Supplementary Methods.

Confirmation of genotypes

DNA was extracted from tail or ear of mice following the manufacturer's instructions of Viogene Genomic DNA Extraction (Taiwan),and subjected to either Sanger sequencing at Kyoto University using sequencing primers Seq F1: 5'-TAACTGCTGAACCAGCTCTCCAGGC-3'; Or polymerase chain reaction using primers Seq F1 and R1: 5'-ACGCTGAGCAGCAGAATAACTCCT-3', followed by restriction digest by HpyCH4III enzyme (Amplicon: 510 base pair or bp; After digestion-Wild type: 275 and 237bp; Heterozygotes: 275, 237, 161, and 74bp; Mutants: 275, 161 and 74bp), and analyzed using electrophoresis on a 3% TBE agarose gel.

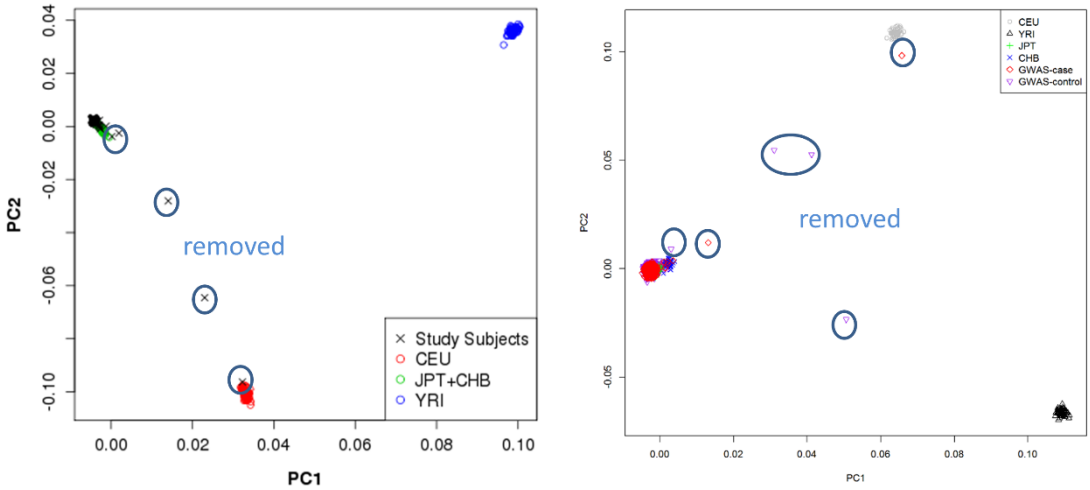
Antibodies, cell culture and flow cytometric analysis

The following monoclonal antibodies were purchased: APC-conjugated anti-CD4 (or L3T4,BioLegend, U.S.), FITC-conjugated anti-CD4 (L3T4,BioLegend), FITC-conjugated-anti-B220 (BD Pharmingen, U.S.), PerCP-Cy5.5-conjugated anti-CD19 (eBioscience, U.S.), PE-conjugated anti-CXCR5 (BioLegend), FITC-conjugated anti-PD1 (clone 29F1A12, BioLeged), APC-conjugated anti-CD95 (or GL7, eBioscience),FITC-conjugated anti-CD93 (or AA4.1, eBioscience), PE-conjugated anti-CD23 (eBioscience), FITC-conjugated anti-CD21 (BIoLegend), PE-conjugated anti-CD3 (BioLegend), APC-conjugated anti-SiglecH (BioLegend), PE-conjugated anti-CD11c (eBioscience), FITC-conjugated CD11b (BioLegend), and PE-conjugated anti-F4/8 (BioLegend), APC-anti-CD8 (BioLegend), PE-conjugated anti-CD62L (or MEL-14, eBioscience), FITC-conjugated-anti-CD69 (clone H1.2F3, eBioscience), Biotin-conjugated anti-peanut agglutinin (PNA, BioLegend), PE-conjugated streptavidin (BioLegend). .

Gene expression analysis

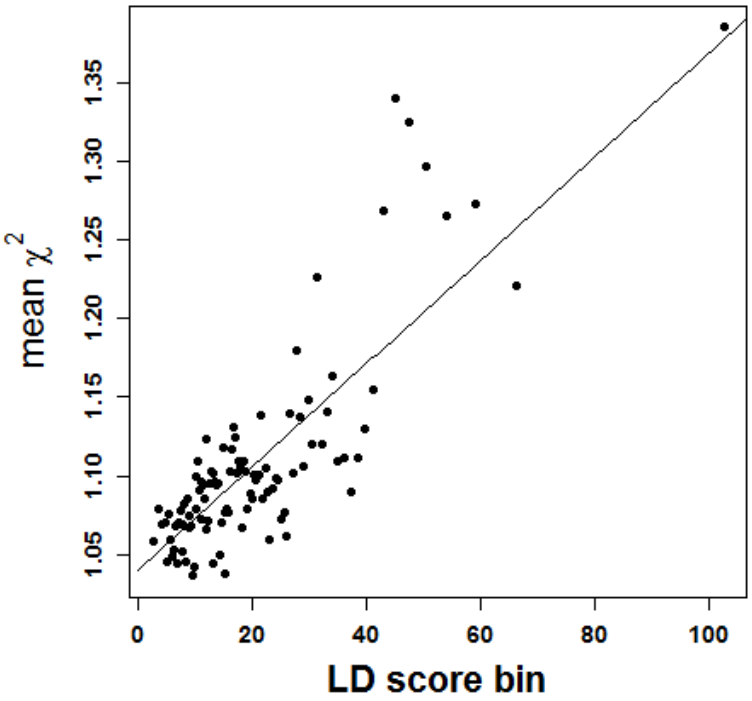
Control glyceraldehyde-3-phoshate dehydrogenase (GAPDH) and target cDNAs were amplified using SYBR green method (Thunderbird qPCRMix,Toyobo,Japan) with specific primer sets (ThermoFisher Scientific, U.S.): Gapdh (5'-ATGTTCGTCATGGGTGTGAA,GGTGCTAAGCAGTTGGTGGT-3'), Isg15 (5'-AGCAAGCAGCCAGAAGCAGACTC,GGAAAGCCGGCACACCAATC-3'), Oas2 (5'-CCGGGCCAGTGCACAAGTTAG,CGATGGCACCGAGGACACC-3'), Irf4 (5'-CTCTTCAAGGCTTGGGCATT,TGCTCCTTTTTTGGCTCCCT-3'), Ifna (5'-CCTGAGAGAAGAAACACAGC,GAGGAAGACAGGGCTCTCC-3').

