

Supplemental Information

Aberrant TAL1 activation is mediated by an interchromosome interaction in human T-cell acute lymphoblastic leukemia

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Supplemental Methods:

Antibodies:

Antibodies against H3K9/14Ac, H3K4me2, H3K4me3, H3K9me2, H3K27me3, and CTCF were purchased from Millipore. hSET1, ASH2L, TAF3 antibodies were purchased from Bethyl Laboratories. TAL1 antibody was obtained from Santa Cruz Biotechnology. Antibodies against RNA polII was from Abcam.

ChIP-seq:

Primary human CD34+ cells were isolated and differentiated to CD36+ cells as described¹. ChIP-Seq and RNA-seq assays were performed as outlined previously¹ and described briefly below. For ChIP-Seq analysis, the cells were cross-linked with 1% formaldehyde, followed by sonication to fragment chromatin to sizes ranging from 200 to 500bp.

Chromatin fractions from 1 to 5 million cells were used for chromatin immunoprecipitation using 2 micrograms of specific antibodies. Following reverse cross-linking and purification, the ChIP DNA was ligated to Illumina ChIP-Seq adaptors, amplified using the Illumina primers, and sequenced on the Illumina GAII platform. Sequence reads of 25-bp were obtained, mapped to the human genome (hg18) and processed as described previously². The sequence reads have been deposited in the NCBI Short Read Archive (GSE12646).

Chromosome conformation capture (3C) and circular chromosome conformation capture (4C) assays

3C assay was performed as described previously with minor modifications³. In brief, 2 x 10⁷ cells were cross-linked with 2% formaldehyde for 10 minutes and stopped by the addition of glycine at a final concentration of 0.125M. Cells were pelleted and washed twice with cold PBS and lysed in lysis buffer (10mM Tris, pH 8.0, 10mM NaCl, 0.2% Nonidet P-40, and protease inhibitors pepstatin, leupeptin, aprotinin, and 0.2mM PMSF) at 4°C for 90 minutes with gentle rotation. Nuclei were collected and washed with appropriate 1× restriction buffer (NEB buffer 3 for *Bam*HI and NEB buffer 3 for *Nla*III) and then resuspended in restriction enzyme buffer containing 0.3% SDS at 37°C for 1 hour with shaking. Triton X-100 was then added to a final concentration of 1.8% to sequester SDS at 37°C for 1 hour with shaking. Chromatin was then digested with 800U of restriction enzyme at 37°C overnight with shaking. Next day the reaction was stopped by adding SDS to a final concentration of 1.6% at 65°C for 30 minutes. The digested chromatin was then diluted in 1 ml of T4 DNA ligation buffer (NEB) containing 1% Triton X-100 and incubated at 37°C for 1 hour with shaking. 400 U of T4 DNA ligase (NEB) were added and the ligation was carried out at 16°C for 5 hours followed by 30 minutes at room temperature. The ligated chromatin was then reverse crosslinked overnight by adding 200 µg of

Proteinase K (Invitrogen) at 65°C followed by phenol chloroform extraction to purify 3C DNAs. Purified 3C ligated DNA was amplified using PCR and the products were cloned into pCR-TOPOII vector (Invitrogen) for sequencing. To control for primer efficiency, BAC template containing 1.82 Mb of the *TAL1* locus was generated and used as a standard. PCR reaction was performed in parallel for BAC standard and 3C ligated DNA. Furthermore, to control for differences in cell-type specific chromatin organization, the interactions at the *TAL1* locus were normalized to ERCC3 locus. Real-time PCR was performed to quantitate 3C interactions using SYBR after validation of each primer pair as described previously⁴. Relative crosslinking frequencies were calculated and plotted after normalization to loading control and ERCC3 control as described previously⁵.

4C assay was performed as described previously⁶ with minor modifications. In brief, 5×10^5 cells were cross-linked with 2% formaldehyde for 10 minutes and lysed with digest buffer containing 2% SDS at 37 °C overnight with shaking. Chromatin was then digested with 300U of *NlaIII* (NEB) at 37°C for 4 hour with shaking. The reaction was stopped by adding SDS to a final concentration of 1.6% at 65°C for 20 minutes. The digested chromatin/DNA was diluted in ligation buffer containing 6000 U of T4 DNA ligase at 16°C. The ligated chromatin was then reverse crosslinked by adding 200 µg of Proteinase K (Invitrogen) overnight and the 4C DNA was purified by phenol chloroform following by Qiagen PCR kit and amplified by inverse PCR using the first inverse primer and nested primer sets. The PCR products were cloned into pCR-TOPOII vector (Invitrogen) for sequencing.

Supplemental Table S1: Summary of the sequencing data of the Jurkat 4C library

Element	#	Gene name	Loci	Function
Intergenic DNA element	1	15 Kb downstream of CD2BP2	chromosome 16	The CD2BP2 protein is originally identified as a binding partner of the T cell adhesion protein CD2 in the context of T cell signaling. The TIL16 element comprises transcription factors, MEIS1, HOXA9, and c-Maf, as well as coactivator, p300, binding motifs. c-Maf is a T-cell specific TF and MEIS1 and HOXA9 is leukemia oncoprotein involved in acute leukemia.
Oncogene	1	Genebody of Rap2A	chromosome 13	Member of RAS oncogene superfamily of small GTP-binding proteins. In it is involved in several signaling cascades that regulate cytoskeletal rearrangements, cell migration, cell adhesion and cell spreading.
Unknown	1	Genebody of IQCA1	chromosome 2	
self-ligated	30			
Junk	24			
Total	57			

Supplemental Table S2: List of primers:

	<i>Primer</i>	<i>Primer sequences (5'- 3')</i>
shRNA	Hs SET1-1	Target: GGAAAGAGCCATCGGAAAT
	Hs SET1-2	Target: GACAACAACGAATGAAATA
	Hs SET1-3	Target: CAACGACTCAAAGTATATA
	Hs c-Maf-1	Target: TGGTTCTCCATGACTGCAAAT
	Hs c-Maf-2	Target: AACTTCTCGTATTTCTCCTTG
	Hs c-Maf-3	Target: ACTTCTCGTATTTCTCCTTGT
	Hs c-Maf-4	Target: TCCAGTAGTAGTCTTCCAGGT
	Hs c-Maf-5	Target: TCATCCAGTAGTAGTCTTCCA
RT-PCR	Mm β -actin	For: GTGGGCCGCTCTAGGCACCA

