Supplemental materials and methods

Supplemental Methods

Information of SLE patients and healthy controls (HCs)

This study was approved by the ethics committees and institutional review board of the Second Xiangya Hospital of Central South University (No.20193044), and all study participants signed a written informed consent. Blood samples were obtained from patients fulfilling the diagnosis of SLE according to the criteria established by the American College of Rheumatology.[1] Lupus disease activity was assessed using the SLE Disease Activity Index (SLEDAI).[2]Age and sex-matched healthy controls were recruited for reasons not related to cancer, cardiovascular diseases, autoimmune diseases or known infectious diseases. The information of SLE patients and HCs are presented in the Supplemental Table S1.

Patient and public involvement

Patients were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Isolation of peripheral $CD4^+$ T cells

A sum of 60 mL of peripheral venous blood from each patient and healthy subject was preserved with heparin. Peripheral blood mononuclear cells (PBMCs) and $CD4^+$ T cells were isolated by density gradient centrifugation (GE Healthcare, Switzerland) and by positive selection using Miltenyi beads (Miltenyi, Germany) respectively. The purity of $CD4^+$ T cells was generally >95%.

Hi-C library preparation

We performed in situ Hi-C with 5-10 million cells. Briefly, Cells were crosslinked at a final concentration of 2% formaldehyde for 10min in room temperature, and quenched by 200mM glycine. After the completion crosslinking and lysis, chromatin was digested with 400 U MboI restriction enzyme (NEB) at 37 °C. DNA ends were labeled with biotin-14-dATP using Klenow large fragment for 45 min at 37 °C overnight and the enzyme was inactivated with 20% SDS solution. DNA ligation was performed by the addition of T4 DNA ligase (NEB) and incubation at 16°C for 4-6 h. After ligation, proteinase K was added to reverse cross-linking during incubation at 65 °C overnight. DNA fragments were purified and dissolved in water. DNA was

treated with T4 DNA polymerase to remove unligated biotinylated ends and sheared to 300-500bp by bioruptor (time on: 15s，time off: 45s，cycle：7), and DNA ends were then repaired. DNA fragments labeled by biotin were separated on Dynabeads® M-280 Streptavidin (Life Technologies) and ligased with adapters. PCR amplification were performed with NEB Next Ultra lI DNA Library Prep Kit for llumina. Hi-C libraries were controlled for quality and sequenced on an Illumina NovaSeq 6000 platform to obtain 150 bp paired-end reads.

Construction of interaction map

The sequencing adaptor and low-quality base were trimmed using Trimmomatic (version 0.38)[3]. Clean Hi-C data were iteratively mapped to the human genome hg19 using the hiclib software package (version 1f8815d0cc9e)[4] and dandling ends and other unusable data were filtered. A Hi-C map is a list of DNA-DNA contacts produced by a Hi-C experiment. The valid pairs after pooling were binned into 100kb, 40kb, 20kb, and 10kb nonoverlapping genomic intervals to generate contact maps. Raw Hi-C contact maps were normalized using an iterative normalization method to eliminate systematic biases.

Compartment A/B analysis

The CscoreTool (v 1.1)[5] software was applied to identify A and B compartments on 100kb resolution. For each individual chromosome, genomic bins with a positive or negative c-score signa were divided into the A or B compartment. The active “A” compartments are gene-dense euchromatic regions, whereas the inactive “B”-compartments are gene-poor heterochromatic regions.

Topologically associated domains (TADs) analysis

The TADs were identified using insulation score algorithm[6] on 40kb normalized contact maps. The border of all the samples were merged as all borders collection. The appearance (as value 1) or not (as value 0) of each border in each sample was used to take PCA analysis with pcomp R package.

Calculation of intra-and inter-chromosome interactions

The contacts between 10kb bins of intra-chromosome and inter-chromosome interactions of each sample were transferred to Ay's Fit-Hi-C software (v1.0.1) (with parameter settings -L 20,000 -U 2,000,000 -p 2 -b 200) [7] to calculate the corresponding cumulative probability P value and false discovery rate (FDR) q value. After calculation, the interactions in which both the P value and q value were less than 0.01, and contact count > 2 were identified as significant interactions.

Loops analysis

Loops were identified using mustache software (v 1.0.2) [8] on 10 kb contact maps with parameter: -pt 0.1 -st 0.88. Loops of all samples were merged as all loops collection. To calculate loops strength, as the figure, the loops were mapping on 20kb z-transferred contact map and merge with same contact. The loop strength is the mean contact value of a 140kb (7 bins) on each side square area with the loop contact at center. The strength of each loop in each sample was used to take PCA analysis with pcomp R package.

RNA-seq library preparation and data analysis

The sorted $CD4^+$ T cells were isolated using a TRIzol (Life Technologies). The total RNA was quantified and qualified by Agilent 2100 Bioanalyzer (Agilent Technologies, CA, USA). A total amount of 1 μg RNA per sample was used and mRNA was purified using poly-T oligo-attached magnetic beads. First strand cDNA was synthesized using random hexamer primer. Second strand cDNA synthesis was subsequently performed using DNA Polymerase I. The library fragments were purified with AMPure XP system (Beckman Coulter, Beverly, USA). The sequencing was performed by Illumina Noveseq.

Raw data of fastq format were firstly processed by removing reads containing adapter, reads containing ploy-N and low-quality reads. And paired-end clean reads were aligned to the reference genome using Hisat2 v2.0.5.[9] The reads numbers were mapped to each gene. And then FPKM of each gene was calculated based on the length of the gene and reads count mapped to this gene. Differential expression analysis of two conditions was performed using the DESeq2 R package[10] (1.16.1). Genes with an adjusted P-value <0.05 found by DESeq2 were assigned as differentially expressed. Gene Ontology (GO) and Reactome pathway enrichment analysis of differentially expressed genes were implemented by R package.[11]

ATAC footprint analysis

The raw ATAC data were filtered to remove reads containing adapter, reads containing ploy-N and low quality. Filtered reads were aligned to refence genomes hg19. The peaks were called using MACS2 [12](v 2.1.1, -f BED --nomodel --shift -75 --extsize 150 -B --SPMR --keep-dup=all). The Transcription factors footprint were analyzed using HINT[13] (v0.13.0).

Quantitative RT-PCR

1μg RNA was extracted from cells infiltrated in TRIzol reagent (Thermo Fisher Scientific). Additionally, cDNA was generated by reverse transcription with a PrimeScript RT reagent kit, following the manufacturer's instructions. The transcript was analyzed for the expression of genes with a CFX96 Touch (Bio-Rad). Primer sequences were listed in Supplemental Table S6.

CRISPR/Cas9 mediated genomic DNA fragment knock out in Jurkat cell line

The Cas9 stably expressed Jurkat cell line was purchased from Yuanjing biology corporation. Each gRNA with chemical modifications comprising 2'-O-methyl and phosphonothioate modifications at 5' and 3' ends was synthesized by GenScript corporation. sgRNA sequences were listed in Supplemental Table S5. Two gRNA (50 pmol) were transfected into 3×10^6 Cas9 stably expressed Jurkat cells in 100 μl opti-MEM solution by Lipofectamine 3000 (Thermo Fisher). After 3 days of culture, the cells were harvested to detect gene expression.

Luciferase reporter assay

Candidate gene promoter and/or promoter looping interaction regions were cloned into the pGL3-basic vector (Promega). Basal gene promoter construct or empty basic pGL3-basic vector were controls. Renilla luciferase plasmid was used as a normalization control. Luciferase reporter activity was measured in 293T cells by the Dual-Luciferase Reporter Assay System (Promega) using a Luminoeter (Promega). The DNA sequences for luciferase reporter assay were shown in Supplemental Table S7

Transfection of SPI1 siRNA

Purified $CD4^+$ T cells were transfected with a Human T cell Nucleofector Kit and an Amaxa nucleofector (Lonza). $CD4^+$ T cells were then resuspended in human T cell nucleofector solution, and SPI1-siRNA was added. SPI1 siRNA and Entransfer-R (Engreen) reagents were prepared by

mixing them with Opti-MEM. Following incubation at room temperature for 5 minutes, the siRNAs and transfection reagents were mixed and incubated at room temperature for 30 minutes. The transfection cocktail was added to each well and cells were incubated at 37°C. The complete medium was replaced after 6 hours.

