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RESEARCH ARTICLE

Role of CTCF Binding Site Mutations in Oncogene Activation via Enhancer Hijacking

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ABSTRACT

Somatic mutation of CTCF binding motifs at topologically associating domain (TAD) boundaries has emerged as a recurrent, non-coding mechanism of oncogene activation in cancer, in which boundary erosion permits otherwise insulated enhancers to contact and inappropriately activate a neighbouring proto-oncogene, yet how individual patient-derived CTCF motif mutations quantitatively affect boundary strength and downstream oncogene expression has rarely been tested by direct genetic reconstruction. Here we used CRISPR base editing to introduce four recurrent, patient-derived CTCF motif point mutations found near the TAL1 and LMO2 oncogenes in T-cell acute lymphoblastic leukemia (T-ALL) into an isogenic human T-cell progenitor line, and profiled the consequences using in situ Hi-C, CTCF ChIP-seq, ATAC-seq and RNA-sequencing. Base editing of the strongest of the four motifs, located at a boundary immediately downstream of TAL1, reduced CTCF occupancy at that site by 71% and produced a marked increase in inter-domain Hi-C contact frequency spanning the boundary, consistent with partial TAD fusion; the three weaker motifs produced smaller but still significant reductions in local boundary insulation. RNA-sequencing showed that TAL1 expression increased 8.3-fold following the strongest motif's disruption, with smaller but significant increases following disruption of the weaker motifs, and that this increase was accompanied by de novo ATAC-seq accessibility gain at TAL1's promoter matching the accessibility signature of a nearby stem cell-specific enhancer normally insulated from it. Combinatorial disruption of two motifs produced TAL1 induction greater than either single mutation alone but less than additive, indicating partial redundancy between boundary elements. A matching CTCF motif mutation near LMO2 similarly increased LMO2 expression and induced ectopic enhancer contact, reproducing the two most common enhancer-hijacking events reported in primary T-ALL. These results establish a direct, quantitative relationship between individual CTCF motif mutations, boundary insulation strength, and oncogene induction, with direct relevance for interpreting non-coding mutation burden in cancer genomes.

Keywords: CTCF; enhancer hijacking; TAD boundary; oncogene activation; T-cell acute lymphoblastic leukemia; base editing; Hi-C

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1. INTRODUCTION

Topologically associating domains (TADs), self-interacting chromosomal neighbourhoods bounded by convergently oriented CTCF binding sites, constrain which enhancers can productively contact which promoters, and disruption of TAD boundaries has been increasingly recognised as a non-coding mechanism of oncogene activation across a range of cancers [1,2]. In this enhancer-hijacking model, a somatic mutation that weakens or abolishes a boundary CTCF motif permits an enhancer normally insulated within a neighbouring domain to establish aberrant contact with a proto-oncogene promoter, driving its inappropriate, tissue-inappropriate expression [3,4].

T-cell acute lymphoblastic leukemia (T-ALL) has provided some of the clearest examples of this mechanism, with recurrent somatic mutations and small deletions affecting CTCF motifs near the TAL1 and LMO2 oncogenes reported across independent patient cohorts, each associated with aberrant oncogene expression in the corresponding leukemic blasts [5,6]. However, most evidence for these events has come from correlative genomic and expression profiling of primary patient samples, in which the specific contribution of an individual motif mutation to boundary insulation and oncogene induction is confounded by the substantial additional genetic and epigenetic heterogeneity present in any given leukemia, leaving open whether the association between a given motif mutation and oncogene overexpression reflects a direct causal, quantitatively predictable relationship.

A related open question concerns the consequence of the multiple CTCF motif mutations frequently observed at a single boundary in some patient genomes: whether combining mutations at more than one motif within the same boundary produces an additive increase in oncogene expression, consistent with each motif contributing independently to insulation, or a sub-additive relationship consistent with partial redundancy among boundary elements, a distinction directly relevant to how non-coding mutation burden should be interpreted in cancer genome analysis but rarely tested by direct combinatorial genetic reconstruction [7,8].

