

Exploring Cancer Genomes in 3D

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Challenges in Data-Driven Genomic Computing – Mar. 6-8, 2019

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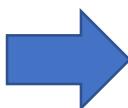
oricchiolab.epfl.ch



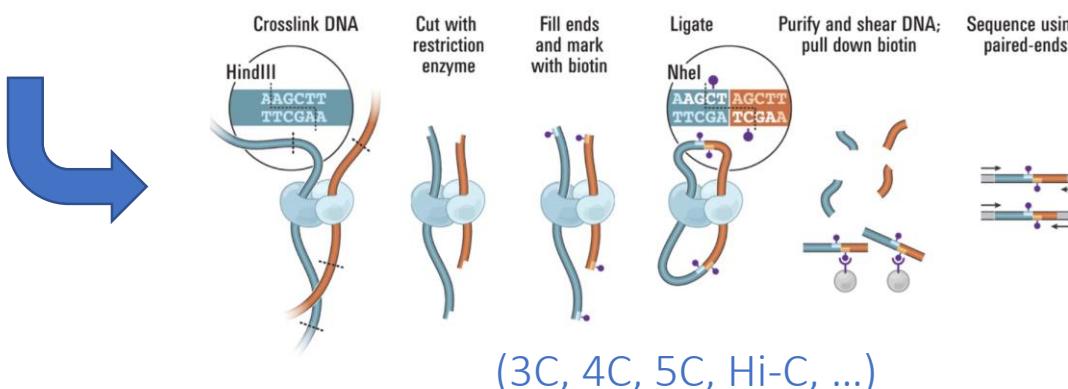
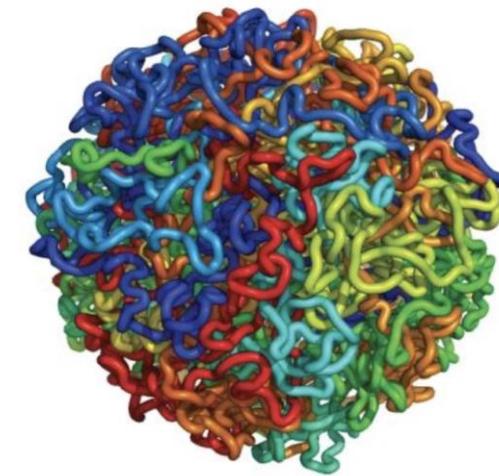
@elisa_oricchio