3C assay

3C experiments were constructed according to previous studies[14]. Briefly, samples were crosslinked with 1% formaldehyde for 10 min and then quenched with 0.125 M glycine at room temperature. The cross-linked samples were subsequently lysed. Endogenous nuclease was inactivated with 0.3% SDS, then chromatin DNA were digested by 100 U Hind III (NEB), and ligated by 50 U T4 DNA ligase (NEB). After reversing cross-links, the ligated DNA was extracted through QIAamp DNA Mini Kit (Qiagen) according to manufacturers' instructions. 3C-qPCR was then carried on the 3C DNA at the regions of interest and normalized to loading controls. Primers used in the 3C assay are listed in Supplemental Table S6.

Chromatin immunoprecipitation PCR

$CD4^+$ T cells transfected with 200nM SPI1 siRNA or negative controls (RiboBio) were isolated for chromatin immunoprecipitation (ChIP) with anti-H3K4me1, anti-H3K4me3 and anti-H3K27ac antibody (Active Motif) and anti-SPI1 antibody（CST）using the ChIP kit (Millipore). The detailed protocol has been described in our previous study.[15] Immunoprecipitated DNA and input DNA were assessed by real-time PCR. The resulting DNA fragments were purified and subjected to PCR with the use of primers encompassing *DDX60L* promoter regions. Primer sequences are listed in Supplemental Table S6.

In vitro Th9 cell differentiation

Naive $CD4^+$ T cells were purified from PBMC cells of health adults and were cultured in the presence of plate-bound anti-CD3 (5μg/mL) plus soluble anti-CD28 (5 μg/mL) and Th9-polarizing cytokines TGF-β (5 ng/mL) and IL-4 (10 ng/mL). Cell cultures were transfected with control siRNA (si-NC) and SPI1 siRNA (si-SPI1) respectively. After 3 days of culture, the cells were harvested for subsequent analysis.

Statistical analysis.

Statistical analyses were performed in the SPSS 25.0 software. All data are presented as the mean ± S.E.M. All statistical analyses were calculated using paired or unpaired two-tailed Student's *t* test, unless otherwise mentioned. Asterisks define the significance level (*P < 0.05; **P < 0.01; ***P < 0.001).

Supplemental Tables

Table S1. Demographics and characteristics of subjects

Demographics	SLE1	SLE2	SLE3	SLE4	SLE5	SLE6	SLE7	HC1	HC2	HC3	HC4	HC5
Sex	F	F	F	F	F	F	F	F	F	F	F	F
Age (years)	31	19	43	38	41	32	58	26	37	40	29	35
SLEDAI-2K score	4	13	20	8	6	6	0	-	-	-	-	-
course (months)	2	18	185	96	126	5	100	-	-	-	-	-
Clinical manifestations												
Proteinuria	+	-	+	+	+	-	-	-	-	-	-	-
Alopecia	-	+	+	+	-	-	-	-	-	-	-	-
Arthritis	-	-	-	-	-	+	-	-	-	-	-	-
Rash	-	-	-	-	-	+	-	-	-	-	-	-
Laboratory tests												
C3, g/L	0.31↓	0.43↓	0.47↓	0.78	0.65↓	0.62↓	1.17	-	-	-	-	-
C4, g/L	0.28	0.07↓	0.13	0.18	0.19	0.48	0.27	-	-	-	-	-
ANA	+	+	+	+	+	+	+	-	-	-	-	-
Anti-dsDNA	-	+	+	-	-	+	-	-	-	-	-	-
WBC, $*10^9$/L	15.47↑	2.2↓	5.36	10.5↑	9.02	3.67↓	7.52	-	-	-	-	-
RBC, $*10^{12}$/L	4.97	3.67	4.51	3.98	3.76	4.03	4.29	-	-	-	-	-
HGB, g/L	145	114	135	121	120	115	139	-	-	-	-	-
PLT, $*10^9$/L	300	125	227	219	210	243	129	-	-	-	-	-
Treatment												
Glucocorticoid dose, prednisolone(mg /day)	50	10	10	20	10	0	10	-	-	-	-	-
Immunosuppressor (CTX or Tacrolimus)	-	-	-	+	+	-	+	-	-	-	-	-
HCQ	+	+	+	+	-	+	+	-	-	-	-	-

SLEDAI: SLE Disease Activity Index, C3: complement 3, C4: complement 4, ANA: anti-nuclear antibody, WBC: white blood cell, RBC: red blood cell, HGB: hemoglobin, PLT: blood platelet, HCQ: hydroxychloroquine, CTX: Cyclophosphamide.

Table S2. Samples data information

Sample ID	Hi-C data (raw reads)	RNA-seq data (raw reads)
HC1	2,378,413,632	-
HC2	1,985,010,151	92,328,206
HC3	1,570,793,350	-
HC4	1,637,397,857	85,430,604
HC5	2,004,764,210	102,037,078
SLE1	2,326,628,278	91,302,090
SLE2	2,255,780,626	-
SLE3	1,794,534,212	-
SLE4	2,076,796,696	89,617,234
SLE5	1,999,428,313	-
SLE6	2,149,074,761	-
SLE7	2,255,088,114	89,468,246

Table S3. Loops that strength correlated with SLEDAI overlap DEG. (Excel file)

Table S4. Loops that strength correlation with other clinical parameters of SLE patients. (Excel file)

Table S5. GO and pathway enrichment analysis in SLE looping associated genes. (Excel file)

Table S6. Primer sequences and sgRNA sequences

Sequence name	**Sequence (5' to 3')**
RT-qPCR primers	
β-actin-F	CATGTACGTTGCTATCCAGGC
β-actin-R	CTCCTTAATGTCACGCACGAT
SPI1-F	GTGCCCTATGACACGGATCTA
SPI1-R	AGTCCCAGTAATGGTCGCTAT
DDX60L-F	AAAGCCTCATACAACACTTGGAA
DDX60L-R	CCGATCCTTCTGACCATAGGTG
LTBP1-F	GCGATGAGTTGAACAACCGGATGTC
LTBP1-R	TCAAGGCGGTATTCATCGGAGTGC
CXCL13-F	GAGGCAGATGGAACTTGAGC
CXCL13-R	CTGGGGATCTTCGAATGCTA
SLC8A-F1	ACAACATGCGGCGATTAAGTC
SLC8A-R1	GCTCTAGCAATTTTGTCCCCA
IFIT1-F	TTGATGACGATGAAATGCCTGA
IFIT1-R	CAGGTCACCAGACTCCTCAC
ATG5-F	GCAGATGGACAGTTGCACACAC
ATG5-R	GAGGTGTTTCCAACATTGGCTCA
HDC-F	CAACTTCTCACTCCGAGGG
HDC-R	GTTGCACAGACAAAGACGG
FCER1A-F	AGTCTTCAGTGACTGGCTG
FCER1A-R	TACACATCCCAGTTCCTCC
IL9-F	CTCTGTTTGGGCATTCCCTCT
IL9-R	GGGTATCTTGTTTGCATGGTGG
IRF1-F	CTGTGCGAGTGTACCGGATG
IRF1-R	ATCCCCACATGACTTCCTCTT
ETV5-F	TCAGCAAGTCCCTTTTATGGTC
ETV5-R	GCTCTTCAGAATCGTGAGCCA
BATF-F	TATTGCCGCCCAGAAGAGC
BATF-R	GCTTGATCTCCTTGCGTAGAG
FOXO1-F	TCGTCATAATCTGTCCCTACACA
FOXO1-R	CGGCTTCGGCTCTTAGCAAA

