

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Hom G, Graham RR, Modrek B, et al. Association of systemic lupus erythematosus with *C8orf13*-*BLK* and *ITGAM*-*ITGAX*. *N Engl J Med* 2008;358:900-9. DOI: 10.1056/NEJMoa0707865.

## SUPPLEMENTARY INFORMATION

### METHODS

#### DATA QUALITY FILTERS

Samples with an average call rate of  $\leq 95\%$  (N=42) or where the reported sex of the individual was discordant with observed sex (N=21) were excluded from the analysis. The identity by state (IBS) across the genome was estimated for each sample, and the samples examined for cryptic relatedness. One sample from each pair estimated to be duplicates or 1st-3rd degree relatives was removed ( $\hat{P}_i > 0.10$  and  $Z_1 \geq 0.15$ , N=161). Three of these pairs were comprised of both a case and a control; the control was removed. SNPs with a frequency in cases of  $< 1\%$  (N=21,644) or a HWE  $P \leq 1 \times 10^{-6}$  in controls (N=2819) were removed from the analysis. SNPs with missingness  $> 5\%$  (N=6074) were removed. SNPs were tested for the probability of a significant difference in missingness between cases and controls; SNPs with  $P \leq 1 \times 10^{-5}$  (N=7646) were removed. SNPs were also tested for batch effects: for example, between ABCoN samples and all other cases; SNPs with  $P < 1 \times 10^{-9}$  (N=13) were removed.

Population outliers were detected using EIGENSTRAT.<sup>1</sup> Samples more than 6 standard deviations from the mean along any of the top 10 principal components

were excluded from the analysis (N=141). Data from the 3340 remaining control samples were randomly assigned to each SLE case series proportionately, resulting in a ~2.5 control:case ratio.

## DATA ANALYSIS

After removing low quality data using the QC filters above to minimize technical artifacts, evidence of inflation was noted for each series: 1.14, 1.18, and 1.11, respectively, for Series 1, 2 and 3. To correct for the presence of population stratification, principal components for each series were calculated using a subset of SNPs in EIGENSTRAT.<sup>1</sup> SNPs with case MAF < 2% (5011), control HWE  $P \leq 1 \times 10^{-4}$  (1792), or missing data > 1% (50414) were removed, as were SNPs in regions of abnormal LD patterns due to structural variation on chromosomes 6 (from 24-36 Mb), 8 (8-12 Mb), 11 (42-58 Mb), and 17 (40-43 Mb). The remaining 440,202 SNPs were used to calculate principal components. In each series, the first 4 principal components were used to adjust the association statistic for all 502,033 SNPs. After adjustment for population stratification, the  $\lambda_{gc}$  for each series approached 1.0. The corrected association statistic for each series was combined by the weighted merging of the Z-score incorporating  $\lambda_{gc}$  (Supplementary Figure 1).

To test for heterogeneity between the three case-control studies for the most significantly associated variants, we ran the Breslow-Day test implemented in PLINK for the SNP with the best association in each of these regions: HLA DRB,

STAT4, IRF5, BLK, and ITGAM/ITGAX. No significant heterogeneity was detected (each  $P > 0.2$ ).

Associations between individual SNPs and subphenotypes were calculated for the combined dataset (Supplementary Table 6), using the Mantel-Haenszel heterogeneity test and combined odds ratio implemented in Stata 9.2 (<http://www.stata.com/>). In the Swedish samples, 521 cases were examined for an association to the ACR criteria. Statistical significance was assessed by 2x2 contingency tables and a chi square test (Supplementary Table 7). The calculated P-values were not adjusted for multiple testing, since the ACR criteria are known to be correlated and a simple Bonferroni correction of  $\alpha=0.05/11=0.0045$  would likely be overly conservative.