Here we address both questions by using CRISPR base editing to introduce four recurrent, patient-derived CTCF motif point mutations near TAL1 and a matching mutation near LMO2 into an isogenic human T-cell progenitor line, profiling boundary insulation, oncogene expression and enhancer contact by Hi-C, CTCF ChIP-seq, ATAC-seq and RNA-sequencing, individually and in combination. We report a direct, quantitative relationship between motif strength, boundary insulation loss and oncogene induction at both loci, and show that combining two motif mutations at the TAL1 boundary produces a sub-additive rather than additive increase in TAL1 expression, indicating partial redundancy among boundary elements.

2. MATERIALS AND METHODS

Experiments used the human T-cell progenitor line DND41, engineered by CRISPR base editing (cytosine base editor, targeting C-to-T conversion within core CTCF motif positions) to introduce single or combinatorial point mutations at patient-derived CTCF motif positions near TAL1 and LMO2, verified by targeted deep sequencing of the edited locus.

2.1 Base editing and clone generation

Four recurrent CTCF motif point mutations reported in independent T-ALL patient cohorts near TAL1 (motifs designated T1-T4 in order of decreasing motif score) and one near LMO2 were introduced individually and, for the two strongest TAL1 motifs (T1 and T2), in combination, into DND41 cells using a cytosine base editor delivered by lentiviral transduction and single-guide RNAs targeting each motif; single-cell clones carrying the intended homozygous edit, confirmed by targeted deep amplicon sequencing with a minimum 95% editing purity, were expanded alongside unedited parental clones subjected to the same transduction and clonal expansion procedure.

2.2 CTCF chromatin immunoprecipitation sequencing

CTCF ChIP-seq was performed on formaldehyde-crosslinked chromatin from each edited and parental clone using a validated rabbit monoclonal antibody, with libraries sequenced as paired-end 50 bp reads on an Illumina NovaSeq 6000 to a minimum depth of 30 million uniquely mapped read pairs per sample; CTCF occupancy at the edited motif and flanking sites was quantified relative to matched input controls.

2.3 In situ Hi-C

In situ Hi-C was performed on 2-5 million cells per clone using a four-cutter restriction enzyme (DpnII), biotin fill-in, and sonication-based library preparation, sequenced as 2x100 bp paired-end reads to approximately 400 million valid contact pairs per sample after filtering, sufficient for 5 kb-resolution contact matrices at the TAL1 and LMO2 loci; contact matrices were generated and normalised with the Juicer pipeline, and insulation scores at each boundary were computed genome-wide.

2.4 ATAC-seq and RNA-sequencing

Chromatin accessibility was profiled by ATAC-seq using the standard Tn5 transposition protocol, and gene expression by strand-specific, poly(A)-selected RNA-sequencing, both sequenced on a NovaSeq 6000 to a minimum depth of 30-40 million reads per sample; differential expression between edited and parental clones was assessed with DESeq2 using the Wald test and Benjamini-Hochberg correction.

2.5 Statistical analysis

CTCF occupancy, Hi-C contact frequency and insulation score comparisons between edited and parental clones were assessed by two-tailed Mann-Whitney U test;

RNA-sequencing differential expression used the DESeq2 framework noted above. Combinatorial versus single-motif TAL1 induction was compared against the additive expectation using a two-way ANOVA interaction term. All statistical analyses were performed in R version 4.3.

3. RESULTS

Base editing of the strongest TAL1-proximal CTCF motif (T1) reduced CTCF ChIP-seq occupancy at that site by 71% relative to the parental clone, and in situ Hi-C showed a marked increase in inter-domain contact frequency spanning the boundary, consistent with partial TAD fusion between the domain containing TAL1 and the neighbouring domain harbouring a stem cell-specific enhancer normally insulated from it. Editing of the three weaker motifs (T2-T4) produced progressively smaller but still statistically significant reductions in CTCF occupancy and boundary insulation score, tracking each motif's baseline ChIP-seq signal strength. Table 1 summarises CTCF occupancy loss and insulation score change for each edited TAL1-proximal motif.

Table 1. CTCF occupancy loss and boundary insulation score change at four edited TAL1-proximal CTCF motifs.