NFATC2-F	GAGCCGAATGCACATAAGGTC
NFATC2-R	CCAGAGAGACTAGCAAGGGG
ChIP-qPCR primers	
DDX60L promoter loci 1-F	AAGGCTTTCCATATACATGCCCA
DDX60L promoter loci 1-R	ACCATTTTATTCACTGGGTCATCC
DDX60L promoter loci 2-F	TCTTAACTCCTTTAGCCACCAACT
DDX60L promoter loci 2-R	GCCTTGCTCAACAGATAATTCAGG
DDX60Lpromoter-SpiI ChIP-F	AGGCCTTTTCGATTTCCGCA
DDX60Lpromoter-SpiI ChIP-R	TGCTTAGCGTGCTGCATTTAC
sgRNA sequence for CRISPER-Cas9	
DDX60L-enhancer1-left	TCAGCGTTAGCACTAGCCGCAGG
DDX60L-enhancer1-right	ACGACACCCTTCGCGATGAATGG
DDX60L-enhancer2-left	TAGGAGTCTGAGTAGCCGCAGGG
DDX60L-enhancer2-right	TATGAATCTACTGCGAGCTCAGG
CXCL13 enhancer-left	AAGCATTACTGACCAGTACT GGG
CXCL13 enhancer-right	GGCCACATGAATACCAACAC TGG
3C-qPCR primers	
P	GGGTATGAACCATCCTGAGGCA
A	GGACCCCAATAGCTCAGCTT
B	GGCACAGATATTTTCACAGCCAT
C	CCTATTTGCTGACTTCCCATCAAGT
D	GCGACTTTGATGCTTGCTTTCACTT
E	GACTTGCCTAAGGTTACACAGCTAGT
F	GAACATACTCGGGCTTTGTCAA
G	GCCTATGCAAGCCTTTTAGCAAT
GAPDH-R	CCACATCGCTCAGACACCAT
GAPDH-F	CCCGCAAGGCTCGTAGAC

Table S7. The inserted DNA sequences in luciferase reporter vector

Target regions	Position	DNA sequences
DDX60L promoter	GRCh38 chr4:168480520-168481202	CTAGGGAGTTAGTTTCGGTTTCTTTTCTCCACCGCGAGGCCT TTTCGATTTCCGCAGTTTTCTGGAGGTAGAATATAGGTCTGC ATTGGTTTACTCTGAGAATCTTAGGGAAGTAATAGTAGAAG CGATGATATGCTATCTGGGACATGCATGTAATTGTAAAGGG AAAGAAAGCAGAGAAATCTGGGACTCTAAACAAGGAATTG AGGCTGAGAGTAAATGCAGCACGCTAAGCACTATGAAAGTC TGCGGTGAGGTGTGGCGTTTTTCTTTTCTGGCAAGGTACTGG ACAGGCAAAAATGGAGTAAAAAAGGATTAGGGGCTTTGAG TTTCTGTCCTAAGAAGTTCATTTTATGAAAAATTTCCAATAG TATAACTGTCCAGTGTGAACATTTGAAAGACCAATCATCTAT CACAGAGAATTTAAATTGAGAAGAAGAATGCTCTTTAGTTT TGTCATCAAGCTCATTAATGTTTGAAATTCGAGTTTCAACCC CAGCCCATCATGGTCTTTAGTGCTCCAGACGCTTAATTCCAT GACGTTATGCATGTGCAGAATATATTGAGATTCAAGGTGGT GGTGAGGGTGCCCCAGTAACGGCATGGGGTAATAAATGGA GAGAAATCGAAACCGGAAGTTCTGTCTTCAAGAAAAGGAA AGGGTGGAAGTGACTTGTTCACA
DDX60L enhancer	GRCh38 chr4:169009969-169010486	TTTGGCCCCTTCCAGGTTTCTGGCAATGACCGCCAGTCGGTA GCCTTTCCGGGCCATTAACTGGGCCACAGCTCTGCCAATGCC TCGGGAGCCTCCAAAAACAGCACACACTTTGTCCATCTCGG AGTCACAAACTCGGAGGAAAGAGGGTAGGGAGTGGGAGCC CCTCTCCAGGTTCCCTCAGGCTTTTAAACAACCGCGGTTCCA AAAAAAAAAAAAAAGAAAAAAAAAGGCAAACCGCAAAAAA AAATAACGCCGCTCGACACCTCCTGCAGCCGCACAATAGTA ATGCAAGACGCCGTGAAAAGGAGGAAGAGCTCGACGTCGC CGCGTCGACGTCATCACGCACGGACTCTTCCGCGCCACACC TAACAAATACGCCGACGAGAGCTCCCCGCCGGCGGAAGAAT GGCCTGGAGAGGGCCTCGATGCTTGCTGGGACCTGTAGTCT TGACGCATGAGAGCAACTGGCGCAGGCGCGCTGCTCGGTGG GGAATGTACTTGTGGCACTGAGGGGG
CXCL13 promoter	GRCh38 chr4: 77601816-77602542	TTACTGATACTGGTGGCCTGGGGAAGTTAACAAGGCAAATA AGTGTTGGAGTCGGGATACAAACCGAGCCAGTCTGATTTCA GAGCCTGAGCTCTCACCTCCAAGGTTATAATACTTTTCTATT GTGCTGAAAGTTATGTGGGAGCAAACAGATGTCAGATGTTC AGCAGGTTAAAACATGTGTTAACAGGATACAGTAAGTTTCT GTTTTCTAGTTGAGTGGCATGAAAGAAAATGTTCTCAATTGT ATCACAGTGACATTTGTCCTATCTCTTACTACAAACTACTTT ATTTAATCACTGTGAAACTCTACCGTTAACTCTCTGTTTAAT ACCTGTTGACTACCTAGATTGTCAGATACTTTGTCCAATTAT GCCATCTCACTGTTTTAGTGACATTTCACTTTTTGATATCTTG AGAGAGAGTTTCCTTCTTGTCACTGCTCTGCATTTAGATGTC AGTGAGTACTGACATCTACAGTGGATGTGTCCTGTCCACTTT TACTAAAATAAGGTATCTATGCATCATTTTCTGAGGAAATGT CTTGTCCAAACATATCTCTGAAGATAATTTGAATGTGCATAA TATCTTTATCCAGAAATAGCATGCCACAGCAAACTATGCAG CTTATGTTAGACCAGGCCCATGCATTCAAACCACCTGAGAA TCTCGTTGAATGCAGGACCTGAGATTCTACATTTTAAACTAG CTCTCGGGTGAAGTTAA
CXCL13 enhancer	GRCh38 chr4:77384967-77385764	GGGCTATGCCTGCATGTTCTGGGGGAGTGCTAGTGAGCCAT ATTTGGTGTTATGGGTTATGGAATAGGATATCACTGTTCTGT GGCACAGCTATACATTCTATATTTTGCTTCTAAATTGATCAT CTTTTATATTGTGGGGCAGGCAAGTGTGTAAGTTAGAGCCTT

		GACCTTGGTAAAGGTTGCTTGGCACTTGGCACTTTGTTTTTT GGGGAACCAAGAGTTTATTTCTGCTTTTTAATCAGGGACTCA CTCAACAGAGGTCTCCATGTGAAAGCAAGTCTGTACTAAAA AGCTAAACAGCACTTCTGTGGACCTCTCAGTGGTTATTTGAT TGGATGGCTCAAAGTGTATCAGATCATGAGTTTAACTTCCTG TATGAGGGAGATGGCTTTAGAGTCCAGGATGAGGTATCTGA GACCACAGGACACTGCTAGAAACTGACTCGCTGACTTCTAT GCTTCACGAGATATGAGTGGTCTTGTGCATCCCTCCCAGGGT TTCTGGAAGTGCATGTGGGGTGTGAAAGAATCAGACAAGTC CCAAAGGTAAACTGCCAGGGCAGAAACTCTGAAACCTGATT CACTGTGTTGGCCAGAAGAGGGCAGCACTCACACAGCAGAA CAACTTTACGCATTCAGTGACTTCAAGGAGGATCCATACTC AGAGCCAACGATCCCTGAGAAAGCCTGGAGAGGGGTTGGG GCCTCAAATGAGCAGCTTCTTAGTGATGTTTCTGGGAAGAA AGAATGGACAAGTGAGTGGCCTCTTGGCCTGATAAGTACTT TGCACTAAAAGA

Figure S1. Gene expression difference between SLE patients and health controls before excluding SLE7 and HC5.