#### GENE EXPRESSION ANALYSIS

Gene expression measurements of Epstein-Barr Virus transformed B cell lines from 210 unrelated, healthy HapMap individuals from a publicly available dataset (GENEVAR project, <http://www.sanger.ac.uk/humgen/genevar/>) were examined for a correlation to variants significantly associated with SLE.<sup>2</sup> Specifically, the median fluorescence intensity of 4 measurements from probes for *BLK* (GI\_33469981-S), *C8orf13* (GI\_32698772-S), *ITGAM* (GI\_6006013-S), *ITGAX* (GI\_34452172-S), *ACTB* (beta-actin, GI\_5016088-S), and *GAPDH* (GI\_7669491-S) from 60 U.S. residents with northern and western European ancestry (CEU), 60 Yoruba (YRI), 45 Han Chinese individuals from Beijing (CHB) and 45 Japanese individuals from Tokyo (JPT) were examined. The expression data for

*BLK*, *C8orf13*, *GAPDH* and *ACTB*, in Epstein-Barr Virus transformed B cell lines from 210 unrelated, healthy HapMap individuals, were stratified by rs13277113 genotype (obtained from the HapMap (<http://www.hapmap.org>)), and the significance of the differential expression was measured by a 2-tailed t-test assuming an equal variance. Similarly, the expression data for *ITGAM*, *ITGAX*, *GAPDH* and *ACTB* were stratified by genotype at rs11574637 and tested for significance using a t-test. Expression data normalized on a log scale across the HapMap populations as described by the GENEVAR project yielded similar results to the median fluorescence intensity.

The association of *BLK* and *C8orf13* expression to cis-genetic variation in an independent set of 400 EBV-transformed B cells was obtained by the examination and data-mining of a recently published study (<http://www.sph.umich.edu/csg/liang/asthma/>).<sup>3</sup> Specifically, the association of a proxy for rs13277113 (rs4840568) to the expression levels of *BLK* (probe 206255\_at) and *C8orf13* (probe 226614\_s\_at) was measured as described by Dixon et al.<sup>3</sup>

## SUPPLEMENTARY RESULTS

### ASSOCIATIONS WITH SLE CLINICAL FEATURES

Finally, we examined the associations between the two top SNPs, rs11574637 (*BLK*) and rs13277113 (*ITGAM*), and the presence of individual ACR criteria, using the combined case series 1-3 (Supplementary Table 6, and see Supplementary Methods). The strongest association was an inverse relationship between the rs11574637 minor allele and the presence of arthritis, OR=0.73 (95% CI = 0.59-0.91, P = 0.0045). Both variants were modestly associated with hematologic criteria: rs11574637, OR=1.21 (95% CI = 1.00-1.47, P = 0.04) and rs13277113, OR = 1.23 (95% CI = 1.03-1.46, P = 0.02). However, in 521 Swedish cases, no significant associations of *BLK* and *ITGAM* variants were observed (Supplementary Table 7).

## SUPPLEMENTARY REFERENCES

1. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet* 2006;38(8):904-09.
2. Stranger BE, Nica AC, Forrest MS, et al. Population genomics of human gene expression. *Nat Genet* 2007;39(10):1217-24.
3. Dixon AL, Liang L, Moffatt MF, et al. A genome-wide association study of global gene expression. *Nat Genet* 2007;39(10):1202-07.

## SUPPLEMENTARY TABLES

Supplementary Table 1: Frequency of clinical characteristics in SLE Series 1-3 and Swedish cases.

