

3D Genome Analysis Identifies Enhancer Hijacking Mechanism for High-Risk Factors in Human T-ALL

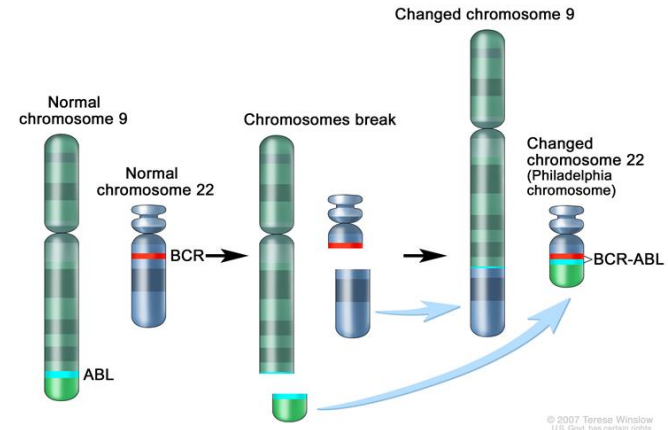
Fengling Chen

Supervisor: Michael Q. Zhang & Yang Chen

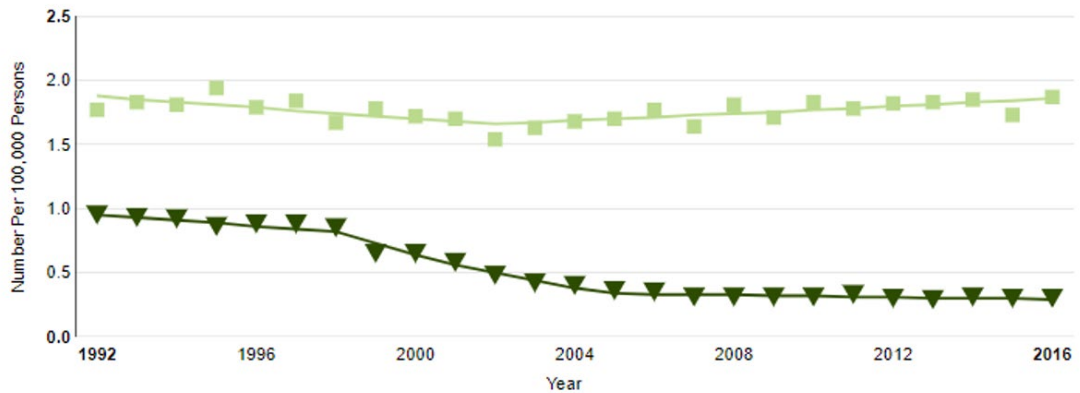
Bioinformatics Division and Center for Synthetic and Systems Biology,
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2020-12-05

CML and GLIVEC

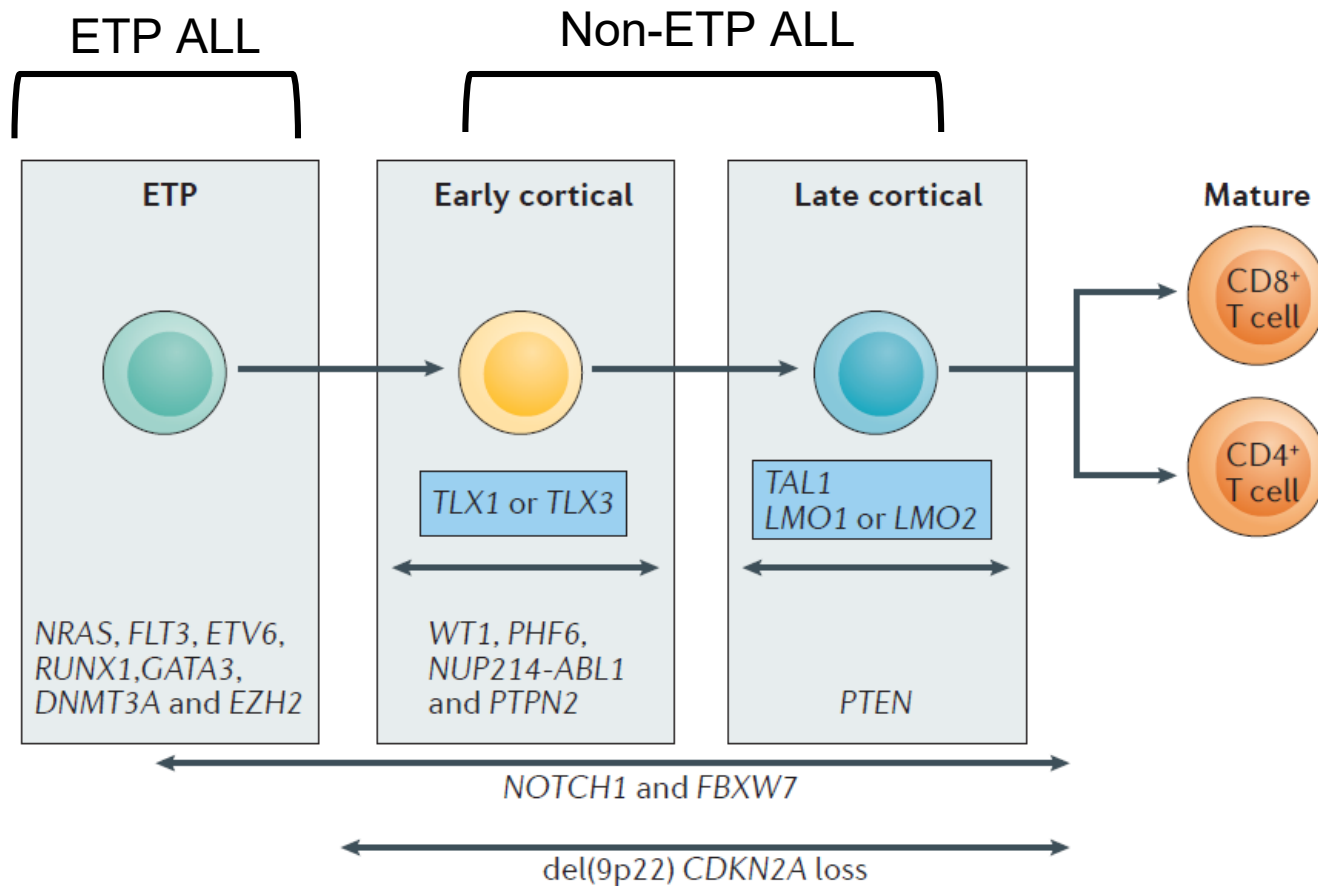


Chronic myelogenous leukemia (CML)
90% CML patients have BCR-ABL translocation;
GLIVEC can turn the five-year survival rate from 30% to 90%.



■ New Cases - SEER 13 ▼ Deaths - U.S.

T-ALL: T-cell acute lymphoblastic leukaemia



ETP-ALL

1. Block at the earliest stages of T cell differentiation;
2. High-risk subtype

Motivation of studying T-ALL with 3D genome data

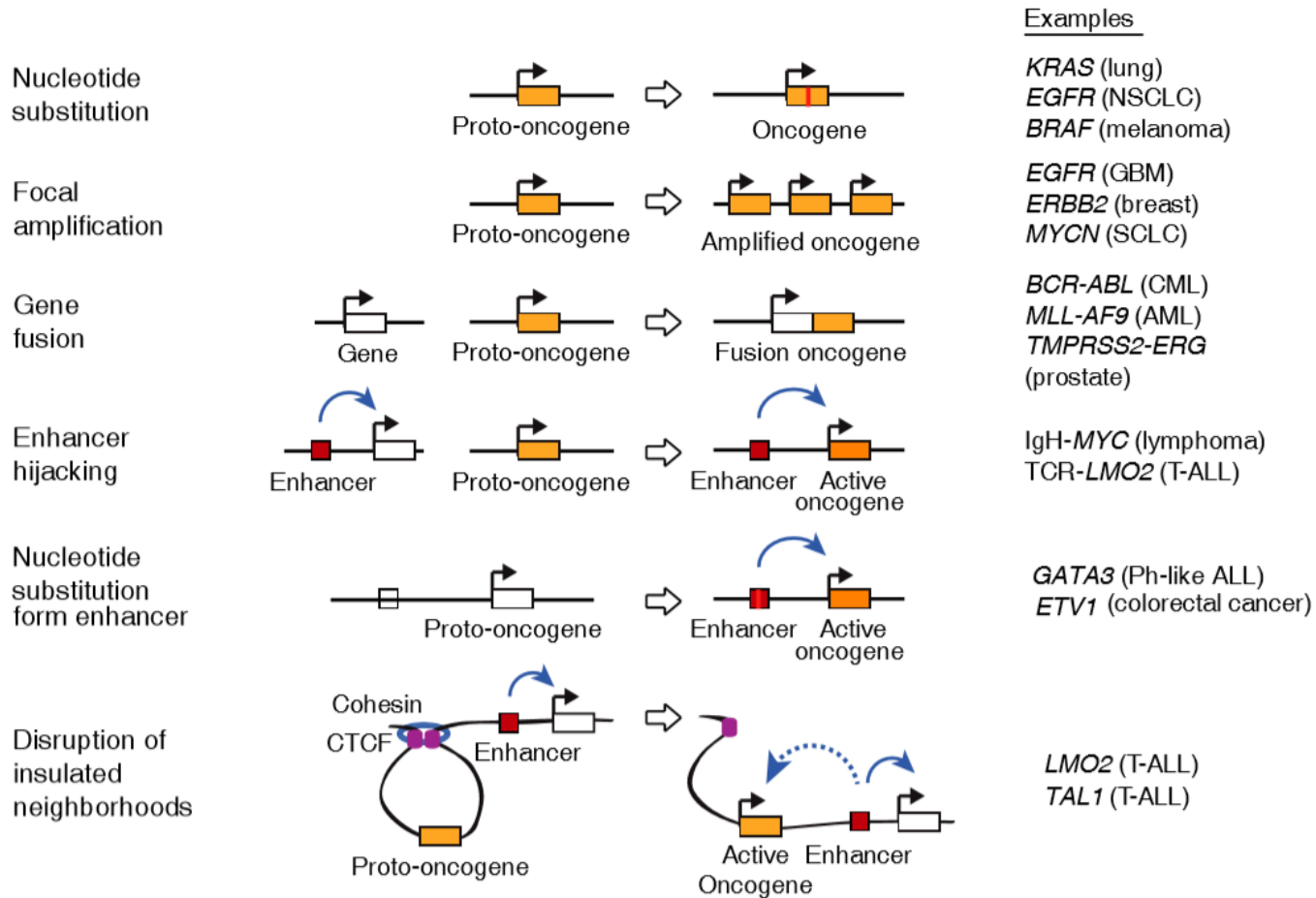
Whole-exome and RNA sequencing analyses of large T-ALL cohorts

Liu, Yu, et al. *Nature genetics* (2017). The US
Seki, Masafumi, et al. *Nature genetics* (2017). Japan
Chen, Bing, et al. *PNAS* (2018). China

- Focusing on coding region of genome.
- Identification of T-ALL associated mutations and dysregulated genes.
- Non-coding region account for 98% genome, regulatory elements locate in non-coding region.