(A)The Correlations between the six samples.

(B)Heat map represent different expressed genes between SLE patients (SLE1, SLE4, SLE7) and health controls (HC2, HC4, HC5).

Figure S2. SLE loops were identified by SLEDAI scores and gene expression profile.

(A)The distribution of Pearson correlation coefficient between loop strength and SLEDAI score. red bars indicate positive correlation loops (Pearson value > 0.6), green bars indicate negative correlation loops (Pearson value < -0.6).

(B) GO functional enrichments of the genes overlapped with loops (241 in all) which strength high correlated (both positive and negative) with SLEDAI score.

(C)The percentages of loop interaction type from 391 SLE associated loops.

(D) Heat map showing relative gene expression of DEGs genes from $CD4^+$ T cell RNA-seq data of SLE in this study and public GEO dataset (GSE97263).

(E) RT-qPCR results of SLE associated gene expression in $CD4^+$ cells of SLE (n=18) and HCs (n=18). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ by unpaired two-tail Student's *t* test.

Figure S3. Long term interaction around gene *DDX60L*

(A) Relative luciferase activity was measured in 293T cells transfected luciferase reporter vector containing *DDX60L* promoter region with or without promoter looping interaction regions. The results are normalized to internal Renilla activity.

(B) RT-qPCR analysis showing the relative *DDX60L* mRNA level in Jurkat cells, which were transfected with 2 pairs of sgRNA targeting *DDX60L* looping interaction regions, respectively. *** $P < 0.001$ by paired two-tail Student's *t* test.

(C)ChIP-qPCR analysis of the enrichment of SPI1 bound to the *DDX60L* promoter from $CD4^+$ T cells transfected with SPI1 siRNA or negative control. * $P < 0.05$, ** $P < 0.01$ by paired two-tail Student's *t* test.

(D)Seven primer pairs used for the 3C assay are shown on the diagram. Promoter primer of *DDX60L* is used as an anchor primer (corresponding to P), the primer from *DDX60L* promoter looping regions are marked with "E", and another primers are used for control sites, where

locates at points A, B, C, D, F and G.

(E) Normalized 3C signal ratios were calculated for the *DDX60L* promoter looping interaction (indicated as E) after control siRNA (si-NC) or SPI1 siRNA (si-SPI1) transfected $CD4^+$ T cells. Six regions (A, B, C, D, F, G) were used as an internal genomic control. * $P < 0.05$ by paired two-tail Student's *t* test.

(F) RT-qPCR results of Th9 associated gene expression in $CD4^+$ T cells of SLE (n=18) and HCs (n=18). * $P < 0.05$, ** < 0.01 by unpaired two-tail Student's *t* test.

(G)mRNA expression of Th9 cell-related genes determined by RT-qPCR in Th9 cell differentiation treated with control siRNA (si-NC) and SPI1 siRNA (si-SPI1) respectively. * $P < 0.05$ by unpaired two-tail Student's *t* test.

Figure S4. Long term interaction around gene *CXCL13*.

(A)Genomic features of localize region of gene *CXCL13*. From the top, genomic coordinates, ChIP-seq peaks of H3K4me1, H3K4me3 and H3K27ac in activate $CD4^+$ T cell from public data, Gene location (gene are marked with red), the loops that strength correlated with SLEDAI score and gene expression.

(B)Difference chromatin interaction map of *CXCL13* localized region. The 20kb binned heatmap depicting the Z-score difference between health controls (different rows) and SLE patients (different columns) are shown. The gene is marked at the bottom.

(C)Gene expression level of *CXCL13* in samples of HC2, HC4, HC5, SLE1, SLE4, and SLE7.

(D)Loop strengths of the two loops in all the samples. The points size reflects the SLEDAI scores.

(E)Relative luciferase activity was measured in 293T cells transfected luciferase reporter vector containing *CXCL13* promoter region with or without promoter looping interaction regions. The results are normalized to internal Renilla activity. ** < 0.01 by unpaired two-tail Student's *t* test.

(F)RT-qPCR analysis showing the relative *CXCL13* mRNA level in Jurkat cells, which were transfected with a pair of sgRNA targeting *CXCL13* promoter interaction regions. * < 0.05 by unpaired two-tail Student's *t* test.

Figure S5. Long term interaction around gene *SLC8A1-AS1*.

(A) Genomic features of localize region of gene *SLC8A1-AS1*. From the top, genomic

coordinates, ChIP-seq peaks of H3K4me1, H3K4me3 and H3K27ac in activate $CD4^+$ T cell from public data. Gene location (gene are marked with red), the loops that strength correlated with SLEDAI score and gene expression.

(B)Difference chromatin interaction map of *SLC8A1-AS1* localized region. The 20kb binned heatmap depicting the Z-score difference between health controls (different rows) and SLE patients (different columns) are shown. The gene is marked at the bottom.

(C) Gene expression level of *SLC8A1-AS1* in samples of HC2, HC4, HC5, SLE1, SLE4, and SLE7.

(D)Loop strengths of the two loops in all the samples. The points size reflects the SLEDAI scores.

Figure S6. Long term interaction around gene *DNAJB4.*

(A)Genomic features of localize region of gene *DNAJB4*. From the top, genomic coordinates, ChIP-seq peaks of H3K4me1, H3K4me3 and H3K27ac in activate $CD4^+$ T cell from public data, Gene location (gene are marked with red), the loops that strength correlated with SLEDAI score and gene expression.

(B)Difference chromatin interaction map of *DNAJB4* localized region. The 20kb binned heatmap depicting the Z-score difference between health controls (different rows) and SLE patients (different columns) are shown. The gene is marked at the bottom.

(C) Gene expression level of *DNAJB4* in samples of HC2, HC4, HC5, SLE1, SLE4, and SLE7.

(D)Loop strengths of the two loops in all the samples. The points size reflects the SLEDAI scores.

Figure S7. Long term interaction around gene *CASP5*.

(A)Genomic features of localize region of gene *CASP5*. From the top, genomic coordinates, ChIP-seq peaks of H3K4me1, H3K4me3 and H3K27ac in activate $CD4^+$ T cell from public data, (B)Gene location (gene are marked with red), the loops that strength correlated with SLEDAI score and gene expression.

(C)Difference chromatin interaction map of *CASP5* localized region. The 20kb binned heatmap depicting the Z-score difference between health controls (different rows) and SLE patients (different columns) are shown. The gene is marked at the bottom.

(D)Gene expression level of *CASP5* in samples of HC2, HC4, HC5, SLE1, SLE4, and SLE7. Loop strengths of the two loops in all the samples. The points size reflects the SLEDAI scores.

Figure S8. Local genomic 3D features around SLE risk SNP rs2732549.

(A)Chromatin interaction map of rs2732549 localize region of all the samples. the rs2732549 is indicated at the bottom.