<b>Phenotypes*</b>	<b>All GWAS Subjects</b>	<b>Series 1</b>	<b>Series 2</b>	<b>Series 3</b>	<b>Swedish Cases</b>
Anti-nuclear autoAbs	1193/1301 (91.7%)	385/409 (94.1%)	541/595 (90.9%)	292/297 (98.3%)	758/781 (97.1%)
Arthritis	1023/1303 (78.5%)	310/411 (75.4%)	444/595 (74.6%)	269/297 (90.6%)	594/781 (76.1%)
Photosensitivity	928/1301 (71.3%)	288/411 (70.1%)	469/595(78.8%)	171/295 (58.0%)	528/781 (67.61%)
Immunologic disorder	867/1303 (66.5%)	313/411 (76.2%)	336/595 (56.5%)	218/297 (73.4%)	511/781 (65.4%)
Hematologic disorder	795/1301 (61.1%)	274/411 (66.7%)	368/595 (61.9%)	153/295 (51.9%)	450/781 (57.6%)
Malar rash	635/1270 (50.0%)	235/411 (57.2%)	274/595 (46.1%)	126/264 (47.7%)	452/781 (57.9%)
Oral ulcers	564/1302 (43.3%)	222/411 (54.0%)	183/595 (30.8%)	159/296 (53.7%)	180/781 (23.0%)
Serositis	499/1299 (38.4%)	195/410 (47.6%)	175/595 (29.4%)	129/294 (43.9%)	345/781 (44.2%)
Renal disorder	365/1302 (28.0%)	137/411 (33.3%)	139/595 (23.4%)	89/296 (30.1%)	239/781 (30.6%)
Neurologic disorder	125/1301 (9.6%)	38/411 (9.3%)	59/595 (9.9%)	28/295 (9.5%)	88/781 (11.3%)
Discoid rash	120/1270 (9.5%)	67/411 (16.3%)	39/595 (6.6%)	14/264 (5.3%)	196/781 (25.1%)

\*See <http://www.rheumatology.org/publications/classification/SLE/sle.asp> for phenotype definitions.

Supplementary Table 2. Top 50 loci associated with SLE in a whole genome scan in 1311 cases and 3340 controls.