Exploring the chromatin 3D structure

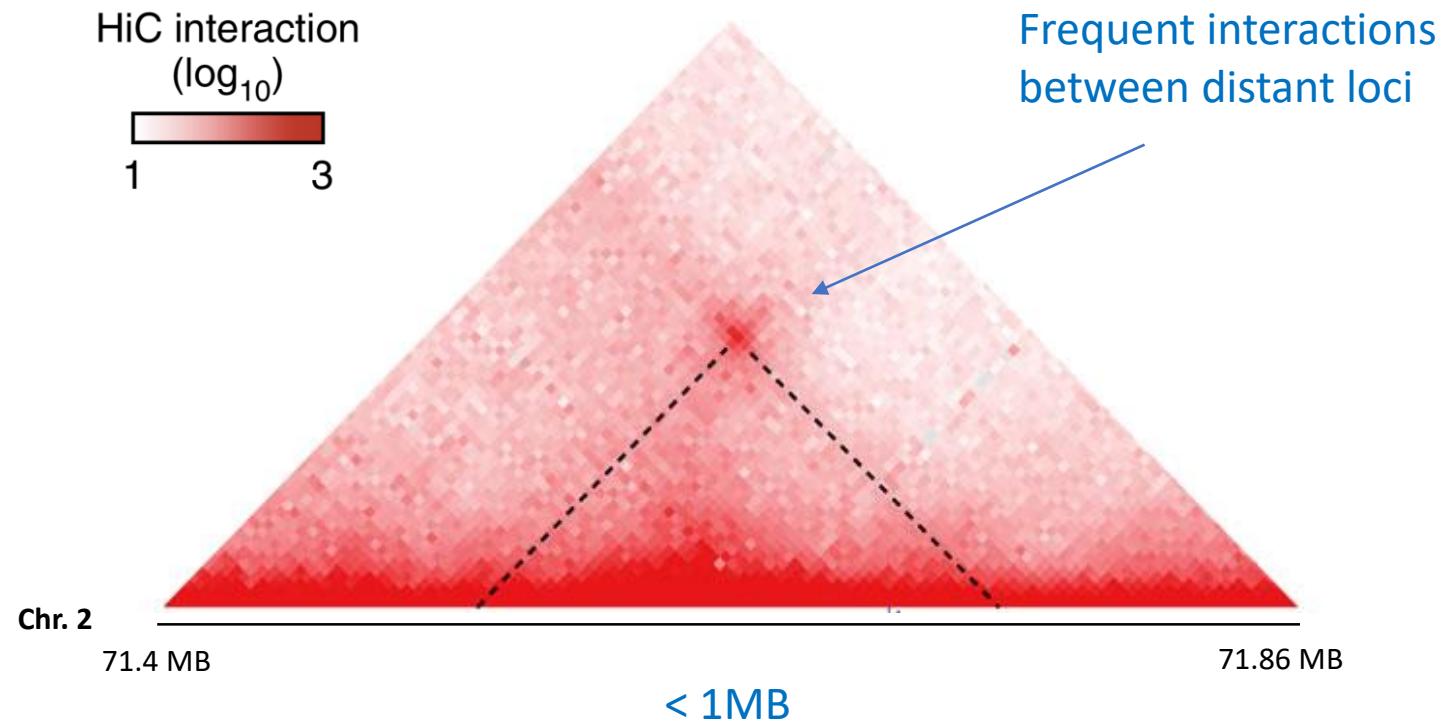
Linear view of the DNA



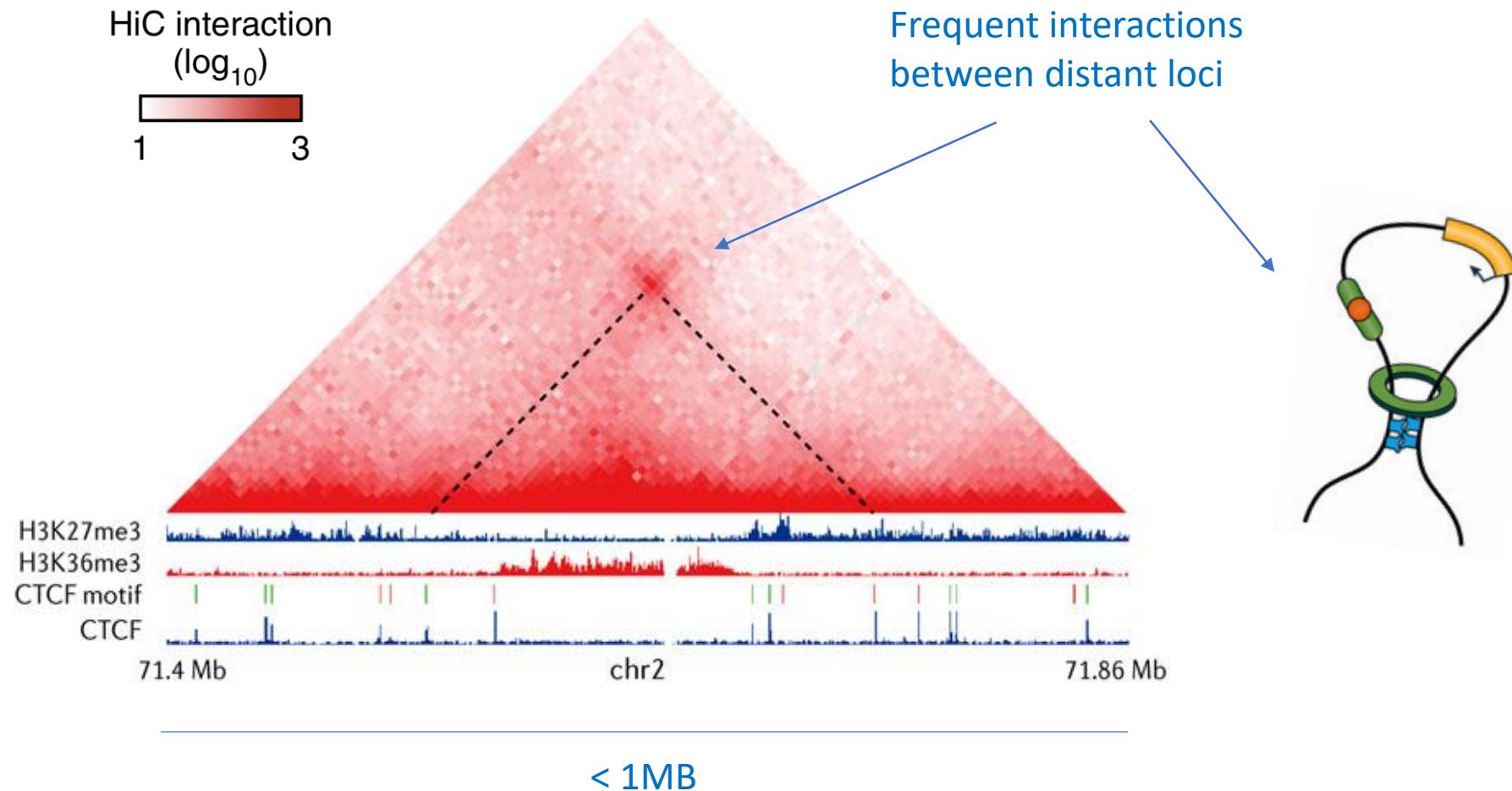
3D view of the DNA



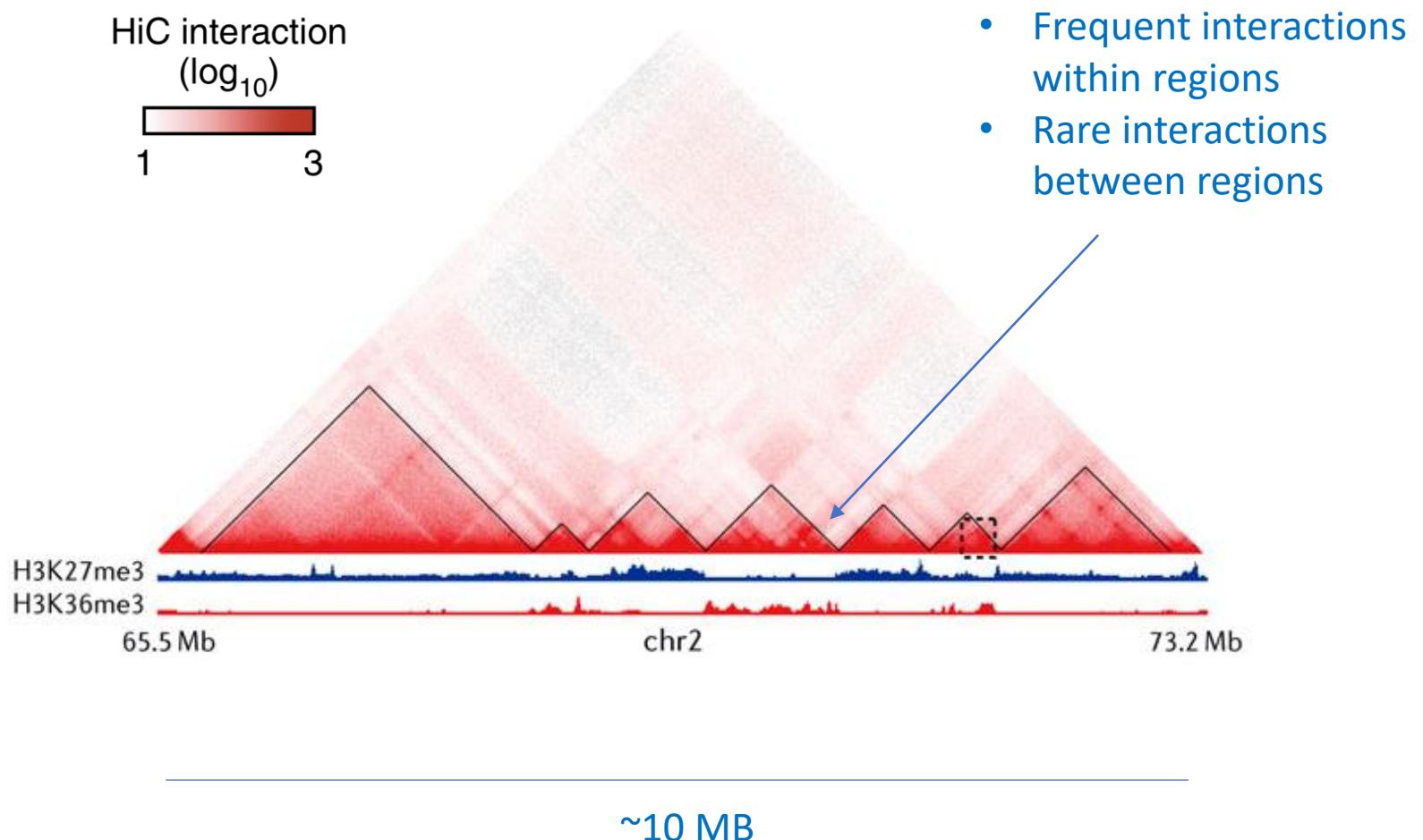
Exploring the chromatin 3D structure



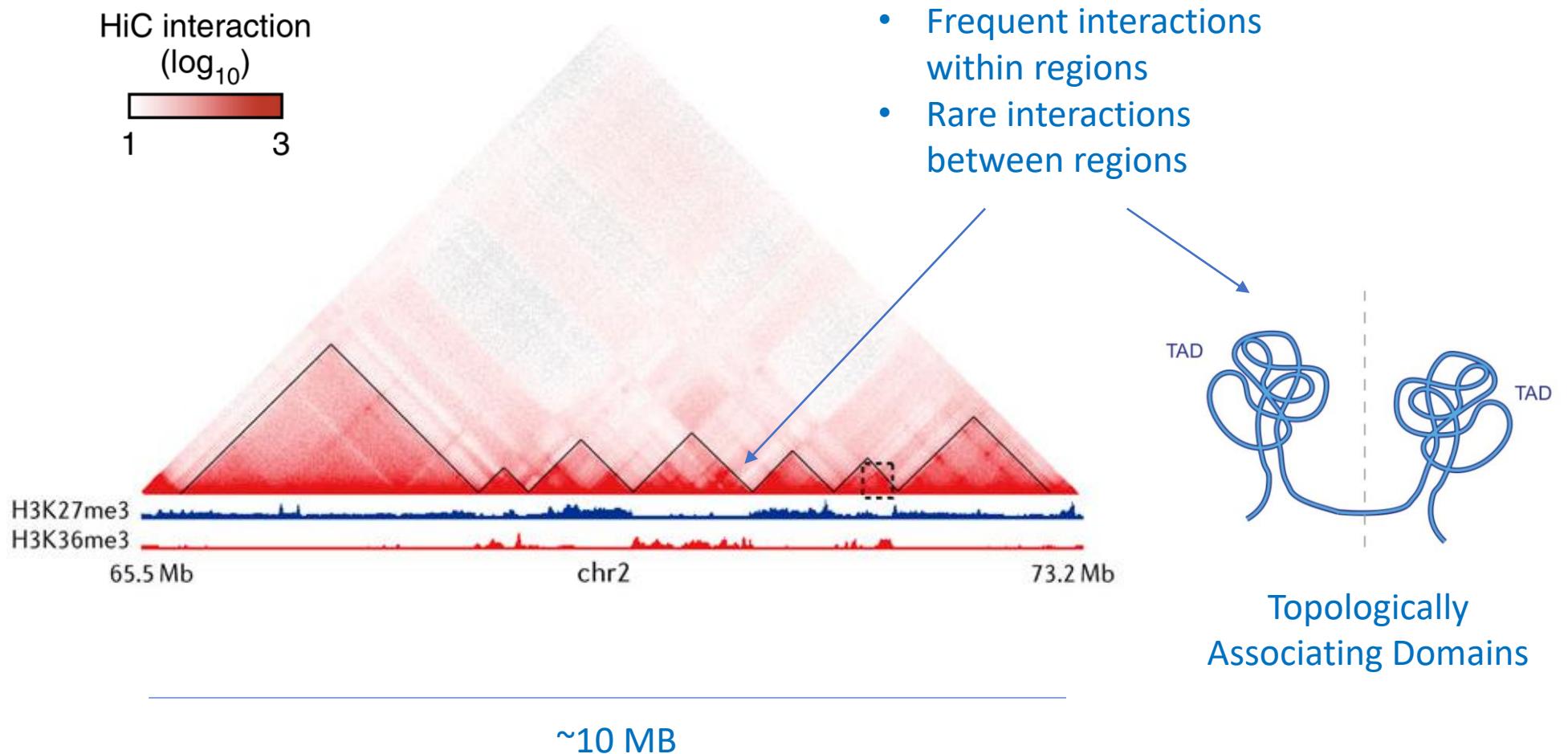
Exploring the chromatin 3D structure



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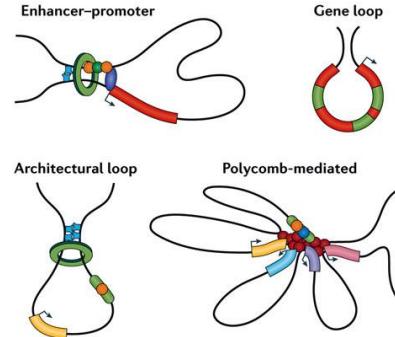
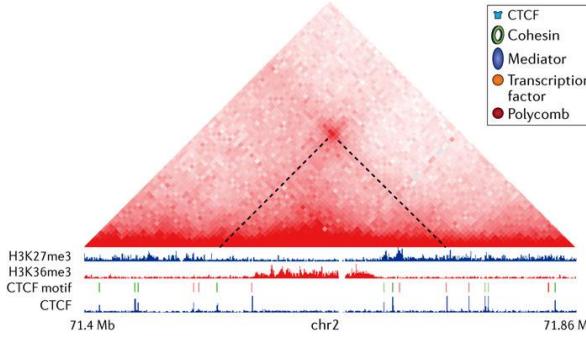


Exploring the chromatin 3D structure

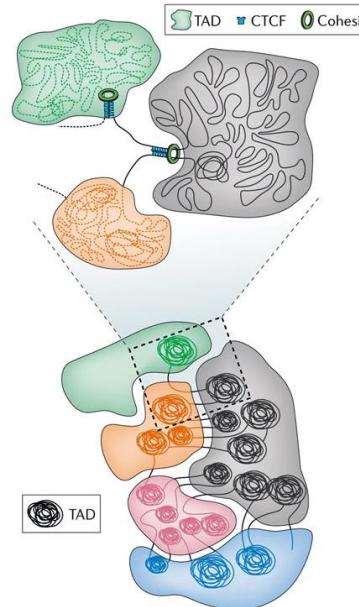
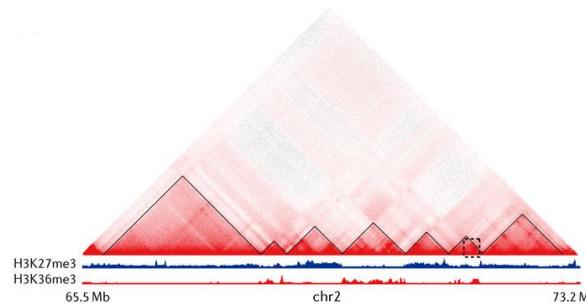


Chromatin Architectural Elements

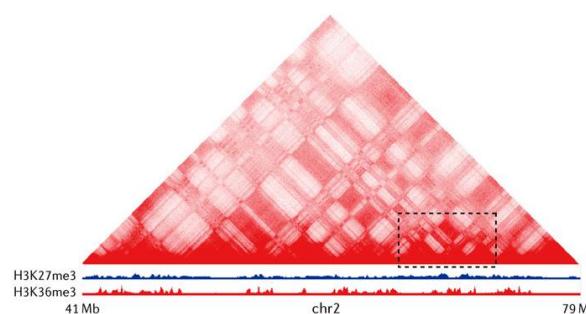