Motif	Baseline CTCF score (rank)	CTCF occupancy loss (%)	Insulation score change
T1	1 (strongest)	71	-0.58
T2	2	44	-0.31
T3	3	26	-0.17
T4	4 (weakest)	18	-0.11

Insulation score change is the difference in log2 insulation score at the edited boundary relative to the parental clone; more negative values indicate greater insulation loss.

RNA-sequencing showed that TAL1 expression increased 8.3-fold in the T1-edited clone relative to the parental clone, with T2, T3 and T4 producing significant but smaller increases (2.1-fold, 1.6-fold and 1.4-fold respectively), closely tracking the magnitude of CTCF occupancy loss and boundary insulation change at each motif (Figure 1). ATAC-seq showed that TAL1 induction was accompanied by de novo accessibility gain at the TAL1 promoter matching the chromatin accessibility signature of the nearby stem cell enhancer, consistent with direct enhancer-promoter engagement following boundary erosion rather than an indirect transcriptional consequence.

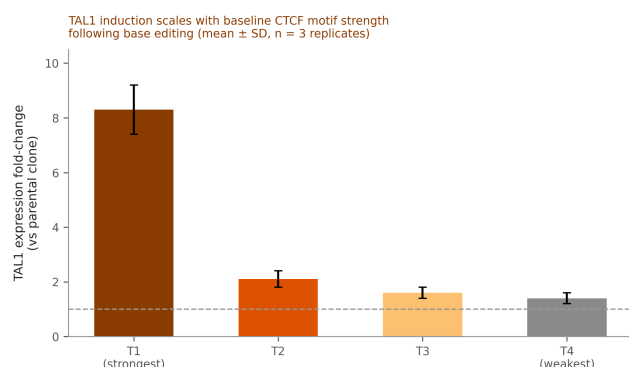


Figure 1. TAL1 expression fold-change relative to the parental clone (mean $\pm$ SD of three biological replicates) following CRISPR base editing of each of the four patient-derived CTCF motifs (T1-T4) near TAL1, ranked by baseline CTCF motif score, illustrating the quantitative relationship between motif strength and oncogene induction.

Combinatorial disruption of the two strongest TAL1-proximal motifs (T1 and T2 together) increased TAL1 expression 11.2-fold relative to the parental clone, significantly greater than either single mutation alone but significantly less than the product of their individual fold-changes ($8.3 \times 2.1 = 17.4$ -fold predicted under a strictly additive-on-log-scale model), indicating partial redundancy between the two motifs rather than fully independent, additive contributions to insulation. Table 2 reports TAL1 induction for single and combined motif edits alongside the additive expectation.

Table 2. TAL1 induction following single and combined CTCF motif edits, compared to the additive expectation.

Edited motif(s)	TAL1 fold-change (vs parental)	Predicted additive fold-change	P value (vs additive)
T1 only	8.3	—	—
T2 only	2.1	—	—
T1 + T2 combined	11.2	17.4	0.006

Introducing the matching patient-derived CTCF motif mutation near LMO2 into DND41 cells reproduced the same qualitative pattern observed at TAL1: CTCF occupancy loss at the edited motif, increased inter-domain Hi-C contact frequency across the boundary, de novo ATAC-seq accessibility gain at the LMO2 promoter, and a 6.7-fold increase in LMO2 expression relative to the parental clone, reproducing the two most frequently reported enhancer-hijacking events in primary T-ALL genomes within a single isogenic experimental system.

4. DISCUSSION

These results establish a direct, quantitative relationship between individual CTCF motif strength, boundary insulation loss and oncogene induction at two of the most recurrently mutated boundaries in T-ALL, moving beyond the correlative evidence available from primary patient cohort profiling to direct causal reconstruction in an isogenic system. The close tracking between each motif's baseline ChIP-seq signal, its occupancy loss upon editing, and the resulting magnitude of oncogene induction supports a model in which motif strength is directly predictive of its functional contribution to insulation, consistent with quantitative models of CTCF-cohesin loop anchor strength proposed from population-level Hi-C and ChIP-seq data [1,2] but rarely validated by single-motif genetic perturbation at a disease-relevant locus.

