

Supplementary Information

Trans-ancestral mapping of the MHC region in SLE identifies new independent and interacting loci at *MSH5*, *HLA-DPB1* and *HLA-G*

Supplementary Methods

Custom iSelect SNP selection

The MHC region SNPs were chosen according to the following criteria: all SNPs put forward were required to have an Illumina designability score >0.8 . All Illumina MHC-Panel SNPs were chosen (~2,360). Additional SNPs were selected from [1] and [2]. Further SNPs were added from HapMap Phase II. In this latter dataset there are 7,574 SNPs that are both designable (score >0.8) and common (minor allele frequency, MAF $>5\%$) in any population. SNPs were included if they were (i) not picked in the above steps, (ii) not in perfect linkage disequilibrium (LD) with any SNP from the above steps and (iii) not in perfect LD with any other picked SNP (LD estimates across CEU, YRI and CHB+JPT). To resolve the phase, haplotypes from the HapMap website were used. Only SNPs with designability-score ≥ 1.0 were allowed to tag other SNPs. SNPs identified from the resequencing of eight homozygous MHC haplotypes were also included [3]. From the 37,535 SNPs called between the eight haplotypes, 11,112 were designable and had their minor allele on at least two haplotypes. From these, a set 309 SNPs were not in perfect LD (on the eight haplotypes) with any HapMap SNP or another SNP from the resequencing project and were added to the dataset. Owing to the small sample size, there will be many false positive instances of perfect LD. To account for this, coding SNPs and SNPs in recombination hotspots were also added.

Supplementary Table 1: Single marker association analysis in Spanish SLE cohort (SNPs with $p < 10^{-5}$)

MARKER	BP	A1	OR	L95	U95	P
RS9268832	32535767	A	1.80	1.45	2.23	7.64E-08
RS1150758	32136127	C	2.61	1.81	3.78	3.34E-07
RS3117213	33172583	A	1.86	1.46	2.35	3.55E-07
RS3130490	31847099	A	2.96	1.95	4.51	3.94E-07
RS7195	32520517	A	1.75	1.41	2.17	3.96E-07
RS2213586	32521072	A	1.75	1.41	2.17	3.96E-07
RS9277545	33163301	A	1.86	1.46	2.37	4.42E-07
RS3117231	33182886	G	1.85	1.46	2.36	4.54E-07
RS1150755	32146528	A	2.58	1.79	3.73	4.71E-07
RS2395314	33170651	A	1.86	1.46	2.36	4.78E-07
RS3131379	31829012	A	2.87	1.90	4.32	5.13E-07
RS3117574	31833209	A	2.87	1.90	4.32	5.13E-07
RS3763327	32521808	G	1.73	1.39	2.14	5.79E-07
RS3131381	31816442	A	2.85	1.89	4.30	5.87E-07
RS2227139	32521437	G	1.73	1.40	2.15	5.96E-07
RS7194	32520458	G	1.72	1.39	2.14	7.14E-07
RS2213585	32521128	G	1.72	1.39	2.14	7.14E-07
RS1270942	32026839	G	2.83	1.87	4.26	7.38E-07
RS389884	32048876	G	2.83	1.87	4.26	7.38E-07
RS3130288	32203979	A	2.82	1.87	4.26	7.46E-07
RS3128972	33166752	G	1.83	1.44	2.32	7.59E-07
RS3130212	33182367	C	1.87	1.46	2.40	7.72E-07
RS9277555	33163583	A	1.83	1.44	2.33	7.87E-07
RS8084	32519013	A	1.70	1.38	2.10	8.45E-07
RS3117222	33168927	A	1.82	1.43	2.31	8.62E-07
RS3130320	32331236	A	1.76	1.41	2.21	9.59E-07
RS2179919	33167240	G	1.82	1.43	2.30	9.72E-07
RS3128919	33169604	A	1.81	1.43	2.30	9.78E-07
RS558702	31978305	A	2.79	1.85	4.20	1.06E-06
RS497309	32000463	C	2.79	1.85	4.20	1.06E-06
RS3117577	31835453	G	2.78	1.84	4.20	1.08E-06
RS3091284	33165222	C	1.82	1.43	2.32	1.25E-06
RS3130455	31233957	T	1.99	1.51	2.63	1.30E-06
RS130065	31230479	A	1.93	1.48	2.52	1.31E-06
RS3130679	31915519	G	2.76	1.83	4.17	1.35E-06
RS3117234	33181962	G	1.83	1.43	2.35	1.39E-06
RS519417	31986412	A	2.74	1.82	4.12	1.46E-06
RS3117226	33165637	A	1.83	1.43	2.34	1.49E-06
RS3094662	31229924	C	1.98	1.50	2.61	1.63E-06
RS3130191	33169849	G	1.79	1.41	2.28	1.64E-06
RS3134942	32276749	A	2.39	1.67	3.42	1.66E-06
RS3132956	32287416	A	2.39	1.67	3.42	1.66E-06