How alternations of the non-coding region contribute to T-ALL progression?

Motivation of studying T-ALL with 3D genome data



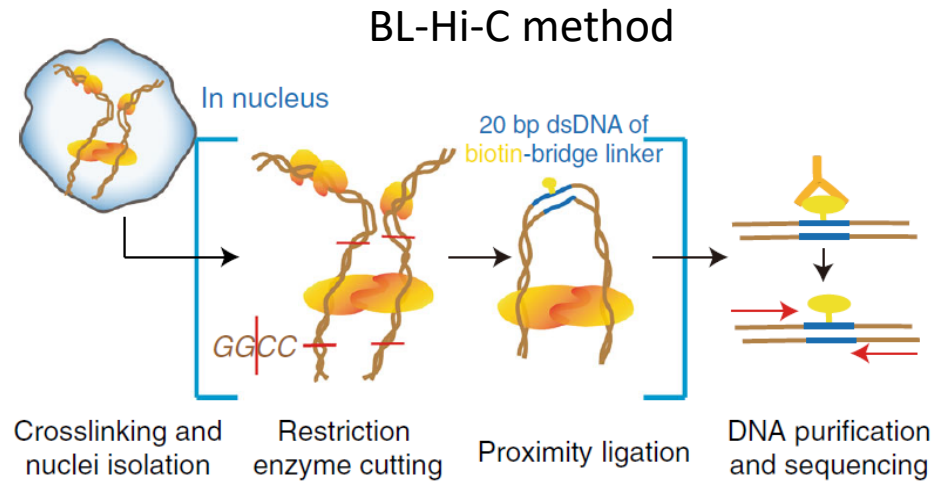
Mechanism of oncogene activation (Hnisz et al. Science, 2016)

3D genome technology is a great tool to detect non-coding alterations and explain the mechanism of oncogene activation.

Experimental design



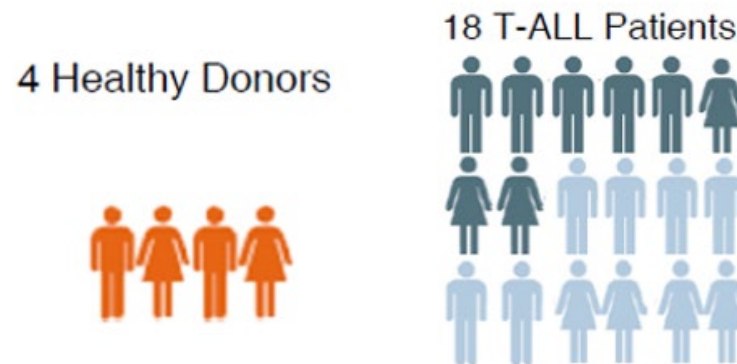
Prof. Hong Wu



Liang et al. Nature communication, 2018

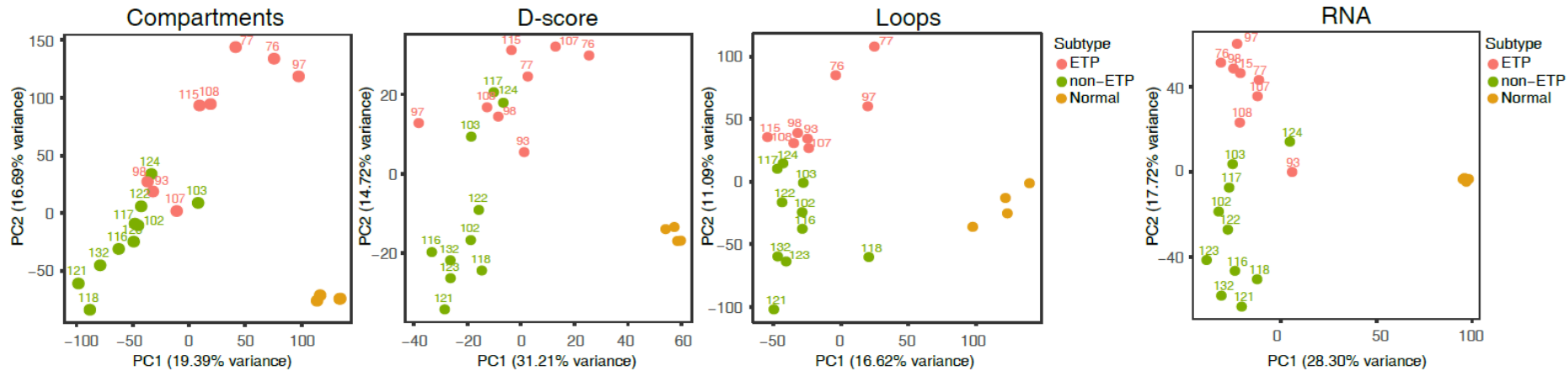


Dr. Lu Yang



Paired BL-Hi-C and RNA-seq experiment

Global reorganization of 3D genome architecture in T-ALL

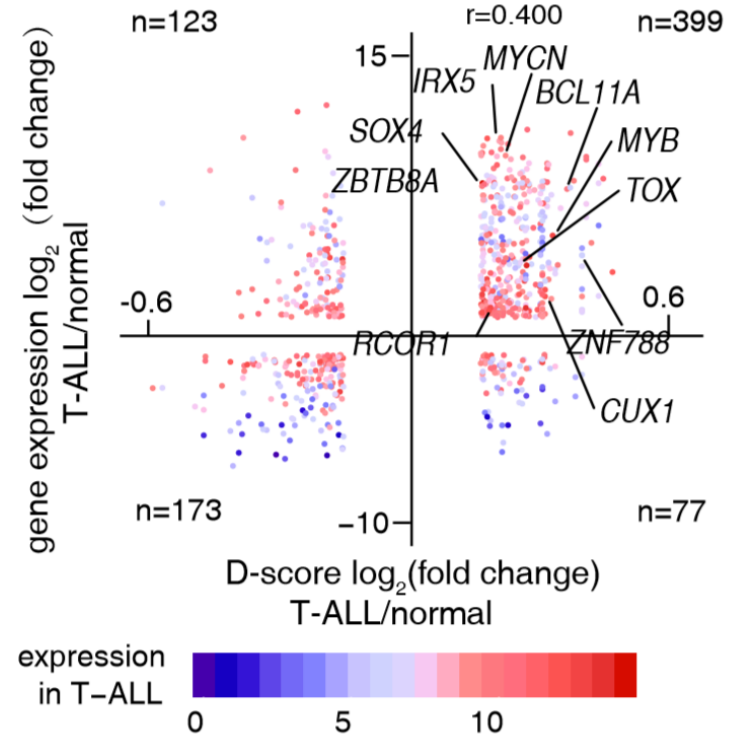
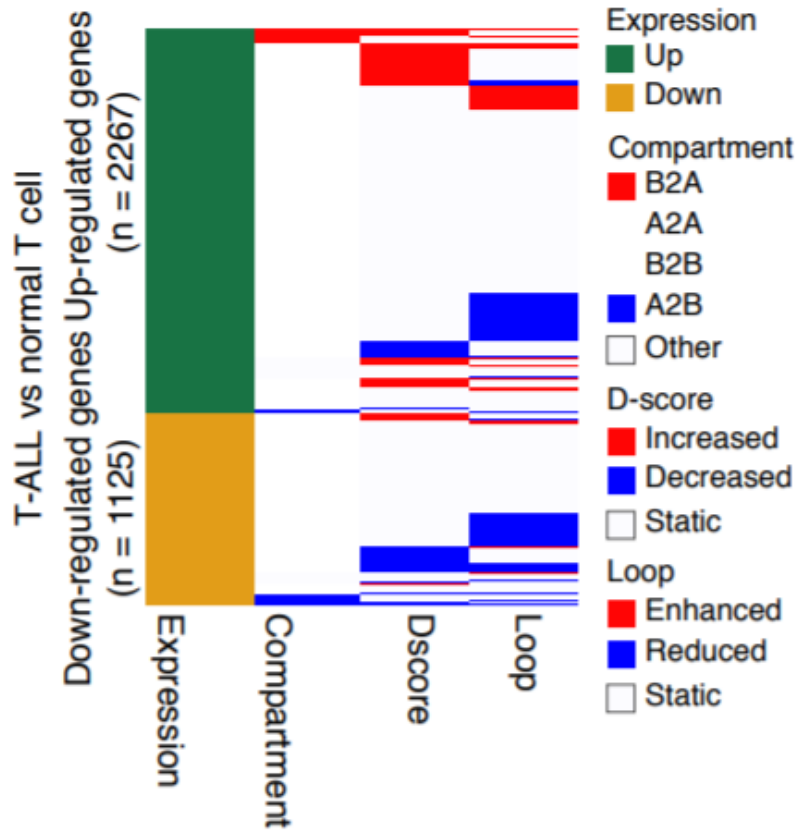


Compartment: B-to-A (1.38%) and A-to-B switches (1.59%)

