients and analysed using Affymetrix HTA2.0 array. Serum cytokines were measured using ultrasensitive quantitative assays.

Results Gene expression profiling demonstrated an elevation of *STAT1*, *STAT2* and multiple interferon (IFN) responsive genes at baseline in patients with SLE. Statistical and gene network analyses demonstrated that baricitinib treatment reduced the mRNA expression of functionally interconnected genes involved in SLE including *STAT1*-target, *STAT2*-target and *STAT4*-target genes and multiple IFN responsive genes. At baseline, serum cytokines IFN- α , IFN- γ , interleukin (IL)-12p40 and IL-6 were measurable and elevated above healthy controls. Treatment with baricitinib significantly decreased serum IL-12p40 and IL-6 cytokine levels at week 12, which persisted through week 24.

Conclusion Baricitinib treatment induced significant reduction in the RNA expression of a network of genes associated with the JAK/STAT pathway, cytokine signalling and SLE pathogenesis. Baricitinib consistently reduced serum levels of two key cytokines implicated in SLE pathogenesis, IL-12p40 and IL-6.

factor (BAFF), a proliferation inducing ligand, interleukin (IL)-6, IL-12, IL-17, IL-23, tumour necrosis factor, as well as deficiency of IL-2 and IL-10.² Treatments are under study that target these cytokines, such as type I IFN, to potentially mitigate against SLE pathogenesis.

Many studies have reported elevation of IFN in SLE either measured directly or more often indirectly through elevation of IFN response gene mRNA expression.^{3 4} Several anti-IFN-specific monoclonal antibodies have been studied in clinical trials to determine their efficacy and safety in SLE. Among these, rontalizumab was not efficacious in treating active SLE,⁵ and only a modest clinical effect was observed in a trial testing another anti-IFN mAb: sifalizumab.⁶ In a phase II trial of a mAb targeting the IFN- α receptor, which blocks all type I IFN species, the mAb anifrolumab met the study primary endpoint of Systemic Lupus Responder Index (SRI)-4 at week 24 with a sustained reduction in oral corticosteroids from weeks 12 to 24.^{7 8} Subsequently, two phase III clinical trials, TULIP 1 and TULIP 2, have been completed using anifrolumab,^{9 10} while one met the primary endpoint of British Isles Clinical Lupus Activity index, a second trial failed to meet its primary endpoint of the SRI-4 response.

In addition to targeting IFNs, a proof of concept study targeting IL-6 has reported potential efficacy,¹¹ and in a phase II study targeting the p40 subunit shared by IL-12 and IL-23, patients treated with mAb ustekinumab



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INTRODUCTION

SLE is an autoimmune disease that is characterised by systemic inflammation in multiple organs.^{1 2} Despite improvements in therapy, substantial unmet medical need exists in SLE. A plethora of cytokines have been implicated in the pathogenesis of SLE, including an excess of interferons (IFNs), B cell activating

10 mg had a higher response rate according to SRI-4 than patients in the placebo group.¹² Nevertheless, a phase III study of ustekinumab has recently been discontinued.¹³ These findings support the concept that multiple cytokines such as IFN, IL-6 and the IL-12p40 pathway may have a role in SLE pathogenesis and could be viable targets for drug therapy.

Baricitinib is approved for the treatment of moderate-to-severe active rheumatoid arthritis in adults in over 65 countries including the USA, Japan and countries in the European Union. Baricitinib inhibits Janus kinase (JAK) 1 and JAK2 signalling¹³ via STAT1 and STAT2 pathways, which may impact the release of several proinflammatory cytokines, including type I IFNs, IFN- γ , IL-6, IL-12, IL-23 and others.^{14,15} In a phase II study of baricitinib, patients with SLE showed improvement in arthritis or rash at week 24, as well as SRI-4 and other secondary endpoints.¹⁶ Baricitinib, therefore, has the potential to simultaneously affect several key cytokines implicated in the pathogenesis of SLE.^{2,15} The goal of the present study was to examine the gene signature profiles and serum cytokines of SLE patients who were treated with baricitinib and to characterise molecular and cellular immune pathways impacted by baricitinib.

PATIENTS AND METHODS

Patient characteristics and study design

SLE patient samples were obtained from the double-blind, randomised, placebo-controlled, 24-week phase II clinical trial, labelled JAHH.¹⁶ Patients were ≥ 18 years of age and had a diagnosis of SLE. At baseline, patients were required to have a positive ANA or a positive antidiagonal stranded DNA (anti-dsDNA), a clinical Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K) of 4 or greater and arthritis or rash as defined by the SLEDAI-2K. Study drug was added to existing stable background standard of care therapy. Prednisone or equivalent was limited to a maximum daily dose of 20 mg at study entry and could not be increased after randomisation. Stable doses of non-steroidal anti-inflammatory drugs, a single immunosuppressant (azathioprine, methotrexate or mycophenolate mofetil) or a single antimarial were allowed. Active severe lupus nephritis or active CNS lupus were not permitted. Patients were randomly assigned to receive once-daily baricitinib 2 mg, baricitinib 4 mg or placebo for 24 weeks. The primary endpoint of the study was the proportion of patients achieving resolution of arthritis or rash as defined by the SLEDAI-2K at week 24.¹⁶ All patients and control subjects provided written informed consent. Full details of the JAHH clinical trial have been published.¹⁶

RNA isolation, analysis and hybridisation

Whole blood was collected in PAX gene tubes (Thermo Fisher Scientific) at baseline and weeks 2, 4, 12 and 24. Total RNA was isolated, and RNA quality was assessed postextraction as previously described.³ Complementary

DNA (cDNA) was prepared as previously described, and labelled cDNA was hybridised to the GeneChip Human Transcriptome Array 2.0 (HTA2.0) according to the manufacturer's instructions.³

Microarray analysis

Microarray analyses were performed on the Affymetrix HTA2.0 array and analysed as recently reported.³ Comparison of patients with SLE with healthy controls was performed with preprocessed array data from a combined data set of ILLUMINATE-1 and ILLUMINATE-2, which were two phase III studies of the anti-BAFF targeting mAb tabalumab compared with healthy controls.³ Analyses from study JAHH were performed with and without correction for total cell count and are shown using corrected counts.

Microarray preprocessing and normalisation

HTA2.0 microarray preprocessing was performed by summarising probe-level microarray data to the 'transcript cluster' (TC) level using TCs as defined by Affymetrix. Background correction and quantile normalisation were carried out using standard robust multiarray average.¹⁷ Summarisation to the TC level was done by estimating sample effects in an analysis of variance model with sample and probe effects using robust regression (rlm function in the R MASS package).

Cytokine expression analysis

JAHH serum samples were analysed for IL-2, IL-3, IL-5, IL-6, IL-10, IL-17A, IL-12p40, IL-12p70, GM-CSF and IFN- γ using a Meso Scale Multiplex cytokine panel and ultrasensitive quantitative assays (Quanterix SiMoA platform).¹⁸ JAHH plasma samples were analysed for IL-21 and IFN- α . Cytokine detection was performed using ultrasensitive quantitative assays.¹⁹ Cytokine concentrations were log-transformed before computing expression changes from baseline. Samples with undetectable analyte levels (concentration below lower limit of quantification (LLOQ)) were imputed to $0.5 \times$ LLOQ. Patients with undetectable cytokine levels at both baseline and week 12 were removed from the analysis.

Gene network analysis

Genes included in this analysis were selected from the list of differentially expressed genes for the baricitinib 4 mg dose at week 12 compared with placebo. The genes were selected by two methods: (1) the 50 genes most significantly changed with baricitinib treatment and (2) genes that interact with JAK1 or JAK2 via transcriptional regulation or phosphorylation as defined by the curated MetaBase (Clarivate) database and had an adjusted $p < 0.05$. In order to graphically show the interactions, these genes, along with STAT1, STAT2, JAK1, JAK2 and TYK2, were queried against the known interactions in MetaBase, and genes with known interactions were connected and displayed using Cytoscape; genes that were not directly connected to this network are not shown.

N-of-1 single subject analyses

Unpaired single-subject analyses were conducted similar to that of Gardeux *et al.*²⁰ Briefly, two gene signatures were defined including JAK1-activated genes or JAK1/JAK2/TYK2-activated genes, according to the gene network information from the MetaBase (Clarivate) database. Baseline expression of all signature genes was analysed from each SLE patient and compared with the mean expression from the patient population by Wilcoxon test.²⁰ Subjects showing statistically elevated or reduced expression of the signature at baseline were included in signature-high and signature-low groups, respectively. For each patient and for each visit, the change in SLEDAI-2K from baseline was computed. Next, for each signature group (high and low), the average SLEDAI-2K change was computed at each visit. Significance was assessed by running Monte Carlo simulations with 10 000 iterations. At each iteration, baseline signature status was randomly shuffled, and average SLEDAI-2K changes for each group and at each visit were computed. Statistical significance was determined by computing the overall difference between average SLEDAI-2K changes from the signature-high and signature-low groups, and then assessing it against the distribution from the Monte Carlo simulations.

Statistical analysis

All variables analysed were quantitative even if there was a categorical version of the variable. Pharmacological analysis was based on microarray data and performed by first fitting a mixed-effect, repeated measures model within each TC separately. The response variable was log₂-expression. Main effects, including treatment and time along with their interactions, were included in the model as fixed discrete effects. Age, sex and cell counts were included in the model as additional control covariates. A spatial correlation structure was used to model the covariance of measurements made on the same patient across different visits/time-points. Pharmacodynamic (PD) effects were estimated based on the difference between the variation in expression for each treatment group at a given time point and baseline and the variation in expression in the placebo group at that same time point and baseline. The MMRM model was fit for each TC separately and comparisons of baricitinib 2 mg and baricitinib 4 mg to placebo were performed at each time point. PD effects were evaluated only on the TCs associated to the top 50 genes according to differences between SLE and controls, and the corrections for multiple comparisons were done by computing FDR adjusted q-values using a Benjamini-Hochberg procedure.²¹

RESULTS

Patient disposition

The demographics of the patients are shown in table 1.¹⁶ Most patients were female with a mean age of 43–46 years and disease duration of 10–12 years. All patients with SLE

included in this analysis participated in the phase II trial of baricitinib (JAHH), had given informed consent for genetic studies and had provided adequate amounts of high-quality RNA available, as well as serum and plasma, at the time of testing (n=274). This resulted in a total of 274 patients, compared with the total number of 314 patients enrolled in the trial for RNA and a total of 270 patients for cytokine testing.

Baseline gene expression in SLE

A comparison yielding a ranked list of the top 50 genes elevated in patients with active SLE at trial enrolment compared with healthy blood donor controls is shown in figure 1A. An extended list of the top 150 genes elevated and a list of the top 150 genes decreased compared with controls is shown in online supplementary tables S1 and S2, respectively. As described in figure 1, there were genes with large fold increases comparing patients to healthy controls in JAHH at baseline, and these were highly statistically significant (online supplementary table S1). These findings were compared with those from the ILLUMINATE study where an independent group of controls was compared with 1760 patients with SLE.³ At baseline, findings from ILLUMINATE were similar to JAHH both in terms of the rank order of genes and the fold changes that are detected (figure 1A). Many of these genes have been defined functionally as IFN responsive genes. Importantly, the STAT1 (figure 1B) gene exhibited significantly elevated expression at baseline among the SLE patients who all had active disease at study entry. Furthermore, among patients with SLE, but not healthy controls, there was significant overexpression of paired STAT1 with STAT2 at baseline ($p<2.0\times10^{-16}$) (figure 1C) consistent with the predominance of IFNs.