(B)Difference chromatin interaction map of rs2732549 localized region. The 20kb binned heatmap depicting the Z-score difference between health controls (different rows) and SLE patients (different columns) are shown. rs2732549 is indicated at the bottom.

(C)Genomic features of localize region of rs2732549. From the top, genomic coordinates, ChIP-seq peaks of H3K4me1, H3K4me3 and H3K27ac in activate $CD4^+$ T cell from public data, gene location, gene expression difference between SLE patients and health controls. Red mean upregulation in SLE sample, blue mean downregulation in SLE sample. The color reflects the log base 10 of interaction's p-value.

Figure S9. Local genomic 3D features around SLE risk SNP rs2245214.

(A)Chromatin interaction map of rs2245214 localize region of all the samples. the rs2245214 is indicated at the bottom.

(B) Difference chromatin interaction map of rs2245214 localized region. The 20kb binned heatmap depicting the Z-score difference between health controls (different rows) and SLE patients (different columns) are shown. rs2245214 is indicated at the bottom.

(C)Genomic features of localize region of rs2245214. From the top, genomic coordinates, ChIP-seq peaks of H3K4me1, H3K4me3 and H3K27ac in activate $CD4^+$ T cell from public data, gene location, gene expression difference between SLE patients and health controls. Red mean upregulation in SLE sample, blue mean downregulation in SLE sample. The color reflects the log base 10 of interaction's p-value.

Supplemental Figures

Figure S1. Gene expression difference between SLE patients and health controls before excluding SLE7 and HC5.

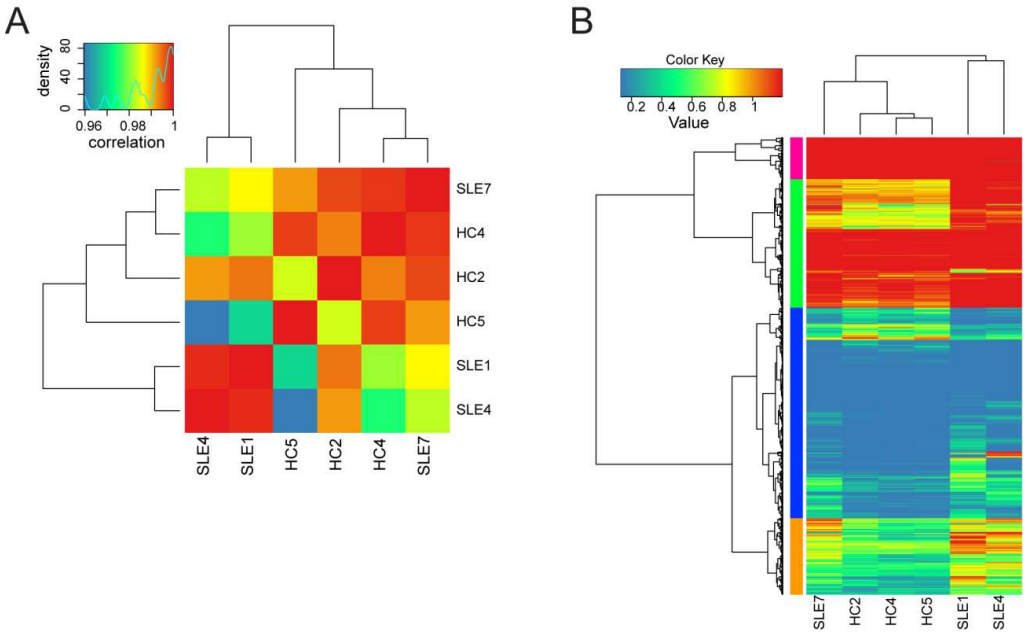


Figure S2. SLE loops were identified by SLEDAI scores and gene expression profile.