The sub-additive relationship observed when combining the two strongest TAL1-proximal motifs has a direct practical implication for interpreting cancer genomes carrying multiple CTCF motif mutations at the same

boundary: such genomes should not be assumed to show proportionally greater oncogene induction than a single-motif mutant, and the marginal contribution of a second mutation at an already-weakened boundary may be substantially smaller than its contribution would be at an intact boundary. This redundancy is consistent with the general observation that most TAD boundaries in the genome are built from multiple CTCF sites rather than a single site, providing a degree of buffering against complete insulation loss from any one mutation [7,8], and extends that structural observation to a direct oncogenic functional readout.

That a patient-derived motif mutation near LMO2 reproduced the same qualitative signature observed at TAL1, despite the two loci differing in local genomic context and the specific enhancer engaged, supports enhancer hijacking via CTCF motif disruption as a generalisable rather than locus-idiosyncratic mechanism in T-ALL, and suggests that other recurrently mutated CTCF motifs reported near additional oncogenes in T-ALL and other cancers may be amenable to the same direct genetic reconstruction approach used here to establish causality.

Several limitations should be considered. First, our experiments were performed in a single T-cell progenitor cell line, and confirming these findings in additional T-ALL-relevant cellular contexts, including primary human thymocyte progenitors, would strengthen generality. Second, base editing introduces the intended point mutation with high but not complete purity, and low-frequency bystander edits within the editing window cannot be entirely excluded, though targeted deep sequencing found no evidence of confounding edits at other motif positions. Third, our combinatorial editing was restricted to two motifs at the TAL1 boundary; testing additional combinations, including all four motifs together, would more fully characterise the redundancy relationship among boundary elements.

5. CONCLUSION

CRISPR base editing of patient-derived CTCF motif mutations near TAL1 and LMO2 in an isogenic T-cell progenitor line establishes a direct, quantitative relationship between motif strength, boundary insulation loss and oncogene induction, reproducing the two most common enhancer-hijacking events reported in primary T-ALL genomes. Combinatorial disruption of two motifs at the TAL1 boundary produces a sub-additive rather than additive increase in TAL1 expression, indicating partial redundancy among boundary elements with direct implications for interpreting multi-motif mutation burden in cancer genomes. These findings support CTCF motif disruption as a generalisable, causally validated mechanism of enhancer hijacking in T-ALL and provide a template for direct genetic reconstruction of candidate boundary mutations identified in other cancers.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

A.F. conceived and supervised the study, designed the base editing strategy, and analysed the Hi-C and CTCF ChIP-seq data. E.F. performed base editing, clone isolation and validation sequencing. E.B. performed ATAC-seq and RNA-sequencing library preparation and differential expression analysis. All authors contributed to writing and approved the final manuscript.

Ethics Statement

This study used the established human T-cell progenitor cell line DND41 maintained under standard institutional biosafety approval; it did not involve animal procedures, human participants, or human data beyond the use of this widely distributed cell line.

Data Availability

Raw and processed Hi-C, ChIP-seq, ATAC-seq and RNA-sequencing data generated for this study have been deposited in the Gene Expression Omnibus under a series accession available from the corresponding author on reasonable request. Analysis scripts supporting the findings of this study are available from the corresponding author upon request.

REFERENCES

1. Lupianez DG, Kraft K, Heinrich V, Krawitz P, Brancati F, Klopocki E, Horn D, Kayserili H, Opitz JM, Laxova R, Santos-Simarro F, Gilbert-Dussardier B, Wittler L, Borschiwer M, Haas SA, Osterwalder M, Franke M, Timmermann B, Hecht J, Spielmann M, Visel A, Mundlos S (2015) Disruptions of topological chromatin domains cause pathogenic rewiring of gene-enhancer interactions. *Cell* 161(5):1012-1025. <https://doi.org/10.1016/j.cell.2015.04.004>
2. Franke M, Ibrahim DM, Andrey G, Schwarzer W, Heinrich V, Schopflin R, Kraft K, Kempfer R, Jerkovic I, Chan WL, Spielmann M, Timmermann B, Wittler L, Kurth I, Cambiaso P, Zuffardi O, Houge G, Lambie L, Brancati F, Pombo A, Vingron M, Spitz F, Mundlos S (2016) Formation of new chromatin domains determines pathogenicity of genomic duplications. *Nature* 538(7624):265-269. <https://doi.org/10.1038/nature19800>