Baricitinib induces change in gene expression

For genes that were upregulated, baricitinib treatment induced statistically significant changes in gene expression, which was most notable with the 4 mg dose (figure 2). The heatmap in figure 2A shows the top 50 genes with elevated expression in SLE versus controls, ranked by fold change. The subsequent columns show changes for baricitinib 2 mg and 4 mg treated patients at weeks 4, 12 and 24 compared with baseline. The heatmap demonstrates the quantitative reduction in gene expression with baricitinib treatment for many of the genes elevated in SLE versus controls, with many IFN responsive genes represented among the top 50. Consistent with the phosphorylation-mediated mechanism of STAT1 activation,²² there was no statistically significant downregulation of STAT1 RNA in samples from baricitinib-treated patients (figure 2A and online supplementary table S3).

The effect of baricitinib on the JAK/STAT signalling pathway and the association with SLEDAI-2K was further investigated. At week 0, patients with elevated (signature-high) or reduced (signature-low) expression of JAK1-activated genes were identified using an N-of-1-pathway single-subject analysis. Next, changes in the SLEDAI-2K

**Table 1** Baseline characteristics and disease activity*

	Placebo (n=90)	Baricitinib 2 mg (n=92)	Baricitinib 4 mg (n=92)
Age, years, mean (SD)	45.5 (12.6)	43.4 (11.0)	46.2 (12.0)
Female, n (%)	85 (94.4)	83 (90.2)	88 (95.7)
Time since onset of SLE, years, mean (SD)	10.2 (8.0)	11.8 (9.4)	12.1 (10.4)
SLEDAI-2K score, mean (SD)	8.9 (2.9)	8.6 (3.2)	8.8 (3.1)
SLEDAI-2K \geq 10, n (%)	39 (43.3)	28 (30.4)	37 (40.2)
SLEDAI-2K organ system involvement, n (%)			
Musculoskeletal	79 (87.8)	82 (89.1)	87 (94.6)
Mucocutaneous	79 (87.8)	73 (79.3)	81 (88.0)
Immunological	53 (58.9)	53 (57.6)	57 (62.0)
Haematological	12 (13.3)	7 (7.6)	3 (3.3)
Renal	8 (8.9)	8 (8.7)	4 (4.3)
Vascular	1 (1.1)	3 (3.3)	3 (3.3)
CNS	2 (2.2)	0	2 (2.2)
Cardiovascular and respiratory	2 (2.2)	1 (1.1)	1 (1.1)
Constitutional	1 (1.1)	2 (2.2)	0
≥1A or ≥2B BILAG scores, n (%)	52 (57.8)	49 (53.3)	62 (67.4)
Physician's Global Assessment, mean (SD)	48.7 (16.9)	48.7 (16.1)	51.9 (16.1)
CLASI activity score, mean (SD)	5.2 (5.9)	4.0 (5.7)	3.9 (3.4)
Tender joint count, mean (SD)	7.7 (5.9)	8.6 (6.5)	8.6 (5.9)
Swollen joint count, mean (SD)	5.4 (4.7)	5.2 (4.6)	5.8 (4.2)
Urine protein:creatinine ratio, n (%)			
≤50 mg/mmol	85 (94.4)	89 (96.7)	86 (93.5)
>50 mg/mmol	5 (5.6)	3 (3.3)	6 (6.5)
eGFR (MDRD), mL/min/1.73 m ² , mean (SD)	92.5 (22.8)	96.0 (21.7)	91.1 (24.2)
SLICC/ACR Damage Index score, mean (SD)	0.6 (1.0)	0.4 (0.6)	0.4 (0.9)
Haematological, mean (SD)			
Haemoglobin, mmol/L-Fe	8.0 (0.9)	8.1 (0.9)	7.9 (0.9)
Platelets, 10 ⁹ /L	239.7 (65.5)	250.0 (77.4)	245.6 (72.7)
Leucocytes, 10 ⁹ /L	5.5 (2.1)	6.2 (2.6)	5.9 (2.4)
Neutrophils, 10 ⁹ /L	3.7 (1.7)	4.3 (2.2)	4.0 (2.1)
Lymphocytes, 10 ⁹ /L	1.3 (0.6)	1.4 (0.7)	1.4 (0.7)
Monocytes, 10 ⁹ /L	0.3 (0.1)	0.3 (0.1)	0.3 (0.1)
Immunologic			
ANA titre \geq 1:80, n (%)	89 (98.9)	91 (98.9)	87 (94.6)
Anti-dsDNA, IU/mL, mean (SD)	83.9 (133.6)	115.5 (190.3)	140.1 (300.1)
Anti-dsDNA \geq 30 IU/mL, n (%)	42 (46.7)	47 (51.1)	46 (50.0)
C3, g/L, mean (SD)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)
C3 <90 mg/dL, n (%)	24 (26.7)	24 (26.1)	28 (30.4)
C4, g/L, mean (SD)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)
C4 <10 mg/dL, n (%)	11 (12.2)	22 (23.9)	13 (14.1)
Anti-Sm \geq 30 AU/mL, n (%)	9 (10.8)	5 (6.0)	6 (7.2)
Anti-RNP \geq 30 AU/mL, n (%)	24 (28.9)	18 (21.4)	24 (28.9)
Anti-SSA/Ro 52 \geq 30 AU/mL, n (%)	28 (33.7)	22 (26.2)	24 (28.9)
Anti-SSA/Ro 60 \geq 30 AU/mL, n (%)	45 (54.2)	36 (42.9)	34 (41.0)

Continued

Table 1 Continued

	Placebo (n=90)	Baricitinib 2 mg (n=92)	Baricitinib 4 mg (n=92)
Anti-SSB/LA \geq 30 AU/mL, n (%)	13 (15.7)	12 (14.3)	13 (15.7)
Antiphospholipid positive, n (%)	16 (19.0)	23 (27.1)	19 (23.2)
Anticardiolipin IgG >14 GPL, n (%)	6 (7.1)	6 (7.1)	4 (4.9)
Anticardiolipin IgM >12 MPL, n (%)	13 (15.5)	20 (23.5)	18 (22.0)
Serum IgG, g/L, mean (SD)	14.1 (6.3)	13.9 (3.7)	13.6 (4.9)
Serum IgM, g/L, mean (SD)	1.1 (1.7)	1.0 (0.6)	1.0 (0.7)
Concomitant medications			
Corticosteroids, n (%)	66 (73.3)	70 (76.1)	66 (71.7)
Prednisone dose (or equivalent; of those taking corticosteroids), mg/day, mean (SD)	7.9 (4.6)	8.4 (5.7)	8.5 (4.4)
Prednisone dose (or equivalent; of those taking corticosteroids), \geq 7.5 mg/day, n (%)	31 (47.0)	33 (47.1)	35 (53.0)
Antimalarials, n (%)	65 (72.2)	61 (66.3)	67 (72.8)
Immunosuppressants, n (%)	39 (43.3)	41 (44.6)	43 (46.7)
MTX	11 (12.2)	15 (16.3)	13 (14.1)
AZA	13 (14.4)	8 (8.7)	9 (9.8)
MMF	10 (11.1)	8 (8.7)	14 (15.2)
NSAID, n (%)	24 (26.7)	25 (27.2)	27 (29.3)

*For patients included in the gene expression analyses.

ACR, American College of Rheumatology; AZA, azathioprine; BILAG, British Isles Lupus Assessment Group; C, complement; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; CNS, central nervous system; dsDNA, double-stranded DNA; eGFR, estimated glomerular filtration rate; Ig, immunoglobulin; MDRD, Modification of Diet in Renal Disease Study equation; MMF, mycophenolate mofetil; mmol/L-Fe, mmol/L (Fe); MTX, methotrexate; n, number of patients in the specified category; N, number of patients in analysis population; NSAID, nonsteroidal anti-inflammatory drug; RNP, ribonucleoprotein; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2000; SLICC, Systemic Lupus International Collaborating Clinics.

were calculated from baseline for each patient in the signature-high group versus signature-low group across the three treatment arms. SLEDAI-2K trajectories were aggregated according to the baseline grouping (signature high vs low groups) and smoothed by LOESS. This analysis (**figure 2B and C**) revealed that patients with a relative elevation of JAK1-target genes at baseline had an overall better response to treatment with baricitinib 4 mg. Interestingly, patients from the placebo group exhibited overlapping SLEDAI-2K changes over time independent of the relative expression of the JAK1 signature at baseline (week 0). Similar results were obtained when baseline patients were grouped based on an expanded list of genes, including targets of JAK1, JAK2 and TYK2 (**figure 2C**), but the placebo response in this analysis was higher after week 12. These results are consistent with the observation that multiple JAK/STAT-target genes showed changes on treatment that correlated with changes in SLEDAI-2K (online supplementary table S4).

Gene network analysis

Baricitinib induced changes in gene expression, regardless of mechanism, by inhibiting JAK1 and JAK2 signalling. **Figure 3** shows genes whose expression changed based on baricitinib's inhibition of JAK1 and JAK2 signalling and the most significantly baricitinib-induced changed genes.

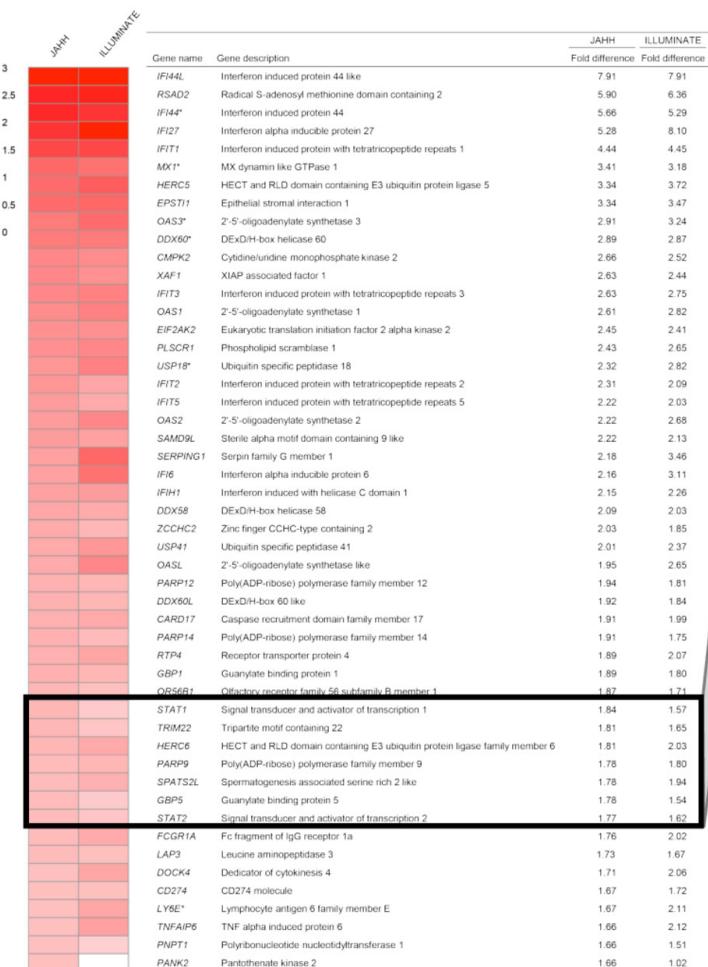
Baricitinib altered the expression of genes involved in immune pathways, including multiple genes for key cytokines (STAT 1, 2 and 4), cytokine receptors, T cells, regulatory cells and cytokine regulators that are associated with the immune pathogenesis of SLE.

Serum cytokine expression

At baseline, expression levels of many cytokines were detectable in a small fraction of healthy control samples, although some cytokines, such as INF- γ , IL-12p40 and IL-17A and IL-21, were routinely detected (**figure 4A**). The fraction of SLE patients with detectable cytokine levels was higher than controls for IFN- α , IFN- γ , IL-10, IL-5, IL-6 and IL-12p40, and the mean serum concentrations were higher in SLE (**figure 4A**).

Cytokine levels were analysed for changes in the serum of JAHH patients by treatment arm (**figure 4B**). There were significant changes in IL-12p40 and IL-6, whose protein levels were reduced in the baricitinib 4mg treatment arm but not in the placebo arm (**figure 4B**). The baricitinib-induced reduction of IL-12p40 ($p=0.016$) and IL-6 ($p=0.001$) was most pronounced at 12 weeks of treatment (**figure 4B**). A similar trend was observed also after 24 weeks of treatment (not shown), but the changes did not meet statistical significance.