Supplementary Figure 1. PCA to exclude outliers from Asian cluster.



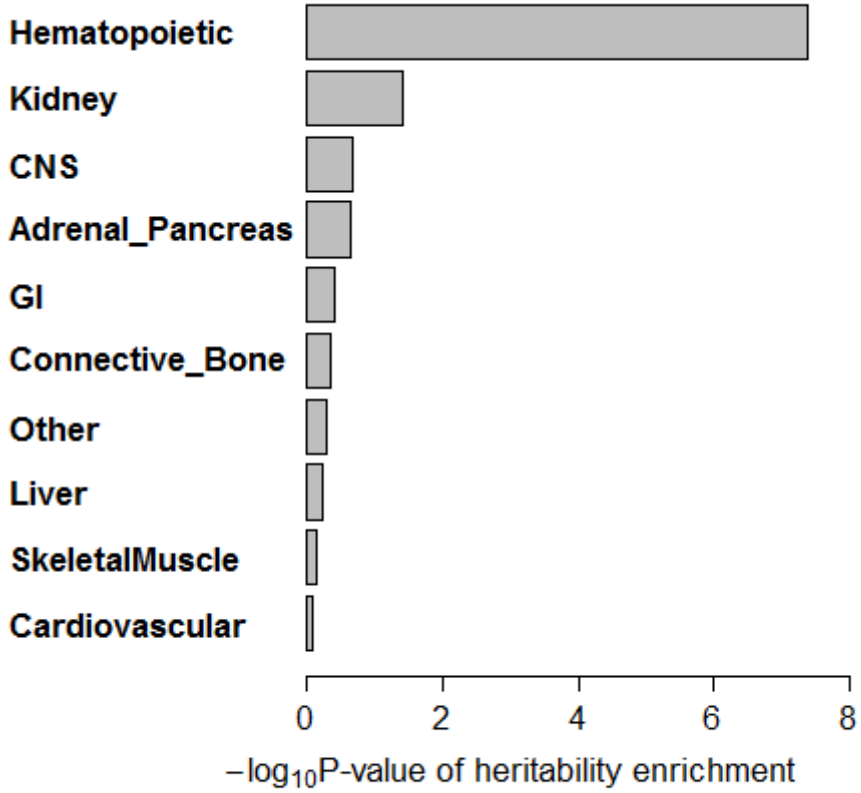
Study subjects in Study 1 and 2 are shown in left and right panels, respectively.

Supplementary Figure 2. Polygenicity found in SLE GWAS.



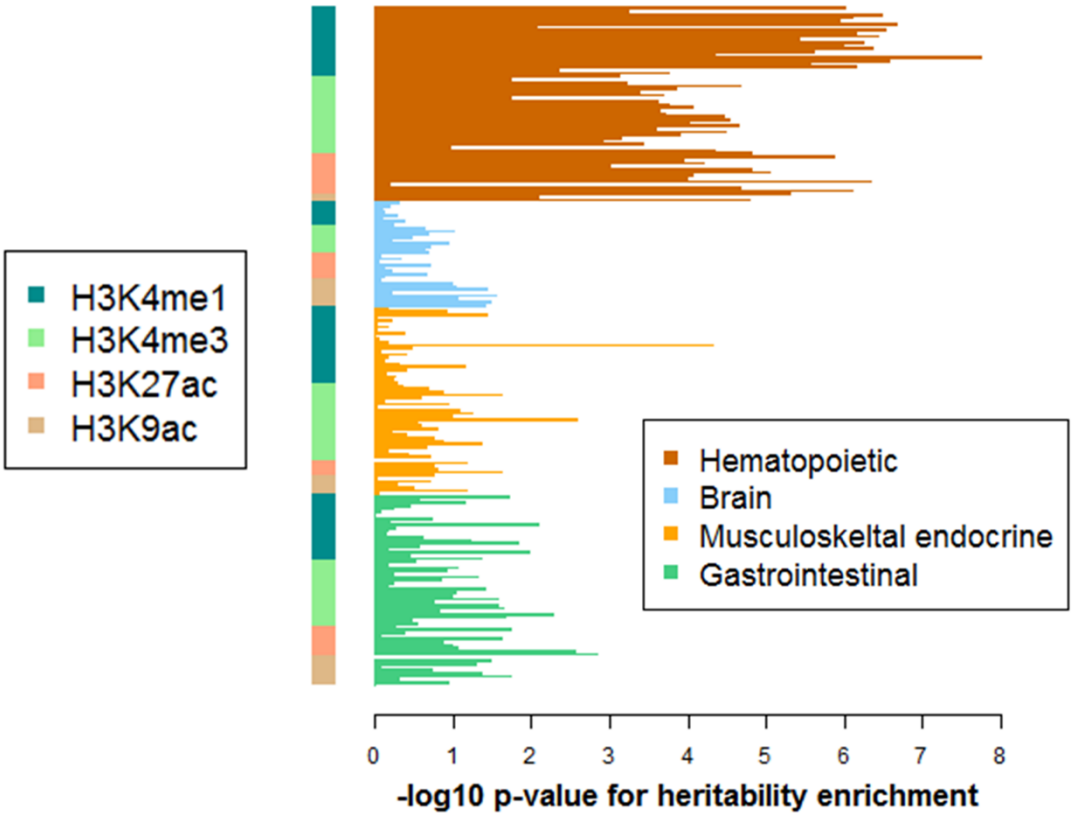
Correlation between LD score bins and mean chi-square statistics in the current study is indicated. The SNPs in the HLA region are excluded from calculation.