		Rev: TGGCCTTAGGGTGCAGGGGG
	Hs β -actin	For: AGAAAATCTGGCACCACACC
		Rev: AGAGGCGTACAGGGATAGCA
	HoxB4	For: TGGATGCGCAAAGTTCACG
	(both for Hs & Mm)	Rev: GGTCTTTTTTCCACTTCATGCG
	Mm Tal1	For: TAGCCTTAGCCAGCCGCTCG
		Rev: GCGGAGGATCTCATTCTTGC
	Hs Tal1	For: GGATGCCTTCCCTATGTTCA
		Rev: AAGATACGCCGCACAACCTT
ChIP	HoxB4 Promoter	For: GCCTCTAACTTTGTTCACTTGAC
	(both for Hs & Mm)	Rev: AGCCATTAATTTCTGGGAATTGC
	Hs HoxB4 3'UTR	For: CCCCGGAAAATCTATCTGC
		Rev: CCAAAGCTGAAAACGAGGAG
Hs TAL1 locus primers	STIL Promoter	For: CCGCAGTTCTCCAAGAAGACTT
		Rev: GGTCGCCGTTACGTATTGGT
	Region -16Kb	For: CAGTAGCAAGCCCAAGTGTAGTAACA
		Rev: GGAAAGATGCACTAACTGGTCCAT
	CTCF site -31Kb	For: ACCTGATGTACCTGTGTTCTTTCC
		Rev: CCCTGTTGGTCCAGTCTGTAAA
	Enhancer -4Kb	For: TGGCTGCCTGACTGTCAGAA
	Rev: CGTTCACCAACCCTCCAATT	
	Region -10Kb	For: CAAATCAGAAGAAAAGACCTGCAA
		Rev: TTTCATTTTCCTTCCCTCAATCTC
	Upstream1a region	For: AGGGAGACTGCCCATTTGAAAT

CpG island	Rev: CCTCCCAGGGCTTCTTTCTT For: CCCTTCTGCGTTTTCTTCGT Rev: CAGAATCAGATCCCTGCTGAGA
TAL1 Prom1a	For: CTAGCGCCGCTCAACCA Rev: TGGGCCAAATGATTCATTTAAT
TAL1 Prom1b	For: CCGCCTCGGAGACTCTCTT Rev: CACAGCCTCGCGCATTT
TAL1 PromIV	For: CGTTTTAAACCCAGTGGCTCTAG Rev: CACGCACACTCTCTCTCACAGAA
Enhancer +19	For: TCCAGGAGGGAGTGCCATT Rev: GCCTGCATCCCCCATTG
CTCF site +40Kb	For: TTTTCTCAGGCTAAGCTCTTTGC Rev: GCAAAGTTAGCCAGAGTGTTGACTC
Map17promoter Upstream region	For: GCGTGGAAGGCACTGAA Rev: GCCCCGCCAAGCTAAACT
Map17promoter Down region	For: CCCACATCTGCTTGTTCTCAT Rev: GCTGGCATTGAGGTCATCT
Enhancer +51Kb	For: GCCTCCTAAGCTTCCTTGATGTC Rev: CAGAAGTGAGACCAATGAGATCGT
CTCF site +53Kb	For: TGGCAGTCCTTCAGTTTCG Rev: CTCTCATCAATCTACGCTTCCTT
CTCF site +57Kb	For: GTGAATGACAGCCATCGTGAT Rev: GGGAGAAGGAGGTGGAGTC
Region +70Kb	For: GTGGCCACAAAGCAAGGAAT Rev: TCTCTGGAATCTCCAAGGCAA
hHS2- β globin	For: AGTGTTTAGCATCCAGCAGGT

		Rev: GAAGGGATAGAGGGAGCTGAG
	TIL16	For: CGAGATGAGGACACAGAG
		Rev: GTAGAATGAGAGGCTGCTT
	+2.7	For: GCGGAAGTATGCGATAAG
		Rev: GCCTCTACTGCTTGAATG
	+10	For: TGGAGATTGGAAGCCTATT
		Rev: TCACAGAGACACAGGATG
	TSS	For: GGAGGAGGATGATGATGATG
		Rev: TTCCAGCAGAGTGTATTCTT
4C		
NlaIII	First round	For: CACTCCCTCCGGTCAAATTG
		Rev: CCCATCTCTAATCCCAAGGC
	Second round	For: GAATCATTGGCCATAAT
		Rev: AACCTCAGTCCCTAACCTTTC
3C		
A) BamHI		
	Prom1aCE	Rev: CTGCTCTAGCGGTGGATTCCTGAGAGGC
	+40.4KbCE	For: GTTGATCACCTGGTGTCTTCCTGTTTCAT
	Enh+51CE	For: ACTCGTGAATCCTGCCCTCCTTCAGAA
		Rev: CAGCCAGCCCAGCTTCTCCACTCACTGA
	Prom1abait_L	For: GTGATGCAGCTTAGTCGCCAACAACCATC
	Prom1abait	For: GACCTCTGGCTGGTAATC
	Enh+51	Rev: GAGTGACCTGACTCGAAC
	+40.4Kb	For: GCCAAGCAAGGACAGACTTAAGGAGGGTG
	TAL1proIV	For: CGTTTTAAACCCAGTGGCTCTAG
		Rev: CACGCACACTCTCTCACAGAA

	ERCC3	For: CACATAACCATAAACTCAGTAGGGTCAGG Rev: ATTAGGAGTGGCTGTGCATGGATG
B) NlaIII	Enh+51	Rev: GAGTGACCTGACTCGAAC
	Prom1a	For: CACTCCCTCCGGTGAAATTG
	+40.4Kb	Rev: GCCCCGCCAAGCTAAACT
	TAL1pro1a	For: CTAGCGCCGCTCAACCA Rev: TGGGCCAAATGATTCATTTAAT
	TIL16 1 ST	For: AAGCAGCCTCTCATTCTA Rev: TAACCTTTCAGACACC
	TIL16 2 ND	For: GAGACCCAGAAAGAGGAA Rev: TTTCTTCAGCGACTCTCA
C) DpnII	TAL1proIV	For: CGTTTTAAACCCAGTGGCTCTAG Rev: CACGCACACTCTCTCTCACAGAA
	CTCF-31_3C	For: GGCTGTTGAGGAGTAGTAGTGTA Rev: CCTTCTCGCAAATGGACAAATCA
	CTCF-31_CE	Rev: TGGAACAGGAAGGAGGAACT
	CTCF+40_3C	Rev: CGGAGGAAGTGCTGAACC
	CTCF+53_3C	For: TGGGAGGAAACAGAGATGACA Rev: AGATTCCTCTCGCAGATGTGA
	CTCF+53_CE	For: TCTCCCTCCAGGTTCTTTCC
	CTCF+57_3C	For: CAAATCAGAAGAAAAGACCTGCAA
	CTCF+57_CE	For: GAAAGGCGCCAGAATGCTCACGTTTTT Rev: GAAGCCATGGGAGGTGACGATTTTGGTA
Luciferase	Tal11a	For: GAAAGGCGCCAGAATGCTCACGTTTTT Rev: GAAGCCATGGGAGGTGACGATTTTGGTA
Reporter		For: TGGGAGGAAACAGAGATGACA Rev: AGATTCCTCTCGCAGATGTGA
Assay	TIL16	For: TGGGAGGAAACAGAGATGACA Rev: TCTCCCTCCAGGTTCTTTCC
		For: CAAATCAGAAGAAAAGACCTGCAA Rev: GAAAGGCGCCAGAATGCTCACGTTTTT
		For: TGCCTAGCCTCCCAAAGTGCTAGGATTA Rev: CGCAGTAAGCACCATTATCA