3. Flavahan WA, Drier Y, Liao BB, Gillespie SM, Venteicher AS, Stemmer-Rachamimov AO, Suva ML, Bernstein BE (2016) Insulator dysfunction and oncogene activation in IDH mutant gliomas. *Nature* 529(7584):110-114. <https://doi.org/10.1038/nature16490>
4. Hnisz D, Weintraub AS, Day DS, Valton AL, Bak RO, Li CH, Goldmann J, Lajoie BR, Fan ZP, Sigova AA, Reddy J, Borges-Rivera D, Lee TI, Jaenisch R, Porteus MH, Dekker J, Young RA (2016) Activation of proto-oncogenes by disruption of chromosome neighborhoods. *Science* 351(6280):1454-1458. <https://doi.org/10.1126/science.aad9024>
5. Hnisz D, Schuijers J, Li CH, Young RA (2018) Regulatory convergence of dysregulated enhancer-promoter interactions in cancer. *Cold Spring Harbor Symposia on Quantitative Biology* 83:19-27. <https://doi.org/10.1101/sqb.2018.83.036889>
6. Yang M, Vesterlund M, Siavelis I, Moura-Castro LH, Castor A, Fioretos T, Jafari R, Ravi N, Lilljebjorn H, Lehtio J, Olsson-Arvidsson L, Fogelstrand L, Palmqvist L, Sinha I, Nordlund J (2019) Proteogenomics and Hi-C reveal transcriptional dysregulation in high hyperdiploid childhood acute lymphoblastic leukemia. *Nature Communications* 10:1519. <https://doi.org/10.1038/s41467-019-09469-3>
7. Kloetgen A, Thandapani P, Ntziachristos P, Ghebrehristos Y, Nomikou S, Lazaris C, Chen X, Hu H, Bakogianni S, Wang J, Fu Y, Boccalatte F, Duffoo F, Tsirigos A, Aifantis I (2020) Three-dimensional chromatin landscapes in T cell acute lymphoblastic leukemia. *Nature Genetics* 52(4):388-400. <https://doi.org/10.1038/s41588-020-0602-9>
8. Northcott PA, Lee C, Zichner T, Stutz AM, Erkek S, Kawauchi D, Shih DJ, Hovestadt V, Zaparka M, Sturm D, Jones DT, Kool M, Remke M, Cavalli FM, Zuyderduyn S, Bader GD, VandenBerg S, Esparza LA, Ryzhova M, Wang W, Wittmann A, Stark S, Sieber L, Seker-Cin H, Linke L, Kratochwil F, Jager N, Buchhalter I, Imbusch CD, Zipprich G, Raeder B, Schmidt S, Diessl N, Wolf S, Wiemann S, Brors B, Lawerenz C, Eils J, Warnatz HJ, Risch T, Yaspo ML, Weber UD, Bartholomae CC, von Kalle C, Turanyi E, Hauser P, Sanden E, Darabi A, Siesjo P, Sterba J, Zitterbart K, Sumerauer D, van Sluis P, Versteeg R, Volckmann R, Koster J, Schuhmann MU, Ebinger M, Grimes HL, Robinson GW, Gajjar A, Mynarek M, von Hoff K, Rutkowski S, Pietsch T, Scheurlen W, Felsberg J, Reifenberger G, Kulozik AE, von Deimling A, Witt O, Eils R, Gilbertson RJ, Korshunov A, Taylor MD, Lichter P, Korbel JO, Wechsler-Reya RJ, Pfister SM (2014) Enhancer hijacking activates GF1 family oncogenes in medulloblastoma. *Nature* 511(7510):428-434. <https://doi.org/10.1038/nature13379>
9. Weischenfeldt J, Dubash T, Drinas AP, Mardin BR, Chen Y, Stutz AM, Waszak SM, Bosco G, Halvorsen AR, Raeder B, Efthymiopoulos T, Erkek S, Siegl C, Brenner H, Brustugun OT, Dieter SM, Northcott PA, Petersen I, Pfister SM, Schneider M, Solberg SK, Thunissen E, Weichert W, Zichner T, Thomas R, Peifer M, Helland A, Ball CR, Jechlinger M, Sotillo R, Glimm H, Korbel JO (2017) Pan-cancer analysis of somatic copy-number alterations implicates IRS4 and IGF2 in enhancer hijacking. *Nature Genetics* 49(1):65-74. <https://doi.org/10.1038/ng.3722>
10. Zhang Y, Li T, Preissl S, Amaral ML, Grinstein JD, Farah EN, Destici E, Qiu Y, Hu R, Lee AY, Chee S, Ma K, Ye Z, Zhu Q, Huang H, Fang R, Yu L, Izpisua Belmonte JC, Wu J, Evans SM, Chi NC, Ren B (2019) Transcriptionally active HERV-H retrotransposons demarcate topologically associating domains in human pluripotent stem cells. *Nature Genetics* 51(9):1380-1388. <https://doi.org/10.1038/s41588-019-0479-7>