TAD boundaries: total: 3421; T-ALL-specific: 377; normal-specific: 315

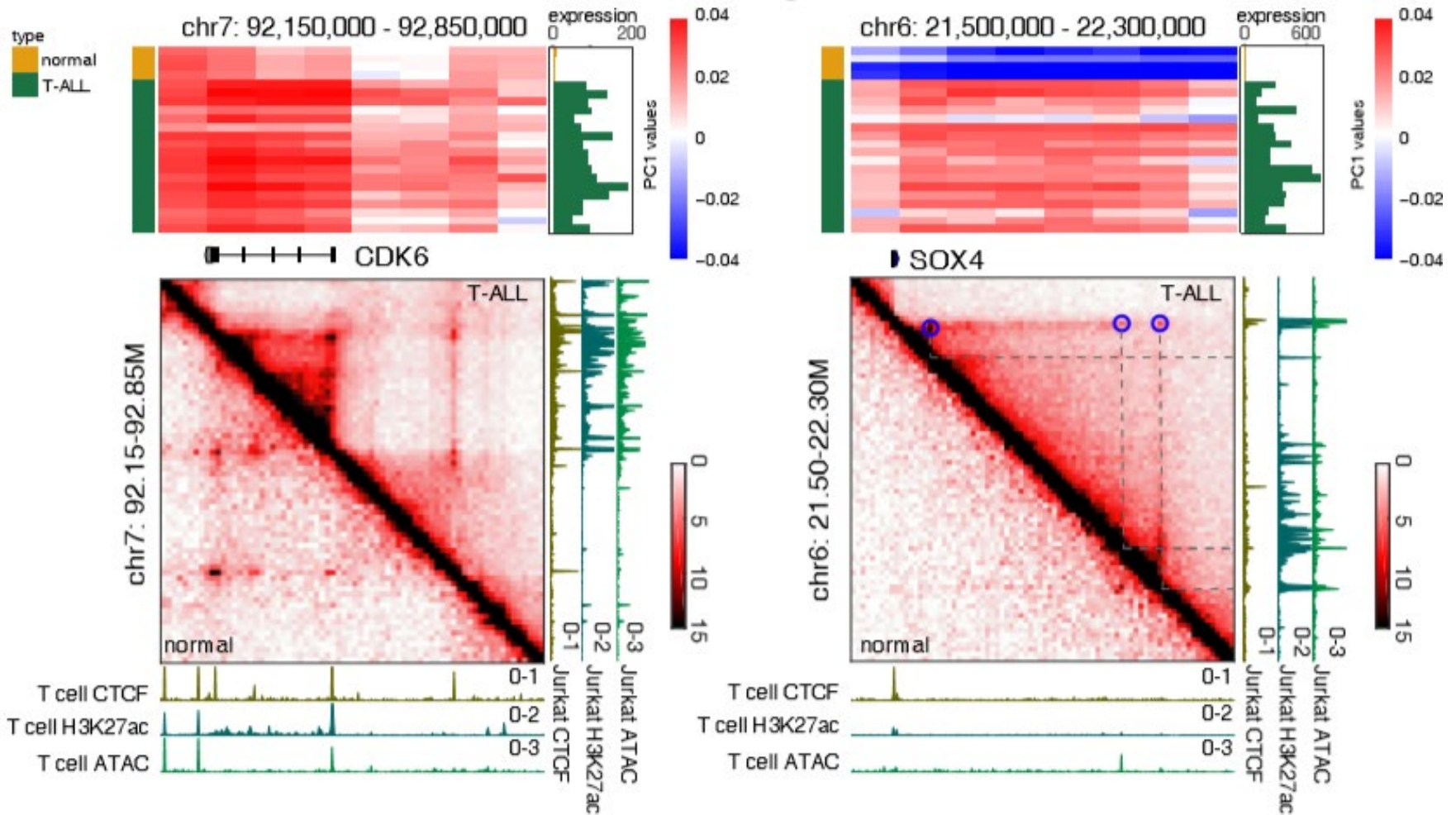
Loops: total: 38464; enhanced: 2330; reduced: 4073

Chromatin structure changes coincide with oncogenic transcription factor aberrant expression



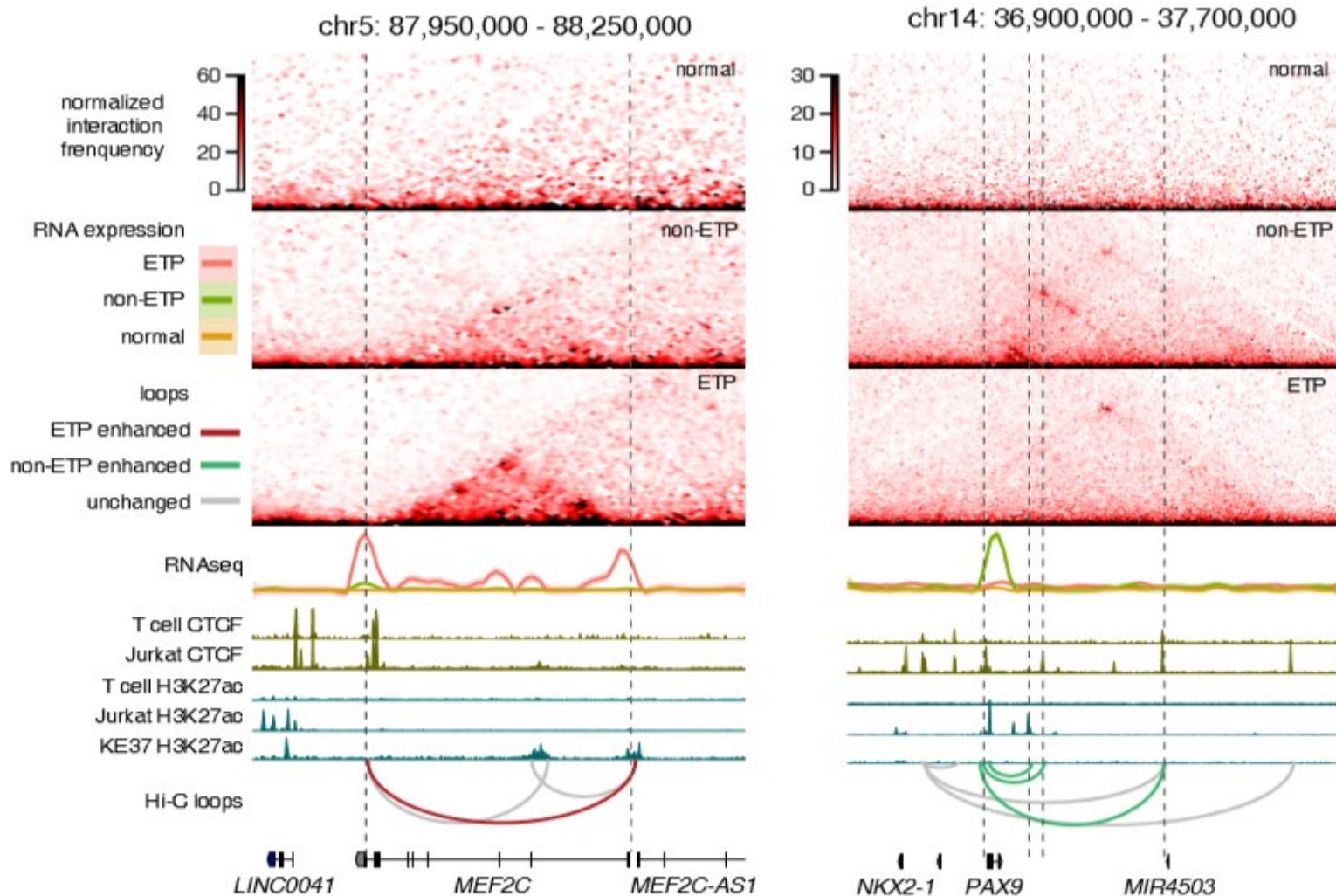
29.4% (996 /3392) of DEGs between normal and T-ALL were associated with consistent 3D genome alterations.

Chromatin structure changes of T-ALL-associated genes



CDK6 is a potential target for T-ALL treatment

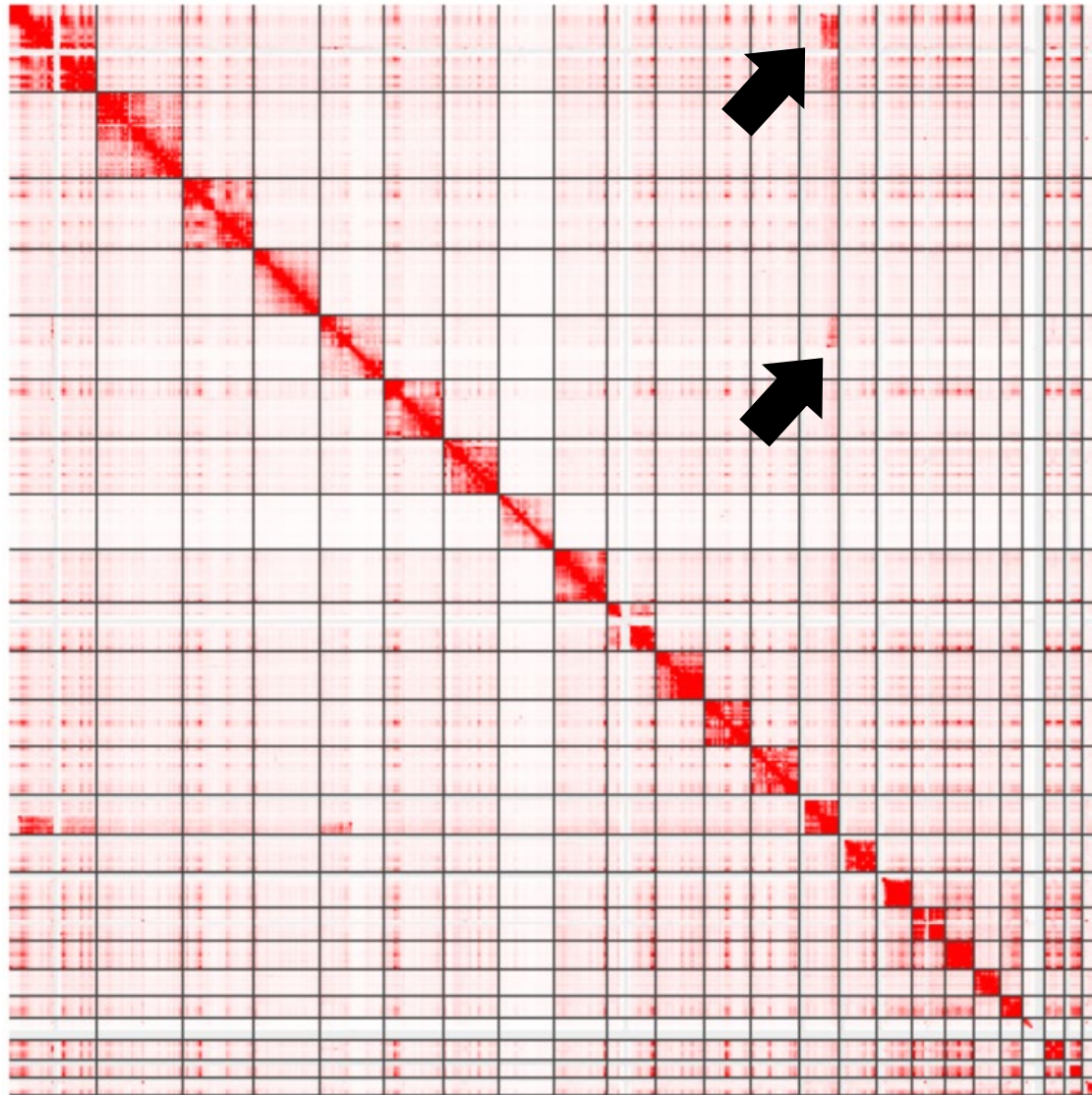
Key TFs have distinct chromatin structures in T-ALL subtypes



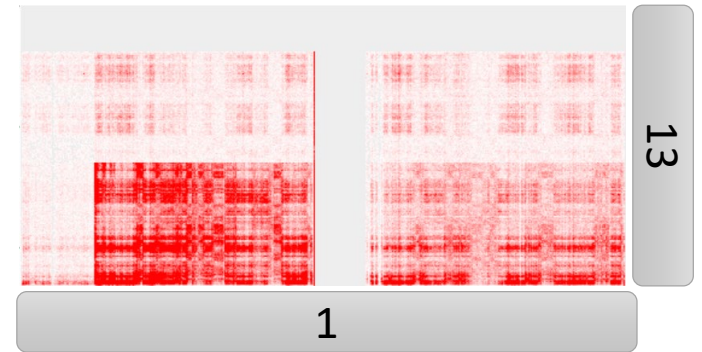
These could be the downstream of genetic variation.