c-Maf deletion 1	For: AAGAGAACTTGGCAGCGCCTCTCATTCTACGG Rev: CCGTAGAATGAGAGGGCGCTGCCAAGTTCTCTT
c-Maf deletion 3	For:GAAGAGAACTTGGCAGCCAAAGCAGCCTCTCATT Rev: AATGAGAGGCTGCTTTGGCTGCCAAGTTCTCTTC
+51(0.7)	For: ATGCACGCGTCTTTATGTTATGGCCATTG Rev: ATGCCTCGAGAGAGATCCAGGCTGGTA
+51(4.2)	For: ATGACGCGTCCCCATGTTCTGCC Rev: ATGCCTCGAGCAACTCCTGGCTGGAAG

Supplemental Figure Legends:

Figure S1. Histone modification patterns in the *TAL1* locus in leukemia cells. (A)

ChIP analysis of histone modifications across the *STIL-TAL1-MAP17* loci in Rex and

HPB-ALL cells. (B) Comparison of H3K27 trimethylation in the *TAL1* locus in K562,

Jurkat, and HL-60 cells. *TAL1* is expressed in K562 and Jurkat cells, but is silenced in

HL-60 cells.

Figure S2. Colocalization of *TAL1* and hSET1 in the *TAL1* locus and other

genomic intergenic regions. (A) Global colocalization of *TAL1* and hSET1 at

intergenic regions of human genome by ChIP-seq analysis. (B) ChIP analysis showed

that TAL1 is bound to the +51 enhancer and the TAL1 promoter 1 only in K562 cells but not in Jurkat cells.

Figure S3. *TAL1* enhancer and promoter interact in erythroid cells but not in T-ALL cells. (A) 3C analysis of the interaction between the *TAL1* promoter 1 and the +51 enhancer in K562 cells using *BamHI* restriction enzyme. (B) Sequencing analysis of the predicted PCR 3C product from K562 cells using *NlaIII* restriction enzyme showed that includes both +51 Kb enhancer and the *TAL1* promoter 1 sequences. (C) 3C analysis of the +51 enhancer and the *TAL1* promoter 1 interaction in Rex and HBP-ALL cells using *NlaIII* restriction enzyme.

Figure S4. Knockdown of hSET1 affects hematopoietic cell growth and differentiation. (A) Western blotting analysis of hSET1 levels in the vector control and the hSET1 KD K562 cells. (B) Western blotting analysis of hSET1 levels in the vector control and the hSET1 KD Jurkat cells. (C) RT-qPCR analysis of TAL1 mRNA levels in the vector control and the hSET1 KD Jurkat cells. (D) Western blotting analysis of hSET1 levels in the vector control and the hSET1 KD CD34+ HSCs.

Figure S5. CTCF dictates enhancer and promoter interaction in the *TAL1* locus. (A) ChIP analysis showed that CTCF binds to the *TAL1* locus in K562 and Jurkat cells. (B) 3C analysis of CTCF mediated chromatin loop between -31 and +53 CTCT motifs in

the vector control and the hSET1 KD K562 cells. **(C)** Quantitation of the 3C CTCF interaction between -31 and +53/or +57 CTCF motifs in the vector control and the hSET1 KD K562 cells.

Figure S6. 4C analysis revealed that a T-cell specific DNA regulatory element in chromosome 16 associates with the *TAL1* promoter 1 in T-ALL. (A) PCR analysis of restriction digestion efficiency in the *TAL1* locus in K562 and Jurkat cells. **(B)** Sequencing analysis of the predicted PCR products from 4C library showed that it includes both *TIL16* sequence in chromosome 16 and the *TAL1* promoter 1 in chromosome 1. **(C)** Sequencing analysis of the predicted PCR products from 4C library showed that includes both *RAP2A* gene sequence in chromosome 13 and the *TAL1* promoter 1 in chromosome 1. **(D)** 3C analysis confirms that *TIL16* element associates with the *TAL1* promoter 1 in Jurkat but not in K562 cells. **(E)** Sequencing analysis of the predicted 3C PCR product showed that it includes both *TIL16* element and the *TAL1* promoter 1 sequences.

Figure S7. Computational analysis predicts transcription factor binding sites in the *TIL16* DNA element in T-lymphocytes. (A) Computational analysis of transcription factor binding sites in the *TIL16* element. **(B)** A long non-coding RNA located 2136 bp downstream of the *TIL16* element is highly expressed in T-lymphocytes and Burkitts lymphoma (<http://biogps.org/#goto=genereport&id=595101>). **(C)** CD2BP2

located ~15K upstream of the *TIL16* element is highly expressed in T-lymphocytes (<http://biogps.org/#goto=genereport&id=10421>).