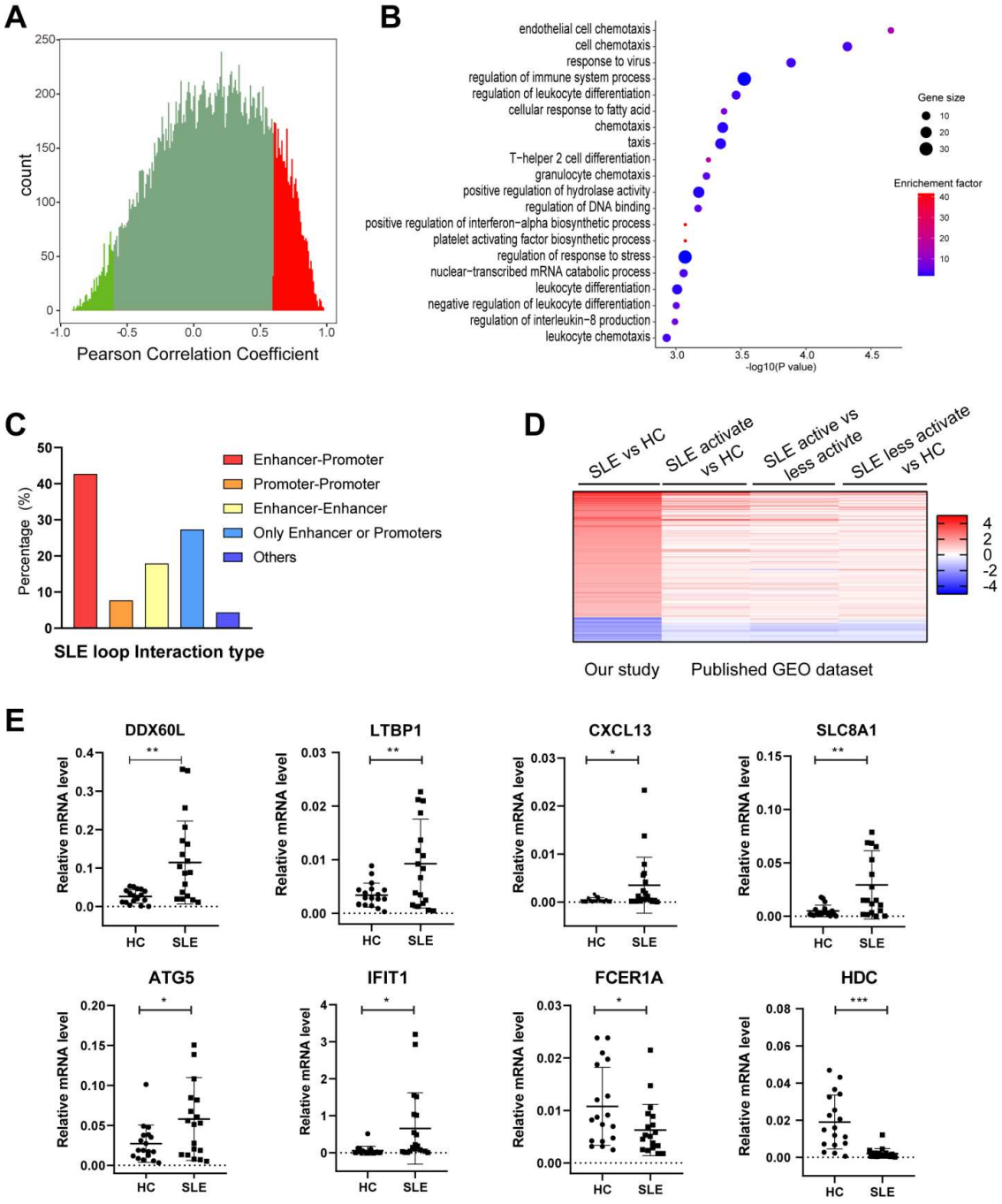


Figure S3. Long term interaction around gene *DDX60L*

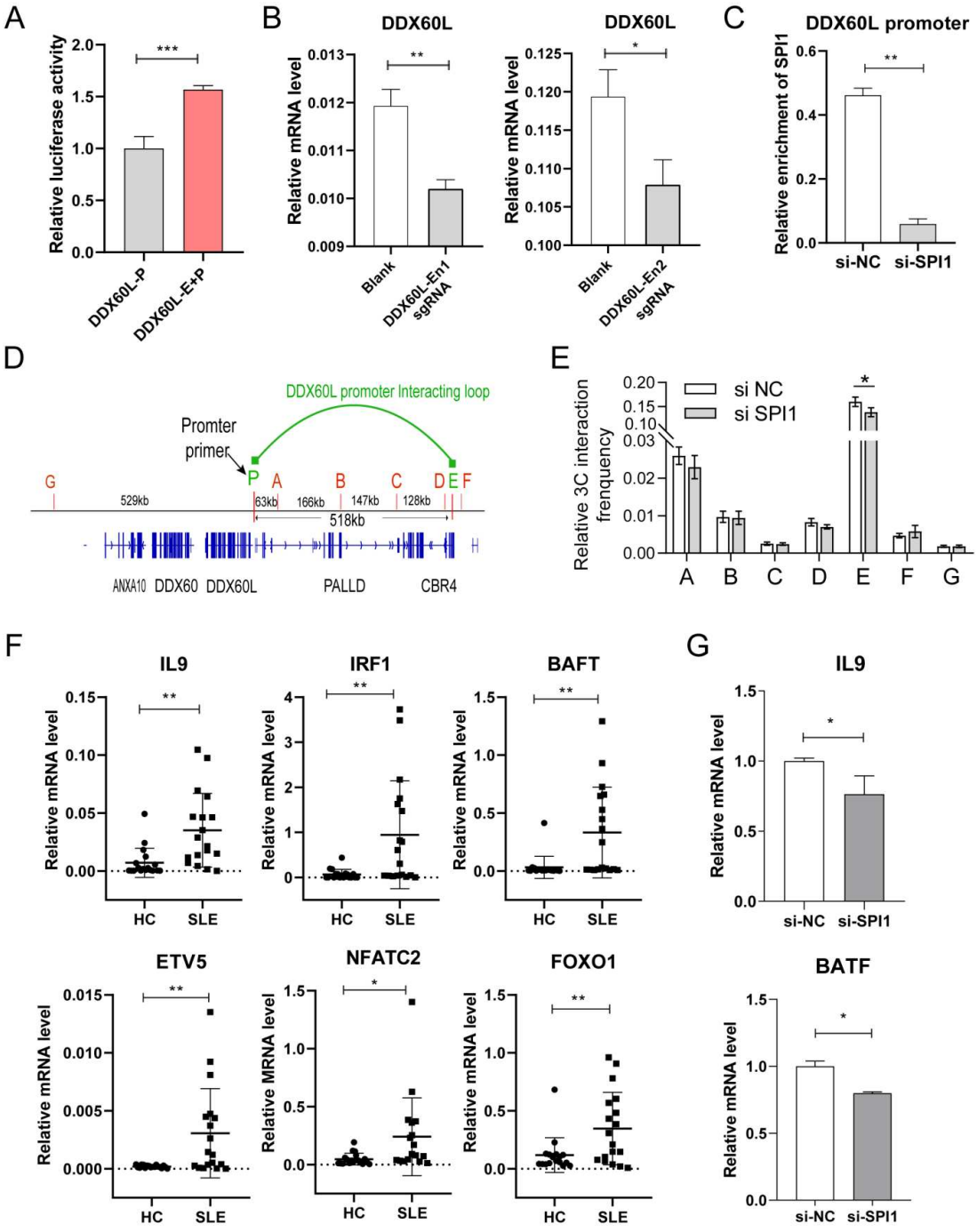


Figure S4. Long term interaction around gene *CXCL13*.

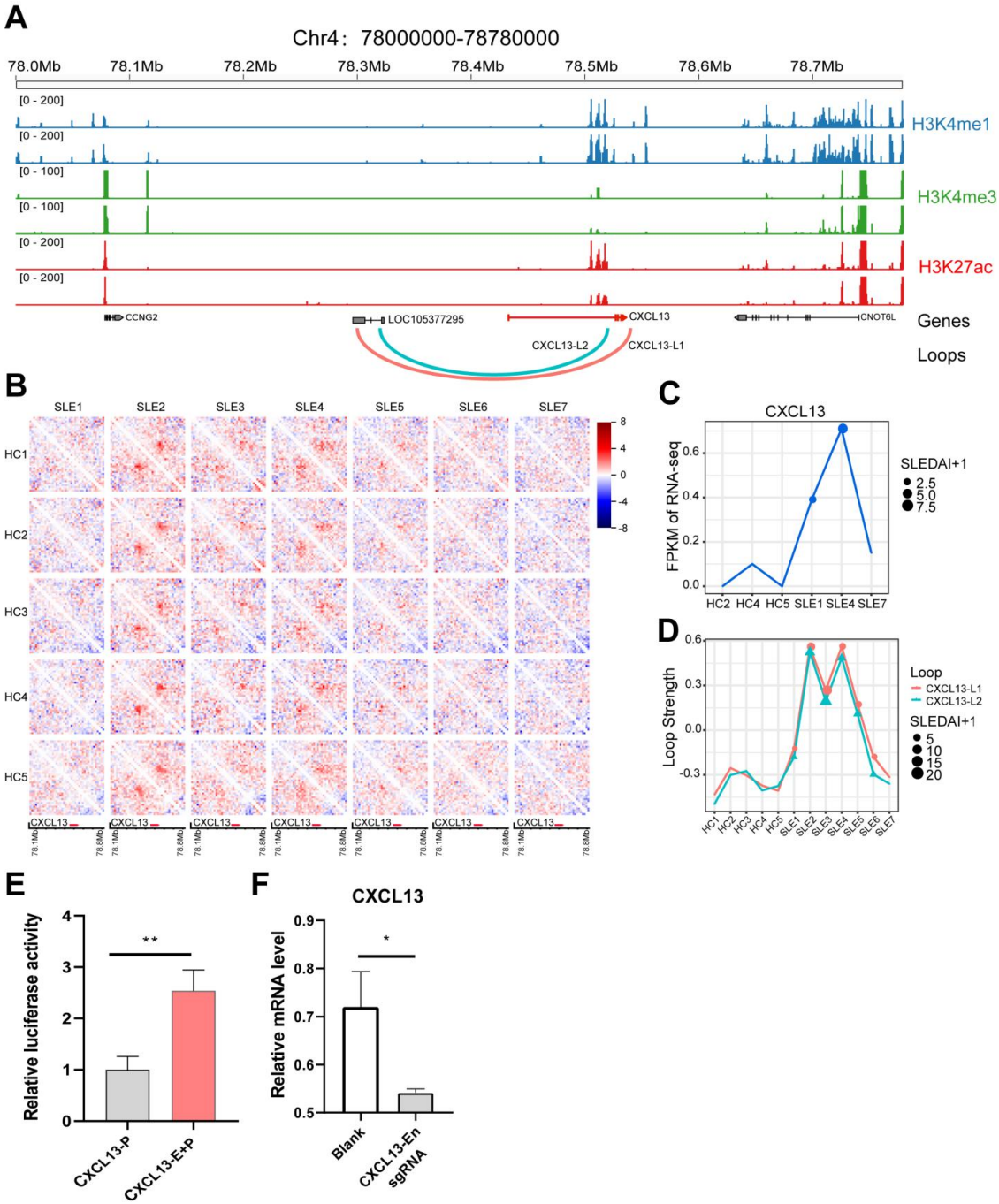


Figure S5 Long term interaction around gene *SLC8A1-AS1*.