CHR	Band	SNP *	Position (build 35)	Locus	Series 1: 411 cases, 1047 controls				Series 2: 595 cases, 1516 controls				Series 3: 305 cases, 777 controls				Combined: 1311 cases, 3340 controls			
					Allele	Case	Control	$\chi^2$ ^	Allele	Case	Control	$\chi^2$	Allele	Case	Control	$\chi^2$	Allele	Case	Control	P *
6	6p21.32	rs2187668	32,713,863	HLA-DQA1	A	0.18	0.11	27.1	A	0.19	0.12	29.0	A	0.21	0.11	34.6	A	0.19	0.11	2.71E-21
2	2q32.2	rs7574865	191,790,140	STAT4	T	0.31	0.22	27.2	T	0.30	0.24	14.3	T	0.33	0.24	16.1	T	0.31	0.23	8.96E-14
7	7q32.1	rs10488631	128,188,135	IRF5/TNPO3	C	0.17	0.12	12.1	C	0.17	0.11	23.9	C	0.17	0.11	13.0	C	0.17	0.11	1.65E-11
8	8p23.1	rs13277113	11,386,596	BLK/C8orf13	A	0.29	0.24	5.3	A	0.28	0.22	12.8	A	0.31	0.22	12.5	A	0.29	0.23	7.57E-08
16	16p11.2	rs11574637	31,276,376	ITGAM/ITGAX	C	0.20	0.18	1.7	C	0.24	0.19	18.4	C	0.25	0.20	10.9	C	0.23	0.19	5.35E-07
9	9q34.13	rs11243676	132,126,322	NTNG2	A	0.05	0.07	6.7	A	0.05	0.06	2.7	A	0.04	0.07	13.3	A	0.05	0.07	2.65E-06
5	5p12	rs979233	42,411,001	GHR	T	0.50	0.46	12.2	T	0.47	0.46	3.5	T	0.49	0.44	6.6	T	0.48	0.45	3.85E-06
18	18q22.3	rs17083844	66,993,224	SOCS6	A	0.04	0.03	4.0	A	0.04	0.03	2.8	A	0.06	0.03	14.5	A	0.05	0.03	6.05E-06
1	1p31.1	rs12141391	71,986,495	NEGR1	A	0.04	0.02	5.7	A	0.04	0.02	7.4	A	0.04	0.02	7.5	A	0.04	0.02	6.99E-06
17	17q11.2	rs1019412	28,512,867	ACCN1	T	0.26	0.23	2.5	T	0.26	0.22	3.4	T	0.31	0.23	15.1	T	0.27	0.23	1.12E-05
7	7p14.3	rs729804	31,712,622	PDE1C	T	0.51	0.47	3.7	T	0.49	0.47	4.7	T	0.55	0.47	11.3	T	0.51	0.47	1.27E-05
2	2q36.3	rs4675077	227,063,536	IRS1	C	0.17	0.14	0.6	C	0.18	0.15	8.0	C	0.19	0.13	14.9	C	0.18	0.14	1.37E-05
4	4q21.23	rs1921880	85,314,378	MGC11324	A	0.08	0.14	9.0	A	0.11	0.13	1.3	A	0.09	0.13	9.7	A	0.09	0.13	1.49E-05
12	12q14.2	rs7956933	61,631,286	AVPR1A	G	0.01	0.02	5.2	G	0.01	0.02	7.1	G	0.01	0.02	6.8	G	0.01	0.02	1.59E-05
20	20q13.12	rs6094661	45,387,700	PRKCBP1	T	0.13	0.10	6.9	T	0.10	0.08	3.9	T	0.12	0.08	7.6	T	0.12	0.09	1.83E-05
17	17p11.2	rs4404112	16,789,646	TNFRSF13B	G	0.18	0.17	1.9	G	0.20	0.18	3.9	G	0.23	0.15	14.8	G	0.20	0.17	1.86E-05
2	2q31.1	rs1386354	172,837,045	DLX2	A	0.12	0.17	15.5	A	0.15	0.16	2.1	A	0.12	0.16	3.8	A	0.13	0.16	1.97E-05
5	5q33.3	rs254850	158,599,310	UBLCP1	T	0.21	0.17	6.9	T	0.24	0.18	18.9	T	0.21	0.19	0.9	T	0.22	0.18	2.67E-05
10	10p14	rs11255111	7,479,732	SFMBT2	A	0.02	0.04	3.0	A	0.02	0.03	6.8	A	0.01	0.04	8.9	A	0.02	0.03	2.71E-05
5	5p13.1	rs982054	42,163,692	FBXO4	C	0.29	0.29	2.2	C	0.30	0.30	6.2	C	0.34	0.28	10.4	C	0.31	0.29	2.80E-05
12	12q24.23	rs1961707	117,843,445	KIAA1853	T	0.29	0.34	6.3	T	0.29	0.34	13.1	T	0.31	0.34	2.3	T	0.29	0.34	2.90E-05
8	8p23.1	rs656319	9,851,822	MSRA	T	0.45	0.44	0.7	T	0.47	0.43	7.9	T	0.49	0.40	12.5	T	0.47	0.42	3.10E-05
8	8q12.3	rs11783343	62,835,576	ASPH	T	0.11	0.17	16.0	T	0.17	0.17	0.0	T	0.14	0.19	7.5	T	0.14	0.17	3.37E-05
1	1q21.1	rs885239	144,352,419	ACP6	A	0.19	0.16	6.1	A	0.17	0.16	2.9	A	0.18	0.15	8.2	A	0.18	0.16	3.46E-05