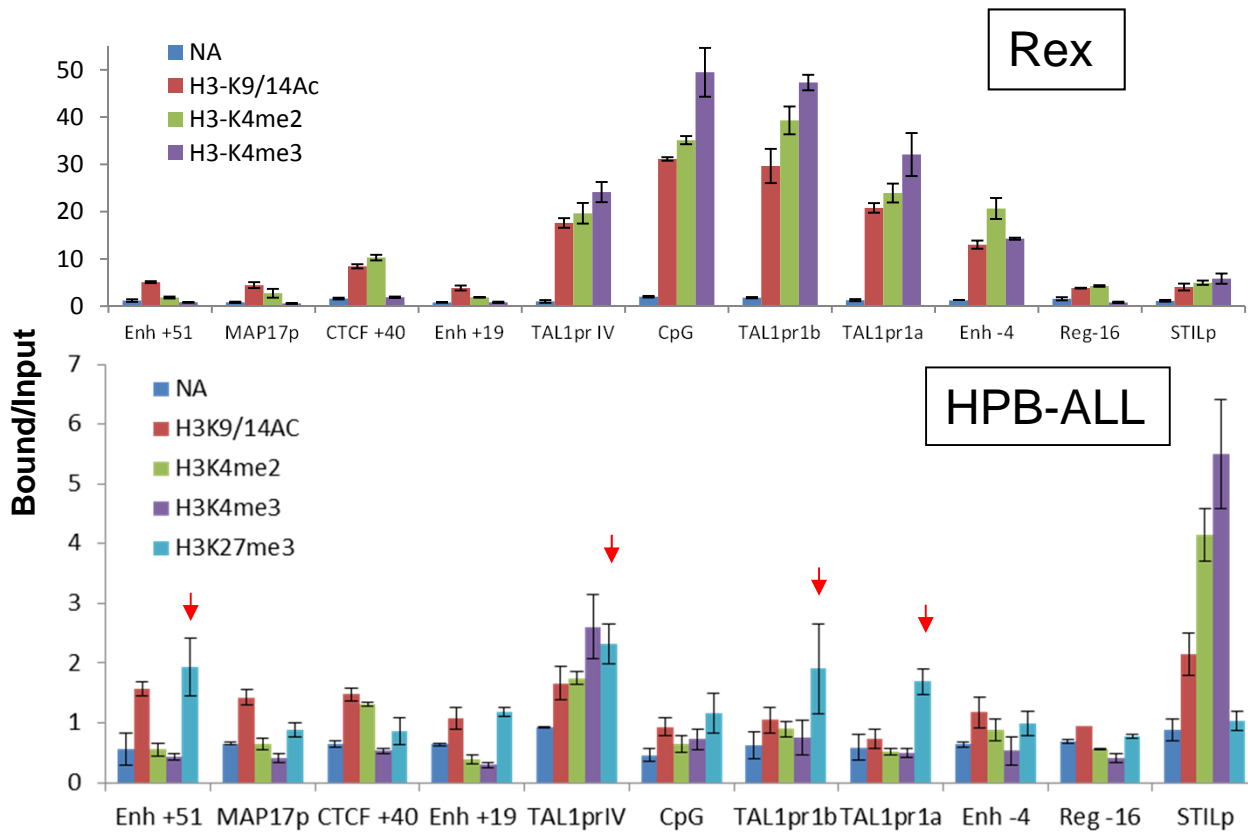
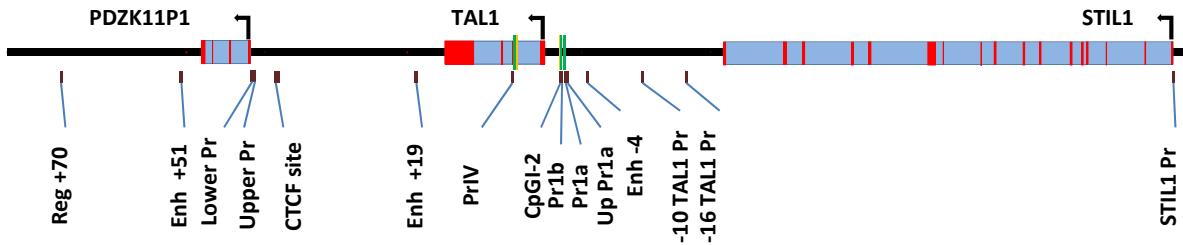
Figure S8. Computational and ChIP-seq analysis reveals that *TIL16* DNA element is active in T-lymphocytes. (A) ChIP-seq analysis of CD4⁺ T cells revealed that the *TIL16* element is highly enriched with H3K4me1, a characteristic epigenetic mark for active enhancer. (B) Computational analysis of transcription factor binding sites in the *TAL1* promoter 1 element.

Figure S9. Molecular characterization of a pediatric T-ALL patient sample. (A) RT-qPCR analysis of *TAL1* mRNA levels in T-ALL patient sample, Jurkat, and HPB-ALL cells. (B) Western blotting analysis of *TAL1* levels in T-ALL patient sample and Jurkat cells. (C) Western blotting analysis of *TAL1* levels in T-ALL patient derived COG-LL-317 cells obtained from Children's Oncology Group and Jurkat cells. (D) PCR analysis to detect potential chromosomal deletion and translocation in the T-ALL patient sample indicated that there is no chromosomal rearrangement in this patient. (E) PCR analysis to detect potential chromosomal deletion and translocation in the T-ALL COG-LL-317 cells indicated that there is no chromosomal rearrangement in this patient. (F) 3C analysis of the interchromosome interaction between the *TAL1* promoter 1 in chromosome 1 and the *TIL16* element in chromosome 16 comparing normal bone marrow and T-ALL COG-LL-317 cells.

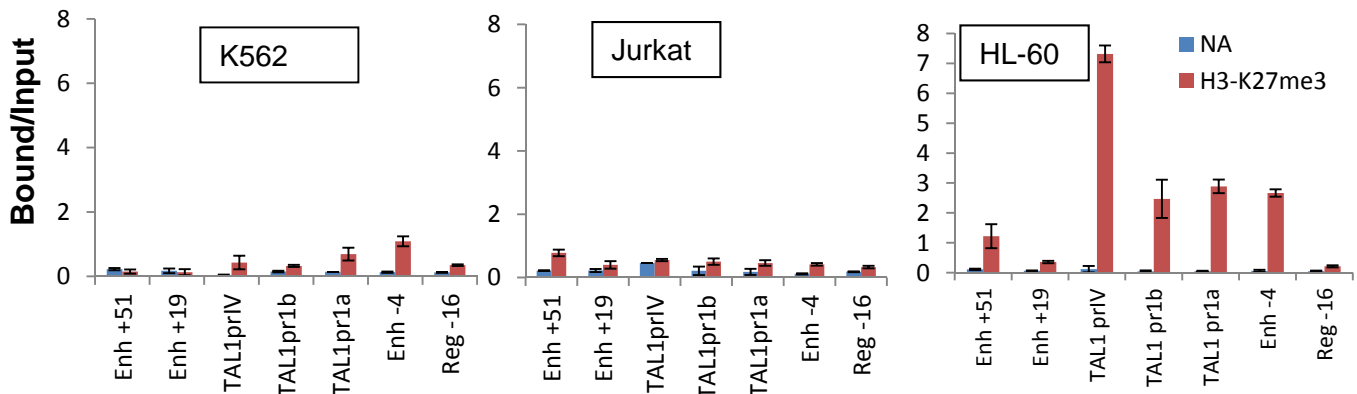
Figure S10. KD of c-Maf disrupts the interchromosomal interaction and impairs T-ALL cell proliferation. (A) Knockdown of c-Maf decreases cell proliferation. **(B)** A soft agar colony formation assay was carried out in Jurkat cells stably expressing c-Maf shRNA or the vector control, KD of c-Maf reduces colony numbers and sizes of Jurkat cells. **(C)** 3C analysis of interchromosomal interaction between the *TAL1* promoter 1 and *TIL16* element comparing the vector control and the *c-Maf* KD Jurkat clones.