A



B

Gene name	JAHH Fold difference	ILLUMINATE Fold difference
STAT1	1.84	1.57
TRIM22	1.81	1.65
HERC6	1.81	2.03
PARP9	1.78	1.80
SPATS2L	1.78	1.94
GBP5	1.78	1.54
STAT2	1.77	1.62

C

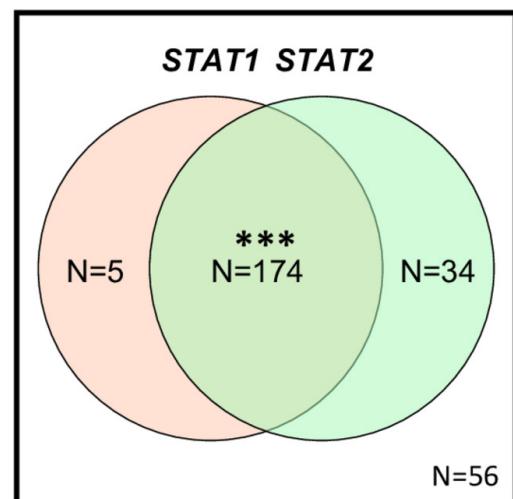


Figure 1 (A) The top 50 genes upregulated (ranked from high to low) based on the difference in expression between patients with SLE from JAHH and healthy control subjects are shown. Gene names were obtained from the MetaBase (Clarivate) database. Findings were compared with those from the ILLUMINATE study, analysed using data deposited in the NCBI Geo database (GSE88887), where an independent group of controls was compared with ILLUMINATE patients with SLE at baseline and expression fold differences are shown. Results shown for patients with SLE from JAHH compared with healthy controls had q -values $<2.7 \times 10^{-8}$. (B) Exploded heatmap showing the top 36th to 42nd top DE genes, which included STAT1 and STAT2. (C) Coordinated mRNA overexpression of signal transducer and activator of transcription (STAT) 1 and STAT2 in patients with SLE. Patients were assigned to the STAT1 high and the STAT2 high groups if their STAT1 and STAT2 mRNA expression at baseline was higher than the 95th percentile of healthy controls. The number of patients in the STAT1 high (orange circle) and STAT2 high (green circle) groups are indicated in the Venn diagram. A total number of 56 patients had normal expression of both STAT1 and STAT2. A total of five patients showed high expression of STAT1 but not STAT2, while 34 patients had increased STAT2 and normal STAT1 expression. A total of 174 patients had increased expression of both STAT1 and STAT2. Asterisks indicate statistically significant association ($^{***} = p < 0.001$). DE, differentially expressed.

DISCUSSION

The goal of this study was to characterise the molecular pathways impacted by the pharmacological effects of the JAK1 and JAK2 inhibitor baricitinib in SLE using RNA and serum samples from a phase II study of baricitinib that successfully met its primary endpoint. Baseline gene expression profiling of patients demonstrated that there was an elevation of *STAT1*, *STAT2* and multiple IFN responsive genes, when compared with healthy controls. Baricitinib treatment reduced the mRNA expression of functionally interconnected genes involved in SLE including *STAT1*-target, *STAT2*-target and *STAT4*-target genes and multiple IFN responsive genes.² Furthermore, the study

demonstrated that treatment with baricitinib 4mg significantly decreased serum IL-12p40 and IL-6 cytokine levels at week 12, which persisted through week 24. Thus, treatment with baricitinib 4mg induced significant reduction in the RNA expression of a network of genes associated with the JAK/STAT pathway, cytokine signalling and SLE pathogenesis, and it consistently reduced serum levels of two key disease-associated cytokines, IL-12p40 and IL-6. In this regard, a *JAK1*-associated gene profile has been identified correlating with treatment-associated changes found for the serum cytokine IL-6 and IL-12p40 responses, which will require further validation/replication. Notably, other cytokine signalling can be influenced indirectly by complex

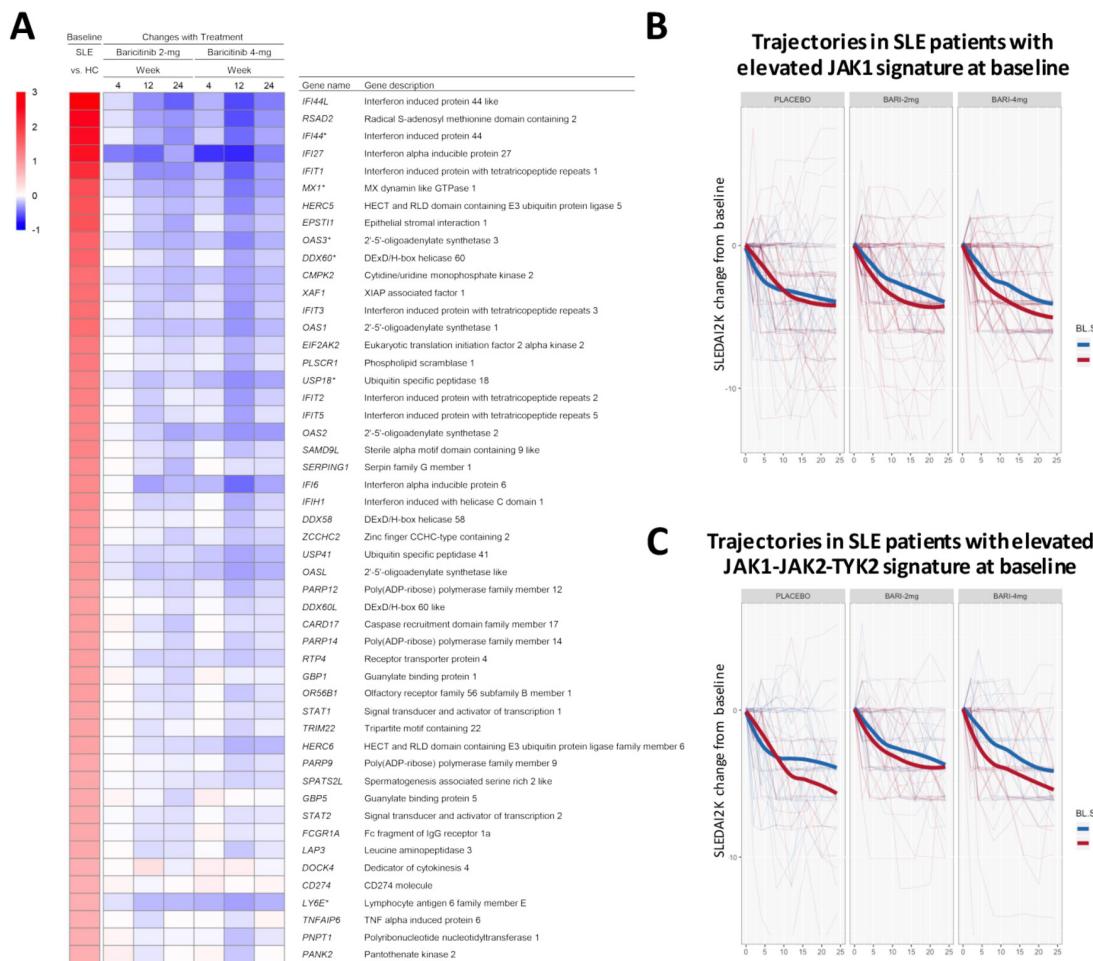


Figure 2 (A) Heatmap of top 50 genes upregulated in patients with SLE (ranked from high to low) showing the difference in expression between patients with SLE and healthy control subjects (far left column) and the corresponding gene expression changes in patients with SLE treated with baricitinib 2 mg and 4 mg at weeks 4, 12 and 24 (right columns) as compared with placebo. Gene name was defined using the MetaBase (Clarivate) database. (B and C) Changes in SLEDAI-2K from baseline for SLE patients with elevated (red) or reduced (blue) expression of the JAK1 (B) or JAK1-JAK2-TYK2 (C) gene signature at baseline. Thin lines correspond to individual patients. Thick lines show the LOESS-smoothed population average by group. Monte Carlo simulations were performed to assess if signature-high averages were overall lower than signature-low averages across visits and by baricitinib treatment group (B, JAK1-signature: placebo, $p=0.80$; baricitinib 2 mg, $p=0.02$; baricitinib 4 mg, $p=0.0003$. C, JAK1/JAK2/TYK2-signature: placebo, $p=0.07$; baricitinib 2 mg, $p=0.07$; baricitinib 4 mg, $p=0.0002$). JAK, Janus kinase; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2000.

interaction of signalling networks that interface with JAK/STAT.

The demographics of patients with SLE in the phase II study JAHH were similar to other recent phase II and III clinical trials suggesting that the baseline findings here may be broadly applicable.^{3 4} The baseline gene expression profiles of the patients studied yielded findings similar to the much larger 1760 patient ILLUMINATE studies, as well as other smaller studies, where large fold differences from healthy controls in expression of type I IFN responsive genes were observed in 50%–75% of patients.^{3 4}

A key finding of the present study was the identification of baseline elevations of *STAT1*, *STAT2* and *STAT4*, and/or downstream genes linked to the JAK/STAT pathway. The observations on *STAT1*, *STAT2* and *STAT4* are distinctive to this study and again

highlight the known importance of these genes and their associated signalling pathways in SLE.^{22 23}

A second important finding of the present study was that pharmacologically induced changes in gene expression following baricitinib therapy resulted in significant reduction in *STAT1*-targets. Of note, patients with a relative elevation in the expression of JAK1 pathway genes at baseline displayed a better response to baricitinib 4 mg according to changes in SLEDAI-2K (figure 2B) or SRI-4 (data not shown) over 24 weeks. While it was anticipated that baricitinib could reduce JAK/STAT targets expression, this is the first publication to directly demonstrate this in a clinical trial linking such changes to clinical improvement.

Gene network analysis revealed further that there were expression changes in genes that are involved directly in classical, canonical JAK/STAT signal