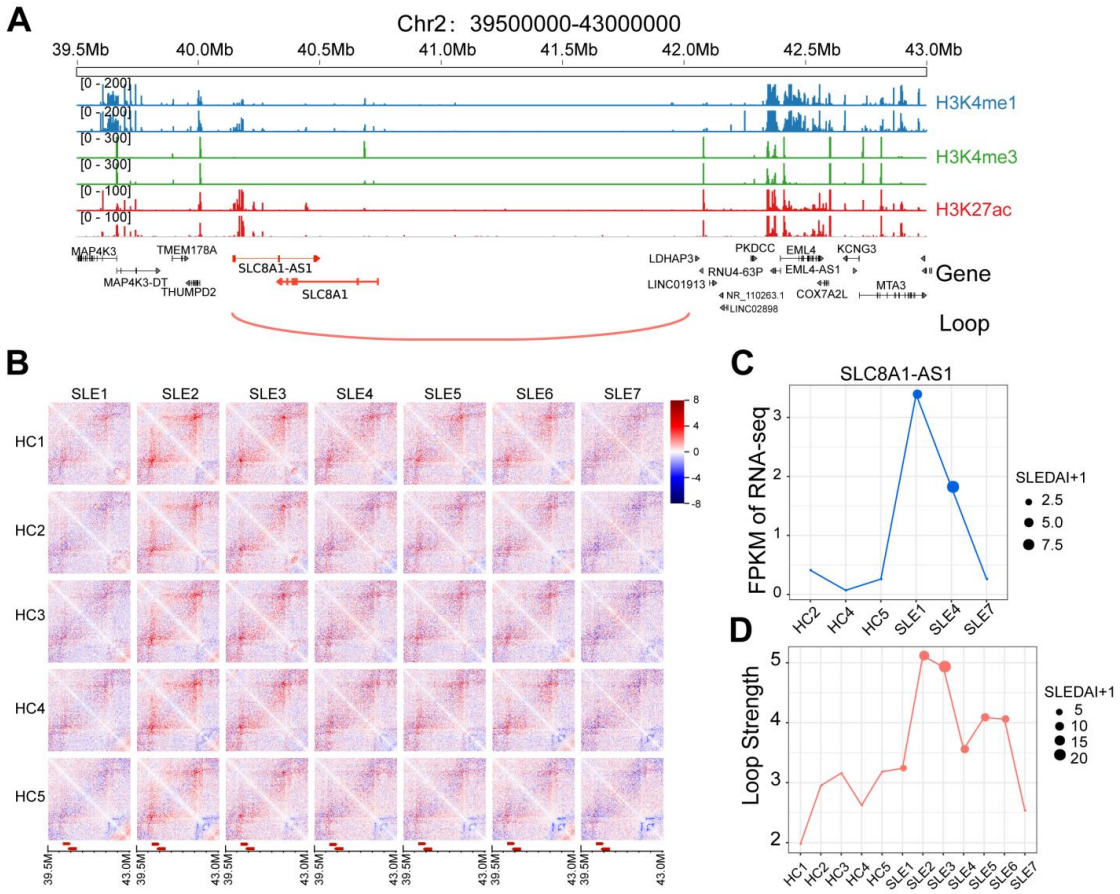


Figure S6. Long term interaction around gene *DNAJB4*.

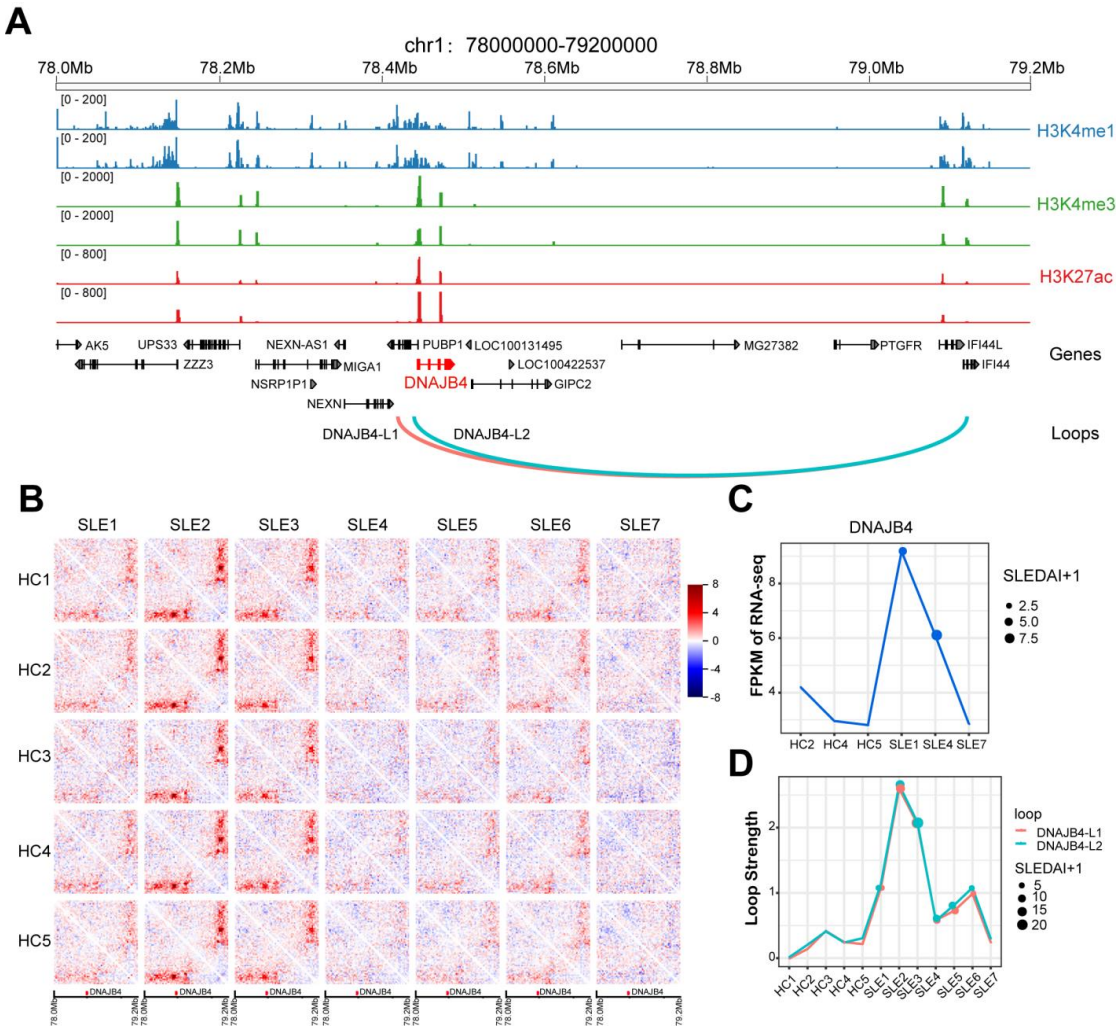


Figure S7. Long term interaction around gene *CASP5*.