Hi-C data reveal massive novel translocations

T-ALL patient



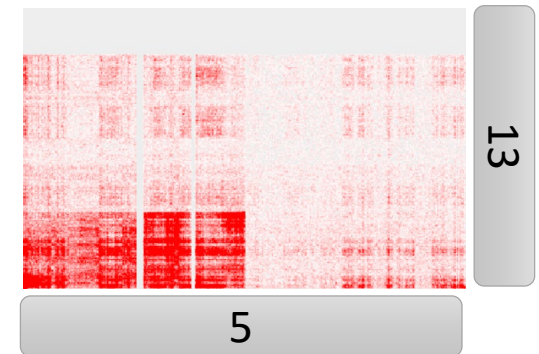
T(1;13)



1

13

T(5;13)

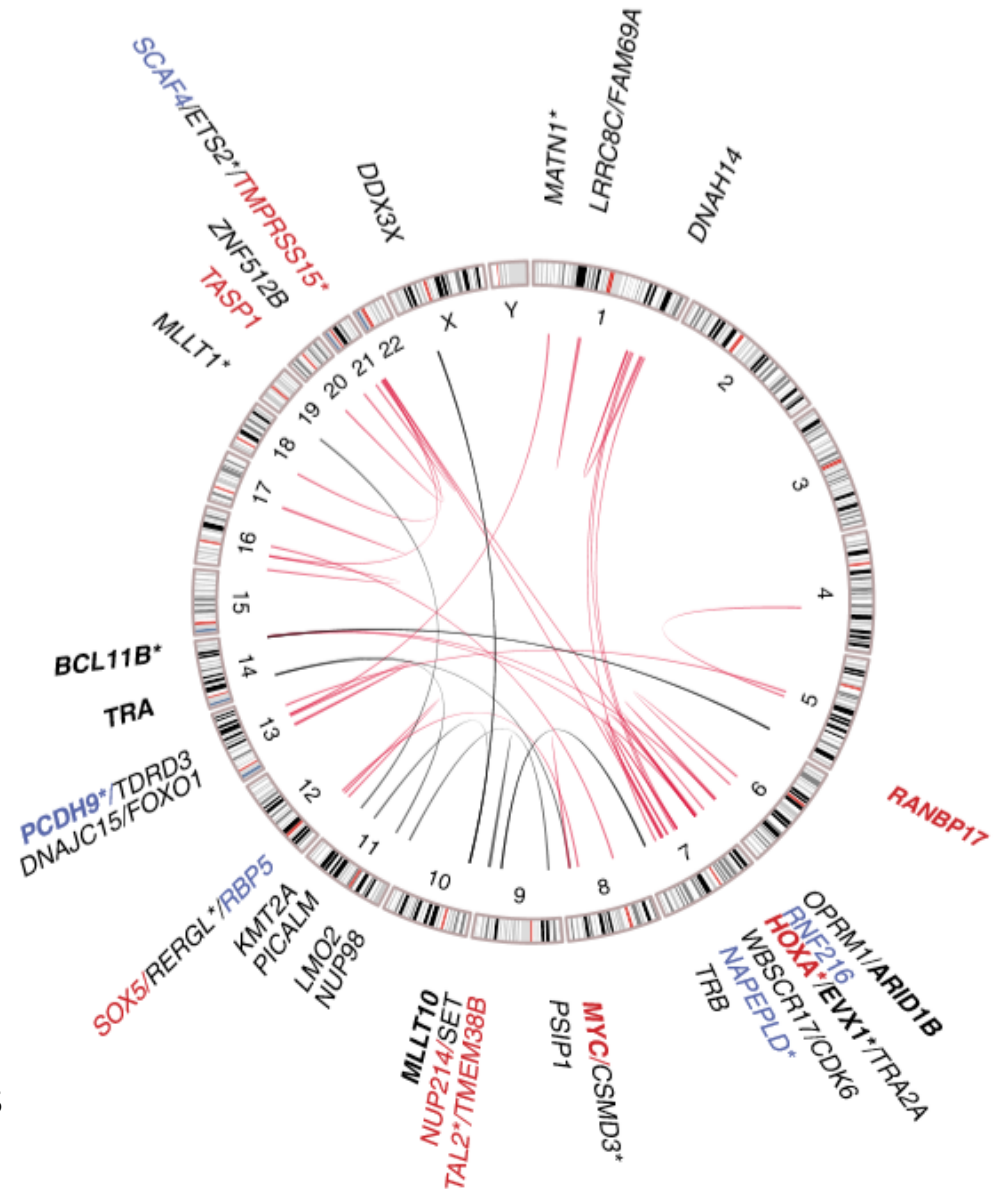


5

13

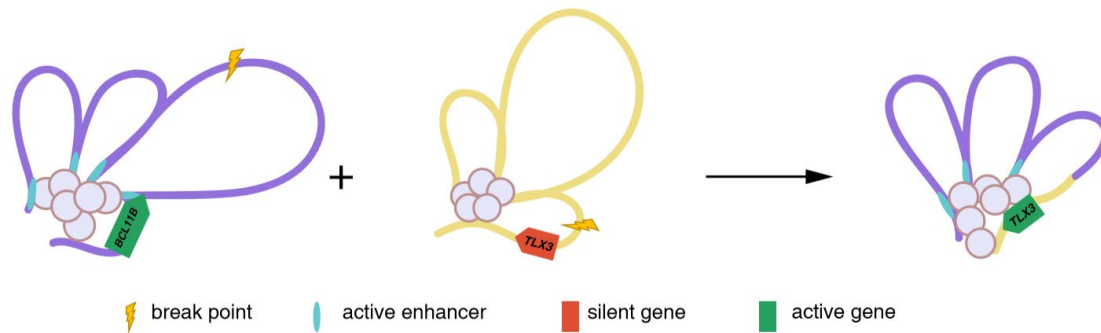
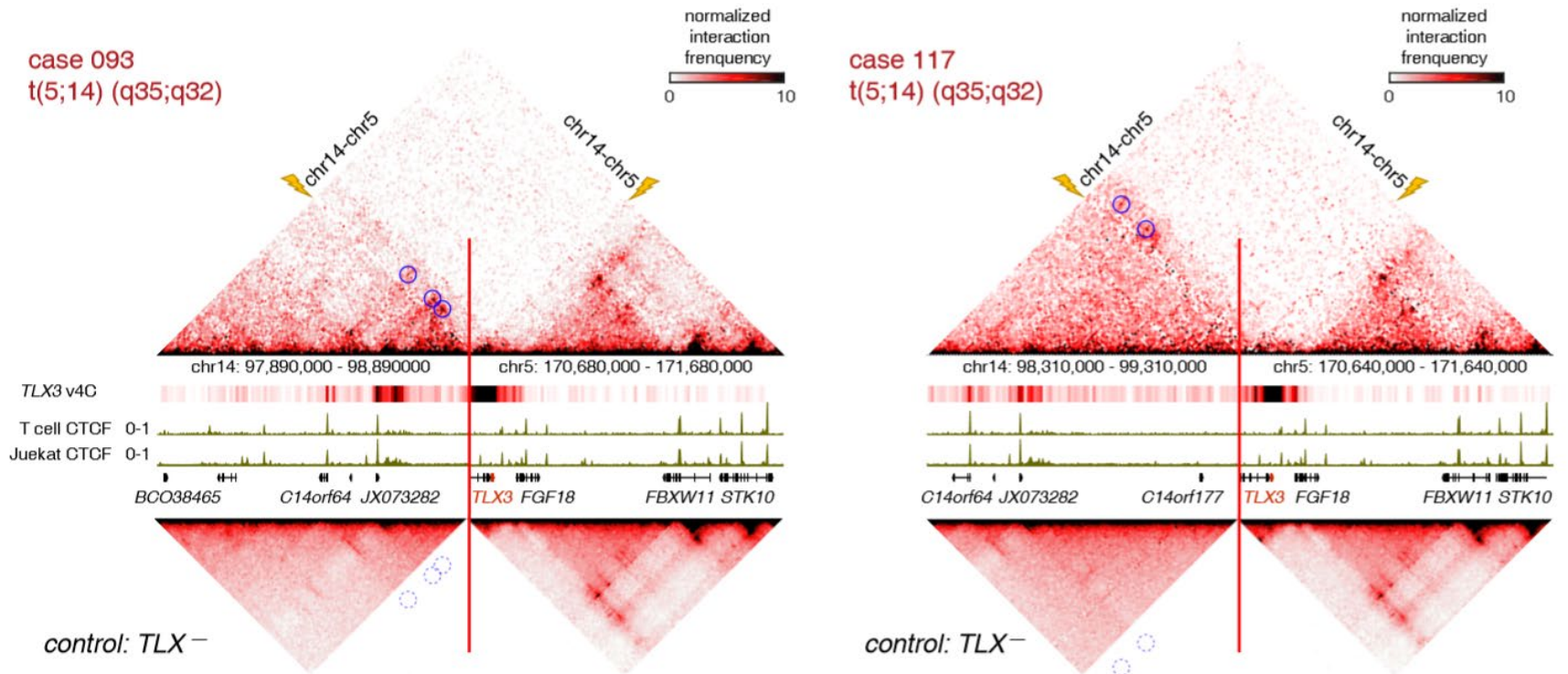
Hi-C data reveal massive novel translocations

Patient Translocation profile
(nearest genes)