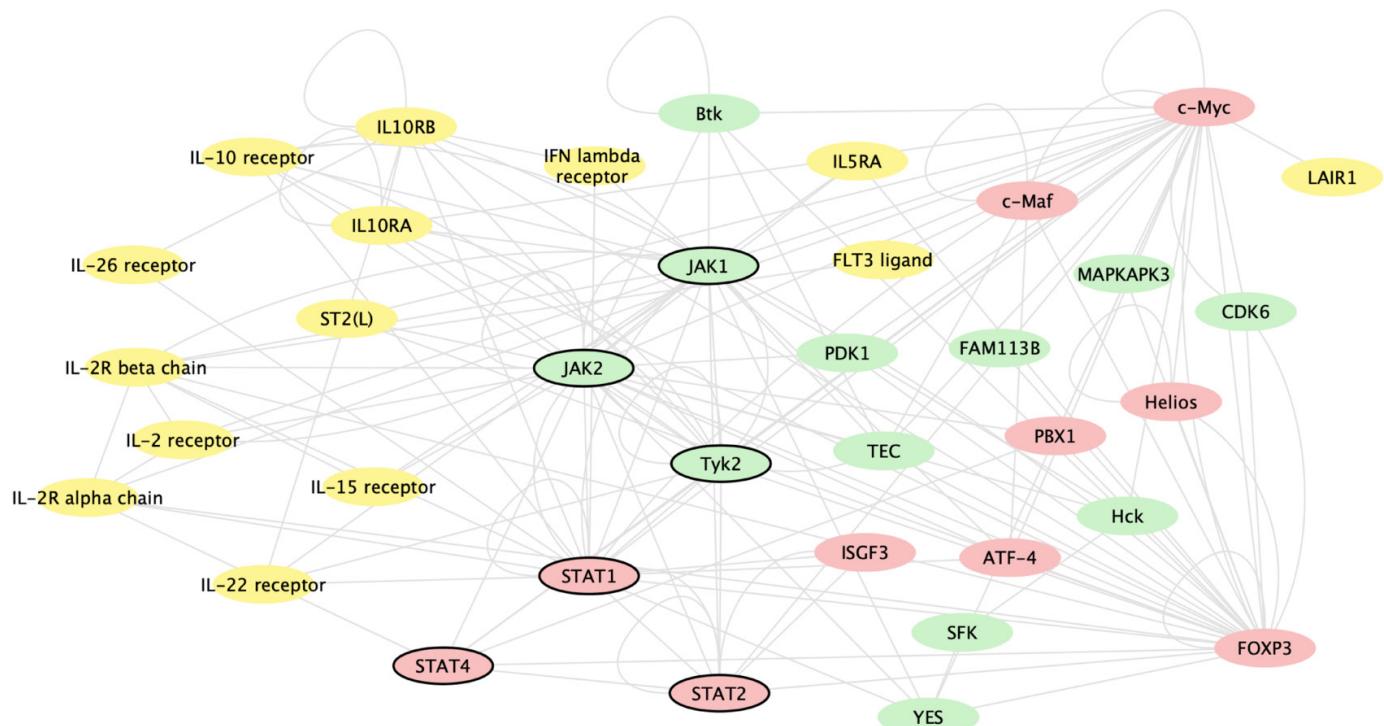


Figure 3 Gene network analysis of genes changed based on baricitinib's inhibition of JAK1 and JAK2 signalling and the most significantly baricitinib-induced changed genes, regardless of mechanism. The analysis includes genes changed with baricitinib 4 mg at week 12 compared with placebo. The genes included were identified by two methods: (1) the 50 genes most significantly changed with baricitinib treatment and (2) genes that interact with JAK1 or JAK2 via transcriptional regulation or phosphorylation as defined by the curated MetaBase (Calarivate) database and had an adjusted $p<0.05$. In order to graphically show the interactions, these genes, along with STAT1, STAT2, JAK1, JAK2 and Tyk2, were queried against the known interactions in MetaBase and kinases (green), ligands/receptors (yellow) and transcription factors (red) with known interactions were connected and displayed using cytoscape (cytoscape.org); genes that were not directly connected to this network or were in other categories are not shown. Genes of key interest in the network are indicated by bold outline, including STAT1, STAT2, STAT4, JAK1, JAK2 and Tyk2. JAK, Janus kinase.

transduction, including *STAT1* and *STAT4*, where genetic polymorphisms have been identified as a risk factor for both disease susceptibility and severity in SLE.^{23 24}

This study is among the largest published surveys that includes both whole blood RNA expression and serum cytokine levels in SLE.^{3 4 25 26} While gene expression studies allow for a comprehensive survey of cellular and molecular immune processes, it is an indirect measure of circulating serum cytokines. Based on precedents in the medical literature, the state of our current understanding of the pathogenesis of SLE and technical feasibility, the study attempted to measure a select number of key cytokines using serum or plasma samples from JAHH. These included: IFN- α , IFN- γ , IL-10, IL-12p40, IL-17A, IL-5 and IL-6 levels. Overall, with few exceptions, the cytokines tested were elevated in patients with SLE at baseline as compared with healthy controls. These results strongly support the hypothesis that SLE is not a single cytokine-driven disease but is characterised by global dysregulation of the cytokine signalling network.² Therefore, a pharmacological approach targeting multiple cytokines at the same time, such as the inhibition of the JAK/STAT axis, could be highly beneficial in the treatment of SLE. In

further support of this, it was found that baricitinib treatment was associated with statistically significant decreases of serum IL-12p40 and IL-6, supporting the concept that reducing the levels of these cytokines may be effective in treating SLE, as was suggested by previous clinical trials targeting these molecules.^{11 12} Various transcription factors have been implicated in the regulation of IL-6 and IL-12p40 expression, including AP-1, C/EBP and nuclear factor- κ B but not the JAK/STAT axis. Therefore, the molecular mechanisms responsible for the baricitinib-induced reduction of cytokine expression are still unclear and may entail cross-talk between STATs and other transcription factors, or suppressive effects on the proliferation and survival of cytokine-producing cells. Changes of *STAT4* possibly linked to IL-12p40 under baricitinib 4 mg provided some confirmation between transcriptional changes and reduced cytokines, which was not seen for *STAT3* connected to IL-6. Although differences between transcriptional changes and related protein expression can be found, the overall findings clearly indicate comprehensive inhibition of inflammatory pathways.

In conclusion, the mechanism of action of baricitinib in SLE may be mediated through the inhibition of multiple immune-related genes and cytokines. The study findings

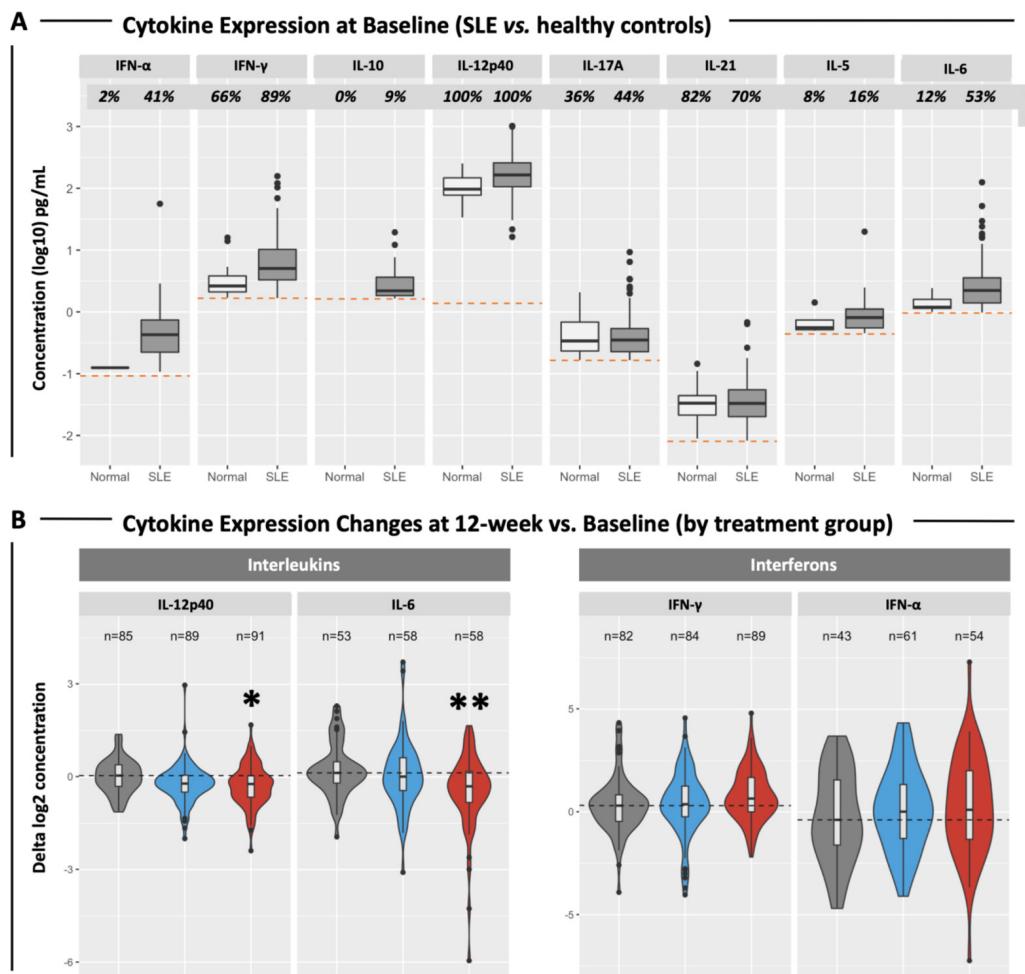


Figure 4 (A) Boxplots showing the expression levels of SLE cytokines in 270 patients at baseline and in 50 healthy controls. Percentages of samples with detectable cytokine levels are reported. Dashed lines indicate the LLOQ for each cytokine. The following cytokines were significantly elevated in SLE samples compared with controls: IFN- α ($p=1.95\times 10^{-7}$), IFN- γ ($p=1.45\times 10^{-7}$), IL-12p40 ($p=2.20\times 10^{-13}$), IL-6 ($p=2.84\times 10^{-7}$). (B) Violin plots showing changes (deltas) in cytokine expression at week 12 compared with baseline. Patients with undetectable levels at both baseline and week 12 were removed from the analysis. The number of subjects included in the analysis is reported. Violin colours indicate treatment groups. Dashed lines indicate the median cytokine expression change detected from baseline in the placebo group. Asterisks indicate statistically significant changes (* $=p<0.05$; ** $=p<0.01$). IL, interleukin; LLOQ, lower limit of quantification.

confirm that the JAK/STAT pathways appear to have a central role in the pharmacological effect of baricitinib in SLE. Baricitinib induced changes in the expression of *STAT1/STAT2* target genes, and these were associated with treatment response. Serum cytokine measurement support the hypothesis that IL-12p40 and IL-6 may have a role in SLE pathogenesis and contribute to the PD effect of baricitinib. Finally, the two ongoing phase III studies of baricitinib in SLE will help to further define the clinical benefits of baricitinib in SLE and the molecular mechanisms of its action.^{27 28}

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for the integrity of the data and the accuracy of the data analysis. Study conception and design: RJB, ERD, REH, RWH, MAP, MES and YT. Acquisition of data: ERD, RWH and MES. Analysis and interpretation of data: all authors. The authors would also like to thank Adam G Abel for his contribution on the interferon signature assay.

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Patient consent for publication Not required.

Ethics approval This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the ethics committee or institutional review board used at each centre. All patients and control subjects provided written informed consent. Full details of the JAHH clinical trial have been published in Wallace *et al.*, 2018.

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Data availability statement Data are available in a public, open access repository. Deidentified data will be deposited in GEO.

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SUPPLEMENTARY FILE
Supplementary Tables

Table S1. Baseline gene expression in SLE patients versus healthy controls, including upregulated genes with the greatest fold change from JAHH*

Gene name	Gene description	JAHH		ILLUMINATE	
		Fold difference	q value	Fold difference	q value
<i>IFI44L</i>	interferon induced protein 44 like	7.91	<1.0e-08	7.91	<1.0e-08
<i>RSAD2</i>	radical S-adenosyl methionine domain containing 2	5.90	<1.0e-08	6.36	<1.0e-08
<i>IFI44</i>	interferon induced protein 44	5.66	<1.0e-08	5.29	<1.0e-08
<i>IFI27</i>	interferon alpha inducible protein 27	5.28	<1.0e-08	8.10	<1.0e-08
<i>IFIT1</i>	interferon induced protein with tetratricopeptide repeats 1	4.44	<1.0e-08	4.45	<1.0e-08
<i>MX1</i>	MX dynamin like GTPase 1	3.41	<1.0e-08	3.18	<1.0e-08
<i>HERC5</i>	HECT and RLD domain containing E3 ubiquitin protein ligase 5	3.34	<1.0e-08	3.72	<1.0e-08
<i>EPSTI1</i>	epithelial stromal interaction 1	3.34	<1.0e-08	3.47	<1.0e-08
<i>OAS3</i>	2'-5'-oligoadenylate synthetase 3	2.91	<1.0e-08	3.24	<1.0e-08
<i>DDX60</i>	DExD/H-box helicase 60	2.89	<1.0e-08	2.87	<1.0e-08
<i>CMPK2</i>	cytidine/uridine monophosphate kinase 2	2.66	<1.0e-08	2.52	<1.0e-08
<i>XAF1</i>	XIAP associated factor 1	2.63	<1.0e-08	2.44	<1.0e-08
<i>IFIT3</i>	interferon induced protein with tetratricopeptide repeats 3	2.63	<1.0e-08	2.75	<1.0e-08
<i>OAS1</i>	2'-5'-oligoadenylate synthetase 1	2.61	<1.0e-08	2.82	<1.0e-08
<i>EIF2AK2</i>	eukaryotic translation initiation factor 2 alpha kinase 2	2.45	<1.0e-08	2.41	<1.0e-08
<i>PLSCR1</i>	phospholipid scramblase 1	2.43	<1.0e-08	2.65	<1.0e-08
<i>USP18</i>	ubiquitin specific peptidase 18	2.32	<1.0e-08	2.82	<1.0e-08
<i>IFIT2</i>	interferon induced protein with tetratricopeptide repeats 2	2.31	<1.0e-08	2.09	<1.0e-08
<i>IFIT5</i>	interferon induced protein with tetratricopeptide repeats 5	2.22	<1.0e-08	2.03	<1.0e-08
<i>OAS2</i>	2'-5'-oligoadenylate synthetase 2	2.22	<1.0e-08	2.68	<1.0e-08
<i>SAMD9L</i>	sterile alpha motif domain containing 9 like	2.22	<1.0e-08	2.13	<1.0e-08
<i>SERPING1</i>	serpin family G member 1	2.18	1.50e -08	3.46	<1.0e-08