Scale of chromatin elements



LOOPS



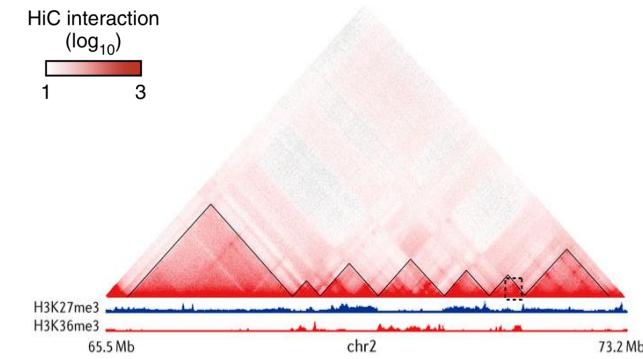
Chromatin
Domains
(TADs)



Chromatin
Compartments

Limits of the current definitions

- Data-driven definition from bulk sequencing

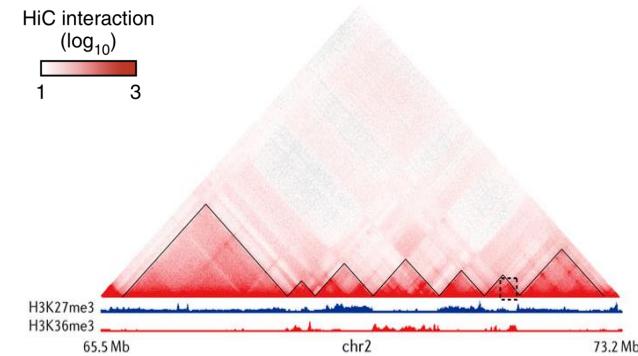


Limits of the current definitions

- Data-driven definition from bulk sequencing



- Sensitive to data quality and resolution
 - Resolution requirements limit applicability
(e.g. loops, sub-compartments)

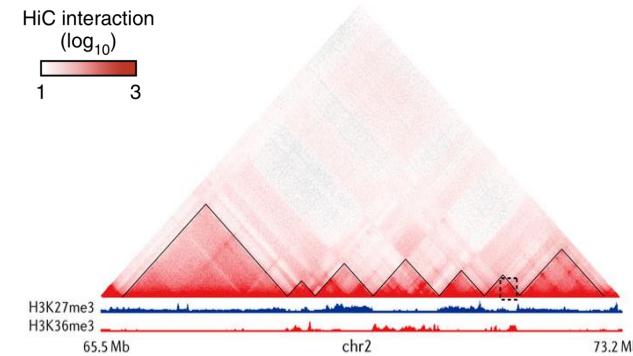


Limits of the current definitions

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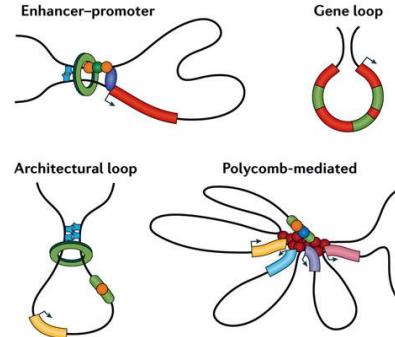
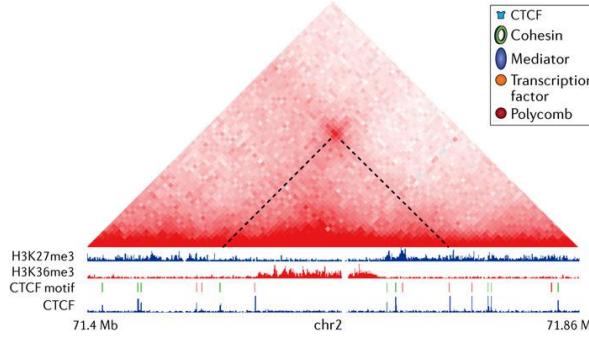