RS1269852	32188169	C	2.76	1.82	4.20	2.02E-06
RS6899657	33158201	A	1.79	1.41	2.27	2.07E-06
RS3132450	31704117	G	2.66	1.77	4.00	2.54E-06
RS3115572	32328462	C	1.67	1.35	2.07	2.64E-06
RS3131296	32280971	A	2.35	1.65	3.36	2.65E-06
RS130076	31230461	A	1.96	1.48	2.60	2.66E-06
RS1367730	33166092	A	1.79	1.40	2.28	2.75E-06
RS1265181	31263764	G	2.00	1.50	2.68	2.90E-06
RS1265178	31269208	A	2.00	1.50	2.68	2.90E-06
RS3117223	33168042	A	1.77	1.39	2.24	3.30E-06
RS6936204	32325070	A	1.72	1.37	2.17	3.44E-06
RS3134796	32297899	G	2.27	1.61	3.21	3.55E-06
RS3130210	33180707	A	1.80	1.40	2.31	3.72E-06
RS910051	32423489	C	2.55	1.71	3.79	4.24E-06
RS3129927	32441805	C	2.55	1.71	3.79	4.24E-06
RS9268165	32380305	G	1.89	1.44	2.48	4.63E-06
RS2523544	31441541	A	2.02	1.49	2.72	4.71E-06
RS1794282	32774504	A	2.51	1.69	3.73	4.73E-06
RS3129890	32522251	G	1.75	1.38	2.23	5.02E-06
RS3129950	32466179	C	2.43	1.66	3.55	5.03E-06
RS2395149	32433540	A	2.52	1.69	3.76	5.47E-06
RS7775397	32369230	C	2.51	1.69	3.75	5.81E-06
RS9268235	32398186	A	2.51	1.69	3.75	5.81E-06
RS1265757	32410360	A	2.51	1.69	3.75	5.81E-06
RS9268208	32388569	G	2.61	1.72	3.95	6.22E-06
RS2064478	33180244	A	1.76	1.38	2.25	6.61E-06
RS3130614	31584437	A	2.54	1.69	3.82	7.79E-06
RS3129962	32487361	A	2.46	1.66	3.65	8.11E-06
RS9268212	32389867	G	1.88	1.43	2.49	8.25E-06
RS1018433	32389488	A	1.86	1.41	2.44	8.71E-06
DRB1_[301]	32600002	C	1.88	1.42	2.48	9.39E-06
RS409558	31816126	G	0.53	0.40	0.71	1.07E-05
RS2293861	31819103	A	0.53	0.40	0.71	1.07E-05
RS2075788	31820160	C	0.53	0.40	0.71	1.07E-05
RS3828922	31821433	A	0.53	0.40	0.71	1.07E-05
RS3864299	32379652	T	1.84	1.40	2.41	1.13E-05
RS9268213	32390059	G	1.84	1.40	2.41	1.13E-05
RS6909790	32390957	G	1.84	1.40	2.41	1.13E-05
RS6915455	32391472	A	1.84	1.40	2.41	1.13E-05
RS9268215	32390449	G	1.83	1.40	2.40	1.21E-05
RS3117230	33183613	G	1.77	1.37	2.29	1.27E-05
RS3821236	191611003	A	1.69	1.34	2.15	1.32E-05
RS2075801	31836246	A	0.54	0.40	0.71	1.34E-05
RS1548306	32535157	T	1.57	1.28	1.93	1.36E-05
RS1986997	31336389	A	1.66	1.32	2.09	1.39E-05
RS9276447	32823547	C	1.60	1.29	1.98	1.51E-05

RS2143462	32443182	A	1.90	1.42	2.54	1.52E-05
RS2179920	33166852	A	1.76	1.36	2.28	1.52E-05
RS4947350	32875598	G	1.82	1.39	2.39	1.52E-05
RS7341328	32383172	A	1.83	1.39	2.40	1.55E-05
RS9268200	32386648	A	1.82	1.39	2.38	1.58E-05
RS9268168	32380488	A	1.82	1.39	2.39	1.59E-05
RS9268192	32385189	A	1.82	1.39	2.39	1.63E-05
RS6934546	32387930	G	1.81	1.38	2.37	1.64E-05
RS3132931	32343873	C	1.82	1.39	2.40	1.84E-05
RS9268137	32363247	A	1.82	1.39	2.40	1.84E-05
RS9268176	32382057	A	1.82	1.39	2.40	1.84E-05
RS6934776	32387794	A	1.82	1.39	2.40	1.84E-05
RS9275602	32790790	A	2.03	1.47	2.81	1.85E-05
RS7742654	32379421	G	1.83	1.39	2.42	1.85E-05
RS7775332	32378341	A	1.78	1.37	2.33	2.03E-05
RS9277385	33158451	G	1.67	1.32	2.11	2.09E-05
RS3115560	32344120	A	1.78	1.36	2.32	2.10E-05
RS3096673	32345991	G	1.78	1.36	2.32	2.10E-05
RS3115553	32353805	A	1.78	1.36	2.32	2.10E-05
RS1264372	30877705	A	1.96	1.44	2.67	2.13E-05
RS652888	31959213	G	1.69	1.33	2.16	2.26E-05
RS3129768	32703061	C	1.82	1.38	2.40	2.37E-05
RS6909427	32376679	C	1.77	1.36	2.31	2.47E-05
RS1018430	32389666	A	1.77	1.36	2.31	2.48E-05
RS9268198	32386165	A	1.80	1.37	2.36	2.50E-05
RS3115563	32341616	A	1.77	1.36	2.31	2.54E-05
RS3864302	32386770	A	1.77	1.36	2.31	2.64E-05
RS1059615	32657541	A	1.84	1.38	2.44	2.71E-05
RS3099844	31556955	A	2.12	1.49	3.01	2.75E-05
RS2734583	31613459	G	2.29	1.56	3.38	2.85E-05
RS9277366	33158085	A	1.60	1.29	2.00	2.86E-05
RS9268167	32380415	A	1.77	1.35	2.30	2.92E-05
RS3024886	191608694	A	1.66	1.31	2.11	2.98E-05
RS9268861	32537872	A	1.71	1.33	2.19	3.03E-05
RS7762279	32863268	G	2.22	1.52	3.22	3.07E-05
RS3130557	31202682	A	2.18	1.51	3.15	3.21E-05
RS6457499	32306926	G	0.65	0.53	0.80	3.28E-05
RS9267488	31622226	G	2.29	1.55	3.38	3.36E-05
RS3129924	32441277	A	1.87	1.39	2.52	3.42E-05
RS3129925	32441397	A	1.87	1.39	2.52	3.42E-05
RS2143461	32443325	A	1.87	1.39	2.52	3.42E-05
RS3129937	32444342	A	1.87	1.39	2.52	3.42E-05
RS7750783	32376058	A	1.78	1.35	2.33	3.49E-05
RS2524054	31360375	A	1.76	1.35	2.29	3.55E-05
RS2647044	32775888	A	1.66	1.31	2.11	3.56E-05
RS9268177	32382860	A	2.35	1.57	3.52	3.67E-05