1. Cui K, Zang C, Roh TY, Schones DE, Childs RW, Peng W *et al.* Chromatin signatures in multipotent human hematopoietic stem cells indicate the fate of bivalent genes during differentiation. *Cell Stem Cell* 2009; 4(1): 80-93.
2. Barski A, Cuddapah S, Cui K, Roh TY, Schones DE, Wang Z *et al.* High-resolution profiling of histone methylations in the human genome. *Cell* 2007; 129(4): 823-37.
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5. Abou El Hassan M, Bremner R. A rapid simple approach to quantify chromosome conformation capture. *Nucleic Acids Res* 2009; 37(5): e35.
6. Gondor A, Rougier C, Ohlsson R. High-resolution circular chromosome conformation capture assay. *Nat Protoc* 2008; 3(2): 303-13.

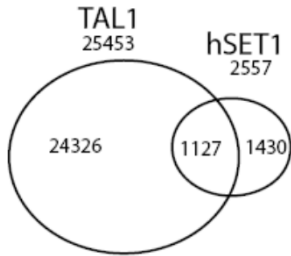
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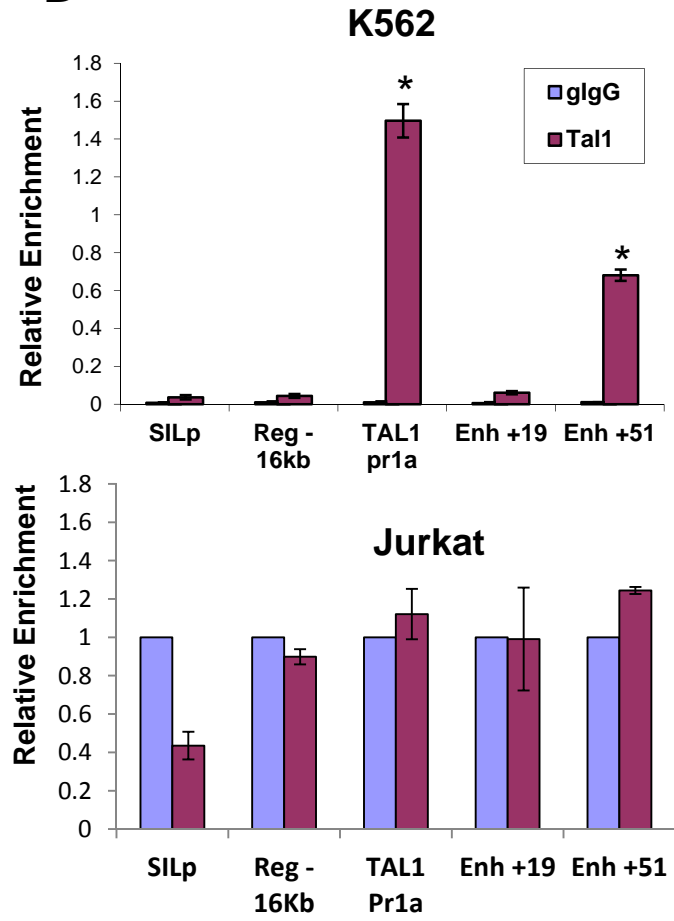
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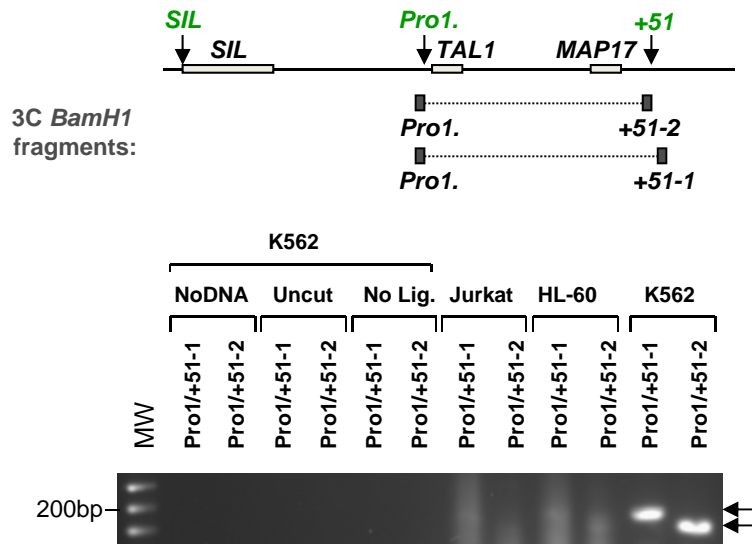
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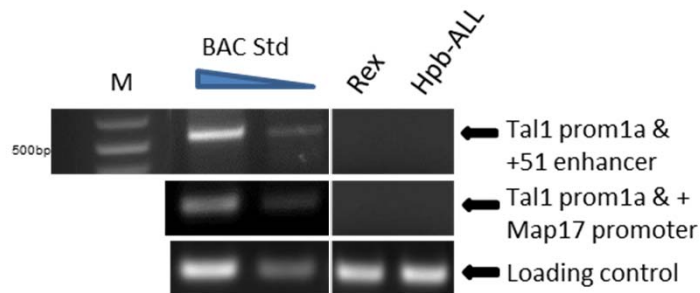
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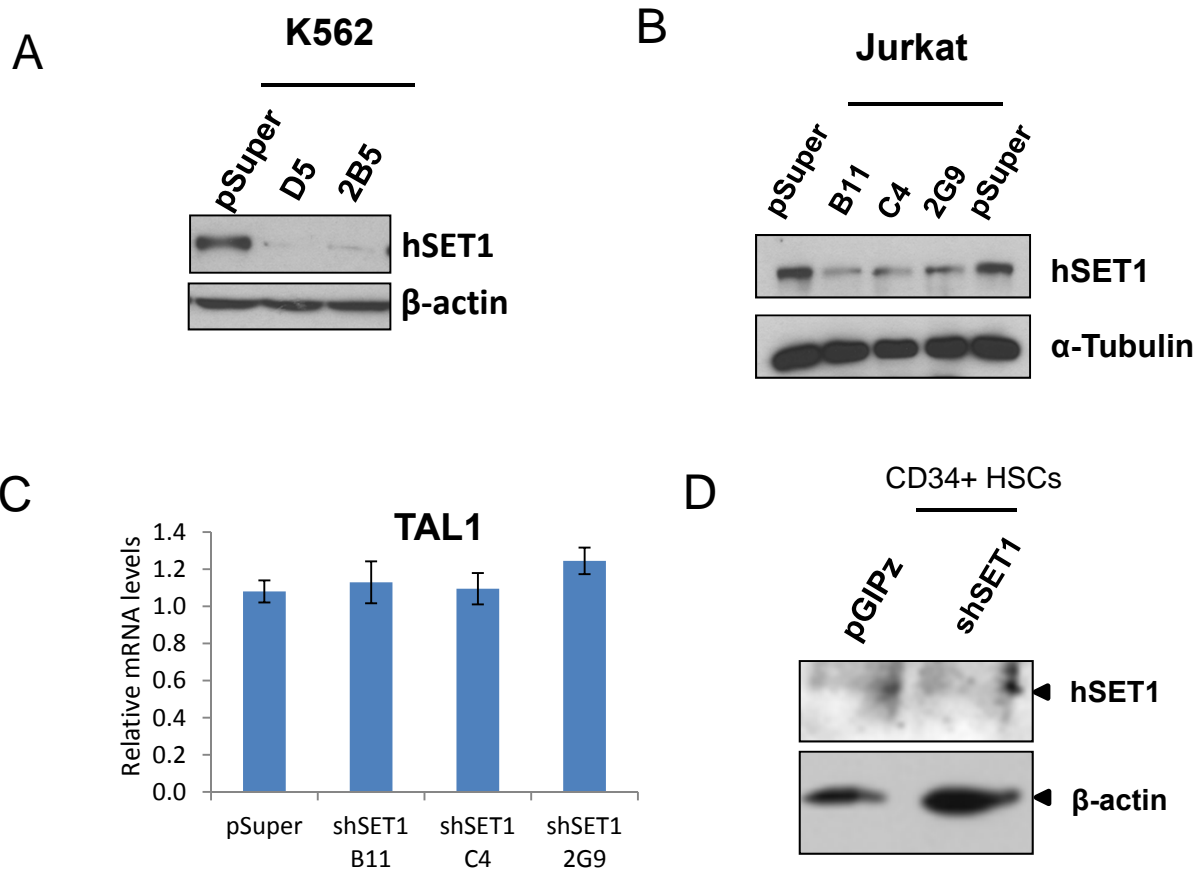