Supplementary Figure 3. Heritability enrichment of SLE GWAS statistics found in 10 cell groups.



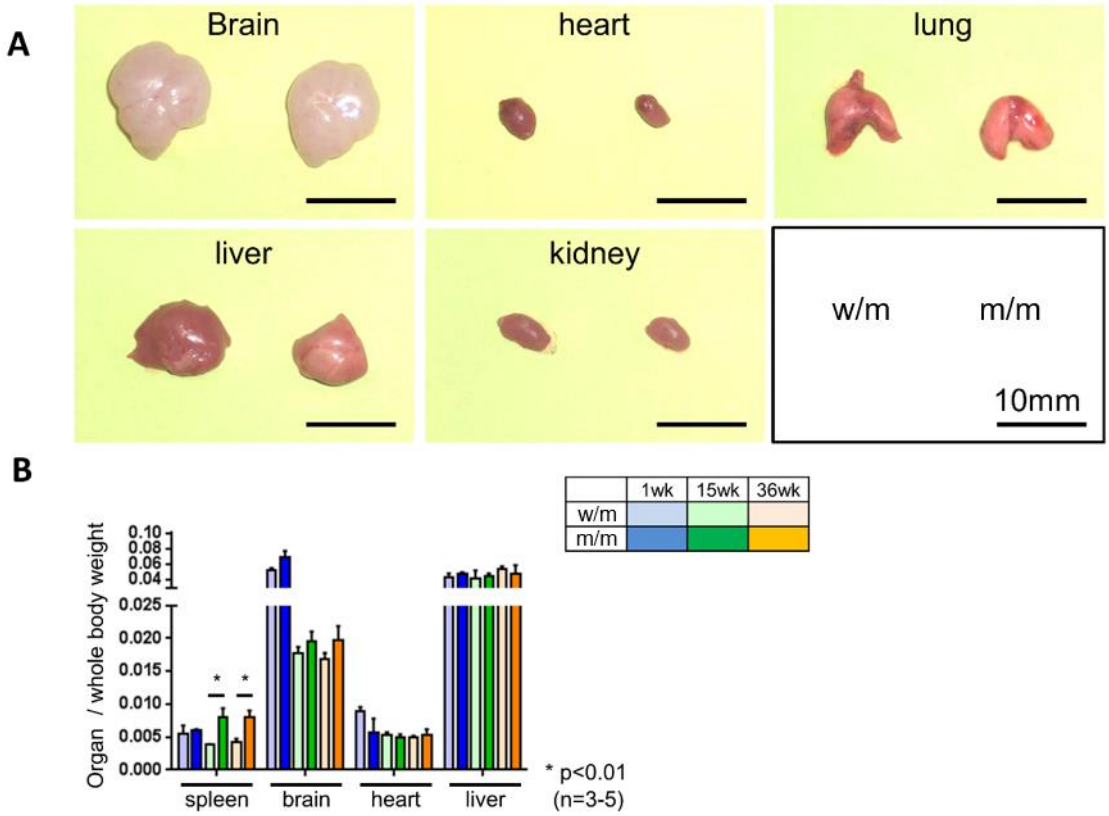
Results of heritability enrichment in cell groups evaluated by LDSC conditioning on basic annotations are indicated.

Supplementary Figure 4. Heritability enrichment in immune cells especially H3K4me1.



Results of heritability enrichment analysis using LDSC for a total of 220 cell types conditioning on basic annotations are indicated.