Gene name	Gene description	JAHH		ILLUMINATE	
		Fold difference	q value	Fold difference	q value
<i>IFI6</i>	interferon alpha inducible protein 6	2.16	<1.0e-08	3.11	<1.0e-08
<i>IFIH1</i>	interferon induced with helicase C domain 1	2.15	<1.0e-08	2.26	<1.0e-08
<i>DDX58</i>	DExD/H-box helicase 58	2.09	<1.0e-08	2.03	<1.0e-08
<i>ZCCHC2</i>	zinc finger CCHC-type containing 2	2.03	<1.0e-08	1.85	<1.0e-08
<i>USP41</i>	ubiquitin specific peptidase 41	2.01	<1.0e-08	2.37	<1.0e-08
<i>OASL</i>	2'-5'-oligoadenylate synthetase like	1.95	<1.0e-08	2.65	<1.0e-08
<i>PARP12</i>	poly(ADP-ribose) polymerase family member 12	1.94	<1.0e-08	1.81	<1.0e-08
<i>DDX60L</i>	DExD/H-box 60 like	1.92	<1.0e-08	1.84	<1.0e-08
<i>CARD17</i>	caspase recruitment domain family member 17	1.91	<1.0e-08	1.99	<1.0e-08
<i>PARP14</i>	poly(ADP-ribose) polymerase family member 14	1.91	<1.0e-08	1.75	<1.0e-08
<i>RTP4</i>	receptor transporter protein 4	1.89	<1.0e-08	2.07	<1.0e-08
<i>GBP1</i>	guanylate binding protein 1	1.89	<1.0e-08	1.80	<1.0e-08
<i>OR56B1</i>	olfactory receptor family 56 subfamily B member 1	1.87	<1.0e-08	1.71	<1.0e-08
<i>STAT1</i>	signal transducer and activator of transcription 1	1.84	<1.0e-08	1.57	<1.0e-08
<i>TRIM22</i>	tripartite motif containing 22	1.81	<1.0e-08	1.65	<1.0e-08
<i>HERC6</i>	HECT and RLD domain containing E3 ubiquitin protein ligase family member 6	1.81	<1.0e-08	2.03	<1.0e-08
<i>PARP9</i>	poly(ADP-ribose) polymerase family member 9	1.78	<1.0e-08	1.80	<1.0e-08
<i>SPATS2L</i>	spermatogenesis associated serine rich 2 like	1.78	<1.0e-08	1.94	<1.0e-08
<i>GBP5</i>	guanylate binding protein 5	1.78	<1.0e-08	1.54	3.30e-06
<i>STAT2</i>	signal transducer and activator of transcription 2	1.77	<1.0e-08	1.62	<1.0e-08
<i>FCGR1A</i>	Fc fragment of IgG receptor Ia	1.76	<1.0e-08	2.02	<1.0e-08
<i>LAP3</i>	leucine aminopeptidase 3	1.73	<1.0e-08	1.67	2.00e-07
<i>DOCK4</i>	dedicator of cytokinesis 4	1.71	<1.0e-08	2.06	<1.0e-08
<i>CD274</i>	CD274 molecule	1.67	<1.0e-08	1.72	1.50e-08
<i>LY6E</i>	lymphocyte antigen 6 family member E	1.67	<1.0e-08	2.11	<1.0e-08
<i>TNFAIP6</i>	TNF alpha induced protein 6	1.66	2.70e-08	2.12	<1.0e-08
<i>PNPT1</i>	polyribonucleotide	1.66	<1.0e-08	1.51	6.60e-07

Gene name	Gene description	JAHH		ILLUMINATE	
		Fold difference	q value	Fold difference	q value
	nucleotidyltransferase 1				
<i>PANK2</i>	pantothenate kinase 2	1.66	<1.0e-08	1.02	8.40e-01
<i>SAMD9</i>	sterile alpha motif domain containing 9	1.65	<1.0e-08	1.60	<1.0e-08
<i>GBP3</i>	guanylate binding protein 3	1.64	<1.0e-08	1.48	1.70e-06
<i>TNFSF13B</i>	TNF superfamily member 13b	1.64	<1.0e-08	1.59	<1.0e-08
<i>ZBP1</i>	Z-DNA binding protein 1	1.63	<1.0e-08	1.63	<1.0e-08
<i>CLEC12A</i>	C-type lectin domain family 12 member A	1.62	2.50e-06	1.17	3.90e-01
<i>SLFN12</i>	schlafen family member 12	1.60	<1.0e-08	1.29	3.60e-04
<i>RNF213</i>	ring finger protein 213	1.60	<1.0e-08	1.53	<1.0e-08
<i>BST2</i>	bone marrow stromal cell antigen 2	1.60	<1.0e-08	1.59	<1.0e-08
<i>SAT1</i>	spermidine/spermine N1-acetyltransferase 1	1.59	<1.0e-08	1.29	3.60e-05
<i>MX2</i>	MX dynamin like GTPase 2	1.58	<1.0e-08	1.58	<1.0e-08
<i>CLEC12B</i>	C-type lectin domain family 12 member B	1.57	2.60e-08	1.21	2.50e-01
<i>SIGLEC1</i>	sialic acid binding Ig like lectin 1	1.56	<1.0e-08	2.01	<1.0e-08
<i>HIST2H4B</i>	histone cluster 2 H4 family member b	1.56	<1.0e-08	1.15	4.20e-02
<i>WSB1</i>	WD repeat and SOCS box containing 1	1.55	<1.0e-08	1.15	1.80e-02
<i>FFAR2</i>	free fatty acid receptor 2	1.53	<1.0e-08	1.54	2.90e-08
<i>CCR1</i>	C-C motif chemokine receptor 1	1.52	1.40e-08	1.85	<1.0e-08
<i>FAM8A1</i>	family with sequence similarity 8 member A1	1.50	<1.0e-08	1.35	<1.0e-08
<i>DHX58</i>	DExH-box helicase 58	1.50	<1.0e-08	1.50	<1.0e-08
<i>TDRD7</i>	tudor domain containing 7	1.50	<1.0e-08	1.47	<1.0e-08
<i>GPR15</i>	G protein-coupled receptor 15	1.49	1.00e-05	1.65	3.50e-04
<i>PGAP1</i>	post-GPI attachment to proteins 1	1.49	<1.0e-08	1.36	1.90e-06
<i>TMEM123</i>	transmembrane protein 123	1.49	<1.0e-08	1.37	1.80e-07
<i>IFI16</i>	interferon gamma inducible protein 16	1.49	<1.0e-08	1.55	<1.0e-08
<i>ABCA1</i>	ATP binding cassette subfamily A member 1	1.48	<1.0e-08	1.61	<1.0e-08
<i>FCGR1B</i>	Fc fragment of IgG receptor Ib	1.48	<1.0e-08	1.44	<1.0e-08
<i>HIST1H4D</i>	histone cluster 1 H4 family member d	1.47	<1.0e-08	1.35	3.30e-06
<i>GK</i>	glycerol kinase	1.47	<1.0e-08	1.23	1.10e-02
<i>ACOT9</i>	acyl-CoA thioesterase 9	1.47	<1.0e-08	1.31	2.70e-07

Gene name	Gene description	JAHH		ILLUMINATE	
		Fold difference	q value	Fold difference	q value
<i>SP100</i>	SP100 nuclear antigen	1.47	<1.0e-08	1.37	<1.0e-08
<i>EVI2A</i>	ecotropic viral integration site 2A	1.46	2.30e-07	1.09	2.00e-01
<i>PTEN</i>	phosphatase and tensin homolog	1.46	<1.0e-08	-1.01	9.40e-01
<i>GBP2</i>	guanylate binding protein 2	1.46	<1.0e-08	1.37	8.90e-08
<i>TRIM38</i>	tripartite motif containing 38	1.46	<1.0e-08	1.30	9.40e-07
<i>NT5C3A</i>	5'-nucleotidase, cytosolic IIIA	1.45	<1.0e-08	1.27	1.90e-04
<i>SP140</i>	SP140 nuclear body protein	1.45	<1.0e-08	1.33	1.40e-05
<i>LTB</i>	lymphotoxin beta	1.45	<1.0e-08	1.14	8.40e-02
<i>TNFSF10</i>	TNF superfamily member 10	1.45	<1.0e-08	1.42	<1.0e-08
<i>NAIP</i>	NLR family apoptosis inhibitory protein	1.45	<1.0e-08	1.40	1.80e-05
<i>TAPI</i>	transporter 1, ATP binding cassette subfamily B member	1.45	<1.0e-08	1.37	<1.0e-08
<i>HIST2H2BF</i>	histone cluster 2 H2B family member f	1.44	<1.0e-08	1.43	1.50e-06
<i>PTP4A1</i>	protein tyrosine phosphatase type IVA, member 1	1.44	<1.0e-08	1.40	5.10e-08
<i>CMTR1</i>	cap methyltransferase 1	1.42	<1.0e-08	1.40	<1.0e-08
<i>AIM2</i>	absent in melanoma 2	1.42	<1.0e-08	1.47	3.00e-08
<i>FAS</i>	Fas cell surface death receptor	1.42	<1.0e-08	1.01	9.50e-01
<i>NABP1</i>	nucleic acid binding protein 1	1.42	<1.0e-08	1.08	4.00e-01
<i>CASP1</i>	caspase 1	1.41	<1.0e-08	1.32	3.50e-06
<i>OTOF</i>	otoferlin	1.41	2.90e-06	1.85	1.80e-06
<i>IFI35</i>	interferon induced protein 35	1.41	<1.0e-08	1.62	<1.0e-08
<i>FAM174B</i>	family with sequence similarity 174 member B	1.41	<1.0e-08	1.32	3.10e-06
<i>UTS2</i>	urotensin 2	1.41	1.80e-03	1.41	6.30e-02
<i>ZNF117</i>	zinc finger protein 117	1.40	9.10e-06	1.03	8.40e-01
<i>CBWD5</i>	COBW domain containing 5	1.40	<1.0e-08	1.12	7.20e-02
<i>SLC26A8</i>	solute carrier family 26 member 8	1.40	<1.0e-08	1.51	3.30e-06
<i>KCNJ15</i>	potassium voltage-gated channel subfamily J member 15	1.39	6.80e-06	1.48	4.10e-05
<i>TMEM62</i>	transmembrane protein 62	1.39	<1.0e-08	1.22	1.90e-04
<i>DHRS9</i>	dehydrogenase/reductase 9	1.39	1.80e-06	1.47	1.80e-05
<i>TLR2</i>	toll like receptor 2	1.39	4.40e-08	1.23	8.80e-03
<i>ACSL1</i>	acyl-CoA synthetase long chain family member 1	1.39	1.20e-07	1.31	2.00e-03
<i>PATL2</i>	PAT1 homolog 2	1.39	<1.0e-08	1.19	2.30e-03
<i>DAPP1</i>	dual adaptor of phosphotyrosine and 3-phosphoinositides 1	1.39	<1.0e-08	1.21	2.70e-04