2	2p14	rs874952	65,520,177	SPRED2	A	0.13	0.15	7.2	A	0.12	0.14	6.4	A	0.12	0.15	4.4	A	0.12	0.14	3.48E-05
8	8p23.1	rs2955587	8,135,490	DEFB4	G	0.47	0.44	0.9	G	0.46	0.41	5.0	G	0.50	0.40	14.4	G	0.47	0.42	3.53E-05
8	8p12	rs4732990	29,592,131	DUSP4	T	0.17	0.14	6.9	T	0.17	0.15	3.7	T	0.18	0.13	6.6	T	0.17	0.14	3.56E-05
3	3p26.3	rs17039471	1,469,265	CNTN6	A	0.07	0.06	1.4	A	0.07	0.07	1.8	A	0.11	0.06	17.2	A	0.08	0.06	3.74E-05
1	1q25.3	rs171980	179,158,255	RGS12	T	0.17	0.23	9.7	T	0.18	0.21	5.4	T	0.18	0.21	3.3	T	0.18	0.21	3.75E-05
14	14q21.1	rs7160383	40,448,684	LRFN5	A	0.35	0.39	6.7	A	0.35	0.39	4.8	A	0.35	0.41	5.7	A	0.35	0.40	3.90E-05
9	9q21.33	rs13297855	84,194,130	SLC28A3	T	0.16	0.12	6.1	T	0.13	0.13	0.0	T	0.18	0.11	15.5	T	0.15	0.12	3.94E-05
18	18p11.21	rs11665283	14,538,205	ANKRD30B	G	0.22	0.20	2.4	G	0.23	0.19	4.5	G	0.23	0.18	11.0	G	0.23	0.19	4.03E-05
17	17q21.31	rs183211	42,143,494	NSF	A	0.23	0.26	2.9	A	0.20	0.25	6.3	A	0.20	0.25	8.5	A	0.21	0.25	4.04E-05
12	12p13.2	rs7980903	12,182,906	BCL2L14	C	0.21	0.18	5.0	C	0.19	0.18	0.4	C	0.24	0.16	14.4	C	0.21	0.18	4.10E-05
14	14q12	rs2180818	25,199,668	STXBP6	A	0.41	0.47	8.6	A	0.41	0.45	5.4	A	0.40	0.47	3.8	A	0.41	0.46	4.34E-05
7	7p15.3	rs1029597	21,536,386	DNAH11	A	0.16	0.19	3.1	A	0.15	0.17	3.4	A	0.13	0.19	11.0	A	0.15	0.18	4.42E-05
17	17q22	rs7503456	50,635,553	STXBP4	C	0.17	0.16	0.4	C	0.19	0.16	8.2	C	0.19	0.13	12.9	C	0.18	0.16	4.43E-05
8	8p23.1	rs12678938	10,054,380	MSRA	T	0.42	0.42	0.0	T	0.41	0.44	3.7	T	0.36	0.47	22.5	T	0.40	0.44	4.45E-05
12	12q23.3	rs7958842	107,166,267	KIAA0789	A	0.10	0.08	2.5	A	0.12	0.09	12.7	A	0.12	0.09	4.7	A	0.11	0.09	4.80E-05
4	4q27	rs17449954	122,965,334	ANKA5	C	0.06	0.05	1.1	C	0.06	0.04	4.1	C	0.09	0.04	13.9	C	0.07	0.05	4.86E-05
3	3p22.1	rs10510732	41,982,344	OIP106	A	0.13	0.17	3.3	A	0.13	0.16	6.1	A	0.12	0.17	7.7	A	0.13	0.17	5.04E-05
17	17q25.2	rs12451573	72,778,745	SEPT9	T	0.09	0.09	0.2	T	0.10	0.08	5.9	T	0.13	0.08	15.9	T	0.11	0.08	5.06E-05
8	8p23.1	rs7814795	10,556,696	RP1L1	C	0.47	0.44	2.4	C	0.47	0.43	3.9	C	0.51	0.42	11.0	C	0.48	0.43	5.24E-05
12	12q12	rs10506202	40,307,616	PDZRN4	G	0.29	0.28	1.8	G	0.31	0.28	7.5	G	0.34	0.27	8.6	G	0.31	0.28	5.58E-05
1	1q25.3	rs12737637	180,458,062	RGL1	G	0.51	0.48	1.9	G	0.51	0.48	3.9	G	0.53	0.46	11.8	G	0.52	0.47	5.63E-05
15	15q15.1	rs8023530	39,435,068	NUSAP1	C	0.29	0.25	4.1	C	0.28	0.27	6.0	C	0.29	0.24	6.5	C	0.29	0.26	5.69E-05
11	11q22.1	rs1021273	98,316,370	CNTN5	G	0.29	0.34	11.5	G	0.32	0.32	0.2	G	0.28	0.34	11.7	G	0.30	0.33	5.88E-05
6	6q22.31	rs6917641	121,305,805	C6orf170	G	0.09	0.11	2.1	G	0.08	0.10	4.6	G	0.07	0.13	10.3	G	0.08	0.11	6.05E-05
1	1p34.1	rs226081	44,515,586	C1orf164	G	0.37	0.31	5.4	G	0.36	0.32	13.2	G	0.34	0.31	1.9	G	0.36	0.31	6.26E-05
8	8q24.23	rs16906782	138,202,322	LOC51059	G	0.10	0.07	8.1	G	0.08	0.08	0.1	G	0.11	0.07	11.2	G	0.09	0.07	6.62E-05
2	2q24.2	rs13023380	162,979,871	IFIH1	G	0.45	0.50	2.6	G	0.44	0.49	5.1	G	0.44	0.52	9.0	G	0.45	0.50	6.85E-05