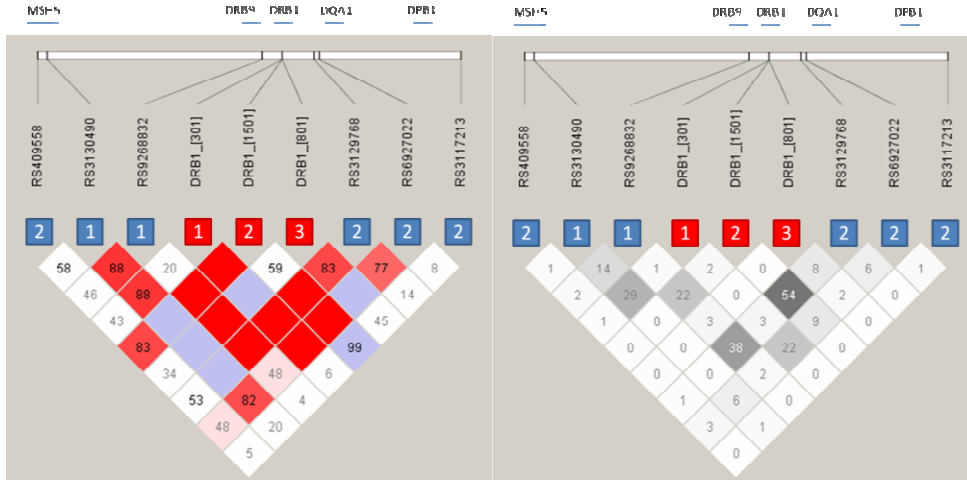
RS2213567	32819633	C	1.55	1.26	1.90	4.14E-05
RS3129939	32444744	G	1.86	1.38	2.50	4.15E-05
RS2239803	32519811	G	1.52	1.24	1.85	4.20E-05
RS2844559	31448054	A	2.14	1.49	3.08	4.25E-05
RS9276731	32873563	A	2.20	1.51	3.20	4.27E-05
RS9276430	32820160	A	1.55	1.26	1.91	4.32E-05
RS3130349	32255674	A	1.83	1.37	2.45	4.39E-05
RS3134940	32257794	G	1.83	1.37	2.45	4.39E-05
RS3129926	32441458	G	1.86	1.38	2.50	4.43E-05
RS2856674	32767623	G	1.77	1.34	2.33	4.89E-05
RS9268197	32385912	A	1.78	1.35	2.35	5.24E-05
RS3134608	32225949	C	1.70	1.31	2.20	5.68E-05
RS1793891	31329677	A	1.62	1.28	2.05	5.80E-05
RS440454	32035321	A	1.63	1.28	2.06	5.96E-05
RS419788	32036778	A	1.63	1.28	2.06	5.96E-05
RS9277565	33164875	A	1.72	1.32	2.25	6.29E-05
RS9277567	33164991	C	1.72	1.32	2.25	6.29E-05
RS931	33162528	A	1.56	1.25	1.94	6.53E-05
RS2064476	33181300	G	1.55	1.25	1.93	6.61E-05
RS2523554	31439808	G	1.60	1.27	2.01	6.87E-05
RS6911419	32517765	A	1.50	1.23	1.84	6.96E-05
RS2239804	32519501	A	1.50	1.23	1.84	6.96E-05
RS3097652	33165813	A	1.56	1.25	1.94	7.31E-05
RS1960278	31377853	C	1.51	1.23	1.84	7.36E-05
RS11860650	31234207	A	1.65	1.29	2.11	7.55E-05
RS3130985	31193335	A	2.07	1.44	2.96	7.90E-05
RS9268220	32392318	A	1.84	1.36	2.50	7.93E-05
RS1264326	30959888	A	2.40	1.55	3.71	7.95E-05
RS4143332	31456344	A	2.13	1.46	3.11	8.06E-05
RS2844531	31461150	G	2.13	1.46	3.11	8.06E-05
RS6931646	32517759	G	1.50	1.23	1.83	8.27E-05
RS9268658	32518694	G	1.50	1.23	1.83	8.31E-05
RS3131788	31132775	A	2.05	1.43	2.94	8.41E-05
RS630379	32030233	A	1.64	1.28	2.10	8.45E-05
RS9268127	32361537	G	1.84	1.36	2.50	8.54E-05
RS9276435	32821845	A	1.73	1.32	2.27	8.58E-05
RS3117225	33165689	A	1.55	1.25	1.93	8.59E-05
RS2858331	32789255	G	0.67	0.55	0.82	8.74E-05
RS3130562	31208953	G	2.08	1.44	3.00	8.87E-05
RS9277394	33158948	A	1.54	1.24	1.91	9.35E-05
RS9277378	33158257	G	1.55	1.24	1.93	9.45E-05
RS9277393	33158855	G	1.54	1.24	1.91	9.49E-05
RS1042544	33162435	G	1.54	1.24	1.91	9.49E-05
RS9277542	33163225	G	1.54	1.24	1.91	9.49E-05
RS3117228	33164413	A	1.54	1.24	1.91	9.49E-05
RS3130188	33165154	G	1.54	1.24	1.91	9.49E-05

RS9277386	33158477	G	1.54	1.24	1.92	9.57E-05
RS3129933	32444139	A	1.83	1.35	2.48	9.70E-05
RS9276689	32859940	A	2.24	1.49	3.36	9.70E-05
RS3134931	32298598	G	0.66	0.54	0.81	9.81E-05