- Sensitive to data quality and resolution
 - Resolution requirements limit applicability
(e.g. loops, sub-compartments)
- Disconnected elements

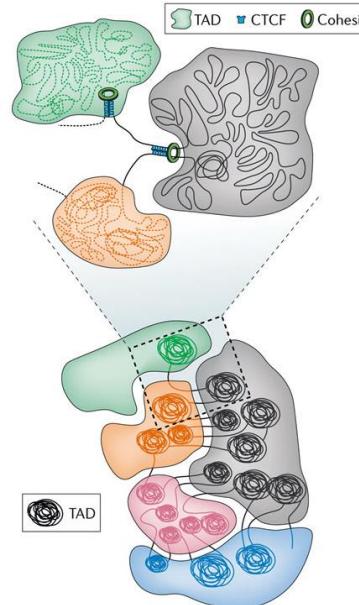
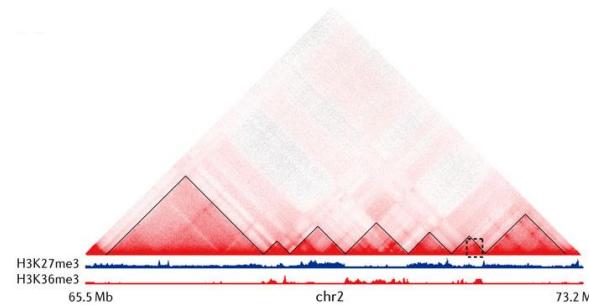


Chromatin Architectural Elements

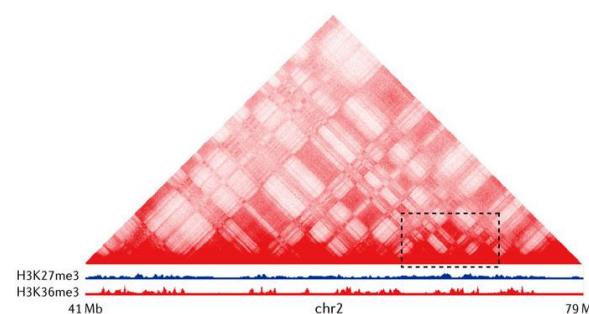
Scale of chromatin elements



LOOPS

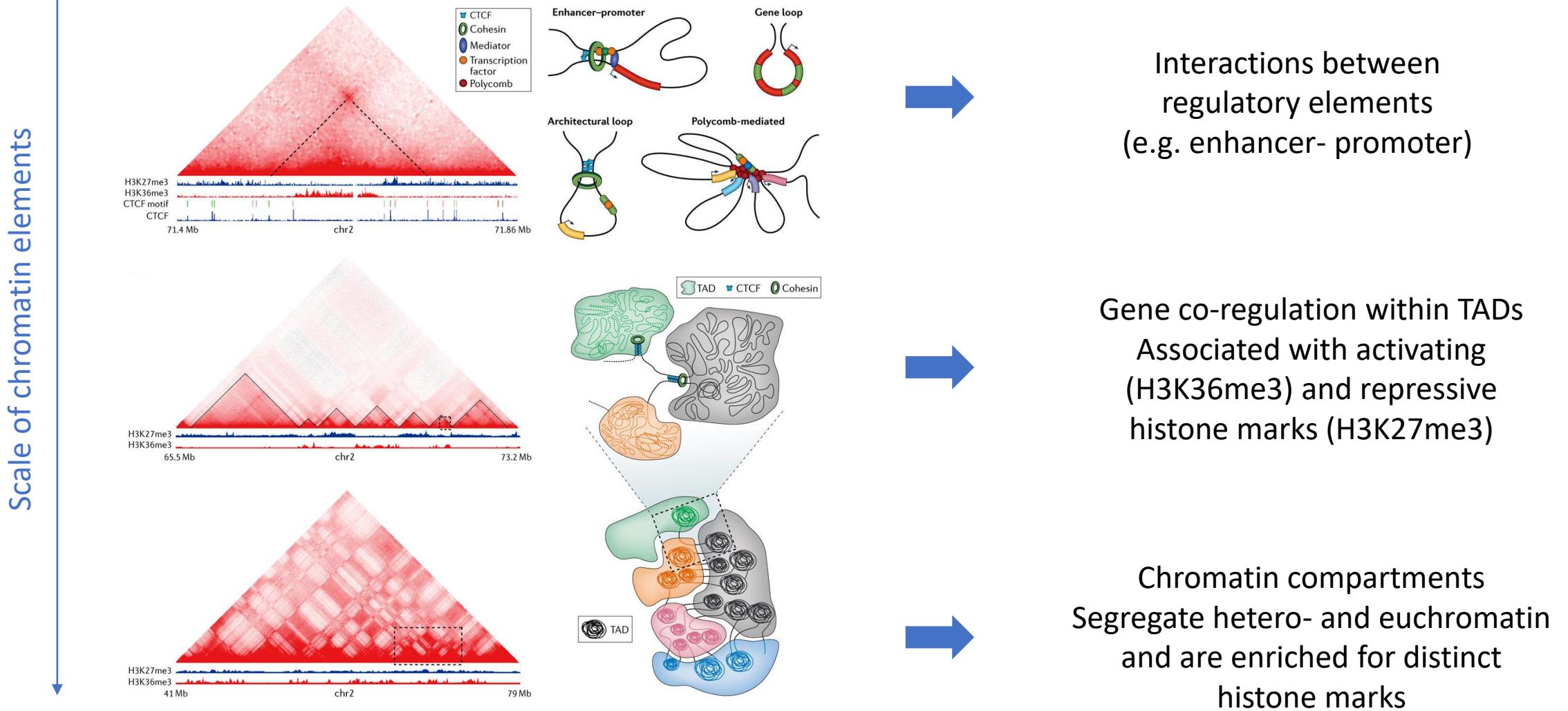


Chromatin
Domains
(TADs)