\* The most associated SNP from the top 50 loci. SNPs within 100kb of the most associated SNP in a region were excluded and only the top HLA region SNP is included. For full results and additional detail, see summary statistics for all SNPs (Supplementary Table 5).

^ The EIGENSTRAT corrected chi square value for each series.

\* The combined P value as described in the methods.

Supplementary Table 3. Expression levels of *BLK*, *C8orf13* and control genes in 210 transformed B cell lines from HapMap individuals.

	Genotype <sup>^</sup>	N	Median Fluorescence Intensity *					P*			
			<i>BLK</i>	<i>C8orf13</i>	<i>ACTB</i>	<i>GAPDH</i>		<i>BLK</i>	<i>C8orf13</i>	<i>ACTB</i>	<i>GAPDH</i>
rs13277113	AA	37	1038.8	400.5	50972.2	27367.8	AAvAG	0.00011	6.1461E-05	0.691	0.746
rs13277113	AG	74	1574.0	275.7	51272.0	27656.2	AGvGG	0.00163	1.01146E-07	0.259	0.835
rs13277113	GG	87	2057.3	165.0	51823.1	27266.8	AAvGG	6.46678E-11	2.33428E-15	0.161	0.894
<p>* Median fluorescence intensity of four measurements for probes for <i>BLK</i> (GI_33469981-S), <i>C8orf13</i> (GI_32698772-S), <i>ITGAM</i> (GI_6006013-S), <i>ITGAX</i> (GI_34452172-S), <i>ACTB</i> (beta-actin, GI_5016088-S), and <i>GAPDH</i> (GI_7669491-S). All expression data is from the GENEVAR project (<a href="http://www.sanger.ac.uk/humgen/genevar/">http://www.sanger.ac.uk/humgen/genevar/</a>) .</p> <p><sup>^</sup> Significance of differential expression as determined by a T-test.</p> <p><sup>^</sup> Genotypes from the International HapMap project (<a href="http://www.hapmap.org">www.hapmap.org</a>)</p>											

Supplementary Table 4. Expression of BLK in transformed B cells from the HapMap populations.

	Genotype <sup>^</sup>	CEU		CHB+JPT		YRI		All Populations		Genotype	CEU	CHB+JPT	YRI	ALL
		N	BLK expression*	N	BLK expression	N	BLK expression	N	BLK expression		P*	P	P	P
rs13277113	AA	2	10.17	33	9.84	2	10.56	37	9.89	AA vs AG	0.3673	0.0021	0.6719	1.9x10 <sup>-5</sup>
rs13277113	AG	26	10.52	41	10.41	7	10.64	74	10.47	AGvsGG	0.0317	0.2319	0.7338	4.5x10 <sup>-5</sup>
rs13277113	GG	31	11.06	9	10.63	47	10.77	87	10.86	AAvsGG	0.0476	0.0015	0.4211	1.1x10 <sup>-12</sup>

\* Normalized expression values for probes for *BLK* (GI\_33469981-S). All expression data is from the GENEVAR project (<http://www.sanger.ac.uk/humgen/genevar/>) .