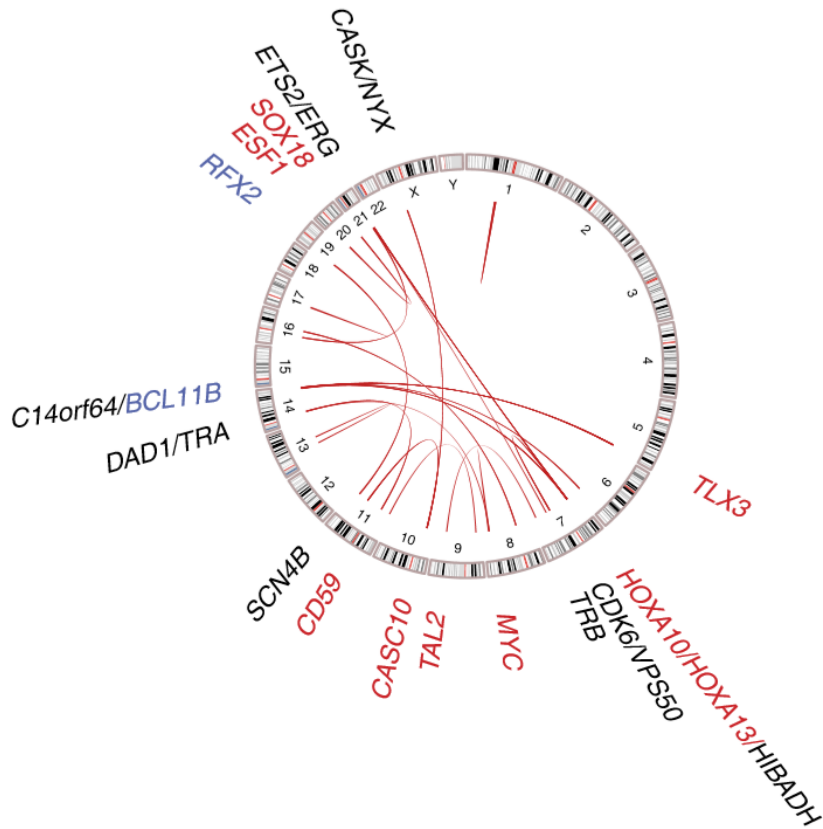
34 (total:46) novel translocation events
37 (total:78) non-coding breakpoints

Trans-loops forms between TLX3 and BCL11B enhancers

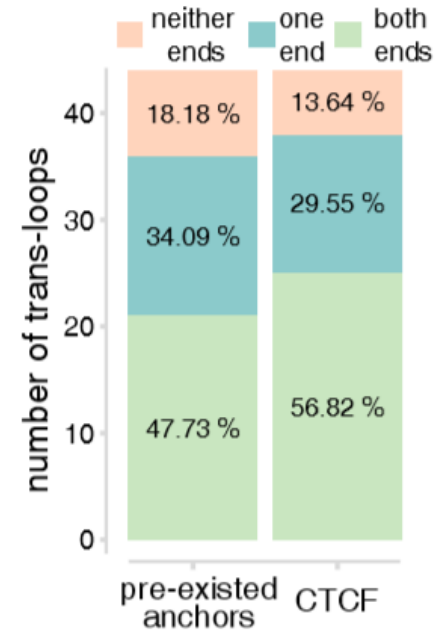


TLX3 and BCL11B are both import TFs in T cell development.

Characteristics of trans-loops

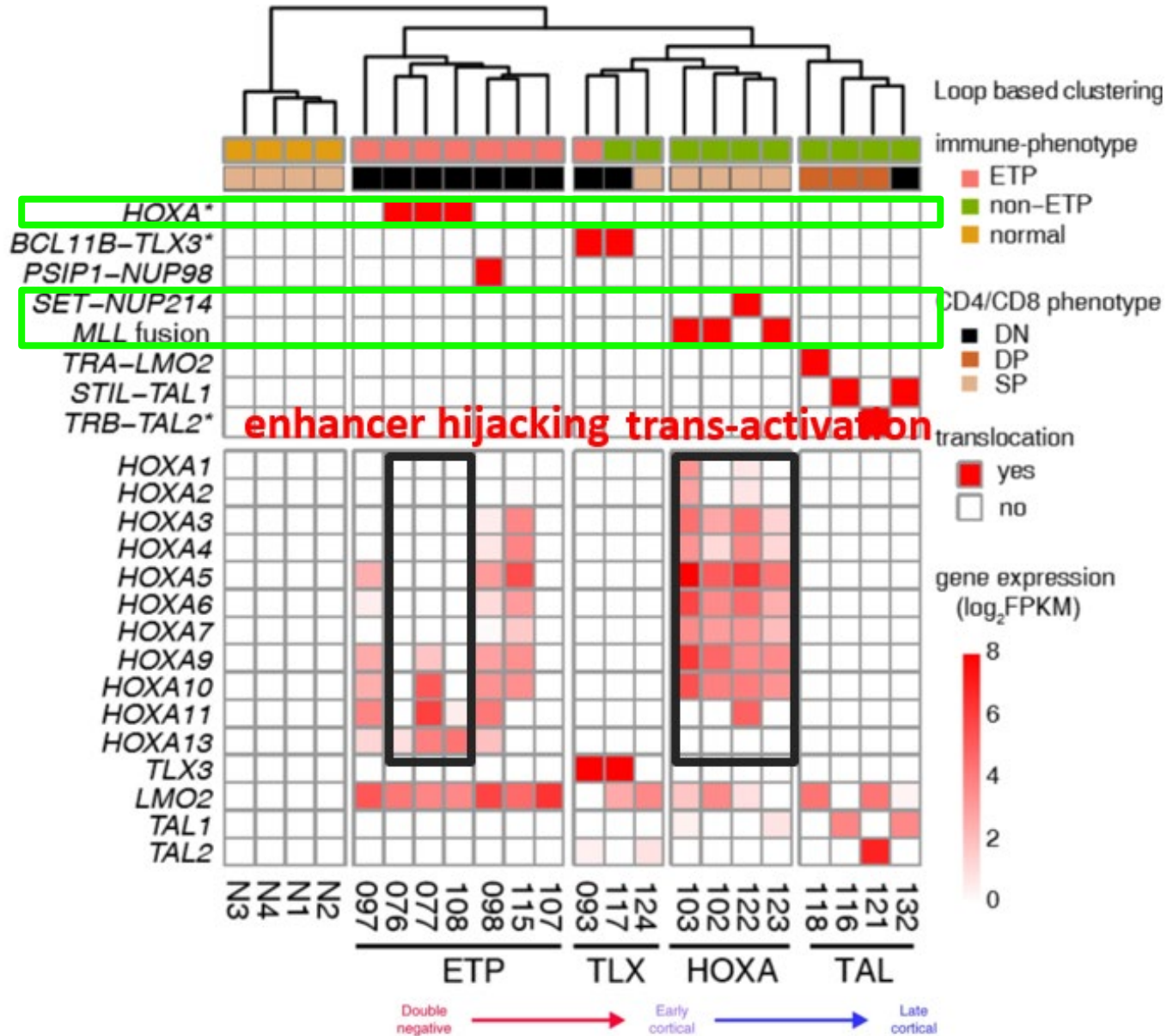


More DEGs can be found using trans-loops

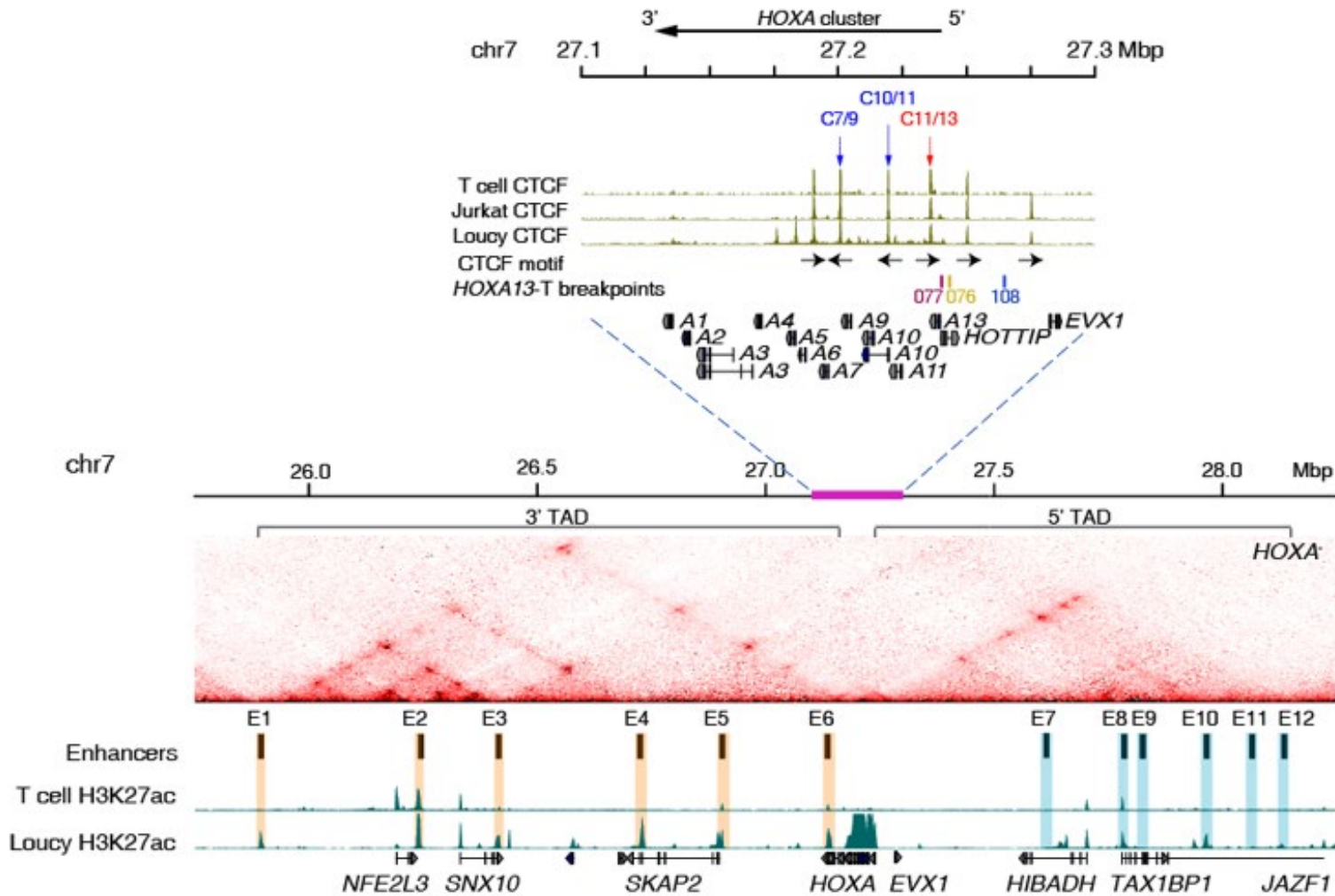


Trans-loop tends to utilize original REs and CTCF binding sites.