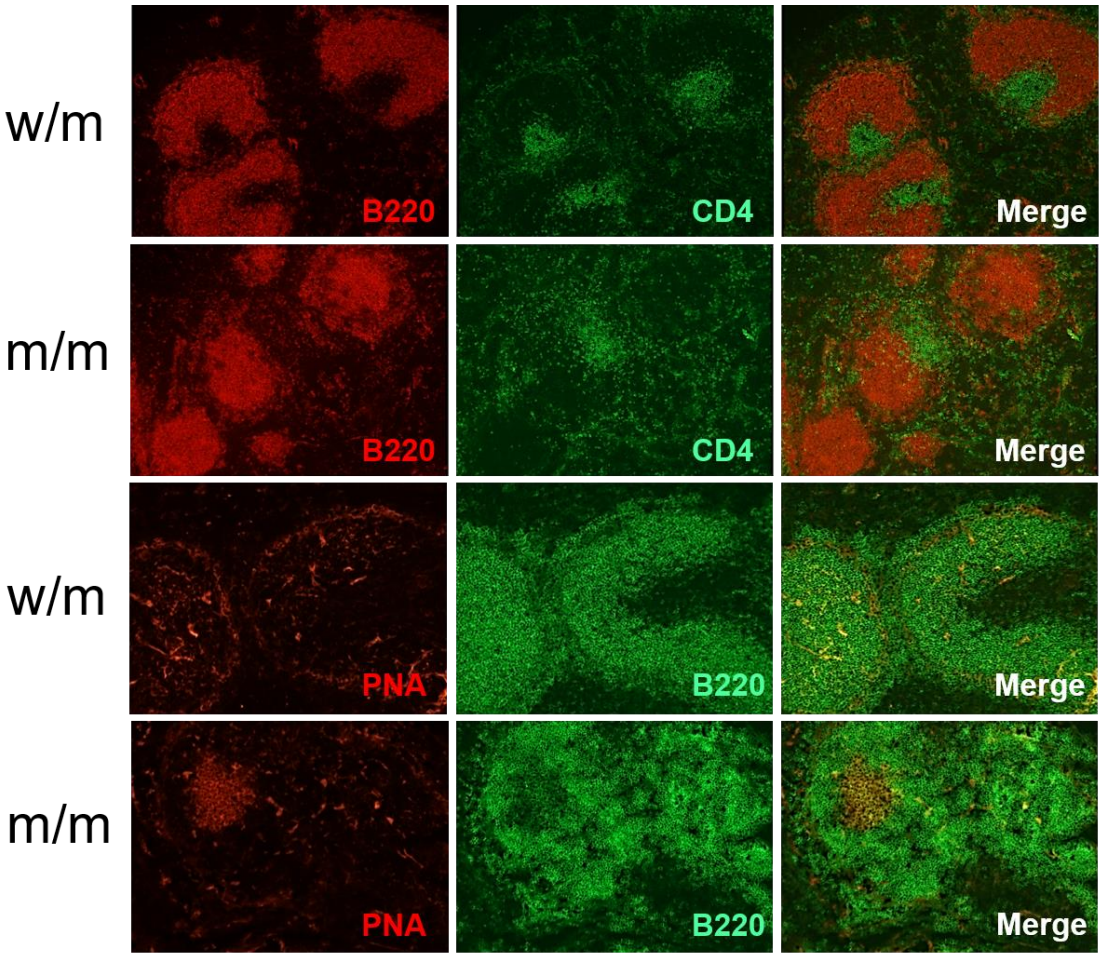
Supplementary Figure 5. No difference in organ size other than spleen and lymph node between mutant mice and heterozygous mice.



A Organs in heterozygous mice and mutant mice are indicated.

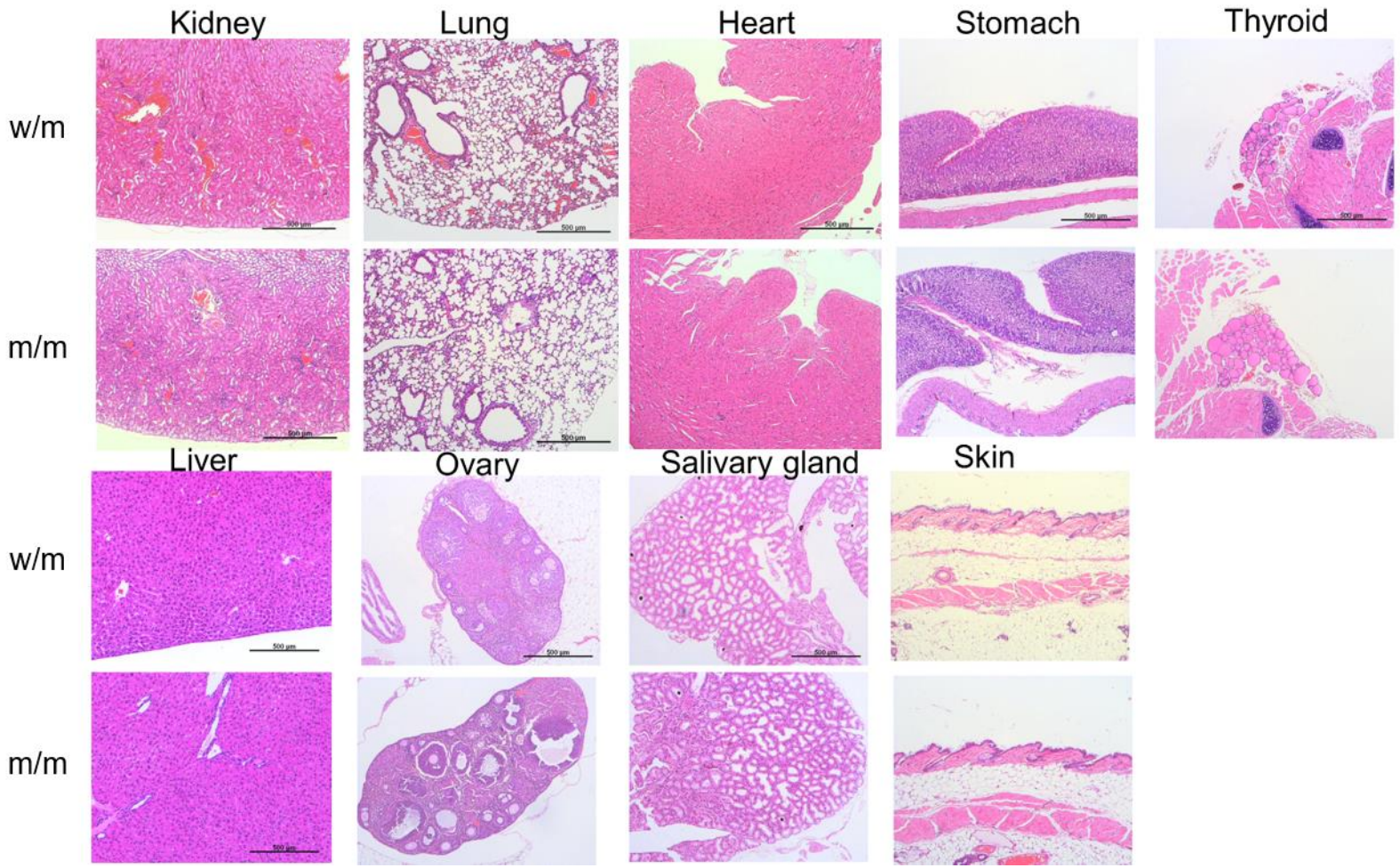
B Proportion of organ over whole body weight is indicated for spleen, brain, heart and liver at 1, 15 and 36 weeks after birth. Data were collected from at least 3 mice, and expressed as mean and S.D.