Supplementary Figure 1: Linkage disequilibrium between top independent MHC SNPs and *HLA-DRB1* alleles in Spanish controls

(a) D' plot

(b) r^2 plot

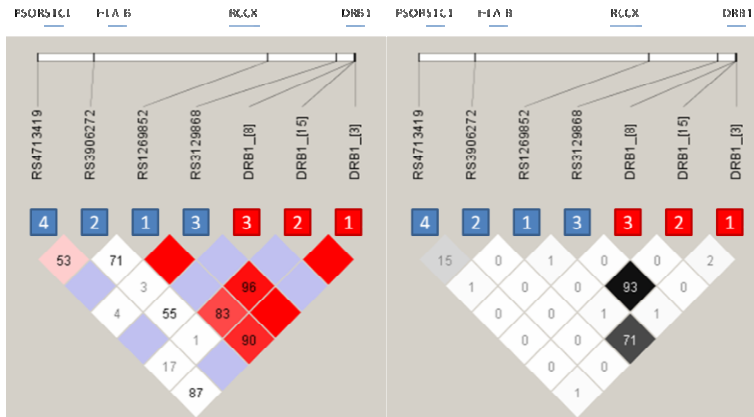


Approximate location of MHC region genes is shown above the plots. SNPs and HLA allele positions are shown to scale. Numbers in boxes denote SNP (blue) and *HLA-DRB1* allele (red) primary (1) and secondary (2-3) signals. Numbers in diamonds denote D' and r^2 values respectively.

Supplementary Figure 2: Linkage disequilibrium between top independent MHC SNPs and *HLA-DRB1* alleles in United Kingdom controls

(a) D' plot

(b) r^2 plot



Supplementary Table 2: *HLA-DRB1* association in Spanish SLE using step-wise conditional logistic regression to assess relative predispositional effects

SNP ID	Position	F_U	OR (95% CI)	P	Other disease
Spanish SLE					
DRB1*03:01	32600000	0.12	1.88 (1.43-2.48)	5.53x10 ⁻⁶	many
<i>DRB1*15:01</i>	<i>32600000</i>	<i>0.09</i>	<i>1.82 (1.30-2.54)</i>	<i>5.00x10⁻⁴</i>	<i>MS, T1D</i>
<i>DRB1*08:01</i>	<i>32600000</i>	<i>0.01</i>	<i>3.67 (1.60-8.38)</i>	<i>0.0021</i>	

Conditional association results are italicised; F_U, frequency in unaffected controls; OR, odds ratio; CI, confidence interval; p, p value (see Methods); MS, multiple sclerosis; T1D, type 1 diabetes.

SLR analyses at the *HLA-DRB1* locus in Spanish SLE reveal significant predisposing effects for the alleles, *HLA-DRB1*03:01*, *HLA-DRB1*15:01* and *HLA-DRB1*08:01*. These data contrast with those of northern European lupus cohorts where *HLA-DRB1*08:01* is uncommon and not associated with SLE [4-5]. However, the *HLA-DRB1*08:01-DQB1*0401* haplotype, inferred using microsatellite markers, was found to be associated with SLE in a previous European-American study. The current data suggest that this association is most likely due to a southern European component within the European-American cohort [6].

Supplementary Table 3: SNP associations following stepwise logistic regression using PC1, *HLA-DRB1*03:01*, *HLA-DRB1*15:01*, *HLA-DRB1*08:01* as covariates in Spanish SLE

MARKER	BP	A1	OR	L95	U95	P
RS3117213	33172583	A	1.81	1.42	2.31	2.28E-06
RS409558	31816126	G	0.55	0.41	0.73	5.31E-05
RS3130490	31847099	A	2.28	1.38	3.77	1.26E-03
RS9268832	32535767	A	1.48	1.14	1.92	3.32E-03
RS3129768	32703061	C	1.72	1.08	2.74	2.22E-02

Supplementary Table 4: SNP associations following stepwise logistic regression using PC1, *HLA-DRB1*03:01*, *HLA-DRB1*15:01* as covariates in United Kingdom SLE

MARKER	BP	A1	OR	L95	U95	P
RS3906272	31370903	A	3.01	2.70	3.32	3.25E-12
RS4713419	31101215	C	0.53	0.18	0.88	3.47E-04
RS1269852	32188169	C	1.66	1.25	2.07	1.65E-02
RS3129868	32512355	T	1.17	0.15	2.20	7.57E-01

Supplementary Table 5: Single marker association analysis in Filipino SLE cohort (SNPs with $p < 10^{-5}$)

MARKER	BP	A1	OR	L95	U95	P
RS9271366	32694832	G	2.46	1.83	3.30	1.97E-09
RS1966002	32689662	C	0.42	0.31	0.55	2.27E-09
RS9270986	32682038	C	0.42	0.31	0.56	2.96E-09
RS615672	32682149	C	0.41	0.30	0.55	5.66E-09
RS2858867	32683303	G	0.41	0.31	0.56	1.01E-08
RS2071351	33151908	A	0.32	0.20	0.52	3.21E-06
RS984778	32508066	A	0.52	0.39	0.69	3.89E-06
RS3135338	32509195	A	0.52	0.39	0.69	4.52E-06
RS3135395	32513170	C	0.52	0.40	0.69	5.01E-06
RS2395173	32512837	G	0.52	0.40	0.69	5.04E-06
RS9258738	29935369	A	0.44	0.31	0.63	6.37E-06
RS2523767	29920786	A	0.45	0.32	0.64	8.17E-06
RS3129768	32703061	A	0.53	0.40	0.71	1.31E-05
RS9501624	32507264	G	3.26	1.91	5.56	1.40E-05
RS6457656	32844956	A	0.37	0.23	0.58	1.58E-05
RS9501259	33163529	G	0.55	0.41	0.72	1.96E-05
RS3129878	32516713	C	0.49	0.35	0.68	2.10E-05
RS9272689	32717083	A	0.54	0.41	0.72	2.18E-05
RS765649	29939037	T	0.47	0.33	0.67	2.90E-05
RS6926336	32515300	G	3.55	1.95	6.44	3.19E-05
RS1611717	29937556	A	0.48	0.34	0.68	3.32E-05
RS9258651	29930334	G	0.48	0.34	0.68	3.46E-05
RS2523756	29928696	A	0.48	0.34	0.68	3.55E-05
RS3094175	29930902	A	0.48	0.34	0.68	3.61E-05
RS1431399	33149012	A	0.42	0.28	0.64	3.85E-05
RS1611737	29939550	C	0.48	0.34	0.68	3.94E-05
RS1611710	29936895	G	0.48	0.34	0.68	4.13E-05
RS9268644	32516022	A	0.44	0.29	0.65	4.69E-05
RS2428510	29931006	G	0.49	0.34	0.69	4.74E-05