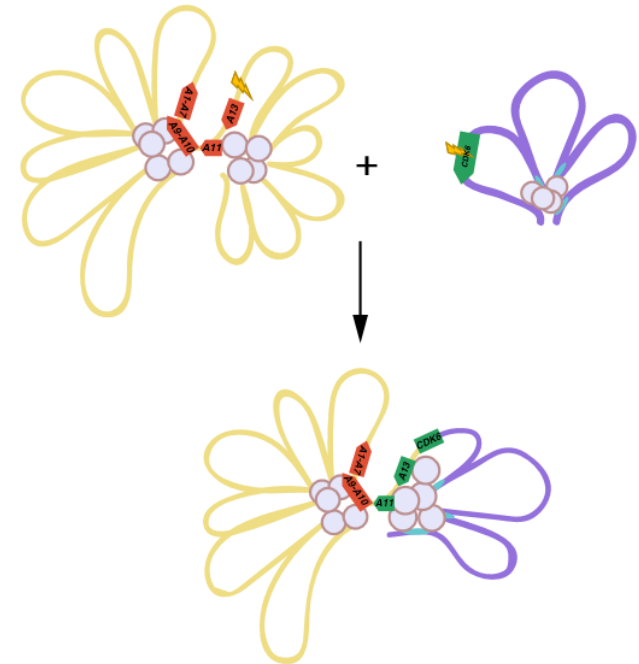
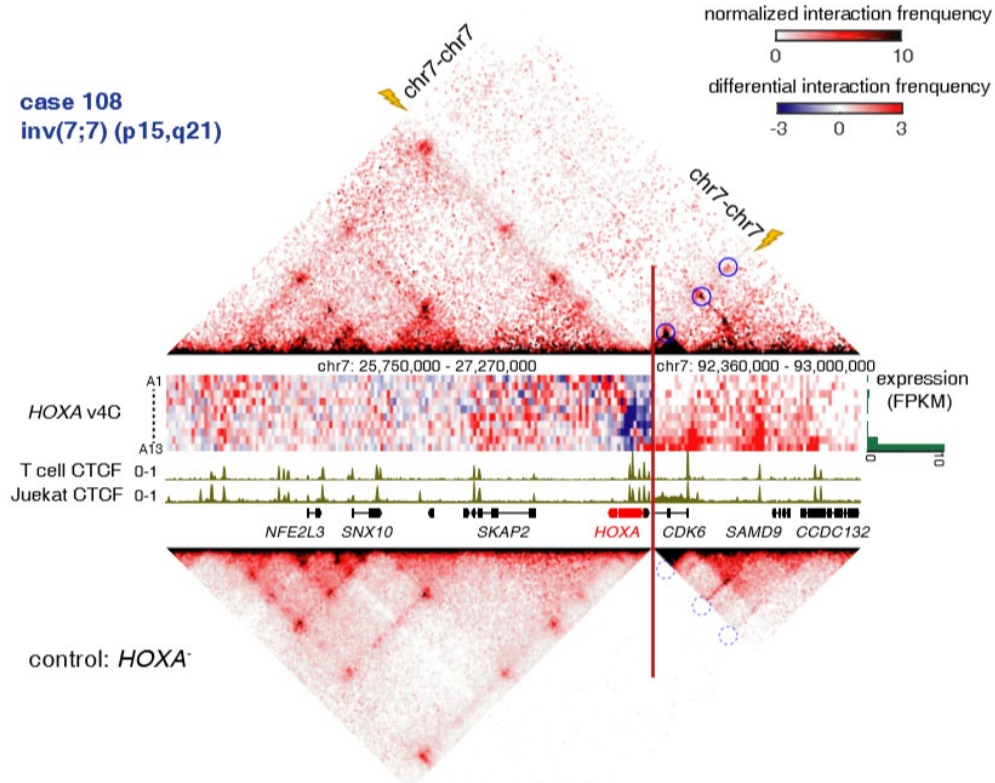
Two HOXA activation mechanism



HOXA genes are partitioned between 2 TADs



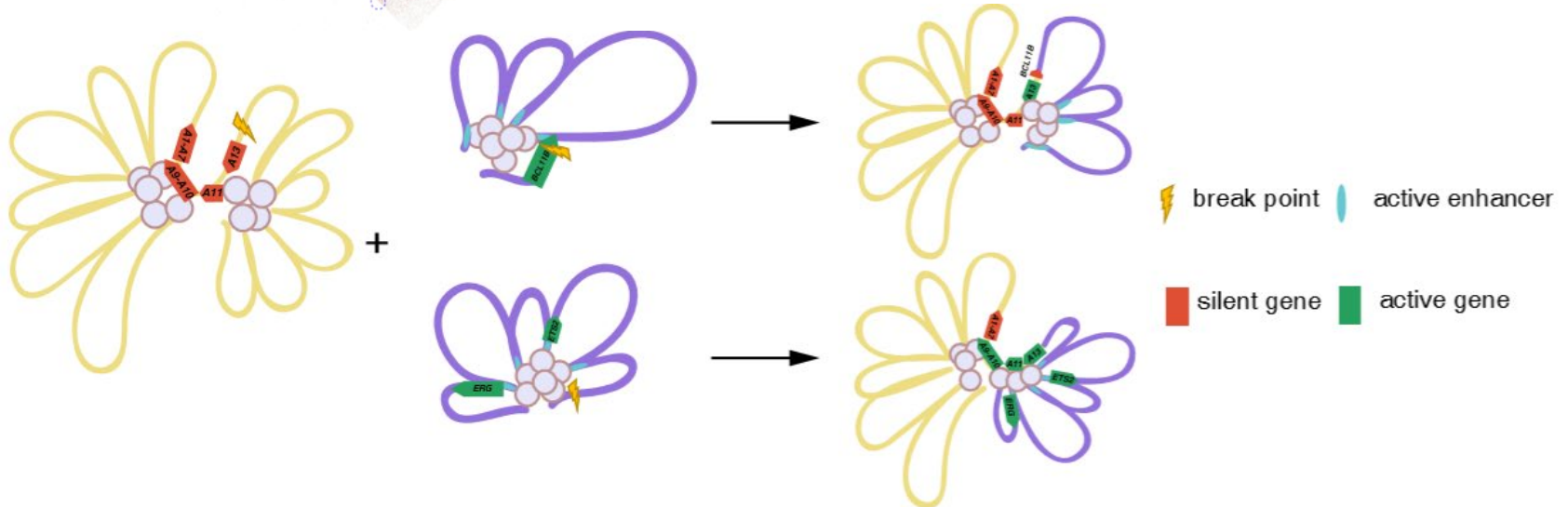
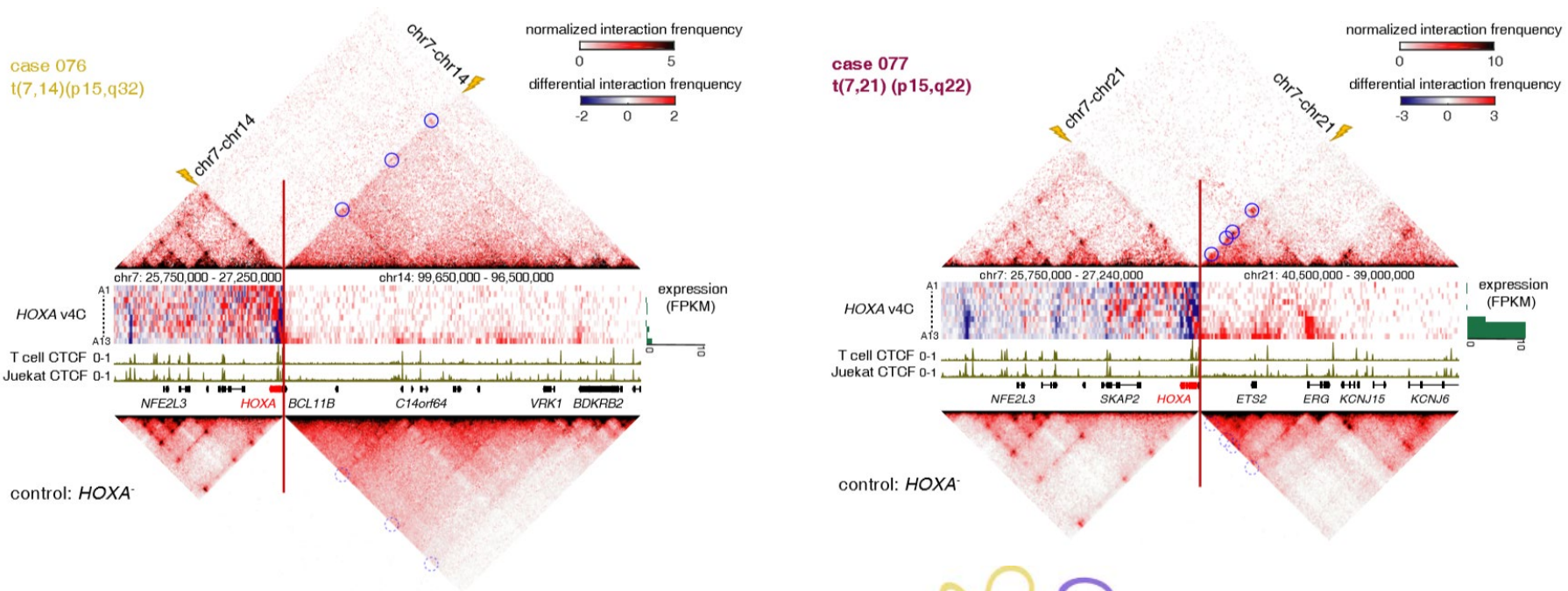
Translocation-mediated enhancer hijack leads to *HOXA13* overexpression