Supplementary Figure 6. Mutant mice demonstrating specific features in spleen

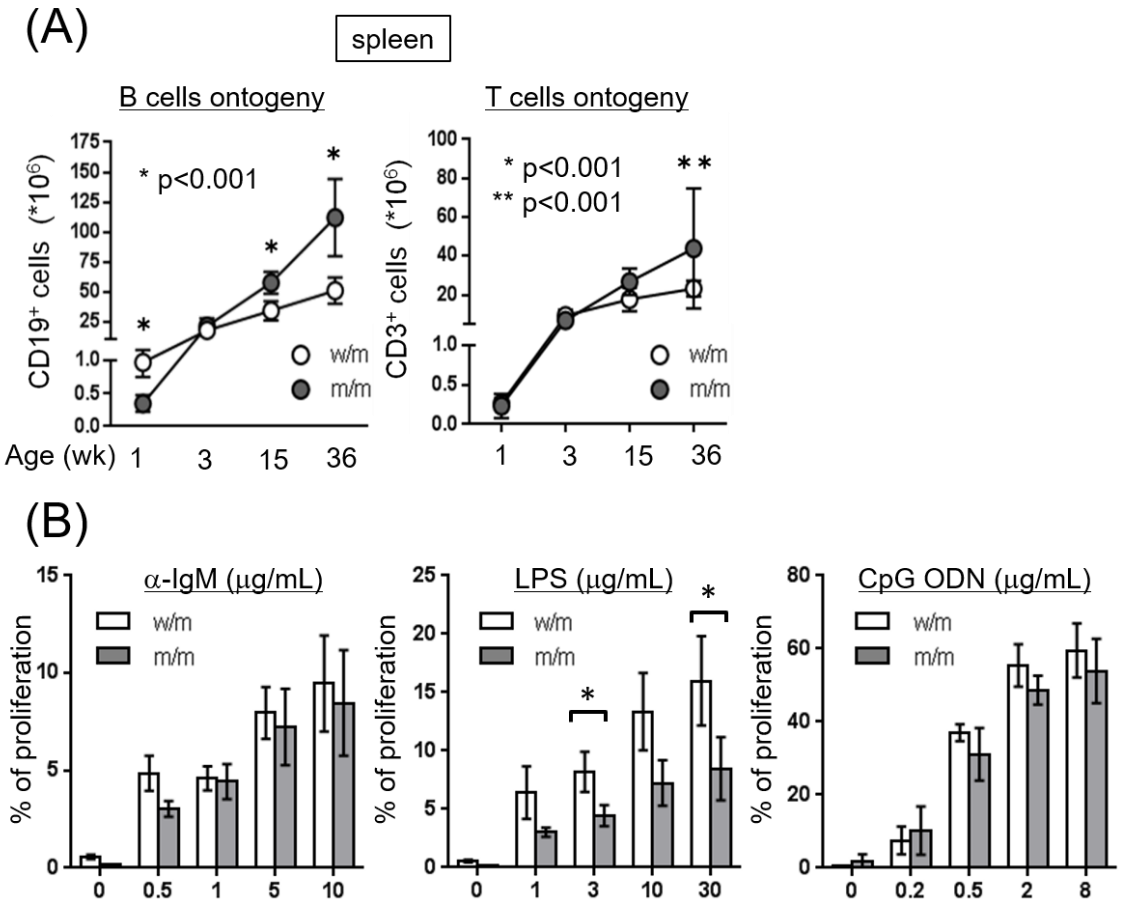


Representative images of spleens from heterozygote and mutant mouse are indicated. Tissue sections were stained with B220 (red) and CD4 (green), or PNA (red), and B220 (green). Altered architectures of splenic white pulp and $PNA^{+}B220^{+}$ cells were noted in the mutant spleens.

Supplementary Figure 7. Histological analysis reveals comparable results between mutant and heterozygous mice for organs other than spleen and lymph nodes.