RS6919513	29931973	G	0.49	0.34	0.69	4.74E-05
RS9258679	29932038	A	0.49	0.34	0.69	4.74E-05
RS3077	33141000	A	0.40	0.25	0.62	5.03E-05
RS3129877	32516575	A	0.44	0.29	0.65	5.13E-05
RS1611732	29938987	G	0.49	0.34	0.69	5.17E-05
RS1978029	32839688	A	0.42	0.27	0.64	5.51E-05
RS9276586	32840915	G	0.42	0.27	0.64	5.51E-05
RS2844827	29919216	A	0.50	0.35	0.70	5.82E-05
RS9469341	33143855	A	0.41	0.26	0.63	6.67E-05
RS1611723	29938484	A	0.50	0.35	0.70	7.04E-05
RS2571391	30031817	C	0.38	0.24	0.62	7.43E-05
RS3129875	32515446	G	0.48	0.33	0.69	7.86E-05
RS1431400	33149154	G	0.41	0.26	0.64	7.92E-05
RS10214910	33145653	C	0.41	0.27	0.64	7.93E-05
RS9348904	33148813	A	0.42	0.27	0.64	8.15E-05
RS7755224	32760295	G	2.48	1.58	3.89	8.39E-05
RS4084096	29919847	C	0.51	0.36	0.71	8.52E-05
RS2395181	32515382	C	0.49	0.34	0.70	9.46E-05
RS9258766	29938390	G	0.51	0.36	0.71	9.48E-05

Supplementary Table 6: *HLA-DRB1* data stratified according to genotype of SNP, *rs9271366*, in 89 subjects of the Filipino SLE cohort

AA HOMs	ALLELES 1&2*	AG HETs	ALLELE 1	ALLELE 2	GG HOMs	ALLELE 1	ALLELE 2
case	15:02, ---	case	15:02	04:05	case	04:01	07:01
case	15:02, ---	case	15:02	14:04	case	07:01	12:02
case	15:02, ---	case	15:02	07:01	case	12:02/20	12:02/20
case	15:02, ---	case	15:02	09:01	case	12:02/20	12:02/20
case	15:02, ---	case	15:02	07:01	case	03:01/20/45/50/51	12:02/19
case	15:02, ---	case	15:02	04:05	case	04:03/52	08:03
case	15:02, ---	case	15:02	08:03	case	12:02	07:01
case	15:02, ---	case	15:02	12:02	case	12:02/19	15:01/35/36/41/42/43
case	15:02, ---	case	15:02	07:01	case	14:04	07:01
case	15:02, ---	case	15:02	12:02	case	04:01	12:02
case	15:02, ---	case	15:02	03:01/34/50/51	case	09:01/02	09:01/02
case	15:02, ---	control	15:02	09:01	case	04:03/52	08:03
case	15:02, ---	control	15:02	12:02	case	04:05	12:02
case	15:02, ---	control	15:02	11:01/75/81	case	04:03/52	08:03
case	15:02, ---	control	15:02	08:03	control	03:01/45/50/51	09:01
case	15:02, ---	control	15:02	12:02	control	04:03/52	11:01/81
case	15:02, ---	control	15:02	12:02	control	08:03	09:01
case	15:02, ---	control	15:02	12:02	control	04:05	09:01
case	15:02, ---	control	15:02	12:02	control	12:02/20	12:02/20
case	15:02, ---	control	15:02	09:01	control	11:01	14:07
case	15:02, ---	control	15:02	16:02	control	12:01/06/10/17	10:01
case	15:02, ---	control	15:02	11:01/75/81	control	04:05/83/89	04:05/80/81N/83/89
case	15:02, ---	control	15:02	10:01	control	04:06	12:02
case	15:02, ---	control	15:02	13:02	control	03:01/45/50/51	11:01/75/81
case	15:02, ---				control	03:01/45/48/50/51	1501/36/41/42/43
case	15:02, ---				control	12:02/20	12:02/20

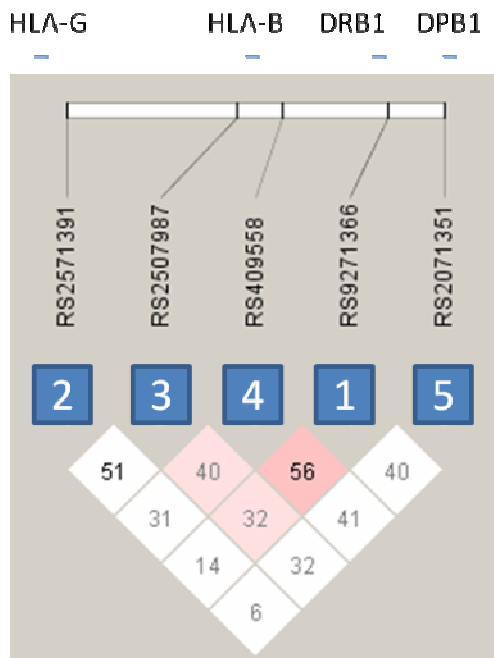
case	15:02, ---
case	15:02, ---
case	15:02, ---
case	15:02, ---
control	15:02, ---
control	15:02, ---
control	15:02, ---
control	15:02, ---
control	15:02, ---
control	15:02, ---
control	15:02, ---
control	15:02, ---
control	15:02, ---