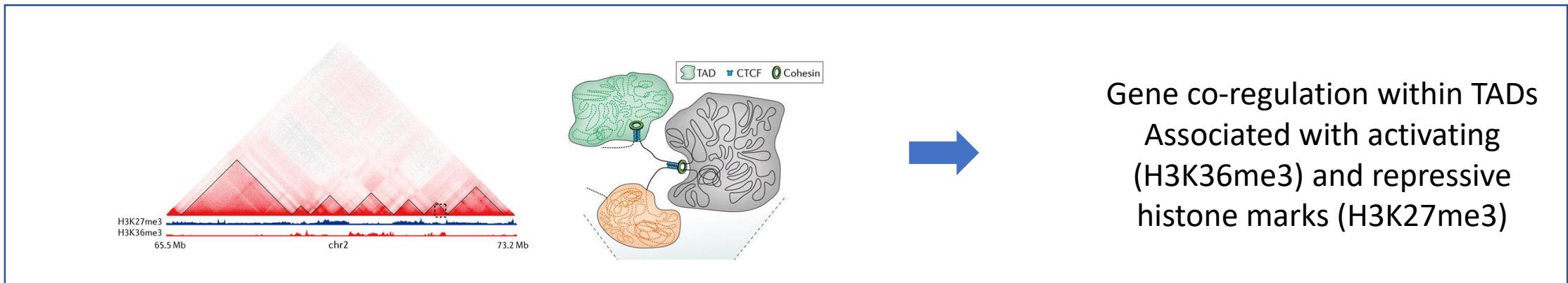


Chromatin
Compartments

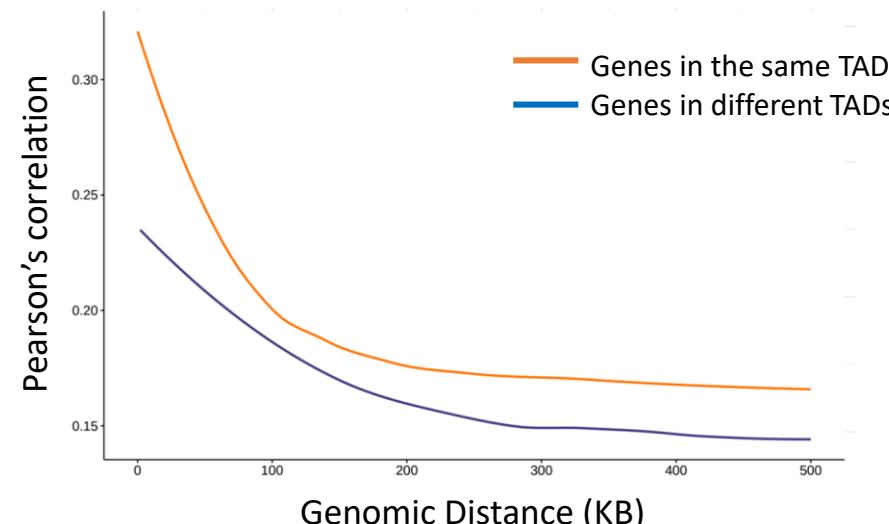
Cell activity is associated with chromatin architectures



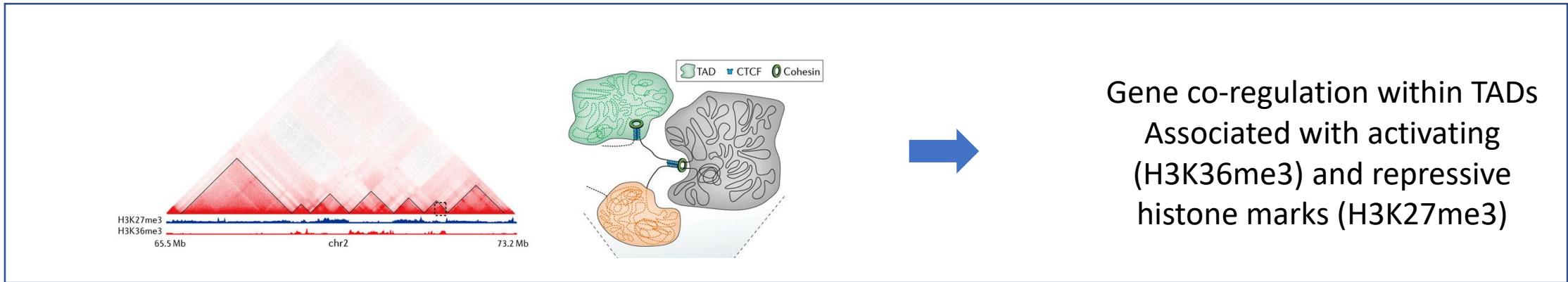
TAD as transcriptional units



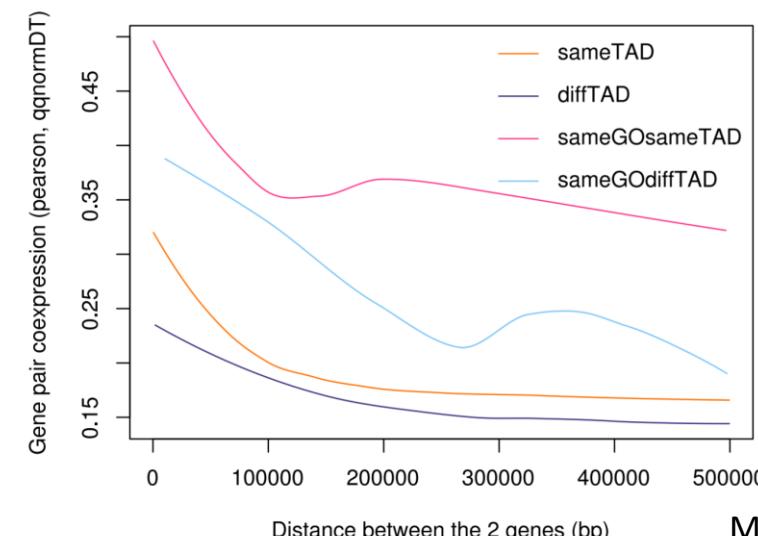
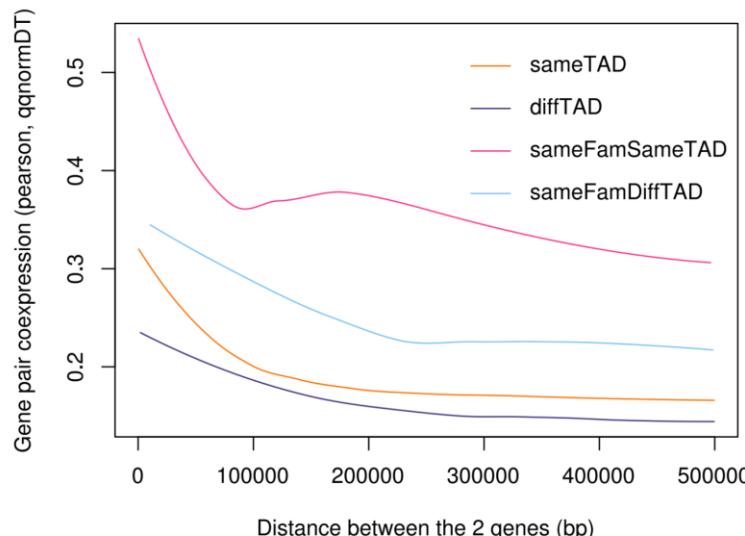
- mRNA expression of genes within the same TAD is more correlated than for genes in different TADs



TAD as transcriptional units



- mRNA expression of genes within the same TAD is more correlated than for genes in different TADs
 - Even after accounting for gene families or Gene Ontology (GO)

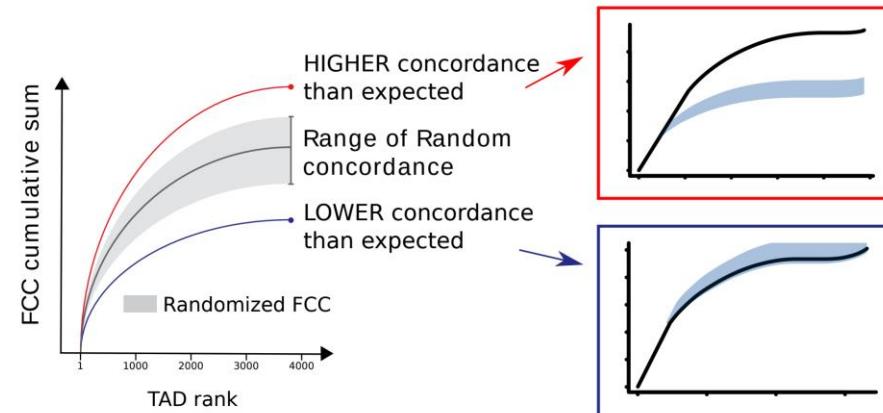


Differentially “expressed” TADs

Given a dataset and 2 conditions to compare

1. Test if expression differences are associated with TADs

$$FCC = \left(2 \frac{\#FC^-}{\#FC} - 1 \right) * \left(2 \frac{\sum |FC^-|}{\sum |FC|} - 1 \right)$$