Supplementary Figure 8. The ontogeny of B and T cells in spleen, and In vitro B cell proliferation assay.

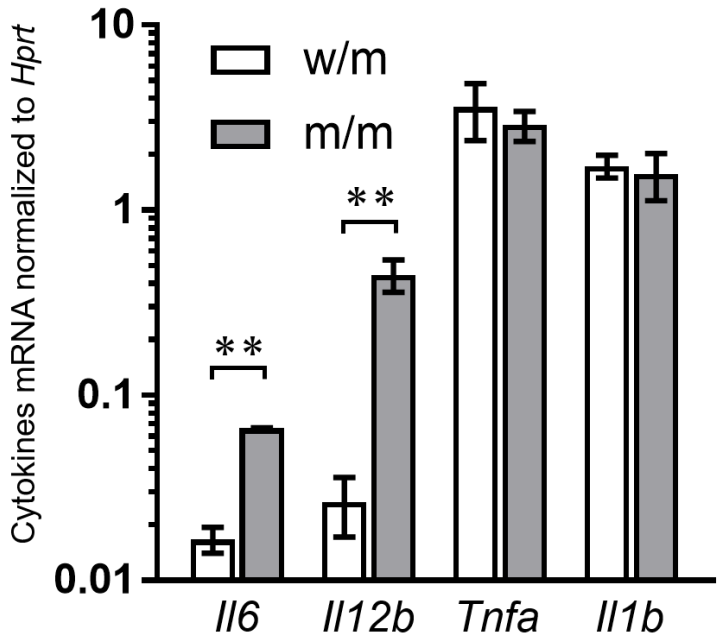


A. The number of CD19$^+$ B cells, CD3$^+$ T cells in spleen Data were collected from at least 4 mice, and expressed as mean and S.D.

B. CFSE labeled purified CD19+ B cell proliferation with indicated doses of anti-IgM (0, 0.5, 1, 5, 10ug/mL), LPS (0, 1, 3, 10, 30ug/mL), CpG ODN2395 (0, 0.2, 0.5, 2, 8ug/mL) were determined at 72 hours by flowcytometry. All experiments were performed with triplicate samples, at least 2 independent experiments, and data were presented as mean and S.D.

* p<0.05, **p<0.01

Supplementary Figure 9. Gene expression analysis of proinflammatory cytokines in spleen.



Supplementary Table 1. Subjects of GWAS meta-analysis of SLE patients

	Case	Control
Study 1		
Number	474	2162
Female Ratio	0.924	0.507
Array	Illumina Human Core Exome	Illumina Human Core Exome
Institution	Kyoto University	Aichi Cancer Center Hospital
Study 2		
Number	889	3374
Female Ratio	0.896	0.445
Array	Illumina HumanHap610-Quad Genotyping BeadChips	Illumina HumanHap550v3 Genotyping BeadChips
Institution	RIKEN	RIKEN

Supplementary Table 2. Criteria of quality controls for samples and SNPs and analyses in the two GWAS.

	Set1	Set2
Samples		
Call Rate	<0.98	<0.98
kinship	PI_HAT>0.25	PI_HAT>0.25
PCA outliers	excluded	excluded
SNP		
Call Rate	<0.98	<0.99
maf	<0.03	<0.01
HWE P	$<1.0x10^{-6}$	$<1.0x10^{-6}$
Rsq	<0.5	<0.5
Analysis		
tool	plink	Mach2dat
covariates	-	PC1-5

Supplementary Table 3. Shared risk alleles between the current study and previous reports in SLE-related loci.

SNP	Chr	Pos	Gene	Risk Allele	Beta	SE	P	Reported Risk Allele	Shared Risk Allele
rs1801274	1	161479745	FCGR2A	G	0.173	0.053	0.0011	G	Y
rs34889541	1	198594769	PTPRC	G	0.166	0.058	0.0040	G	Y
rs2297550	1	206643772	IKBKE	G	0.082	0.044	0.064	G	Y
rs3024505	1	206939904	IL10	A	0.322	0.16	0.044	A	Y
rs9782955	1	236039877	LYST	C	0.186	0.074	0.012	C	Y
rs564799	3	159728987	IL12A	C	0.197	0.084	0.019	C	Y
rs6762714	3	188470238	LPP,	T	0.052	0.057	0.36	T	Y
rs340630	4	87958395	AFF1	A	0.163	0.043	0.00017	A	(Y)
rs10028805	4	102737250	BANK1	G	0.25	0.051	$8.6x10^{-7}$	G	Y
rs7726159	5	1282319	TERT	A	0.172	0.050	0.00055	A	Y
rs7726414	5	133431834	TCF7 SKP1	T	0.284	0.080	0.00042	T	Y
rs10036748	5	150458146	TNIP1	T	0.139	0.049	0.0044	T	Y
rs2421184	5	158886939	IL12B	A	0.166	0.043	0.00013	A	Y
rs2431697	5	159879978	MIR146A	T	0.178	0.058	0.0021	T	Y
rs17603856	6	16630898	ATXN1	G	0.019	0.066	0.78	T	N
rs9462027	6	34797241	UHRF1BP1	A	0.247	0.079	0.0018	A	Y
rs10807150	6	35272274	DEF6	C	0.148	0.045	0.0011	C	Y
rs597325	6	91002494	BACH2	G	0.14	0.043	0.0012	G	Y
rs849142*	7	28185891	JAZF1	T	0.679	0.65	0.30	T	Y