Gene name	Gene description	JAHH		ILLUMINATE	
		Fold difference	q value	Fold difference	q value
<i>CCNL1</i>	cyclin L1	1.39	<1.0e-08	1.03	7.70e-01
<i>PHF11</i>	PHD finger protein 11	1.39	<1.0e-08	1.31	1.40e-07
<i>TRAFD1</i>	TRAF-type zinc finger domain containing 1	1.38	<1.0e-08	1.30	4.80e-08
<i>SRGAP2</i>	SLIT-ROBO Rho GTPase activating protein 2	1.38	<1.0e-08	1.25	8.00e-05
<i>TMEM140</i>	transmembrane protein 140	1.38	<1.0e-08	1.36	5.20e-08
<i>SP110</i>	SP110 nuclear body protein	1.38	<1.0e-08	1.36	<1.0e-08
<i>ZEB2</i>	zinc finger E-box binding homeobox 2	1.38	<1.0e-08	-1.02	8.60e-01
<i>CLEC2B</i>	C-type lectin domain family 2 member B	1.38	<1.0e-08	1.19	3.10e-03
<i>HIST1H1T</i>	histone cluster 1 H1 family member t	1.38	<1.0e-08	1.20	4.80e-03
<i>LAMP3</i>	lysosomal associated membrane protein 3	1.38	<1.0e-08	1.70	<1.0e-08
<i>CLEC7A</i>	C-type lectin domain containing 7A	1.38	<1.0e-08	1.19	9.10e-03
<i>TRIM5</i>	tripartite motif containing 5	1.37	<1.0e-08	1.36	<1.0e-08
<i>KIAA1109</i>	KIAA1109	1.37	<1.0e-08	1.07	3.70e-01
<i>HSH2D</i>	hematopoietic SH2 domain containing	1.37	<1.0e-08	1.16	1.40e-03
<i>TOR1B</i>	torsin family 1 member B	1.37	<1.0e-08	1.45	<1.0e-08
<i>DTX3L</i>	deltex E3 ubiquitin ligase 3L	1.36	<1.0e-08	1.52	<1.0e-08
<i>HIST1H4H</i>	histone cluster 1 H4 family member h	1.36	9.80e-08	1.35	3.90e-03
<i>TAP2</i>	transporter 2, ATP binding cassette subfamily B member	1.36	<1.0e-08	1.11	3.80e-02
<i>DYNLT1</i>	dynein light chain Tctex-type 1	1.36	<1.0e-08	1.20	2.90e-04
<i>NOD2</i>	nucleotide binding oligomerization domain containing 2	1.35	<1.0e-08	1.15	6.80e-02
<i>CBWD1</i>	COBW domain containing 1	1.35	<1.0e-08	1.10	1.10e-01
<i>PRRG4</i>	proline rich and Gla domain 4	1.35	1.00e-04	1.57	6.30e-06
<i>ARRDC3</i>	arrestin domain containing 3	1.35	<1.0e-08	1.17	1.90e-03
<i>ERV3-1</i>	endogenous retrovirus group 3 member 1, envelope	1.35	8.60e-07	1.02	8.50e-01
<i>SMN2</i>	survival of motor neuron 2, centromeric	1.35	5.60e-05	-1.20	3.30e-02
<i>VNN1</i>	vanin 1	1.35	7.70e-04	1.47	2.60e-03
<i>CD44</i>	CD44 molecule (Indian blood group)	1.35	1.40e-06	-1.09	4.40e-01

Gene name	Gene description	JAHH		ILLUMINATE	
		Fold difference	q value	Fold difference	q value
<i>TRIM25</i>	tripartite motif containing 25	1.35	<1.0e-08	1.30	<1.0e-08
<i>JAK2</i>	Janus kinase 2	1.35	<1.0e-08	1.19	4.30e-04
<i>CARD16</i>	caspase recruitment domain family member 16	1.35	8.40e-08	1.40	9.10e-08
<i>ANKRD22</i>	ankyrin repeat domain 22	1.34	1.50e-05	1.61	4.80e-06
<i>MAP2K6</i>	mitogen-activated protein kinase kinase 6	1.34	<1.0e-08	1.28	4.10e-04
<i>NMI</i>	N-myc and STAT interactor	1.34	<1.0e-08	1.33	3.50e-07
<i>ETV7</i>	ETS variant 7	1.34	1.40e-08	1.49	2.10e-08
<i>RICTOR</i>	RPTOR independent companion of MTOR complex 2	1.34	<1.0e-08	1.14	1.30e-02
<i>RNPC3</i>	RNA binding region (RNP1, RRM) containing 3	1.34	<1.0e-08	-1.01	9.50e-01
<i>IL18R1</i>	interleukin 18 receptor 1	1.34	1.60e-04	1.30	3.50e-02
<i>APOL6</i>	apolipoprotein L6	1.33	<1.0e-08	1.34	1.40e-08
<i>RNF149</i>	ring finger protein 149	1.33	<1.0e-08	1.06	5.60e-01
<i>CHMP5</i>	charged multivesicular body protein 5	1.33	1.70e-08	1.44	<1.0e-08

*The top 150 genes upregulated (ranked from high to low) based on the difference in expression between patients with systemic lupus erythematosus (SLE) from JAHH and healthy control subjects are shown. Gene name was defined using the MetaBase (Clarivate) database. Findings were compared to those from the ILLUMINATE study, analyzed using data deposited in the NCBI GEO Database (GSE88887), where an independent group of controls was compared to ILLUMINATE patients at baseline, both in terms of the rank order of genes and the fold changes detected. Statistical significance is shown as q value for patients with SLE compared to healthy controls.

Table S2. Baseline gene expression in SLE patients versus healthy controls, including downregulated genes with the greatest fold change from JAHH*

Gene name	Gene description	JAHH		ILLUMINATE	
		Fold difference	q value	Fold difference	q value
<i>PI3</i>	peptidase inhibitor 3	-1.92	<1.0e-08	1.05	8.40e-01
<i>RELA</i>	RELA proto-oncogene, NF- κ B subunit	-1.92	<1.0e-08	1.07	8.30e-02
<i>KLRB1</i>	killer cell lectin like receptor B1	-1.85	<1.0e-08	-1.85	2.30e-08
<i>RPL26</i>	ribosomal protein L26	-1.76	<1.0e-08	-1.22	1.00e-05
<i>RPL7</i>	ribosomal protein L7	-1.71	<1.0e-08	-1.26	1.00e-06
<i>CD79A</i>	CD79a molecule	-1.70	<1.0e-08	-1.08	6.90e-01
<i>TRAPPC1</i>	trafficking protein particle complex 1	-1.67	<1.0e-08	1.06	1.60e-01
<i>CLIC3</i>	chloride intracellular channel 3	-1.65	<1.0e-08	-1.12	7.30e-02
<i>TCF7</i>	transcription factor 7	-1.60	<1.0e-08	-1.15	1.70e-01
<i>RPL6</i>	ribosomal protein L6	-1.58	<1.0e-08	-1.22	9.50e-04
<i>KLRF1</i>	killer cell lectin like receptor F1	-1.58	2.80e-07	-1.99	2.40e-07
<i>PTPRS</i>	protein tyrosine phosphatase, receptor type S	-1.56	<1.0e-08	-1.36	<1.0e-08
<i>HCST</i>	hematopoietic cell signal transducer	-1.54	<1.0e-08	1.07	3.70e-01
<i>RAD23A</i>	RAD23 homolog A, nucleotide excision repair protein	-1.53	<1.0e-08	-1.10	1.30e-01
<i>RPS28</i>	ribosomal protein S28	-1.52	<1.0e-08	-1.12	8.40e-02
<i>HAT1</i>	histone acetyltransferase 1	-1.52	<1.0e-08	1.01	9.00e-01
<i>RPS27</i>	ribosomal protein S27	-1.52	<1.0e-08	-1.11	2.90e-02
<i>RPS15</i>	ribosomal protein S15	-1.52	<1.0e-08	-1.04	5.30e-01
<i>MED1</i>	mediator complex subunit 1	-1.50	<1.0e-08	1.05	3.70e-01
<i>FCER1A</i>	Fc fragment of IgE receptor Ia	-1.50	7.60e-08	-1.44	1.10e-04
<i>KIAA1324</i>	KIAA1324	-1.48	5.70e-07	-1.38	5.10e-03
<i>SH2D1B</i>	SH2 domain containing 1B	-1.47	<1.0e-08	-1.43	4.40e-04
<i>GSTM4</i>	glutathione S-transferase mu 4	-1.47	<1.0e-08	-1.01	9.40e-01
<i>WASF2</i>	WAS protein family member 2	-1.46	<1.0e-08	-1.06	2.70e-01
<i>EIF4G1</i>	eukaryotic translation initiation factor 4 gamma 1	-1.46	<1.0e-08	1.02	7.20e-01
<i>PSMF1</i>	proteasome inhibitor subunit 1	-1.45	<1.0e-08	-1.21	1.10e-03
<i>CD5</i>	CD5 molecule	-1.44	<1.0e-08	1.01	9.00e-01
<i>RPL4</i>	ribosomal protein L4	-1.43	<1.0e-08	-1.27	5.60e-04
<i>CLPTM1</i>	CLPTM1, transmembrane protein	-1.43	<1.0e-08	1.01	7.70e-01
<i>RBM38</i>	RNA binding motif protein 38	-1.42	8.60e-08	-1.12	2.10e-01
<i>SLC25A39</i>	solute carrier family 25 member 39	-1.42	2.10e-07	-1.14	8.20e-02
<i>WBP2</i>	WW domain binding protein 2	-1.42	<1.0e-08	1.05	3.70e-01
<i>TMEM109</i>	transmembrane protein 109	-1.42	<1.0e-08	-1.02	8.30e-01
<i>CLC</i>	Charcot-Leyden crystal galectin	-1.42	1.60e-03	-1.16	4.20e-01