The associated minor allele is A, the major allele is G

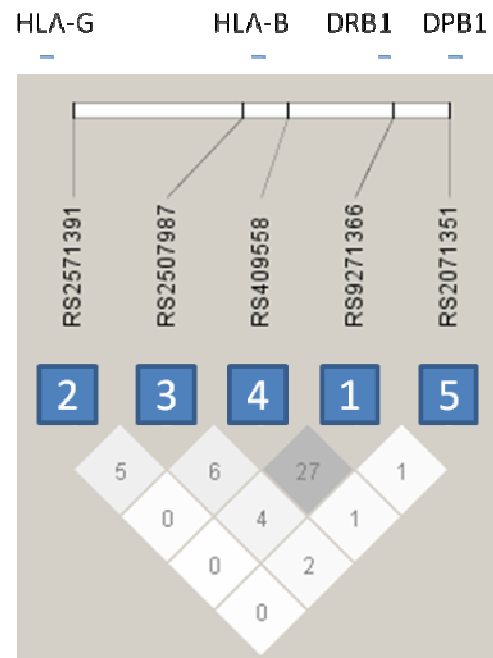
* all samples are homozygous for *HLA-DRB1*15:02*, some sample are homozygous for the string *HLA-DRB1*15:01/02/08*, however as the alleles *HLA-DRB1*15:01* and *HLA-DRB1*15:08* are rare in this cohort, the most likely genotype is homozygous *HLA-DRB1*15:02*

Supplementary Figure 3: Linkage disequilibrium between top independent MHC SNPs and *HLA-DRB1* alleles in Filipino controls

(a) D' plot



(b) r^2 plot



Supplementary Table 7: Association of SNP, rs9271366, in UK, Spanish and Filipino SLE

	UK SLE			Spanish SLE			Filipino SLE			All
	F_U	OR (95% CI)	P	F_U	OR (95% CI)	P	F_U	OR (95% CI)	P	BD P
Primary SMA	0.11	1.32 (1.04-1.66)	0.021	0.10	1.48 (1.09-2.01)	0.012	0.34	2.46 (1.83-3.30)	1.97x10-9	5.25x10-4
Conditional SMA	-	1.63 (1.28-2.07)	7.79x10-5	-	1.55 (1.13-2.11)	0.006	-	NA	NA	-

F_U, frequency in unaffected controls; OR, odds ratio; CI, confidence interval; P, univariate or conditional p-value; BD P, Breslow-Day p value; SMA, single marker association

Supplementary Table 8: Haplotypic association between MHC region SNPs in (a) United Kingdom, (b) Spanish and (c) Filipino SLE

(a) United Kingdom SLE

SNP1	SNP2	SNP3	HAPLOTYPE	F_A	F_U	OR	95% CI	P
RS1269852	RS3906272	RS3129868	CAT	0.000	0.000	NA	NA	NA
RS1269852	RS3906272	RS3129868	GAT	0.016	0.007	NA	NA	NA
RS1269852	RS3906272	RS3129868	CGT	<0.001	0.000	NA	NA	NA
RS1269852	RS3906272	RS3129868	GGT	0.123	0.106	1.2	0.93-1.54	0.15
RS1269852	RS3906272	RS3129868	CAG	0.004	0.001	NA	NA	NA
RS1269852	RS3906272	RS3129868	GAG	0.091	0.048	2.26	1.60-3.18	3.07E-06
RS1269852	RS3906272	RS3129868	CGG	0.239	0.109	2.71	2.17-3.78	8.37E-19
RS1269852	RS3906272	RS3129868	GGG	0.524	0.729	0.37	0.31-0.44	3.72E-28
	RS3906272	RS3129868	AT	0.017	0.006	NA	NA	NA
	RS3906272	RS3129868	GT	0.129	0.105	1.25	0.97-1.61	0.08
	RS3906272	RS3129868	AG	0.097	0.045	2.35	1.64-3.36	2.81E-06
	RS3906272	RS3129868	GG	0.757	0.844	0.59	0.47-0.72	6.52E-07
RS1269852		RS3129868	CT	0.004	<0.001	NA	NA	NA
RS1269852		RS3129868	GT	0.141	0.111	1.29	1.02-1.48	0.03
RS1269852		RS3129868	CG	0.247	0.109	2.74	2.18-3.44	2.96E-18
RS1269852		RS3129868	GG	0.608	0.779	0.44	0.37-0.53	7.94E-19
RS1269852	RS3906272		CA	0.004	<0.001	NA	NA	NA
RS1269852	RS3906272		GA	0.108	0.049	2.37	1.72-3.27	1.59E-07
RS1269852	RS3906272		CG	0.242	0.120	2.42	1.93-3.03	1.48E-14
RS1269852	RS3906272		GG	0.646	0.830	0.36	0.29-0.44	1.23E-23
RS1269852			C (G)		0.110	2.68	2.16-3.33	2.48E-19
	RS3906272		A (G)		0.040	2.84	2.05-3.92	2.95E-10
		RS3129868	T (G)		0.110	1.67	1.29-2.14	8.65E-05