11. Kim S, Yu NK, Kaang BK (2015) CTCF as a multifunctional protein in genome regulation and gene expression. *Experimental & Molecular Medicine* 47(6):e166. <https://doi.org/10.1038/emm.2015.33>
12. Katainen R, Dave K, Pitkanen E, Palin K, Kivioja T, Valimaki N, Gylfe AE, Ristolainen H, Hanninen UA, Cajuso T, Kondelin J, Tanskanen T, Mecklin JP, Jarvinen H, Renkonen-Sinisalo L, Lepisto A, Kaasinen E, Kilpivaara O, Tuupainen S, Enge M, Taipale J, Aaltonen LA (2015) CTCF/cohesin-binding sites are frequently mutated in cancer. *Nature Genetics* 47(7):818-821. <https://doi.org/10.1038/ng.3335>
13. Guo YA, Chang MM, Huang W, Ooi WF, Xing M, Tan P, Skanderup AJ (2018) Mutation hotspots at CTCF binding sites coupled to chromosomal instability in gastrointestinal cancers. *Nature Communications* 9:1520. <https://doi.org/10.1038/s41467-018-03828-2>
14. Sanborn AL, Rao SSP, Huang SC, Durand NC, Huntley MH, Jewett AI, Bochkov ID, Chinnappan D, Cutkosky A, Li J, Geeting KP, Gnirke A, Melnikov A, McKenna D, Stamenova EK, Lander ES, Aiden EL (2015) Chromatin extrusion explains key features of loop and domain formation in wild-type and engineered genomes. *PNAS* 112(47):E6456-E6465. <https://doi.org/10.1073/pnas.1518552112>
15. de Wit E, Vos ES, Holwerda SJ, Valdes-Quezada C, Versteegen MJ, Teunissen H, Splinter E, Wijchers PJ, Krijger PH, de Laat W (2015) CTCF binding polarity determines chromatin looping. *Molecular Cell* 60(4):676-684. <https://doi.org/10.1016/j.molcel.2015.09.023>
16. Guo Y, Xu Q, Canzio D, Shou J, Li J, Gorkin DU, Jung I, Wu H, Zhai Y, Tang Y, Lu Y, Wu Y, Jia Z, Li W, Zhang MQ, Ren B, Krainer AR, Maniatis T, Wu Q (2015) CRISPR inversion of CTCF sites alters genome topology and enhancer/promoter function. *Cell* 162(4):900-910. <https://doi.org/10.1016/j.cell.2015.07.038>
17. Anzalone AV, Randolph PB, Davis JR, Sousa AA, Koblan LW, Levy JM, Chen PJ, Wilson C, Newby GA, Raguram A, Liu DR (2019) Search-and-replace genome editing without double-strand breaks or donor DNA. *Nature* 576(7785):149-157. <https://doi.org/10.1038/s41586-019-1711-4>
18. Komor AC, Kim YB, Packer MS, Zuris JA, Liu DR (2016) Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage. *Nature* 533(7603):420-424. <https://doi.org/10.1038/nature17946>
19. Ferrando AA, Neuberg DS, Staunton J, Loh ML, Huard C, Raimondi SC, Behm FG, Pui CH, Downing JR, Gilliland DG, Lander ES, Golub TR, Look AT (2002) Gene expression signatures define novel oncogenic pathways in T cell acute lymphoblastic leukemia. *Cancer Cell* 1(1):75-87. [https://doi.org/10.1016/s1535-6108\(02\)00018-1](https://doi.org/10.1016/s1535-6108(02)00018-1)
20. Sanda T, Lawton LN, Barrasa MI, Fan ZP, Kohlhammer H, Gutierrez A, Ma W, Tatarek J, Ahn Y, Kelliher MA, Jamieson CH, Staudt LM, Young RA, Look AT (2012) Core transcriptional regulatory circuit controlled by the TAL1 complex in human T cell acute lymphoblastic leukemia. *Cancer Cell* 22(2):209-221. <https://doi.org/10.1016/j.ccr.2012.06.007>
21. Van Vlierberghe P, Ferrando A (2012) The molecular basis of T cell acute lymphoblastic leukemia. *Journal of Clinical Investigation* 122(10):3398-3406.