Gene name	Gene description	JAHH		ILLUMINATE	
		Fold difference	q value	Fold difference	q value
<i>GSPT1</i>	G1 to S phase transition 1	-1.42	2.50e-06	-1.17	3.30e-02
<i>CBLL1</i>	Cbl proto-oncogene like 1	-1.42	<1.0e-08	-1.04	5.80e-01
<i>GMFG</i>	glia maturation factor gamma	-1.42	<1.0e-08	1.07	1.30e-01
<i>GATAD2B</i>	GATA zinc finger domain containing 2B	-1.41	<1.0e-08	-1.04	2.20e-01
<i>AIF1</i>	allograft inflammatory factor 1	-1.41	<1.0e-08	-1.04	4.20e-01
<i>RPS17</i>	ribosomal protein S17	-1.40	1.10e-06	-1.15	7.20e-04
<i>ATP6V0C</i>	ATPase H ⁺ transporting V0 subunit c	-1.40	<1.0e-08	1.01	8.70e-01
<i>HBZ</i>	hemoglobin subunit zeta	-1.40	1.10e-04	-1.16	3.70e-01
<i>FTH1</i>	ferritin heavy chain 1	-1.40	<1.0e-08	1.00	9.70e-01
<i>OR2W3</i>	olfactory receptor family 2 subfamily W member 3	-1.39	7.30e-04	-1.17	2.00e-01
<i>WAS</i>	Wiskott-Aldrich syndrome	-1.39	<1.0e-08	1.06	2.60e-02
<i>SAP130</i>	Sin3A associated protein 130	-1.39	<1.0e-08	-1.01	7.30e-01
<i>MED25</i>	mediator complex subunit 25	-1.39	<1.0e-08	1.01	9.10e-01
<i>SF3A2</i>	splicing factor 3a subunit 2	-1.39	<1.0e-08	-1.04	2.90e-01
<i>CD74</i>	CD74 molecule	-1.39	<1.0e-08	-1.01	9.60e-01
<i>R3HDM4</i>	R3H domain containing 4	-1.39	2.90e-07	1.07	3.90e-01
<i>NRGN</i>	neurogranin	-1.38	1.90e-07	-1.03	7.60e-01
<i>TESPA1</i>	thymocyte expressed, positive selection associated 1	-1.38	1.10e-07	-1.10	3.50e-01
<i>NFIX</i>	nuclear factor I X	-1.38	<1.0e-08	-1.09	1.90e-01
<i>HIST1H4E</i>	histone cluster 1 H4 family member e	-1.38	<1.0e-08	-1.16	3.80e-03
<i>ZFP36</i>	ZFP36 ring finger protein	-1.38	<1.0e-08	1.16	3.10e-05
<i>FCER2</i>	Fc fragment of IgE receptor II	-1.38	<1.0e-08	-1.18	5.20e-02
<i>CD6</i>	CD6 molecule	-1.37	<1.0e-08	-1.01	9.00e-01
<i>CD22</i>	CD22 molecule	-1.37	4.60e-05	-1.21	1.90e-01
<i>NOG</i>	noggin	-1.37	<1.0e-08	-1.33	1.30e-03
<i>S100A12</i>	S100 calcium binding protein A12	-1.37	1.80e-04	1.24	4.80e-02
<i>FAM43A</i>	family with sequence similarity 43 member A	-1.37	<1.0e-08	-1.16	8.70e-04
<i>GZMA</i>	granzyme A	-1.37	5.90e-04	-1.22	1.10e-01
<i>MYADM</i>	myeloid associated differentiation marker	-1.37	<1.0e-08	1.11	3.70e-03
<i>SH3BGRL3</i>	SH3 domain binding glutamate rich protein like 3	-1.37	<1.0e-08	1.02	4.50e-01
<i>SIGLEC10</i>	sialic acid binding Ig like lectin 10	-1.36	<1.0e-08	-1.18	7.50e-04
<i>POLE3</i>	DNA polymerase epsilon 3, accessory subunit	-1.36	<1.0e-08	1.02	7.50e-01
<i>PRKCSH</i>	protein kinase C substrate 80K-H	-1.36	<1.0e-08	-1.09	3.80e-02
<i>KIR3DS1</i>	killer cell immunoglobulin like receptor, three Ig domains and short	-1.35	3.30e-08	-1.11	4.30e-01

Gene name	Gene description	JAHH		ILLUMINATE	
		Fold difference	q value	Fold difference	q value
	cytoplasmic tail 1				
<i>CTSW</i>	cathepsin W	-1.35	3.10e-07	-1.10	3.20e-01
<i>CD27</i>	CD27 molecule	-1.35	<1.0e-08	-1.12	2.30e-01
<i>DAAM1</i>	dishevelled associated activator of morphogenesis 1	-1.35	<1.0e-08	-1.05	4.00e-01
<i>ALG3</i>	ALG3, alpha-1,3-mannosyltransferase	-1.35	<1.0e-08	1.12	2.80e-02
<i>RPL17</i>	ribosomal protein L17	-1.35	4.30e-05	-1.16	2.50e-03
<i>FXYD5</i>	FXYD domain containing ion transport regulator 5	-1.35	<1.0e-08	-1.00	9.60e-01
<i>SLC4A1</i>	solute carrier family 4 member 1 (Diego blood group)	-1.34	2.00e-03	-1.19	2.20e-01
<i>ARHGAP1</i>	Rho GTPase activating protein 1	-1.34	<1.0e-08	1.01	9.10e-01
<i>NDUF55</i>	NADH:ubiquinone oxidoreductase subunit S5	-1.34	<1.0e-08	-1.11	7.10e-03
<i>CCR7</i>	C-C motif chemokine receptor 7	-1.34	5.30e-05	-1.16	2.60e-01
<i>SEPT1</i>	septin 1	-1.34	<1.0e-08	-1.08	2.70e-01
<i>NR1D1</i>	nuclear receptor subfamily 1 group D member 1	-1.34	<1.0e-08	-1.02	7.40e-01
<i>PPP2R1A</i>	protein phosphatase 2 scaffold subunit Aalpha	-1.34	<1.0e-08	1.01	9.00e-01
<i>KIR2DL1</i>	killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 1	-1.33	<1.0e-08	-1.11	3.20e-01
<i>PHB2</i>	prohibitin 2	-1.33	<1.0e-08	-1.06	2.60e-01
<i>IL2RB</i>	interleukin 2 receptor subunit beta	-1.33	<1.0e-08	-1.14	2.80e-03
<i>GUCD1</i>	guanylyl cyclase domain containing 1	-1.33	<1.0e-08	-1.11	9.60e-02
<i>SLC29A3</i>	solute carrier family 29 member 3	-1.33	<1.0e-08	1.02	7.10e-01
<i>PFN1</i>	profilin 1	-1.33	<1.0e-08	1.05	2.70e-01
<i>CS</i>	citrate synthase	-1.33	<1.0e-08	-1.11	1.60e-02
<i>GATA3</i>	GATA binding protein 3	-1.33	<1.0e-08	-1.05	4.40e-01
<i>FECH</i>	ferrochelatase	-1.33	2.70e-04	-1.36	4.20e-04
<i>SF3B4</i>	splicing factor 3b subunit 4	-1.33	<1.0e-08	1.02	2.70e-01
<i>FLT3LG</i>	fms related tyrosine kinase 3 ligand	-1.32	<1.0e-08	-1.02	8.50e-01
<i>PCIF1</i>	PDX1 C-terminal inhibiting factor 1	-1.32	<1.0e-08	-1.01	8.60e-01
<i>SCAMP2</i>	secretory carrier membrane protein 2	-1.32	<1.0e-08	1.04	2.60e-01
<i>EPB42</i>	erythrocyte membrane protein band 4.2	-1.32	2.30e-03	-1.29	5.80e-02
<i>TPP1</i>	tripeptidyl peptidase 1	-1.32	<1.0e-08	1.09	1.50e-02
<i>PRAF2</i>	PRA1 domain family member 2	-1.32	<1.0e-08	1.09	4.60e-05
<i>PRPF8</i>	pre-mRNA processing factor 8	-1.32	<1.0e-08	-1.11	7.10e-02
<i>RAC2</i>	Rac family small GTPase 2	-1.32	<1.0e-08	1.07	1.90e-02

Gene name	Gene description	JAHH		ILLUMINATE	
		Fold difference	q value	Fold difference	q value
<i>ZNF107</i>	zinc finger protein 107	-1.32	5.60e-06	1.02	8.90e-01
<i>APEX1</i>	apurinic/apyrimidinic endodeoxyribonuclease 1	-1.32	<1.0e-08	-1.18	8.90e-03
<i>FLOT1</i>	flotillin 1	-1.32	<1.0e-08	1.09	1.60e-01
<i>HEMGN</i>	hemogen	-1.32	3.50e-05	-1.32	1.40e-04
<i>HCFC1</i>	host cell factor C1	-1.32	<1.0e-08	1.01	8.10e-01
<i>FHL3</i>	four and a half LIM domains 3	-1.32	<1.0e-08	1.03	6.20e-01
<i>CHERP</i>	calcium homeostasis endoplasmic reticulum protein	-1.32	<1.0e-08	1.03	1.70e-01
<i>SELENBP1</i>	selenium binding protein 1	-1.32	2.80e-04	-1.13	3.00e-01
<i>EPB41</i>	erythrocyte membrane protein band 4.1	-1.31	4.90e-08	-1.22	1.90e-04
<i>CITED2</i>	Cbp/p300 interacting transactivator with Glu/Asp rich carboxy-terminal domain 2	-1.31	<1.0e-08	1.05	1.50e-01
<i>SLC9A3R1</i>	SLC9A3 regulator 1	-1.31	<1.0e-08	1.01	7.90e-01
<i>PPBP</i>	pro-platelet basic protein	-1.31	7.30e-03	-1.40	9.70e-04
<i>RSL1D1</i>	ribosomal L1 domain containing 1	-1.31	1.10e-08	-1.11	2.10e-01
<i>SERTAD2</i>	SERTA domain containing 2	-1.31	<1.0e-08	-1.02	6.20e-01
<i>PRKACA</i>	protein kinase cAMP-activated catalytic subunit alpha	-1.31	<1.0e-08	-1.05	5.00e-02
<i>NFATC2</i>	nuclear factor of activated T cells 2	-1.31	<1.0e-08	-1.10	1.40e-01
<i>KIR3DL2</i>	killer cell immunoglobulin like receptor, three Ig domains and long cytoplasmic tail 2	-1.31	<1.0e-08	-1.08	4.60e-01
<i>GYPC</i>	glycophorin C (Gerbich blood group)	-1.31	<1.0e-08	-1.14	2.50e-02
<i>CAT</i>	catalase	-1.31	7.30e-08	-1.19	2.60e-03
<i>PLP2</i>	proteolipid protein 2	-1.31	<1.0e-08	1.17	5.70e-05
<i>SF3A1</i>	splicing factor 3a subunit 1	-1.31	<1.0e-08	1.01	7.10e-01
<i>SIRT2</i>	sirtuin 2	-1.31	<1.0e-08	1.03	4.90e-01
<i>SLC6A8</i>	solute carrier family 6 member 8	-1.31	7.70e-05	-1.03	8.20e-01
<i>MLXIP</i>	MLX interacting protein	-1.31	<1.0e-08	-1.05	1.40e-01
<i>TMEM238</i>	transmembrane protein 238	-1.31	<1.0e-08	1.08	5.10e-02
<i>PHOSPHO1</i>	phosphoethanolamine/phosphocholine phosphatase	-1.31	1.80e-06	-1.02	8.50e-01
<i>KLF2</i>	Kruppel like factor 2	-1.31	<1.0e-08	1.01	8.50e-01
<i>KRT1</i>	keratin 1	-1.30	<1.0e-08	-1.13	6.70e-02
<i>SRM</i>	spermidine synthase	-1.30	<1.0e-08	1.06	2.80e-01
<i>SIGLEC9</i>	sialic acid binding Ig like lectin 9	-1.30	<1.0e-08	1.08	2.20e-01
<i>MAF1</i>	MAF1 homolog, negative regulator of RNA polymerase III	-1.30	<1.0e-08	-1.05	3.60e-01
<i>ZFP36L2</i>	ZFP36 ring finger protein like 2	-1.30	<1.0e-08	-1.03	6.50e-01

Gene name	Gene description	JAHH		ILLUMINATE	
		Fold difference	q value	Fold difference	q value
<i>GSK3A</i>	glycogen synthase kinase 3 alpha	-1.30	<1.0e-08	1.03	4.00e-01
<i>HLA-DRA</i>	major histocompatibility complex, class II, DR alpha	-1.30	1.40e-06	-1.09	4.10e-01
<i>POM121C</i>	POM121 transmembrane nucleoporin C	-1.30	<1.0e-08	-1.09	1.20e-03
<i>DCAF12</i>	DDB1 and CUL4 associated factor 12	-1.30	8.50e-05	-1.11	1.30e-01
<i>RAB1B</i>	RAB1B, member RAS oncogene family	-1.30	<1.0e-08	1.04	9.70E-02
<i>BANF1</i>	barrier to autointegration factor 1	-1.30	<1.0e-08	1.04	2.50e-01
<i>OGFOD1</i>	2-oxoglutarate and iron dependent oxygenase domain containing 1	-1.30	<1.0e-08	1.01	9.40e-01
<i>ANXA1</i>	annexin A1	-1.30	1.80e-05	1.01	8.80e-01
<i>PTBP1</i>	polypyrimidine tract binding protein 1	-1.30	<1.0e-08	-1.03	6.30e-01
<i>KIR2DL3</i>	killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 3	-1.30	2.30e-07	-1.08	5.70e-01
<i>COPE</i>	coatomer protein complex subunit epsilon	-1.30	<1.0e-08	1.12	4.70e-04
<i>CHI3L1</i>	chitinase 3 like 1	-1.30	9.00e-04	-1.17	2.40e-01
<i>SP2</i>	Sp2 transcription factor	-1.30	<1.0e-08	1.06	4.10e-04
<i>KIR2DS4</i>	killer cell immunoglobulin like receptor, two Ig domains and short cytoplasmic tail 4	-1.30	2.10e-05	1.03	8.80e-01
<i>ZHX2</i>	zinc fingers and homeoboxes 2	-1.30	<1.0e-08	-1.06	9.20e-02
<i>BSG</i>	basigin (Ok blood group)	-1.30	1.10e-05	-1.12	1.40e-01
<i>ZNF385A</i>	zinc finger protein 385A	-1.30	<1.0e-08	1.05	3.40e-01
<i>ACTN4</i>	actinin alpha 4	-1.29	<1.0e-08	1.02	6.30e-01
<i>FGFBP2</i>	fibroblast growth factor binding protein 2	-1.29	5.30e-05	-1.19	1.50e-01

*The top 150 genes downregulated (ranked from high to low) based on the difference in expression between patients with systemic lupus erythematosus (SLE) from JAHH and healthy control subjects are shown. Gene name was defined using the MetaBase (Clarivate) database. Findings were compared to those from the ILLUMINATE study, analyzed using data deposited in the NCBI GEO Database (GSE88887), where an independent group of controls was compared to ILLUMINATE patients at baseline, both in terms of the rank order of genes and the fold

changes detected. Statistical significance is shown as q value for patients with SLE compared to healthy controls.