(b) Spanish SLE

SNP1	SNP2	SNP3	HAPLOTYPE	F_A	F_U	OR	95% CI	P
RS3130490	RS3129768	RS3117213	ACA	0.004	0.000	NA	NA	NA
RS3130490	RS3129768	RS3117213	CCA	0.048	0.021	2.46	1.16-5.21	0.02
RS3130490	RS3129768	RS3117213	AAA	0.048	0.014	3.86	2.10-7.08	1.27E-05
RS3130490	RS3129768	RS3117213	CAA	0.190	0.142	1.39	1.07-1.80	0.01
RS3130490	RS3129768	RS3117213	ACC	0.013	0.001	NA	NA	NA
RS3130490	RS3129768	RS3117213	CCC	0.143	0.107	1.65	1.23-2.21	7.12E-04
RS3130490	RS3129768	RS3117213	AAC	0.048	0.027	1.97	1.12-3.47	0.02
RS3130490	RS3129768	RS3117213	CAC	0.506	0.688	0.47	0.38-0.58	3.29E-13
RS3130490	RS3129768		AC	0.017	0.001	NA	NA	NA
RS3130490	RS3129768		CC	0.193	0.128	1.78	1.36-2.38	3.50E-05
RS3130490	RS3129768		AA	0.097	0.041	2.9	1.91-4.42	6.88E-07
RS3130490	RS3129768		CA	0.693	0.830	0.45	0.35-0.57	8.80E-11
RS3130490		RS3117213	AA	0.053	0.014	3.95	2.16-7.23	8.74E-06
RS3130490		RS3117213	CA	0.238	0.164	1.49	1.16-1.91	1.65E-03
RS3130490		RS3117213	AC	0.061	0.027	1.99	1.14-3.46	0.02
RS3130490		RS3117213	CC	0.649	0.795	0.48	0.38-0.61	2.13E-09
	RS3129768	RS3117213	CA	0.053	0.020	2.57	1.22-5.42	1.34E-02
	RS3129768	RS3117213	AA	0.237	0.157	1.75	1.37-2.24	9.58E-06
	RS3129768	RS3117213	CC	0.156	0.109	1.67	1.25-2.23	5.59E-04
	RS3129768	RS3117213	AC	0.553	0.714	0.51	0.42-0.62	6.43E-11
RS3130490			A (C)		0.04	2.96	1.95-4.51	3.94E-07
	RS3129768		C (A)		0.13	1.91	1.44-2.53	7.57E-06
		RS3117213	A (C)		0.18	1.76	1.37-2.25	7.18E-06

(c) Filipino SLE

SNP1	SNP2	SNP3	HAPLOTYPE	F_A	F_U	OR	95% CI	P
RS9271366	RS2571391	RS2507987	GCA	0.017	0.019	0.84	0.20-3.56	0.82
RS9271366	RS2571391	RS2507987	ACA	0.005	0.031	0.002	0.0001-0.06	2.10E-04
RS9271366	RS2571391	RS2507987	GAA	0.262	0.201	1.48	1.04-2.11	0.03
RS9271366	RS2571391	RS2507987	AAA	0.150	0.271	0.44	0.30-0.63	1.14E-05
RS9271366	RS2571391	RS2507987	GCT	0.029	0.029	1.05	0.31-3.59	0.94
RS9271366	RS2571391	RS2507987	ACT	0.026	0.084	0.14	0.06-0.33	5.45E-06
RS9271366	RS2571391	RS2507987	GAT	0.273	0.092	3.45	2.24-5.33	5.69E-11
RS9271366	RS2571391	RS2507987	AAT	0.237	0.274	0.81	0.59-1.12	0.21
RS9271366	RS2571391		GC	0.045	0.048	0.89	0.41-1.95	0.78
RS9271366	RS2571391		AC	0.030	0.116	0.14	0.07-0.29	1.10E-07
RS9271366	RS2571391		GA	0.528	0.296	2.78	2.02-3.83	3.80E-10
RS9271366	RS2571391		AA	0.397	0.539	0.56	0.42-0.75	7.37E-05
	RS2571391	RS2507987	CA	0.022	0.051	0.20	0.07-0.60	3.90E-03
	RS2571391	RS2507987	AA	0.419	0.477	0.80	0.62-1.05	0.11
	RS2571391	RS2507987	CT	0.054	0.113	0.34	0.19-0.62	3.88E-04
	RS2571391	RS2507987	AT	0.505	0.359	1.77	1.33-2.35	7.74E-05
RS9271366		RS2507987	GA	0.283	0.218	1.45	1.04-2.03	0.03
RS9271366		RS2507987	AA	0.157	0.307	0.39	0.27-0.56	3.30E-07
RS9271366		RS2507987	GT	0.300	0.118	4.35	2.73-6.93	6.16E-10
RS9271366		RS2507987	AT	0.260	0.358	0.63	0.46-0.85	2.32E-03
RS9271366			G (A)		0.340	2.46	1.83-3.30	1.97E-09
	RS2571391		C (A)		0.160	0.36	0.22-0.59	6.06E-05
		RS2507987	A (T)		0.480	0.48	0.35-0.66	6.80E-06

F_A, frequency in affected SLE cases; F_U, frequency in unaffected controls; OR, odds ratio; CI, confidence interval; P, nominal p-value; Allele in parenthesis is the unassociated allele in the primary single marker analysis.

Logistic regression interaction and haplotype analysis of top three independent Spanish SNPs

A multiple logistic regression model was fitted with rs3130490, rs3129768 and rs3117213 as explanatory variables. All three SNPs had significant effects (1.45×10^{-06} , 4.04×10^{-06} and 7.28×10^{-06} respectively) with odds ratios of 2.90 (95% CI 1.88-4.48), 1.95 (95% CI 1.47-2.59) and 1.75 (95% CI 1.37-2.24).