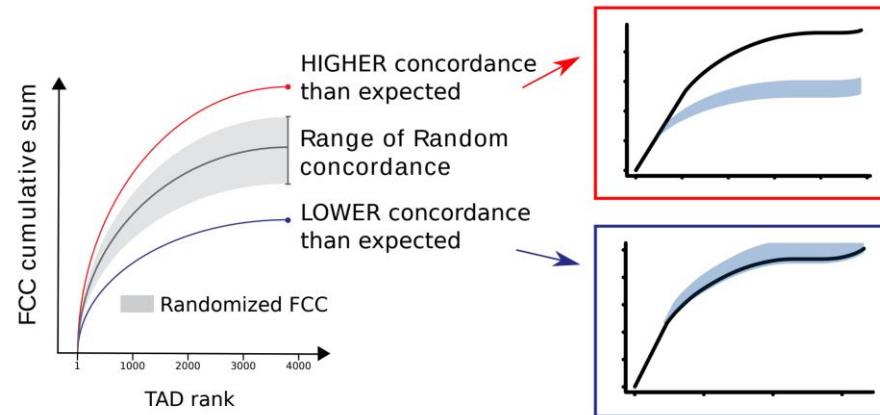


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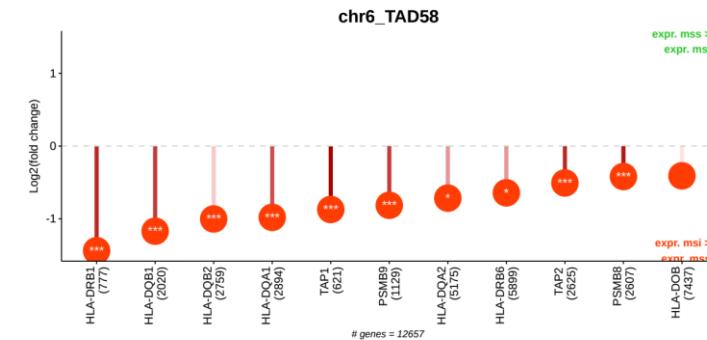
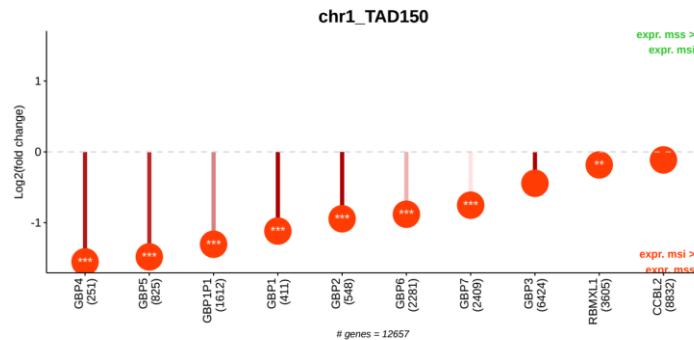
2. Estimate significance of intra-TAD expression fold-change and mRNA expression correlation (empirical p-values combined with Stouffer's method)

Differentially “expressed” TADs

Given a dataset and 2 conditions to compare

1. Test if expression differences are associated with TADs
2. Estimate significance of intra-TAD expression fold-change and mRNA expression correlation (empirical p-values combined with Stouffer's method)

Colorectal Cancer: MSI vs MSS tumors



Cohesin regulates MHC class II genes through interactions with MHC Class II Insulators (Majumder and Boss 2011)

CTCF controls expression and chromatin architecture of the human major histocompatibility complex class II Locus (Majumder and Boss 2010)

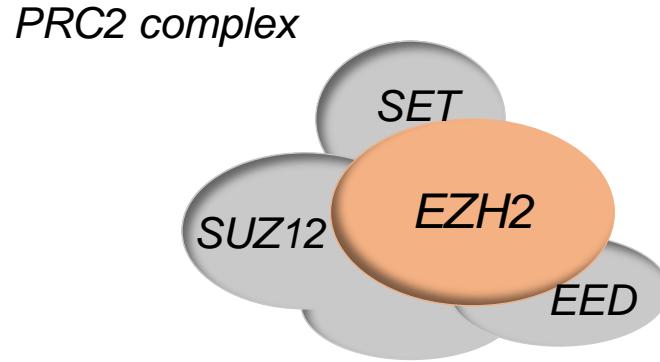
Why exploring cancer genomes in 3D?

Why exploring cancer genomes in 3D?

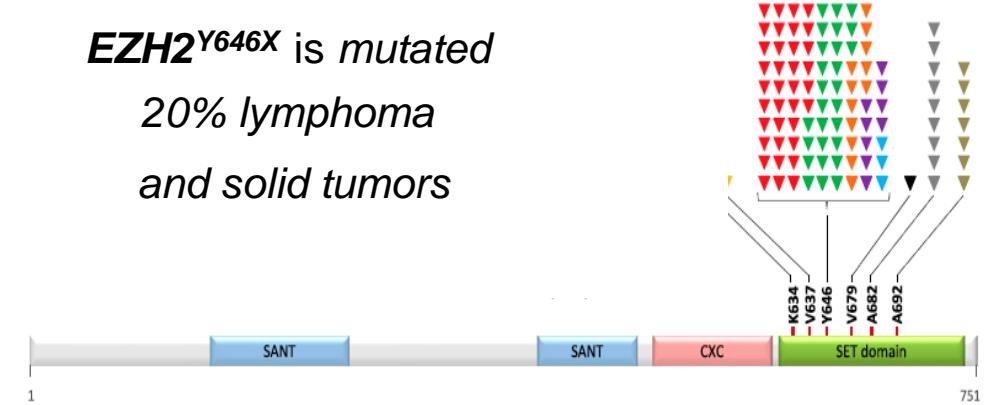


- Frequent mutations across a variety of cancers
- Modify chromatin accessibility and transcription across the whole genome
- Difficult to pin-point specific targets / to understand how their oncogenic potential is implemented

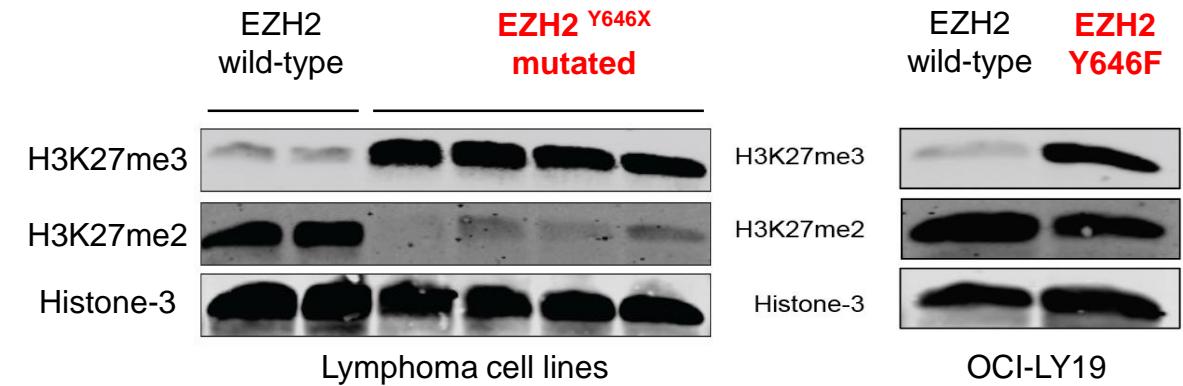
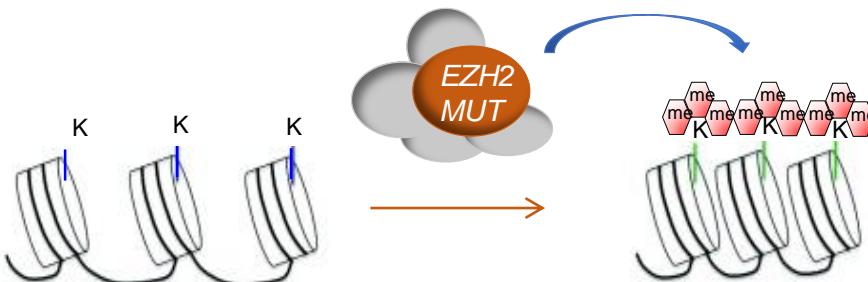
EZH2 mutations in cancer