⚡ break point 🔵 active enhancer
 🟠 silent gene 🟢 active gene

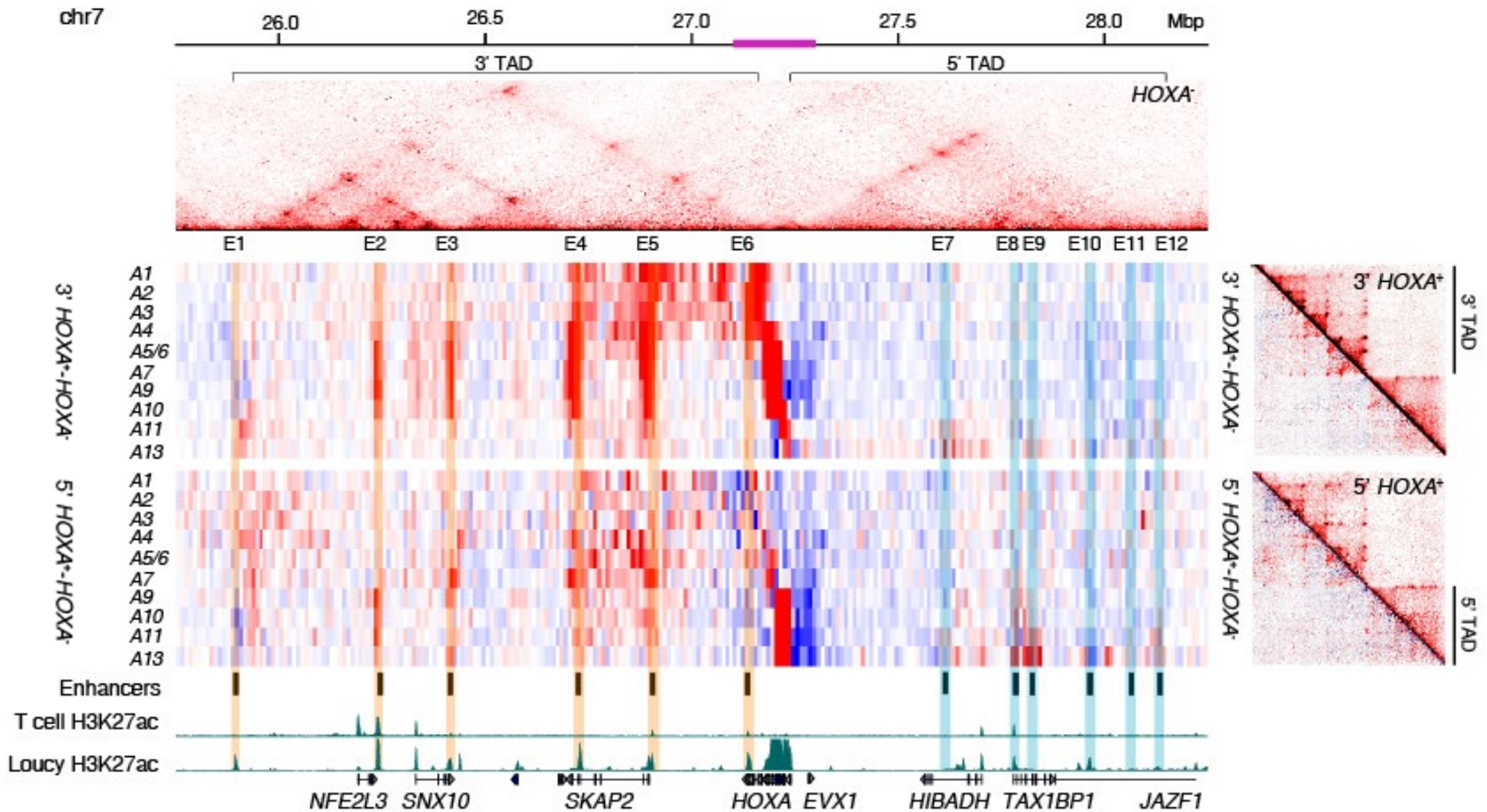
HOXA13 were regulated by *CDK6* enhancers via trans-loops.

Translocation-mediated enhancer hijack leads to *HOXA13* overexpression

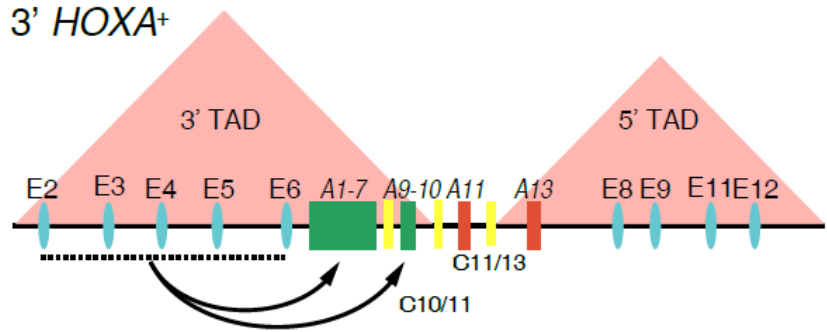


HOXA13 were regulated by *BCL11B* and *ERG* enhancers via trans-loops.

Trans-activation of HOXA related sophisticated loops

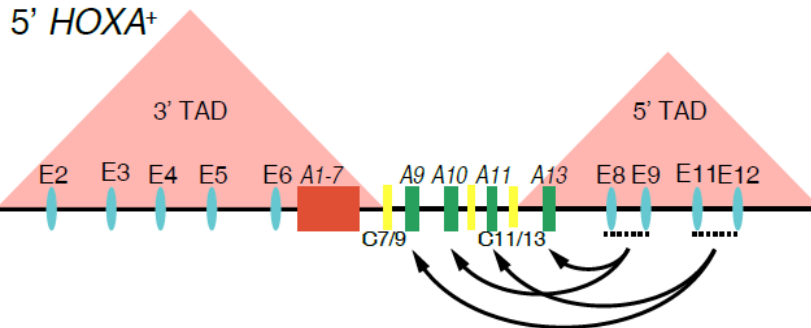


Trans-activation of HOXA related sophisticated loops



Enhanced interactions

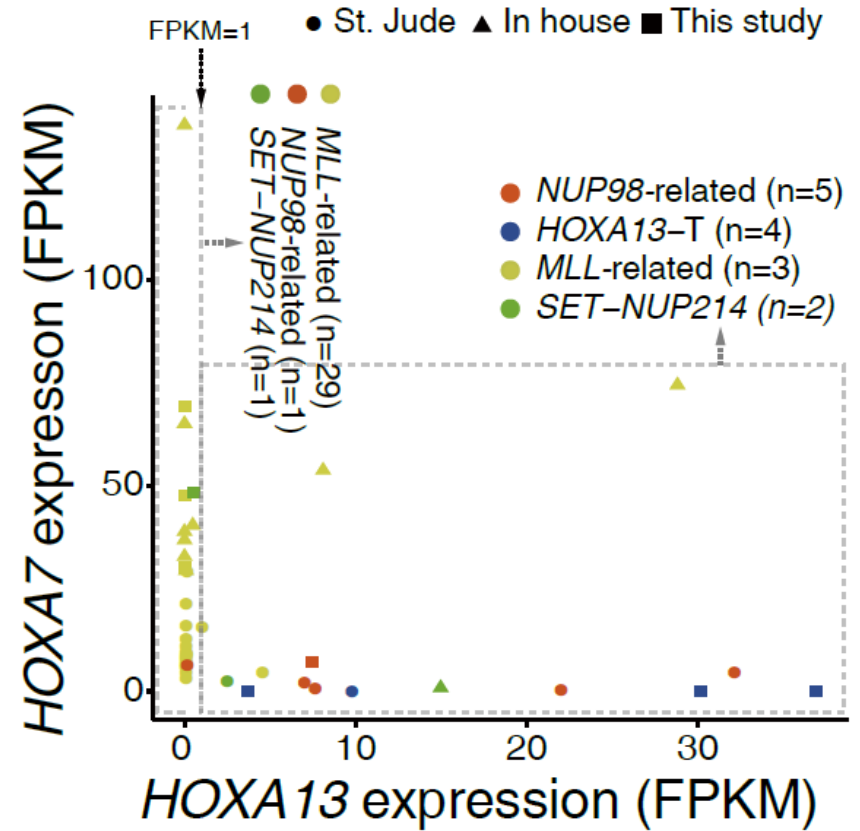
<i>KMT2A-MLLT1</i>	102
<i>PICALM-MLLT10</i>	103
<i>DDX3X-MLLT10</i>	123
<i>SET-NUP214</i>	122



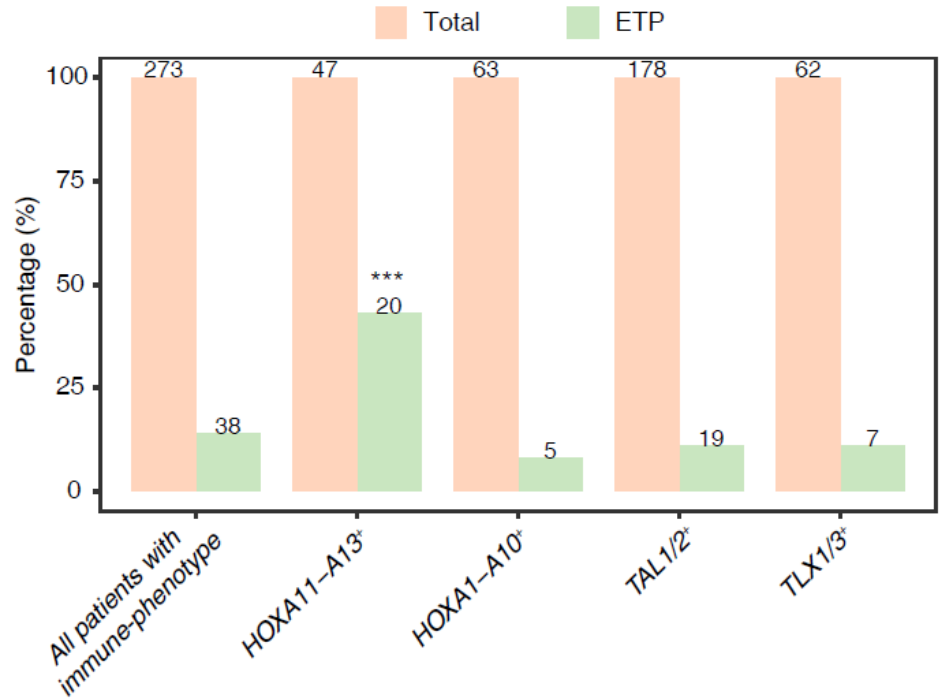
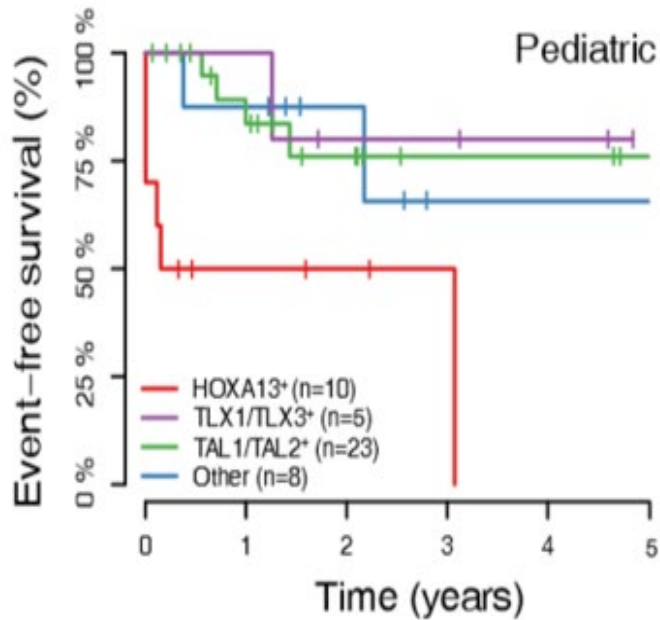
Enhanced interactions

<i>PSIP1-NUP98</i>	098
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Enhancer CTCF Silent gene Active gene