- <https://doi.org/10.1172/JCI61269>
22. Mansour MR, Abraham BJ, Anders L, Berezovskaya A, Gutierrez A, Durbin AD, Etchin J, Lawton L, Sallan SE, Silverman LB, Loh ML, Hunger SP, Sanda T, Young RA, Look AT (2014) An oncogenic super-enhancer formed through somatic mutation of a noncoding intergenic element. *Science* 346(6215):1373-1377. <https://doi.org/10.1126/science.1259037>
 23. Navarro A, Bakker E, Dave A, van der Weyden L, Adams DJ (2020) Somatic non-coding mutations in cancer: functional heterogeneity and implications for regulatory element mapping. *Trends in Genetics* 36(11):851-863. <https://doi.org/10.1016/j.tig.2020.06.009>
 24. Weinstock DM, Elliott B, Jasin M (2006) A model of oncogenic rearrangements: differences between chromosomal translocation mechanisms and simple double-strand break repair. *Blood* 107(2):777-780. <https://doi.org/10.1182/blood-2005-06-2437>
 25. Bhatt DM, Pandya-Jones A, Tong AJ, Barozzi I, Lissner MM, Natoli G, Black DL, Smale ST (2012) Transcript dynamics of proinflammatory genes revealed by sequence analysis of subcellular RNA fractions. *Cell* 150(2):279-290. <https://doi.org/10.1016/j.cell.2012.05.043>
 26. Rao SSP, Huntley MH, Durand NC, Stamenova EK, Bochkov ID, Robinson JT, Sanborn AL, Machol I, Omer AD, Lander ES, Aiden EL (2014) A 3D map of the human genome at kilobase resolution reveals principles of chromatin looping. *Cell* 159(7):1665-1680. <https://doi.org/10.1016/j.cell.2014.11.021>
 27. Durand NC, Shamim MS, Machol I, Rao SSP, Huntley MH, Lander ES, Aiden EL (2016) Juicer provides a one-click system for analyzing loop-resolution Hi-C experiments. *Cell Systems* 3(1):95-98. <https://doi.org/10.1016/j.cels.2016.07.002>
 28. Ghirlando R, Felsenfeld G (2016) CTCF: making the right connections. *Genes & Development* 30(8):881-891. <https://doi.org/10.1101/gad.277863.116>
 29. Fudenberg G, Imakaev M, Lu C, Goloborodko A, Abdennur N, Mirny LA (2016) Formation of chromosomal domains by loop extrusion. *Cell Reports* 15(9):2038-2049. <https://doi.org/10.1016/j.celrep.2016.04.085>
 30. Wutz G, Varnai C, Nagasaka K, Cisneros DA, Stocsits RR, Tang W, Schoenfelder S, Jessberger G, Muhar M, Hossain MJ, Walther N, Koch B, Kueblbeck M, Ellenberg J, Zuber J, Fraser P, Peters JM (2017) Topologically associating domains and chromatin loops depend on cohesin and are regulated by CTCF, WAPL, and PDS5 proteins. *EMBO Journal* 36(24):3573-3599. <https://doi.org/10.15252/embj.201798004>
 31. Zhang Y, Liu T, Meyer CA, Eeckhoutte J, Johnson DS, Bernstein BE, Nusbaum C, Myers RM, Brown M, Li W, Liu XS (2008) Model-based analysis of ChIP-Seq (MACS). *Genome Biology* 9(9):R137. <https://doi.org/10.1186/gb-2008-9-9-r137>