***EZH2^{Y646X}* is mutated
20% lymphoma
and solid tumors**

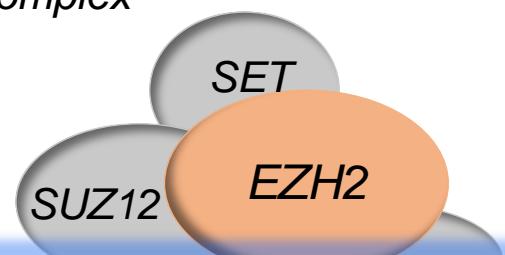


***EZH2^{Y646X}* increases H3K27 tri-methylation**

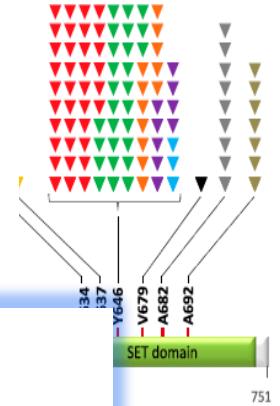


EZH2 mutations in cancer

PRC2 complex

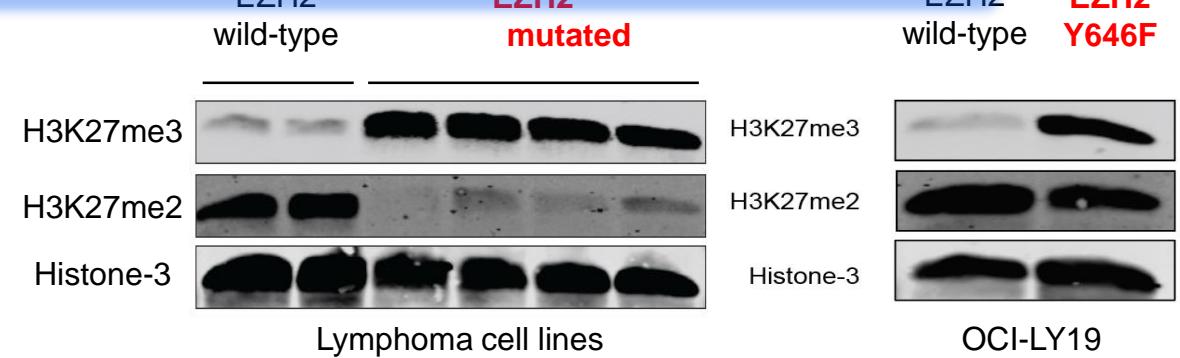
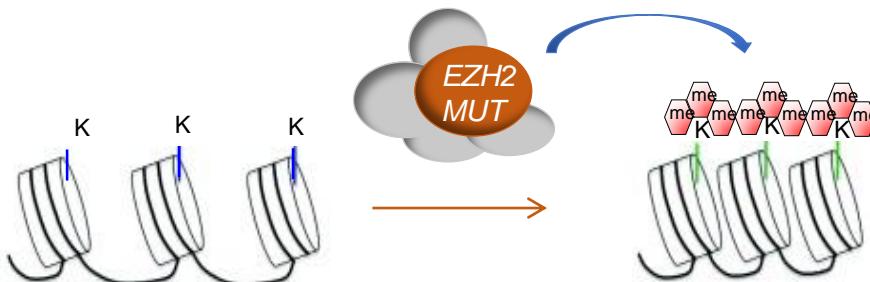


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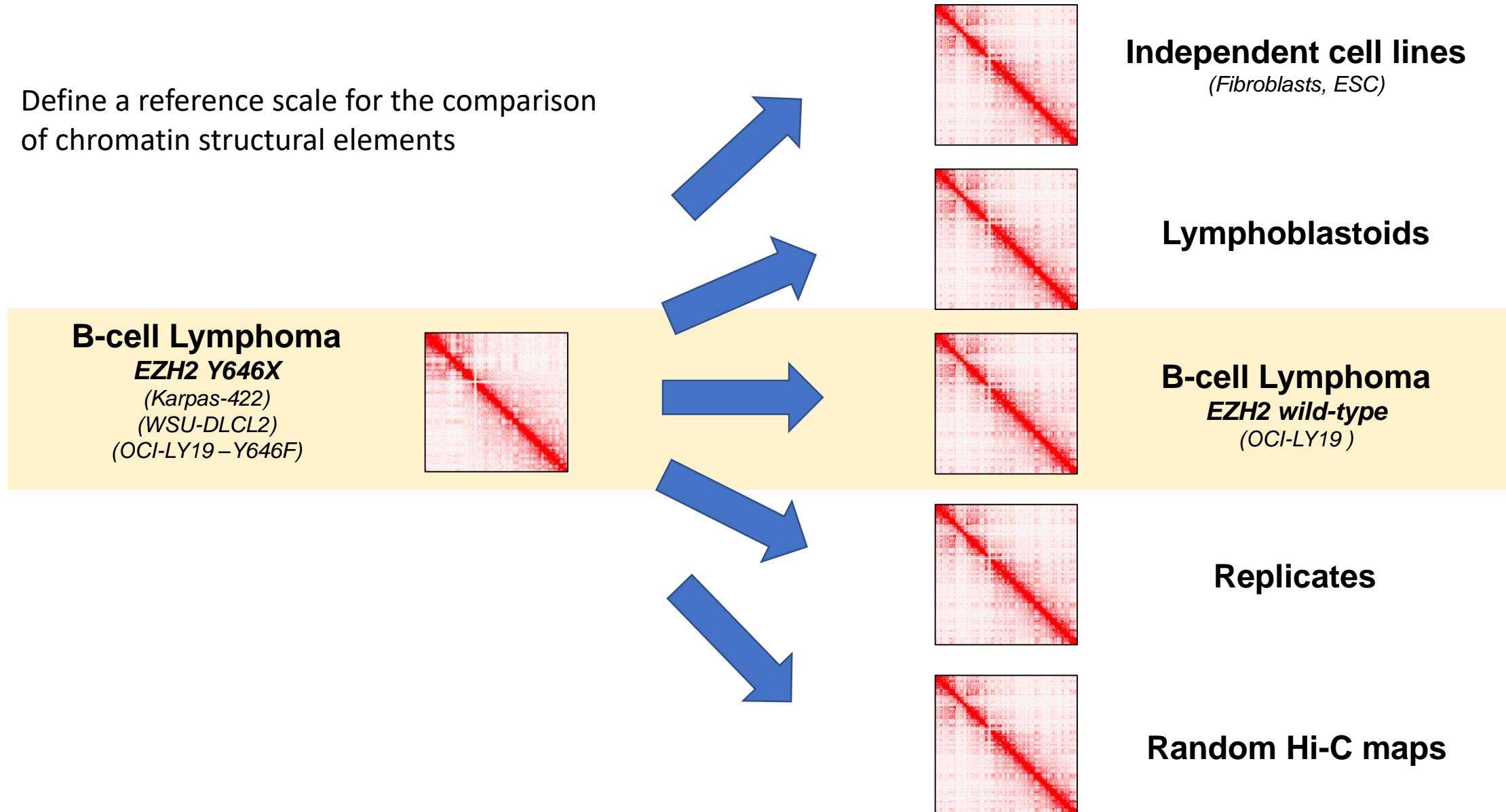
EZH2^{Y646X}

Do epigenetic changes mediated by *EZH2^{Y646X}* alter chromatin domain **structure** and/or **activity**?