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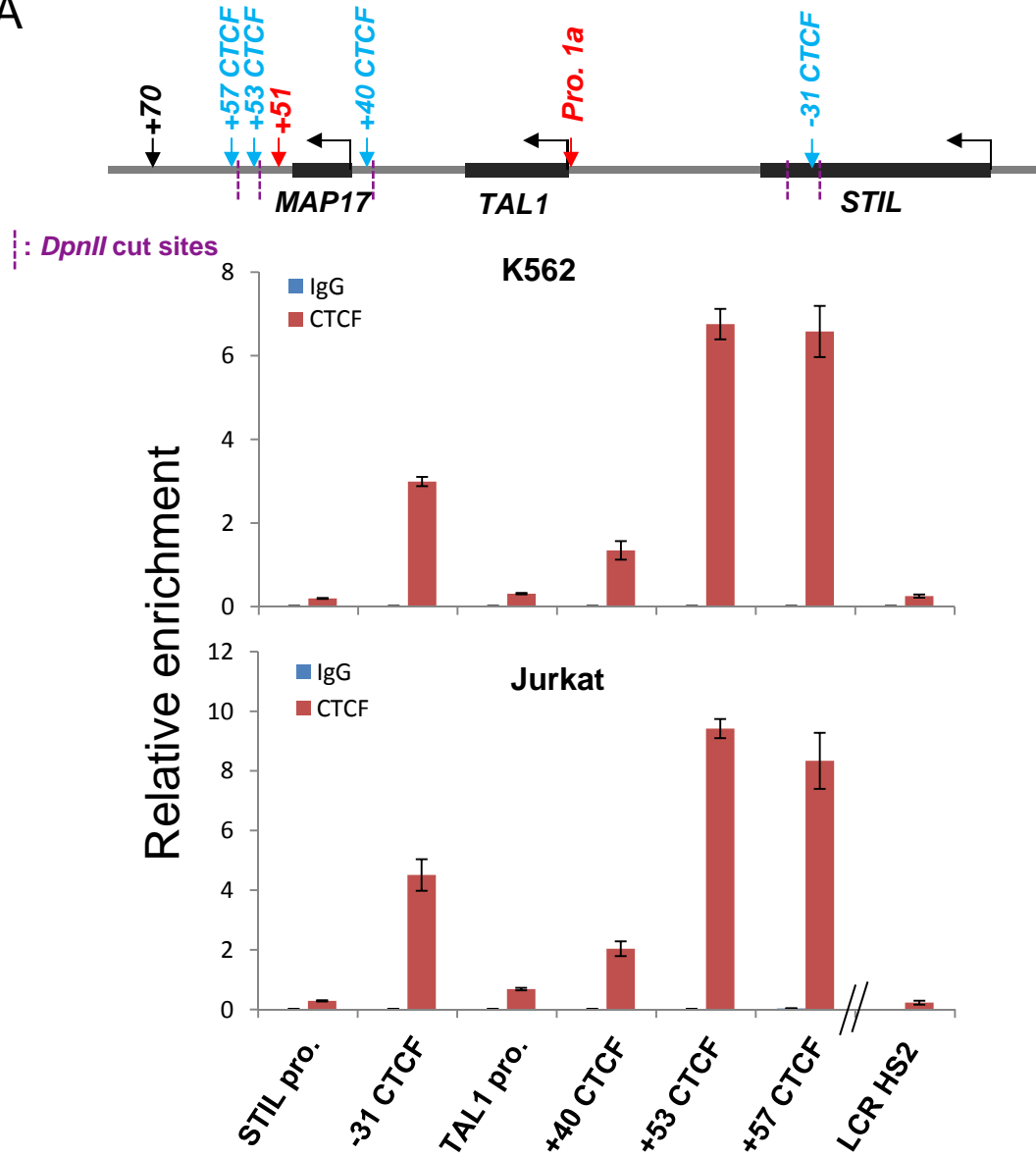
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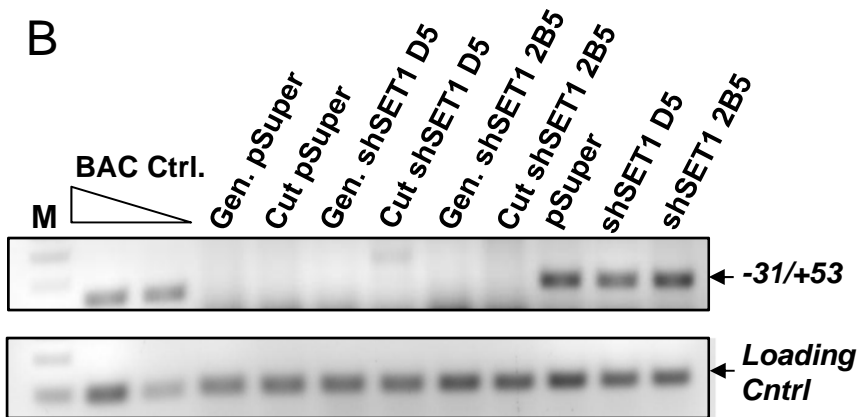