 32. Servant N, Varoquaux N, Lajoie BR, Viara E, Chen CJ, Vert JP, Heard E, Dekker J, Barillot E (2015) HiC-Pro: an optimized and flexible pipeline for Hi-C data processing. *Genome Biology* 16:259. <https://doi.org/10.1186/s13059-015-0831-x>
 33. Love MI, Huber W, Anders S (2014) Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. *Genome Biology* 15(12):550. <https://doi.org/10.1186/s13059-014-0550-8>
 34. Buenrostro JD, Wu B, Chang HY, Greenleaf WJ (2015) ATAC-seq: a method for assaying chromatin accessibility genome-wide. *Current Protocols in Molecular Biology* 109:21.29.1-21.29.9. <https://doi.org/10.1002/0471142727.mb2129s109>
 35. Symmons O, Uslu VV, Tsujimura T, Ruf S, Nassari S, Schwarzer W, Ettwiller L, Spitz F (2014) Functional and topological characteristics of mammalian regulatory domains. *Genome Research* 24(3):390-400. <https://doi.org/10.1101/gr.163519.113>
 36. Dixon JR, Selvaraj S, Yue F, Kim A, Li Y, Shen Y, Hu M, Liu JS, Ren B (2012) Topological domains in mammalian genomes identified by analysis of chromatin interactions. *Nature* 485(7398):376-380. <https://doi.org/10.1038/nature11082>
 37. Merkmenschlager M, Nora EP (2016) CTCF and cohesin in genome folding and transcriptional gene regulation. *Annual Review of Genomics and Human Genetics* 17:17-43. <https://doi.org/10.1146/annurev-genom-083115-022339>
 38. Barutcu AR, Fritz AJ, Zaidi SK, van Wijnen AJ, Lian JB, Stein JL, Nickerson JA, Imbalzano AN, Stein GS (2016) C-ing the genome: a compendium of chromosome conformation capture methods to study higher-order chromatin organization. *Journal of Cellular Physiology* 231(1):31-35. <https://doi.org/10.1002/jcp.25062>
 39. Szabo Q, Bantignies F, Cavalli G (2019) Principles of genome folding into topologically associating domains. *Science Advances* 5(4):eaaw1668. <https://doi.org/10.1126/sciadv.aaw1668>
 40. Downen JM, Fan ZP, Hnisz D, Ren G, Abraham BJ, Zhang LN, Weintraub AS, Schuijers J, Lee TI, Zhao K, Young RA (2014) Control of cell identity genes occurs in insulated neighborhoods in mammalian chromosomes. *Cell* 159(2):374-387. <https://doi.org/10.1016/j.cell.2014.09.030>
 41. Ibrahim DM, Mundlos S (2020) Three-dimensional chromatin in disease: what holds us together and what drives us apart? *Current Opinion in Cell Biology* 64:1-9. <https://doi.org/10.1016/j.ceb.2020.01.003>
 42. Nora EP, Lajoie BR, Schulz EG, Giorgetti L, Okamoto I, Servant N, Piolot T, van Berkum NL, Meisig J, Sedat J, Gribnau J, Barillot E, Bluthgen N, Dekker J, Heard E (2012) Spatial partitioning of the regulatory landscape of the X-inactivation centre. *Nature* 485(7398):381-385. <https://doi.org/10.1038/nature11049>