HOXA13 correlates with poor prognosis of pediatric T-ALL

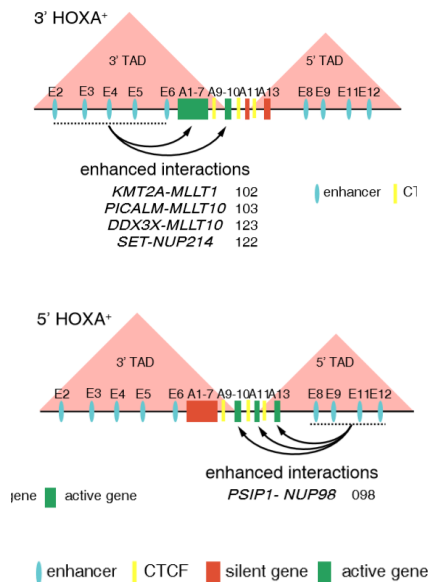


The complete response rates: HOXA13⁺ (50%) and HOXA13⁻ (92%) groups (p-value = 0.007419)

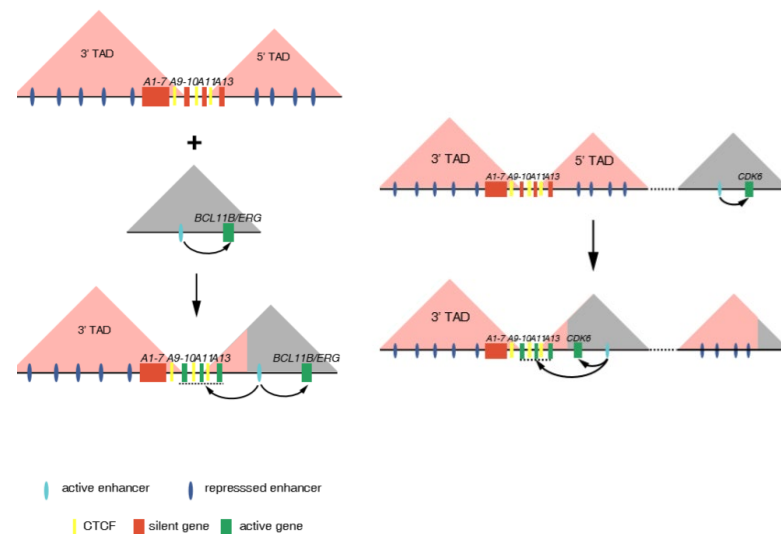
Take home messages

1. Systematically revealed the 3D genome landscape of T-ALL patients.
2. Uncovered novel translocations and neo-loops of T-ALL.
3. Demonstrated gene dysregulation in T-ALL by trans-activation and enhancer hijacking with HOXA as an example.
4. HOXA13 correlates with poor outcome.

Trans-activation of HOXA

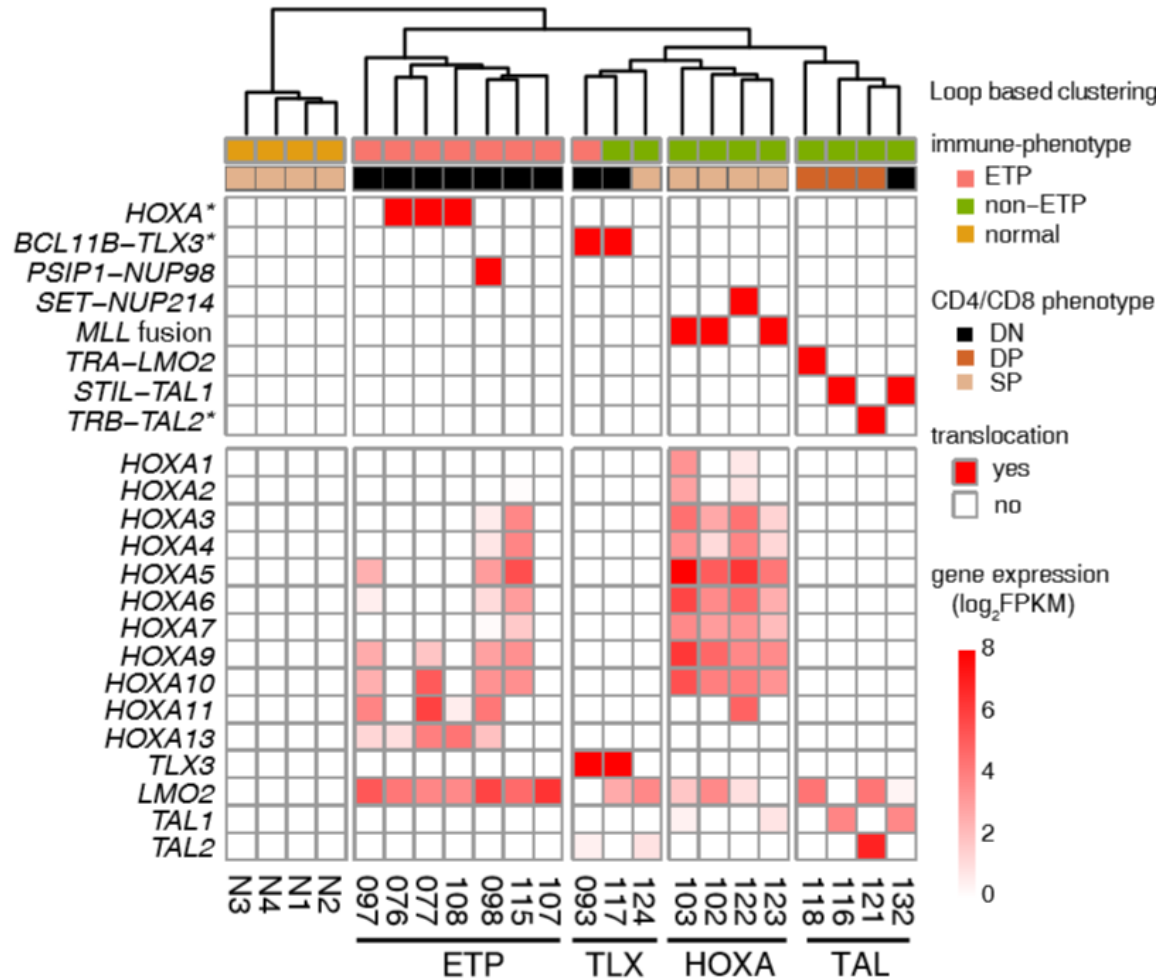


Enhancer hijacking of HOXA



Discussion

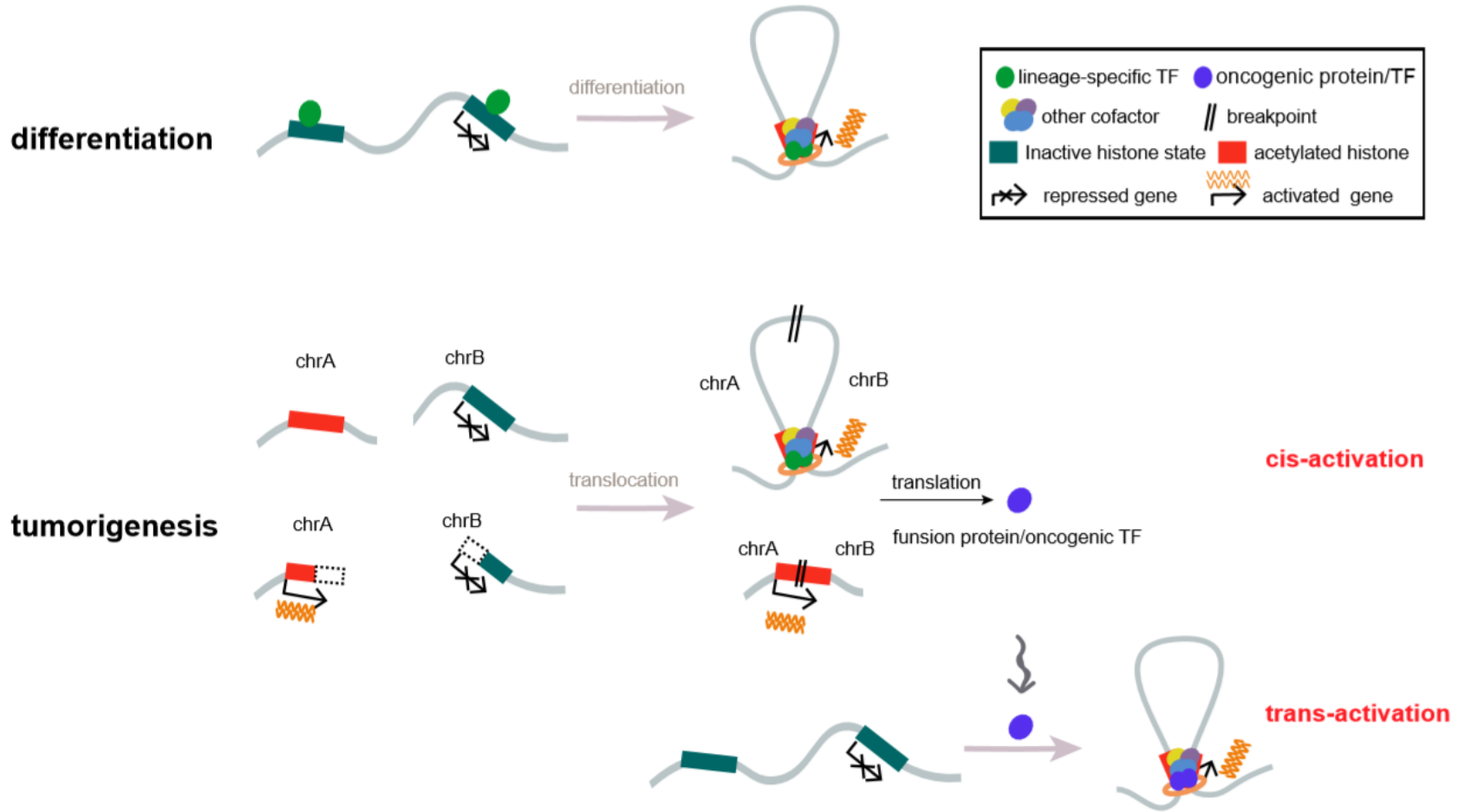
Driver of subpopulation



Chromatin conformation of T-ALL subpopulation is centered on oncogenic TFs ?

Genome variation ->key TF dysregulation->conformation->expression

Discussion



Acknowledgement

Tsinghua University

Prof. Michael Zhang

Yang Chen

Minglei Shi

Key Collaborators

Peking University

Prof. Hong Wu

Lu Yang

Haichuan Zhu

Bingjie Dong



Peking University People's Hospital

Xiaojun Huang

Zongru Li

Yongzhan Zhang

Leping Zhang

Qian Jiang

Yan Chang

National Center for Protein Sciences Beijing

Yan Liu (Tsinghua University)

Fei Wang (Peking University)

Xuefang Zhang (Peking University)