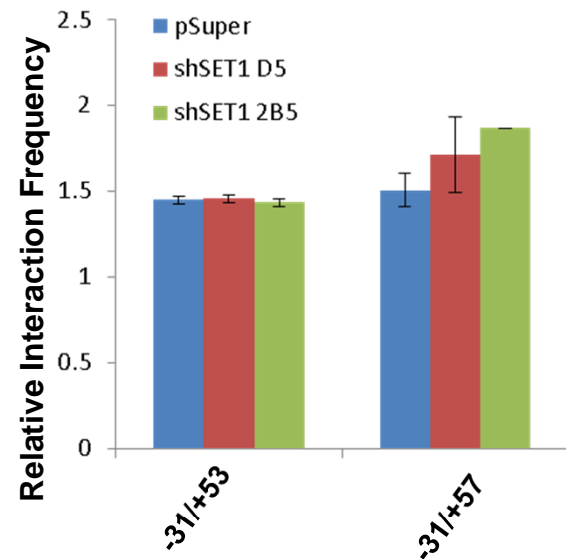
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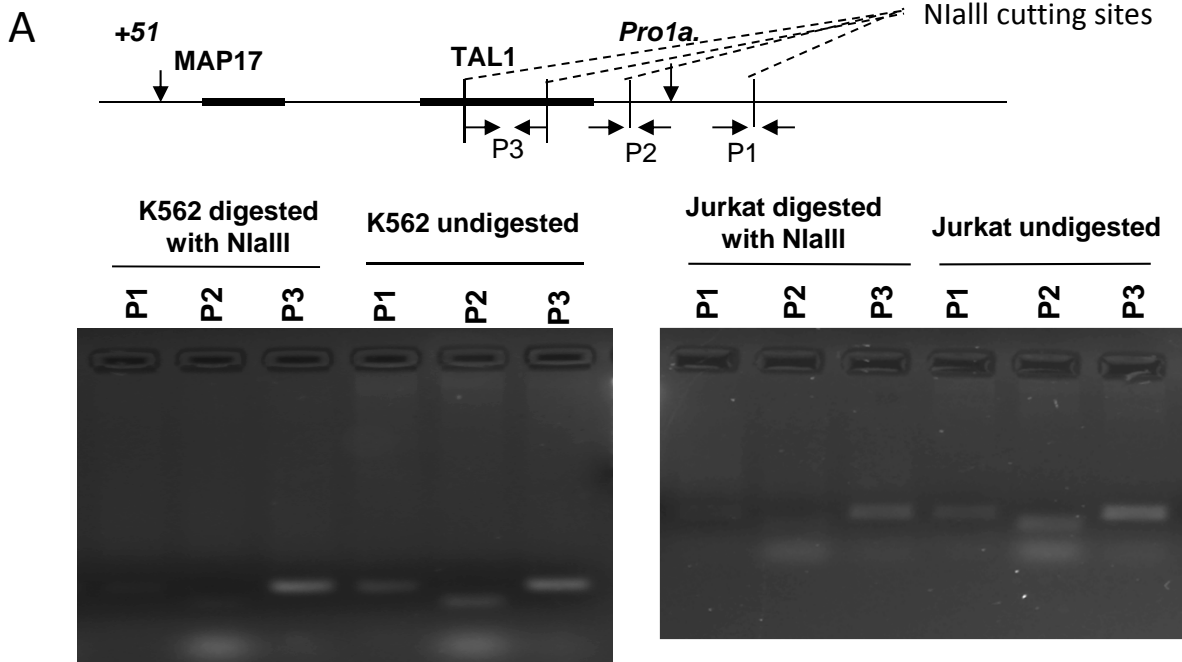


B



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B
TIL16

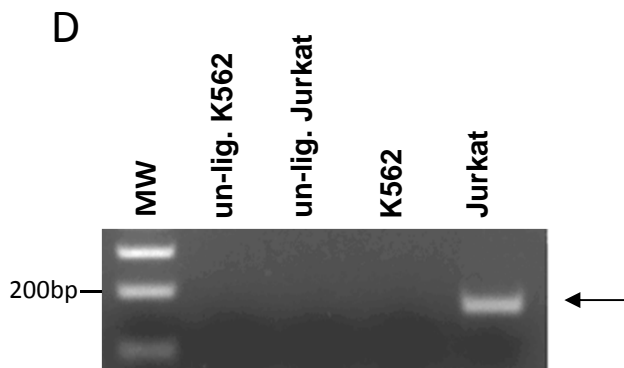
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TAL1 Pro1 primer R

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RAP2A

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TAL1 Pro1 primer R



E

TIL16 primer
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TAL1 pro. primer