rs73135369	7	73940978	GTF2IRD1-GTF2I	C	0.152	0.095	0.11	C	Y
rs3757387	7	128576086	IRF5	C	0.289	0.059	8.9×10^{-7}	C	Y
rs1887428	9	4984530	JAK2	G	0.099	0.047	0.035	G	Y
rs4948496	10	63805617	ARID5B	T	0	0.047	1.0	C	N
rs12802200*	11	566936	IRF7	C	0.802	0.39	0.042	C	Y
rs2732549	11	35088399	CD44	A	0.139	0.053	0.0082	A	Y
rs2009453	11	65399528	PCNXL3	C	0.145	0.045	0.0014	C	Y
rs494003	11	65542298	RNASEH2C	A	0.051	0.070	0.46	A	Y
rs3794060	11	71187679	DHCR7 NADSYN1	C	0.008	0.046	0.86	C	Y
rs1059312	12	129278864	SLC15A4	G	0.165	0.043	0.00013	G	Y
rs4902562*	14	68731458	RAD51B	A	0.101	0.057	0.076	A	Y
rs12900339	15	38927386	RASGRP1	A	0.167	0.046	0.00027	A	Y
rs2289583	15	75311036	CSK	A	0.109	0.053	0.041	A	Y
rs9652601	16	11174365	CIITA SOCS1	G	0.113	0.059	0.055	G	Y
rs1170426	16	68603798	ZFP90	C	0.158	0.054	0.0032	C	Y
rs2286672	17	4712617	PLD2	T	0.018	0.045	0.68	T	Y
rs1610555	18	67543147	CD226	T	0.151	0.045	0.00081	T	Y
rs2304256	19	10475652	TYK2	C	0.048	0.046	0.29	C	Y
rs2305772	19	52033742	SIGLEC6	G	0.167	0.044	0.00014	G	Y
rs61616683	22	39755773	SYNGR1	T	0.184	0.072	0.011	T	Y
rs1734787	23	153325446	IRAK1 MECP2	C	0.219	0.061	0.00035	C	Y

*Results in one of the two Japanese GWAS due to filtering

Previous SLE loci reported by only a manuscript containing part of the Japanese GWAS are excluded from the results except for AFF1.

Supplementary Table 4. SLE-susceptibility SNPs (84 SNPs including the current 2 SNPs) showed enrichment of enhancer histone marks in immune-related cells.

Cell Type	P-value
Primary B cells from peripheral blood	$<1.0x10^{-6}$
Primary Natural Killer cells from peripheral blood	$<1.0x10^{-6}$
GM12878 Lymphoblastoid Cells	$<1.0x10^{-6}$
Primary monocytes from peripheral blood	$<1.0x10^{-6}$
Primary T helper cells PMA-I stimulated	$<1.0x10^{-6}$
Primary neutrophils from peripheral blood	$<1.0x10^{-6}$
Primary T cells from peripheral blood	$<1.0x10^{-6}$
Primary T CD8+ naive cells from peripheral blood	$<1.0x10^{-6}$
Spleen	$<1.0x10^{-6}$
Primary mononuclear cells from peripheral blood	0.000001
Thymus	0.000001
Primary hematopoietic stem cells short term culture	0.000001
K562 Leukemia Cells	0.000002
Primary B cells from cord blood	0.000003
Brain Inferior Temporal Lobe	0.000003
Monocytes-CD14+ RO01746 Primary Cells	0.000006
Primary T cells from cord blood	0.000007
Primary T CD8+ memory cells from peripheral blood	0.000008
Fetal Thymus	0.000012
Primary T helper memory cells from peripheral blood 2	0.000016
NHLF Lung Fibroblast Primary Cells	0.000025
Primary T helper cells from peripheral blood	0.000026
Primary hematopoietic stem cells G-CSF-mobilized Male	0.000027
Lung	0.000042
Sigmoid Colon	0.000046
Primary T helper naive cells from peripheral blood	0.000047
Fetal Heart	0.000095
Brain Cingulate Gyrus	0.00016
Primary hematopoietic stem cells G-CSF-mobilized Female	0.00018

Mesenchymal Stem Cell Derived Chondrocyte Cultured Cells	0.00019
Brain Angular Gyrus	0.00019
Foreskin Melanocyte Primary Cells skin01	0.00021
NH-A Astrocytes Primary Cells	0.00023
Primary T regulatory cells from peripheral blood	0.00026
Adipose Derived Mesenchymal Stem Cell Cultured Cells	0.00027
Osteoblast Primary Cells	0.00032

Cells showing significant results based on Bonferroni's correction are indicated.

Supplementary Table 5. Heritability enrichment in immune-related cells evaluated by LDSC.