Testing for all three 2x2 interaction effects resulted in a significant ($p=0.03$, unadjusted) interaction for rs3130490*rs3129768 where the effect on the odds ratio was positive = 5.1 (95% CI 1.12-23.08). While the raw p-value for this interaction does not withstand a multiple testing adjustment (for the three interaction terms tested), a further analysis looking at all possible models and evaluating using the AIC showed that the model with rs3130490*rs3129768 plus an independent additive term for rs3117213 had the lowest AIC (1017.3). The multiple regression model with three additive terms had AIC=1022.1, while an interaction model with only rs3130490*rs3129768 had AIC=1040.6 and the null model (no markers in the model) had AIC=1101.3.

Evaluated using the BIC, we get the 'rs3130490*rs3129768 plus rs3117213' model has BIC =1060.6 while the multiple regression model with three additive terms has BIC = 1067.435. This equates to a Bayes Factor of 30 in favour of the 'rs3130490*rs3129768 plus rs3117213' model.

We also asked whether a haplotype model for rs3130490*rs3129768 with an independent effect for rs3117213 was a better fit than the interaction model for rs3130490*rs3129768 with an independent effect for rs3117213. To achieve this we phased the data using fastPHASE and coded the four haplotypes for rs3130490*rs3129768 as variables (we counted the observed number of haplotypes - 0, 1, 2). We then fitted the following three models:

- 1) interaction model for rs3130490*rs3129768 with an independent effect for rs3117213
- 2) Protective haplotype for rs3130490*rs3129768 (CA) with an independent effect for rs3117213
- 3) Four haplotypes for rs3130490*rs3129768 (protective used as baseline) with an independent effect for rs3117213

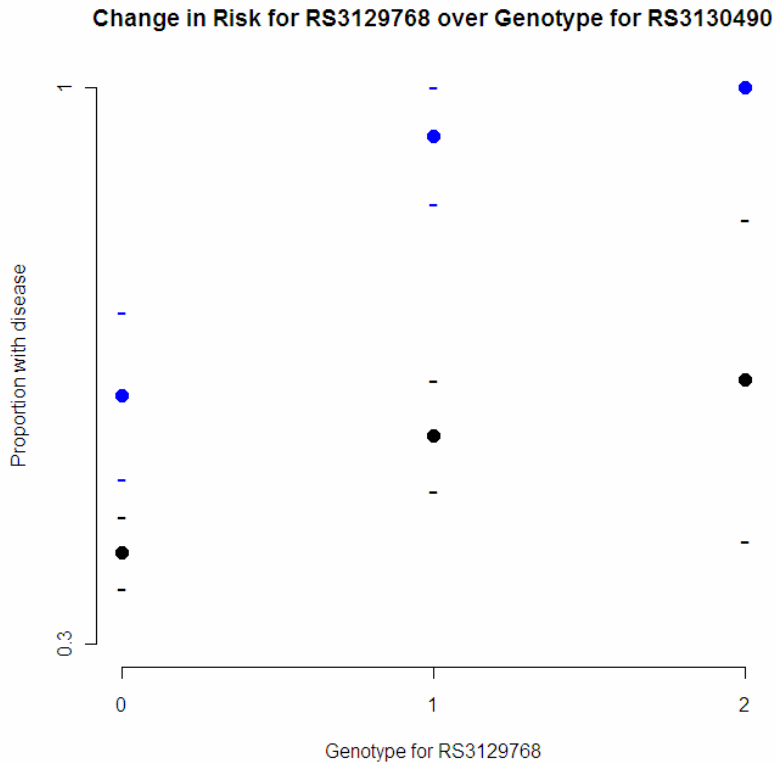
Model -1 has five parameters (intercept + rs3130490 + rs3129768 + rs3130490*rs3129768 + rs3117213), model-2 has three parameters (intercept+protective haplotype+ rs3117213) and model-3 has five parameters(intercept+ 3-non-baseline-haplotypes + rs3117213). We judged the fit of each model by the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC). Model-1 has the lowest AIC and BIC and the difference is >10. Supplementary Table 7 contains these model choice results. We also present the AIC and BIC for the simple 3-snp additive model and the null model (no SNPs included).

	AIC	BIC	Model Details
Model-1	1017.3	1060.6	rs3130490*rs312976 + rs3117213
Model-2	1032.8	1080.2	H(CA) + rs3117213
Model-3	1033.4	1076.8	H(CA) + H(CC) + H(AA) + H(AC) + rs3117213
Model-4	1022.1	1067.4	rs3130490 + rs312976 + rs3117213
Model-5	1101.3	1152.6	Null

Supplementary Table 9: Model choice assessment for top three independently associated Spanish SNPs

Model-1, which has an interaction between rs3130490*rs312976 and an additive effect for rs3117213 has the lowest AIC and BIC. For the haplotype models, H(CA) is a variable with values of 0, 1 or 2 if an individual has 0,1 or 2 copies of the haplotype CA. In model 3 the four haplotypes over determine the model, so we set H(AC) as the baseline.

For a graphical representation of the interaction between rs3130490*rs3129768, see Supplementary Figure 4, where the change in risk for rs3129768 is shown to increase greatly between homozygous and heterozygous individuals for rs3130490. We do not show the points for individuals homozygous for the risk rs3130490 allele as they were very close or equal to 1. In fact an interaction model for rs3130490*rs3129768 with rs3130490 as a dominant term (still with an independent additive effect for rs3117213) could also be fitted (AIC=1019.0, OR for rs3129768 when baseline for rs3130490 = 1.75, OR for rs3129768 when rs3130490 has 1-or-2 risk alleles = 9.92



Supplementary Figure 4: Interaction between rs3129768 and rs3130490: plot of disease risk over genotypes

Black points represent individuals homozygous for the non-risk rs3130490 allele, while the blue points denote individuals heterozygous for rs3130490. The relative risk over rs3129768 changes between the black (OR=1.76) and blue (OR=9.49) points ($p=0.03$ for change in regression coefficient). Points for individuals homozygous for the risk rs3130490 allele are not shown as they were very close or equal to 1.

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