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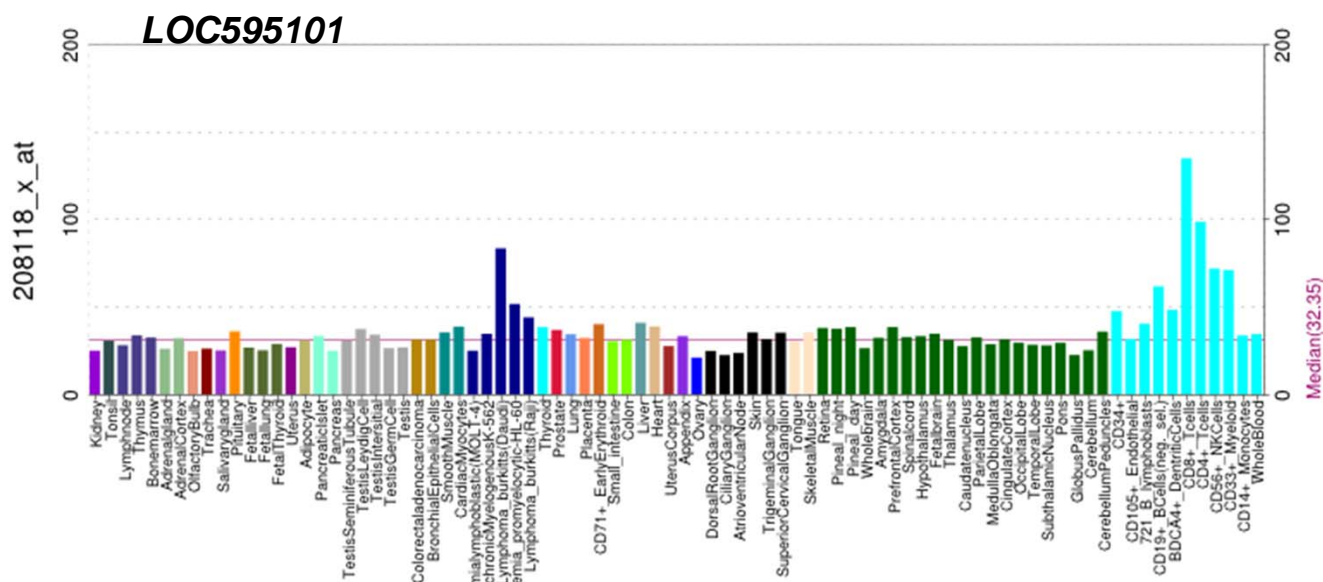
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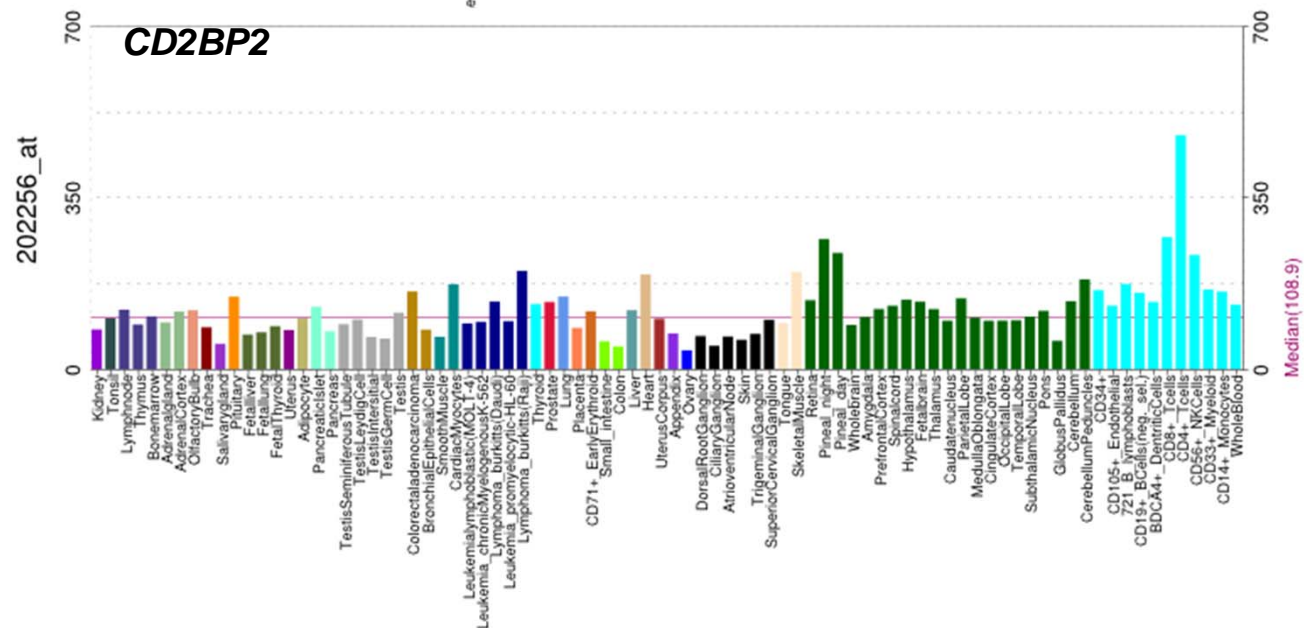
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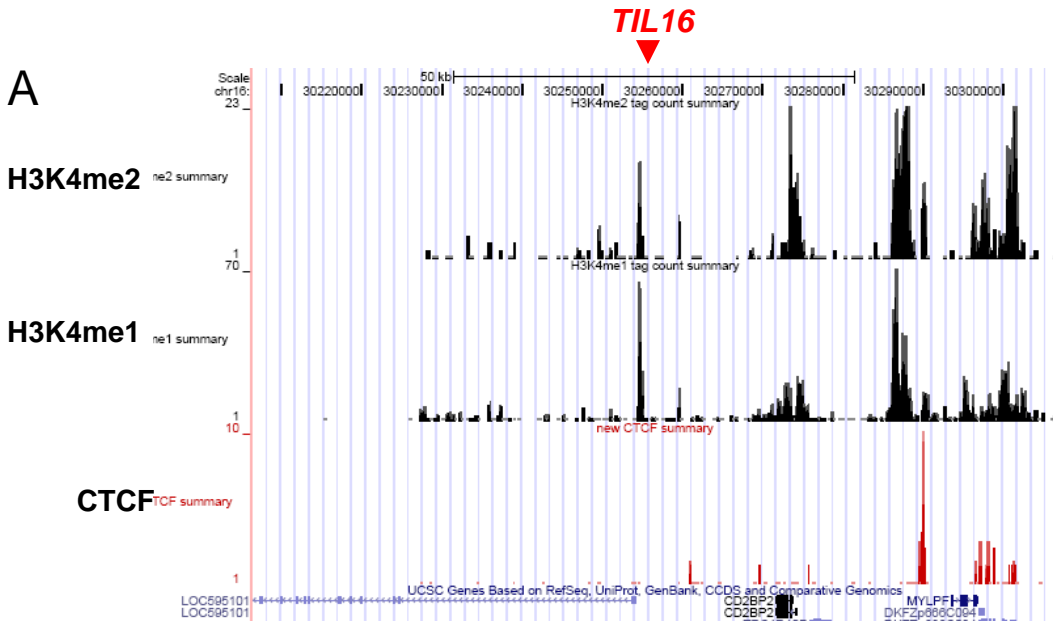
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B



C





B

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69 GGCCGGGCGGGCGCGGGGCGGGGAGCGGGGGCCGCGGGAGGGGCGGGCCGCGCCGC
129 CGCTCAGGACCGGCCTCAAATGGCCACACGCGTACCCCCGTAGCGGAAAAACGTGAGC
189 ATTCTGGC
    
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