\* Significance of differential expression as determined by a T-test.

<sup>^</sup> Genotypes from the International HapMap project ([www.hapmap.org](http://www.hapmap.org))

Supplementary Table 5. Association of C8orf13/BLK and ITGAM/ITGAX region variants with SLE by series.

Locus	Chr	SNP	Position	Series 1: 411 cases, 1047 controls			Series 2: 595 cases, 1516 controls			Series 3: 305 cases, 777 controls			Combined: 1311 cases, 3340 controls		
				Minor Allele Frequency		OR*	Minor Allele Frequency		OR	Minor Allele Frequency		OR	OR (95% c.i.)	$\chi^2$	P <sup>^</sup>
				Case	Control		Case	Control		Case	Control				
C8orf13/BLK	8	rs2736340	11,381,383	0.289	0.242	1.27	0.283	0.226	1.35	0.313	0.228	1.54	1.37 (1.24-1.51)	25.7	4.09x10 <sup>-7</sup>
C8orf13/BLK	8	rs13277113	11,386,596	0.292	0.240	1.30	0.284	0.224	1.37	0.310	0.224	1.55	1.39 (1.26-1.54)	28.9	7.57x10 <sup>-8</sup>
ITGAM/ITGAX	16	rs9937837	31,206,441	0.187	0.127	1.59	0.179	0.135	1.39	0.175	0.128	1.44	1.28 (1.16-1.41)	24.7	6.65x10 <sup>-7</sup>
ITGAM/ITGAX	16	rs11574637	31,276,376	0.202	0.182	1.14	0.244	0.190	1.38	0.253	0.198	1.37	1.30 (1.17-1.45)	25.1	5.35x10 <sup>-7</sup>

\* Odds ratio

<sup>^</sup> Meta P value calculated by the addition of the weighted Eigenstrat corrected Z scores adjusted for residual genomic control inflation factor from each series.

Supplementary Table 6. Association of C8orf13/BLK and ITGAM/ITGAX variants with the 11 ACR clinical criteria for SLE

	<b>C8orf13/BLK: rs13277113</b>			<b>ITGAM/ITGAX: rs11574637</b>		
<b>Phenotypes</b>	<b>P*</b>	<b>Odds Ratio<sup>^</sup> (95% c.i.)</b>	<b>P case series heterogeneity<sup>+</sup></b>	<b>P</b>	<b>Odds Ratio (95% c.i.)</b>	<b>P case series heterogeneity</b>
Immunologic disorder	0.84	-	-	0.12	-	-
Anti-nuclear autoAbs	0.43	-	-	0.21	-	-
Renal disorder	0.56	-	-	0.074	1.20 (0.98 - 1.47)	0.30
Arthritis	0.066	1.22 (0.99 - 1.51)	0.54	<b>0.0045</b>	<b>0.73 (0.59 - 0.91)</b>	0.42
Hematologic disorder	<b>0.024</b>	<b>1.23 (1.03 - 1.46)</b>	0.16	<b>0.044</b>	<b>1.21 (1.00 - 1.47)</b>	0.22
Malar rash	0.46	-	-	0.40	-	-
Serositis	0.068	1.18 (0.99 - 1.40)	0.48	0.63	-	-
Photosensitivity	0.073	1.19 (0.98 - 1.45)	0.84	0.46	-	-
Neurologic disorder	0.70	-	-	0.65	-	-
Discoid rash	0.097	1.27 (0.96 - 1.70)	0.44	0.63	-	-
Oral ulcers	0.17	-	-	0.10	-	-

\* P value for association of the indicated SNP to the 11 ACR clinical criteria in the GWAS sample  
<sup>^</sup> Odds ratio and 95% confidence interval for each phenotype. Only odds ratios and heterogeneity p-values where the association P < 0.1 are displayed.  
<sup>+</sup> P value for the Mantel-Haenszel heterogeneity test

Supplementary Table 7. Association of C8orf13/BLK and ITGAM/ITGAX variants with the 11 ACR clinical criteria for SLE in 521 Swedish cases.