Table S3. Pharmacologically-induced changes in gene expression in response to baricitinib treatment*

Gene name	Gene description	Baricitinib 4-mg					
		Baseline to Week 4		Baseline to Week 12		Baseline to Week 24	
		Fold difference	q value	Fold difference	q value	Fold difference	q value
<i>IFI44L</i>	interferon induced protein 44 like	-1.18	4.0e-01	-1.50	3.1e-03	-1.32	1.2e-01
<i>RSAD2</i>	radical S-adenosyl methionine domain containing 2	-1.15	4.5e-01	-1.48	2.9e-03	-1.25	1.6e-01
<i>IFI44</i>	interferon induced protein 44	-1.11	6.4e-01	-1.38	4.1e-03	-1.21	2.0e-01
<i>IFI27</i>	interferon alpha inducible protein 27	-1.59	2.0e-03	-1.63	2.9e-03	-1.32	1.6e-01
<i>IFIT1</i>	interferon induced protein with tetratricopeptide repeats 1	-1.16	3.8e-01	-1.43	2.9e-03	-1.23	1.6e-01
<i>MX1</i>	MX dynamin like GTPase 1	-1.11	4.9e-01	-1.35	3.2e-03	-1.22	1.2e-01
<i>HERC5</i>	HECT and RLD domain containing E3 ubiquitin protein ligase 5	-1.09	6.4e-01	-1.29	8.2e-03	-1.16	2.1e-01
<i>EPSTI1</i>	epithelial stromal interaction 1	-1.03	9.3e-01	-1.21	2.5e-02	-1.13	2.3e-01
<i>OAS3</i>	2'-5'-oligoadenylate synthetase 3	-1.13	3.0e-01	-1.29	3.1e-03	-1.18	1.3e-01
<i>DDX60</i>	DExD/H-box helicase 60	-1.01	9.8e-01	-1.21	2.8e-02	-1.11	3.2e-01
<i>CMPK2</i>	cytidine/uridine monophosphate kinase 2	-1.13	2.4e-01	-1.23	3.9e-03	-1.16	1.2e-01
<i>XAF1</i>	XIAP associated factor 1	-1.07	4.9e-01	-1.22	3.1e-03	-1.14	1.3e-01
<i>IFIT3</i>	interferon induced protein with tetratricopeptide repeats 3	-1.05	7.8e-01	-1.26	3.9e-03	-1.11	3.1e-01
<i>OAS1</i>	2'-5'-oligoadenylate synthetase 1	-1.12	2.4e-01	-1.25	2.9e-03	-1.16	1.2e-01
<i>EIF2AK2</i>	eukaryotic translation initiation factor 2 alpha kinase 2	-1.05	7.8e-01	-1.18	3.6e-02	-1.10	3.2e-01
<i>PLSCR1</i>	phospholipid scramblase 1	-1.04	7.8e-01	-1.19	2.5e-02	-1.07	4.8e-01
<i>USP18</i>	ubiquitin specific peptidase 18	-1.15	1.1e-01	-1.27	2.3e-03	-1.20	7.6e-02
<i>IFIT2</i>	interferon induced protein with tetratricopeptide repeats 2	-1.05	7.8e-01	-1.24	4.1e-03	-1.11	2.8e-01
<i>IFIT5</i>	interferon induced protein with tetratricopeptide repeats 5	-1.04	8.5e-01	-1.22	8.2e-03	-1.07	4.2e-01

Gene name	Gene description	Baricitinib 4-mg					
		Baseline to Week 4		Baseline to Week 12		Baseline to Week 24	
		Fold difference	q value	Fold difference	q value	Fold difference	q value
<i>OAS2</i>	2'-5'-oligoadenylate synthetase 2	-1.15	3.0e-01	-1.26	8.0e-03	-1.24	7.6e-02
<i>SAMD9L</i>	sterile alpha motif domain containing 9 like	-1.00	9.9e-01	-1.14	9.1e-02	-1.08	4.2e-01
<i>SERPING1</i>	serpin family G member 1	1.02	9.8e-01	-1.06	5.8e-01	-1.07	5.9e-01
<i>IFI6</i>	interferon alpha inducible protein 6	-1.15	3.0e-01	-1.38	2.8e-03	-1.21	1.2e-01
<i>IFIH1</i>	interferon induced with helicase C domain 1	-1.01	9.8e-01	-1.19	2.8e-02	-1.09	4.1e-01
<i>DDX58</i>	DExD/H-box helicase 58	1.01	9.8e-01	-1.14	5.4e-02	-1.06	4.9e-01
<i>ZCCHC2</i>	zinc finger CCHC-type containing 2	-1.04	7.8e-01	-1.13	5.4e-02	-1.10	2.3e-01
<i>USP41</i>	ubiquitin specific peptidase 41	-1.12	1.1e-01	-1.20	2.9e-03	-1.16	7.6e-02
<i>OASL</i>	2'-5'-oligoadenylate synthetase like	-1.14	1.2e-01	-1.22	2.9e-03	-1.17	7.6e-02
<i>PARP12</i>	poly(ADP-ribose) polymerase family member 12	-1.04	6.4e-01	-1.15	8.4e-03	-1.09	2.1e-01
<i>DDX60L</i>	DExD/H-box 60 like	-1.00	9.8e-01	-1.10	1.2e-01	-1.07	4.2e-01
<i>CARD17</i>	caspase recruitment domain family member 17	1.03	9.4e-01	-1.07	3.9e-01	-1.07	4.9e-01
<i>PARP14</i>	poly(ADP-ribose) polymerase family member 14	1.02	9.4e-01	-1.11	1.3e-01	-1.07	4.2e-01
<i>RTP4</i>	receptor transporter protein 4	-1.08	4.5e-01	-1.12	9.1e-02	-1.09	3.0e-01
<i>GBP1</i>	guanylate binding protein 1	1.07	6.4e-01	-1.04	6.2e-01	-1.04	6.1e-01
<i>OR56B1</i>	olfactory receptor family 56 subfamily B member 1	-1.00	9.8e-01	-1.12	2.5e-02	-1.07	3.2e-01
<i>STAT1</i>	signal transducer and activator of transcription 1	1.02	9.4e-01	-1.07	2.7e-01	-1.06	4.2e-01
<i>TRIM22</i>	tripartite motif containing 22	1.04	7.4e-01	-1.09	6.3e-02	-1.03	5.8e-01
<i>HERC6</i>	HECT and RLD domain containing E3 ubiquitin protein ligase family member 6	-1.10	2.7e-01	-1.17	6.1e-03	-1.15	7.6e-02
<i>PARP9</i>	poly(ADP-ribose) polymerase family	-1.01	9.8e-01	-1.09	1.2e-01	-1.06	4.2e-01

Gene name	Gene description	Baricitinib 4-mg					
		Baseline to Week 4		Baseline to Week 12		Baseline to Week 24	
		Fold difference	q value	Fold difference	q value	Fold difference	q value
<i>SPATS2L</i>	member 9 spermatogenesis associated serine rich 2 like	-1.07	3.0e-01	-1.10	4.9e-02	-1.08	2.1e-01
<i>GBP5</i>	guanylate binding protein 5	1.13	3.0e-01	1.02	7.8e-01	-1.01	8.9e-01
<i>STAT2</i>	signal transducer and activator of transcription 2	-1.00	9.8e-01	-1.07	2.0e-01	-1.05	4.5e-01
<i>FCGR1A</i>	Fc fragment of IgG receptor Ia	1.05	7.8e-01	-1.05	5.8e-01	-1.03	7.7e-01
<i>LAP3</i>	leucine aminopeptidase 3	-1.00	9.8e-01	-1.13	2.8e-02	-1.05	4.8e-01
<i>DOCK4</i>	dedicator of cytokinesis 4	1.09	6.4e-01	1.13	1.8e-01	-1.02	8.1e-01
<i>CD274</i>	CD274 molecule	1.11	3.0e-01	1.04	5.8e-01	1.06	4.8e-01
<i>LY6E</i>	lymphocyte antigen 6 family member E	-1.18	7.0e-02	-1.22	2.9e-03	-1.17	7.6e-02
<i>TNFAIP6</i>	TNF alpha induced protein 6	1.02	9.4e-01	-1.07	3.6e-01	1.05	5.8e-01
<i>PNPT1</i>	polyribonucleotide nucleotidyltransferase 1	-1.02	9.4e-01	-1.14	5.4e-02	-1.05	5.3e-01
<i>PANK2</i>	pantothenate kinase 2	1.07	6.4e-01	-1.12	1.3e-01	1.01	9.1e-01

*The top 50 genes upregulated (ranked from high to low) based on the difference in expression between patients with systemic lupus erythematosus (SLE) and healthy control subjects are represented with changes from baseline in gene expression for baricitinib 4-mg at weeks 4, 12, and 24 shown. Gene name was defined using the MetaBase (Clarivate) database. Statistical significance is shown as q value for baricitinib 4-mg compared to placebo.

Table S4. Number of STAT related genes whose variation have statistically significant association to SLEDAI-2K variation*

STAT	Week	Number of downstream genes	Number of downstream genes with FDR $p < 0.1$	Number of downstream genes with $p < 0.05$
<i>STAT1</i>	2	135	30	45
<i>STAT1</i>	4	135	0	5
<i>STAT1</i>	12	135	0	2
<i>STAT1</i>	24	135	0	1
<i>STAT2</i>	2	38	11	13
<i>STAT2</i>	4	38	0	2
<i>STAT2</i>	12	38	0	0
<i>STAT2</i>	24	38	0	0
<i>STAT4</i>	2	6	0	1
<i>STAT4</i>	4	6	0	0
<i>STAT4</i>	12	6	0	0
<i>STAT4</i>	24	6	0	0

*Spearman rank coefficient correlations between variation in Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K) (from baseline) and variation in log2 expression (from baseline) of genes were computed at weeks 2, 4, 12, and 24 with baricitinib 4-mg treatment and tested for statistically significant differences from zero. The genes analyzed were selected from the MetaCore Database for those genes which are downstream of *STAT1*, *STAT2*, or *STAT4*. The number of selected downstream genes for each signal transducer and activator of transcription (STAT) is shown, with the number of statistically significant genes shown according to two different criteria: unadjusted $p < 0.05$ or false discovery rate (FDR) (computed within each STAT and time point) $p < 0.1$. Most of the significant changes occurred at the earliest time point measured, week 2. *STAT1* had the largest number of downstream genes and also the largest number of significantly associated genes according to both criteria.