Cell Type	P
CD56_primary_H3K4me1	$1.7x10^{-8}$
CD3_primary_(UW)_H3K4me1	$2.0x10^{-7}$
CD8_memory_primary_H3K4me1	$2.6x10^{-7}$
CD4_memory_primary_H3K4me1	$2.9x10^{-7}$
CD19_primary_(BI)_H3K4me1	$3.2x10^{-7}$
CD4+_CD25-_CD45R0+_memory_primary_H3K4me1	$3.6x10^{-7}$
CD4+_CD25-_Th_primary_H3K4me1	$4.2x10^{-7}$
CD3_primary_H3K27ac	$4.5x10^{-7}$
CD4+_CD25-_IL17-_PMA_Ionomycin_stim_MACS_Th_sprimary_H3K4me1	$5.4x10^{-7}$
CD4_naive_primary_H3K4me1	$6.7x10^{-7}$
CD8_naive_primary_(UCSF-UBC)_H3K4me1	$7.0x10^{-7}$
Th1_H3K27ac	$7.5x10^{-7}$
CD19_primary_(UW)_H3K4me1	$7.6x10^{-7}$
CD14_primary_H3K4me1	$9.3x10^{-7}$
CD4+_CD25-_IL17+_PMA_Ionomycin_stim_Th17_primary_H3K4me1	$1.0x10^{-6}$
CD3_primary_(BI)_H3K4me1	$1.1x10^{-6}$
CD14_H3K27ac	$1.3x10^{-6}$
CD4+_CD25+_CD127-_Treg_primary_H3K4me1	$2.4x10^{-6}$
CD8_naive_primary_(BI)_H3K4me1	$2.6x10^{-6}$
CD4+_CD25-_CD45RA+_naive_primary_H3K4me1	$3.5x10^{-6}$
Th2_H3K27ac	$4.7x10^{-6}$
CD25-_IL17+_Th17_stim_H3K27ac	$8.5x10^{-6}$
CD25-_IL17-_Th_stim_MACS_H3K27ac	$1.4x10^{-5}$
Treg_primary_H3K4me3	$1.4x10^{-5}$
Peripheralblood_mononuclear_primary_H3K9ac	$1.6x10^{-5}$
CD19_primary_(BI)_H3K4me3	$2.0x10^{-5}$
Th0_H3K27ac	$2.1x10^{-5}$
CD4+_CD25+_CD127-_Treg_primary_H3K4me3	$2.2x10^{-5}$
CD4+_CD25-_IL17+_PMA_Ionomycin_stim_Th17_primary_H3K4me3	$2.8x10^{-5}$
CD56_primary_H3K4me3	$3.2x10^{-5}$

CD4+_CD25-_IL17- _PMA_Ionomycin_stim_MACS_Th_sprimary_H3K4me3	3.3×10^{-5}
CD4+_CD25int_CD127+_Tmem_primary_H3K4me1	4.4×10^{-5}
Peripheralblood_mononuclear_primary_H3K4me3	4.4×10^{-5}
Fetal_thymus_H3K4me1	4.7×10^{-5}
CD20_H3K27ac	5.9×10^{-5}
CD4_primary_H3K4me3	8.4×10^{-5}
CD25+_CD127-_Treg_H3K27ac	8.6×10^{-5}
CD4+_CD25-_Th_primary_H3K4me3	9.3×10^{-5}
CD25int_CD127+_Tmem_H3K27ac	9.8×10^{-5}
CD19_H3K27ac	1.1×10^{-4}
CD8_memory_primary_H3K4me3	1.2×10^{-4}
CD19_primary_(UW)_H3K4me3	1.4×10^{-4}
Peripheralblood_mononuclear_primary_H3K4me1	1.6×10^{-4}
CD4_naive_primary_H3K4me3	1.7×10^{-4}
CD4+_CD25-_CD45RA+_naive_primary_H3K4me3	1.9×10^{-4}
CD3_primary_(UW)_H3K4me3	2.0×10^{-4}
CD4+_CD25-_CD45R0+_memory_primary_H3K4me3	2.2×10^{-4}

Significant results based on Bonferroni's correction ($p>0.05/220$) are indicated.

Supplementary Table 6. Pathways shown by PASCAL.

Database	Pathway	empPvalue
REACTOME	IMMUNE SYSTEM	$3.0x10^{-7}$
REACTOME	ADAPTIVE IMMUNE SYSTEM	$3.3x10^{-5}$
BIOCARTA	NO2IL12 PATHWAY	$3.8x10^{-4}$
BIOCARTA	IL12 PATHWAY	$4.6x10^{-4}$
BIOCARTA	IL22BP PATHWAY	$5.7x10^{-4}$
KEGG	LEISHMANIA INFECTION	$7.3x10^{-4}$
BIOCARTA	NFKB PATHWAY	$7.4x10^{-4}$
REACTOME	SIGNALING BY THE B CELL RECEPTOR BCR	$8.6x10^{-4}$
BIOCARTA	CD40 PATHWAY	$9.2x10^{-4}$
BIOCARTA	IL10 PATHWAY	$1.2x10^{-3}$
REACTOME	INTERFERON ALPHA BETA SIGNALING	$1.3x10^{-3}$
KEGG	NOD LIKE RECEPTOR SIGNALING PATHWAY	$1.4x10^{-3}$
BIOCARTA	PARKIN PATHWAY	$1.6x10^{-3}$
REACTOME	ANTIGEN ACTIVATES B CELL RECEPTOR LEADING TO GENERATION OF SECOND MESSENGERS	$1.9x10^{-3}$
KEGG	PATHWAYS IN CANCER	$2.2x10^{-3}$
BIOCARTA	BIOPEPTIDES PATHWAY	$2.3x10^{-3}$
BIOCARTA	EGF PATHWAY	$2.4x10^{-3}$
BIOCARTA	PDGF PATHWAY	$3.1x10^{-3}$
BIOCARTA	TNFR2 PATHWAY	$3.4x10^{-3}$
REACTOME	INTERFERON GAMMA SIGNALING	$4.4x10^{-3}$

Results with p-values less than 0.005 are indicated