Phenotypes	C8orf13/BLK: rs13277113		ITGAM/ITGAX: rs11574637	
	P*	Odds Ratio <sup>^</sup> (95% c.i.)	P	Odds Ratio (95% c.i.)
Immunologic disorder	0.740	0.94 (0.66-1.34)	0.626	0.91 (0.64-1.31)
Anti-nuclear autoAbs	0.609	0.90 (0.60-1.35)	0.254	1.28 (0.84-1.94)
Renal disorder	0.098	0.73 (0.50-1.06)	0.460	0.87 (0.59-1.27)
Arthritis	0.378	0.88 (0.59-1.32)	0.938	1.02 (0.68-1.53)
Hematologic disorder	0.460	0.86 (0.57-1.29)	0.532	1.14 (0.75-1.74)
Malar rash	0.313	1.20 (0.84-1.70)	0.616	0.91 (0.64-1.31)
Serositis	0.056	1.45 (0.99-2.13)	0.073	1.43 (0.97-2.10)
Photosensitivity	0.975	1.01 (0.57-1.80)	0.363	1.31 (0.73-2.34)
Neurologic disorder	0.269	1.22 (0.86-1.74)	0.068	1.41 (0.97-2.03)
Discoid rash	0.526	0.89 (0.62-1.27)	0.053	1.44 (0.99-2.09)
Oral ulcers	0.500	0.71 (0.27-1.91)	0.318	1.70 (0.59-4.91)

\* P value for association of the indicated SNP to the 11 ACR clinical criteria

<sup>^</sup> Odds ratio and 95% confidence interval for each phenotype.

## SUPPLEMENTARY FIGURES

Supplementary Figure 1. Formula used to combine corrected Z scores weighted for series size and adjusted for residual genomic control inflation factor ( $\lambda_{gc}$ ). The variance ( $\sigma^2$ ) of each series was calculated where  $p$  = the allele frequency in cases and controls. The combined Z score for the 3 SLE series ( $Z^*$ ) was calculated where  $Z_1$ ,  $Z_2$ , and  $Z_3$  equals the Z score based on the EIGENSTRAT corrected chi square for the association of a variant to SLE from each series, and where  $\lambda_1$ ,  $\lambda_2$ , and  $\lambda_3$  is the residual genomic control inflation factor ( $\lambda_{gc}$ ) after EIGENSTRAT correction for each series.

$$Z^* = \frac{\sqrt{\frac{\sigma_{Z1}^2}{\lambda_1}}}{\sqrt{\frac{\sigma_{Z1}^2}{\lambda_1} + \frac{\sigma_{Z2}^2}{\lambda_2} + \frac{\sigma_{Z3}^2}{\lambda_3}}} Z_1 + \frac{\sqrt{\frac{\sigma_{Z2}^2}{\lambda_2}}}{\sqrt{\frac{\sigma_{Z1}^2}{\lambda_1} + \frac{\sigma_{Z2}^2}{\lambda_2} + \frac{\sigma_{Z3}^2}{\lambda_3}}} Z_2 + \frac{\sqrt{\frac{\sigma_{Z3}^2}{\lambda_3}}}{\sqrt{\frac{\sigma_{Z1}^2}{\lambda_1} + \frac{\sigma_{Z2}^2}{\lambda_2} + \frac{\sigma_{Z3}^2}{\lambda_3}}} Z_3$$

$$\sigma_Z^2 = \left( \frac{1}{n_{cases}} + \frac{1}{n_{controls}} \right) * p(1-p)$$