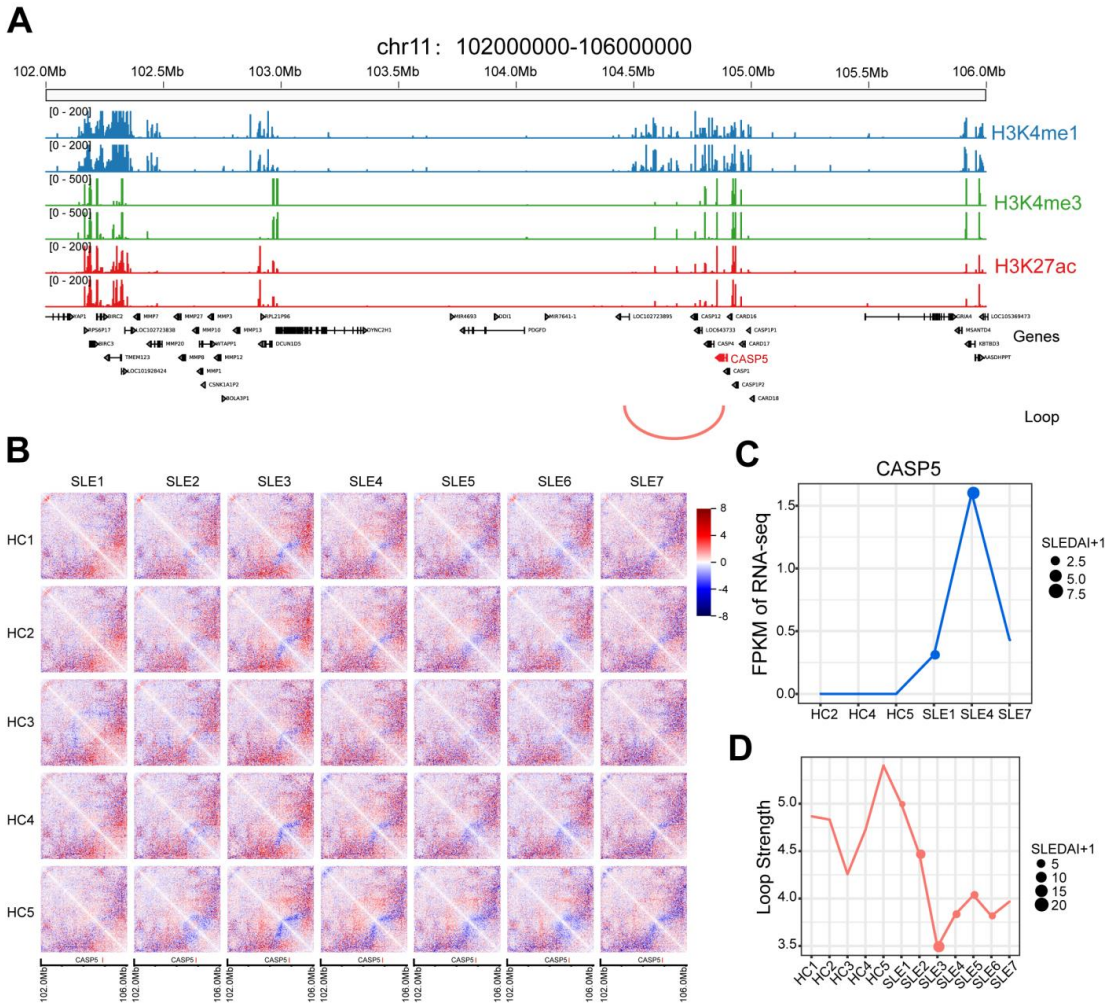


Figure S8. Local genomic 3D features around SLE risk SNP rs2732549.

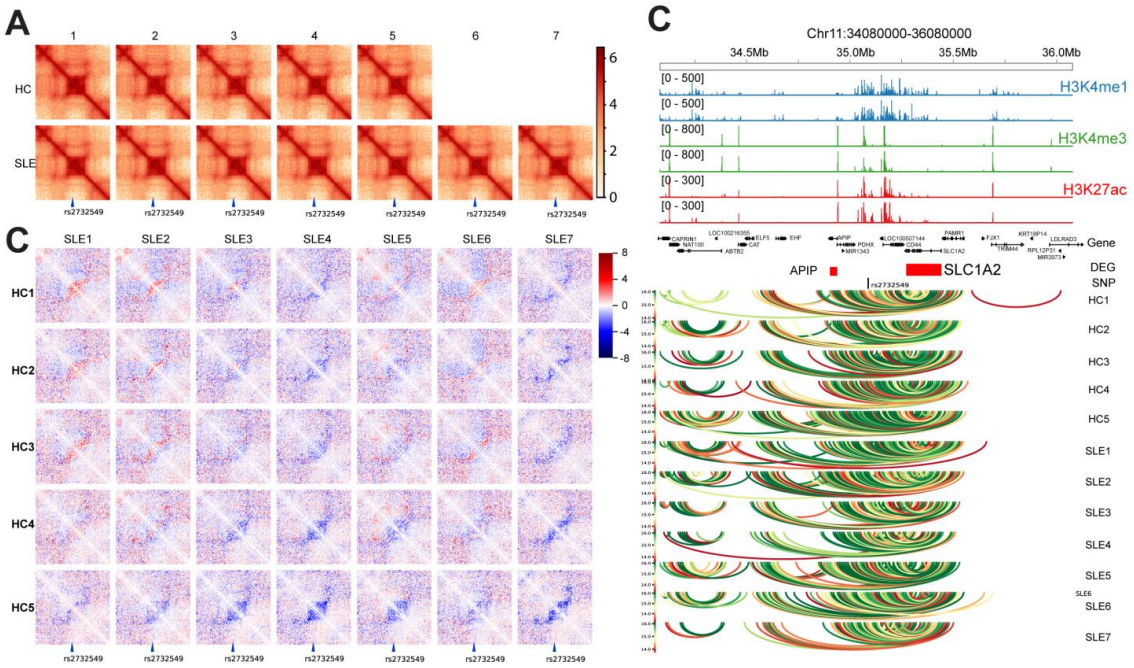
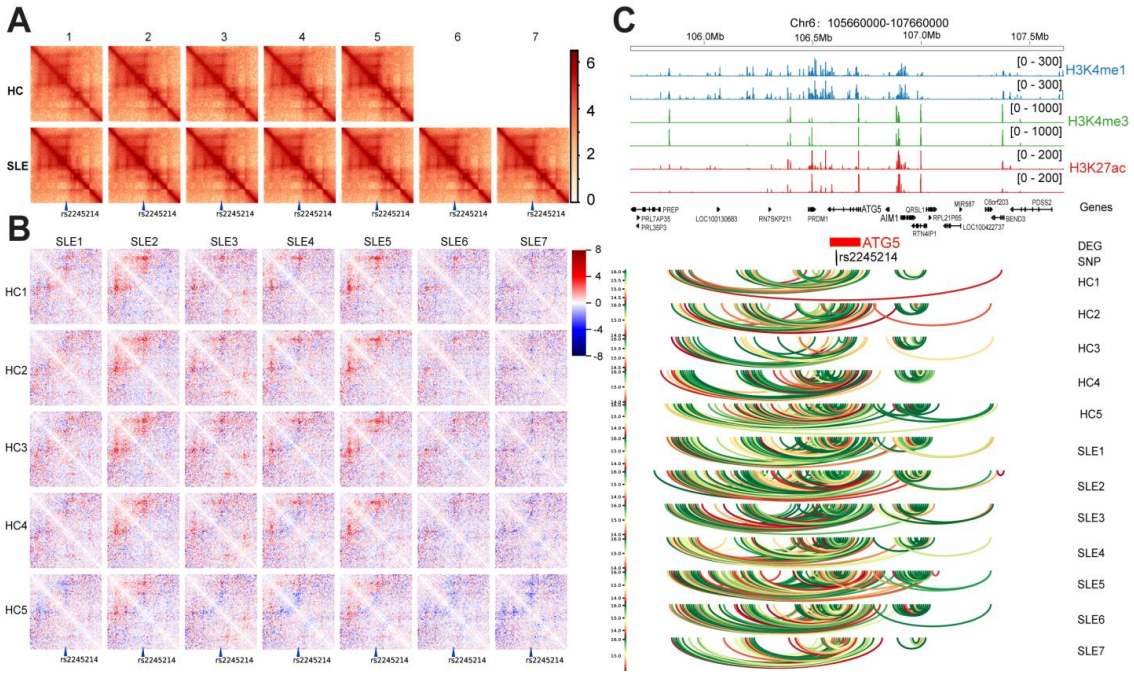


Figure S9. Local genomic 3D features around SLE risk SNP rs2245214.



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