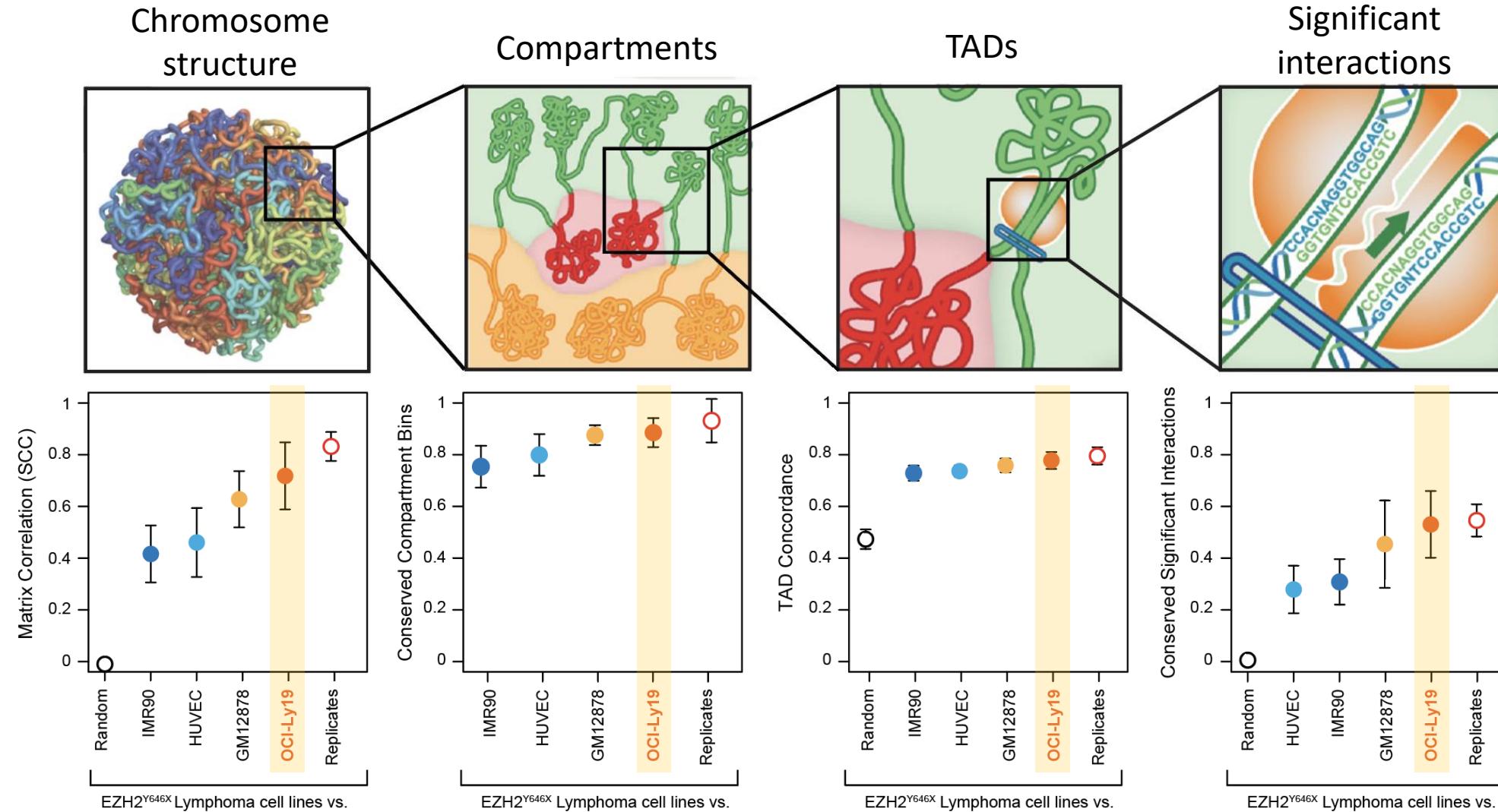
Do EZH2 mutations alter chromatin structure?

Define a reference scale for the comparison
of chromatin structural elements



Do EZH2 mutations alter chromatin structure?

EZH2 mutated cell lines vs. EZH2 wild-type (and others)



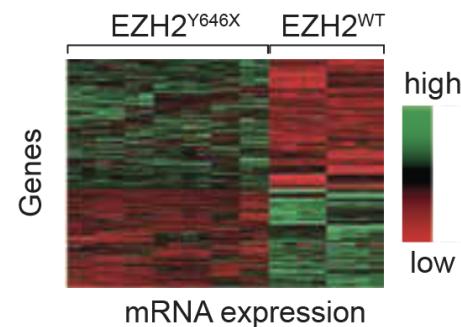
EZH2 mutations do not alter chromatin structure

- In spite of genome-wide changes of H3K27me3, the overall **structural organization** of the chromatin is **highly conserved**
 - **TAD conservation is comparable to what observed between replicates**
- How do **epigenetic and transcriptional changes** induced by EZH2-Y646X distribute across **chromatin domains**?



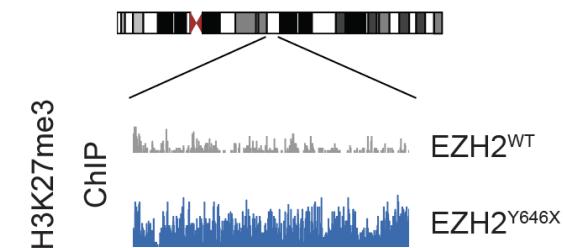
Altered TAD activity?

mRNA expression
($\text{EZH2}^{\text{Y646X}}$ vs. EZH2^{WT})

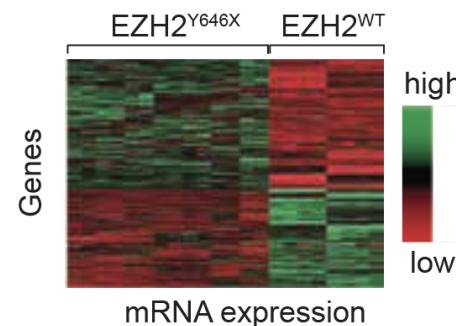


TADs

H3K27me3
($\text{EZH2}^{\text{Y646X}}$ vs. EZH2^{WT})

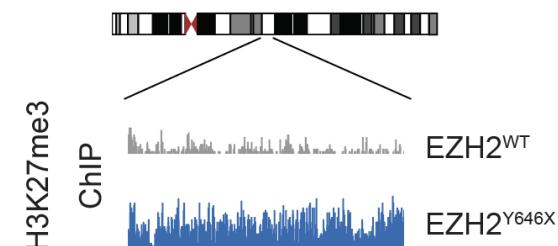


mRNA expression
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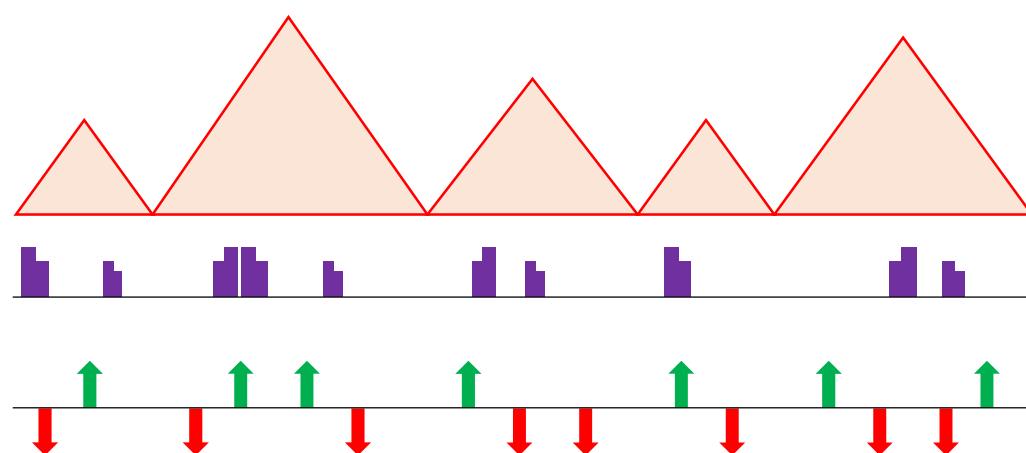


TADs

H3K27me3
($\text{EZH2}^{\text{Y646X}}$ vs. EZH2^{WT})



Expected Distribution

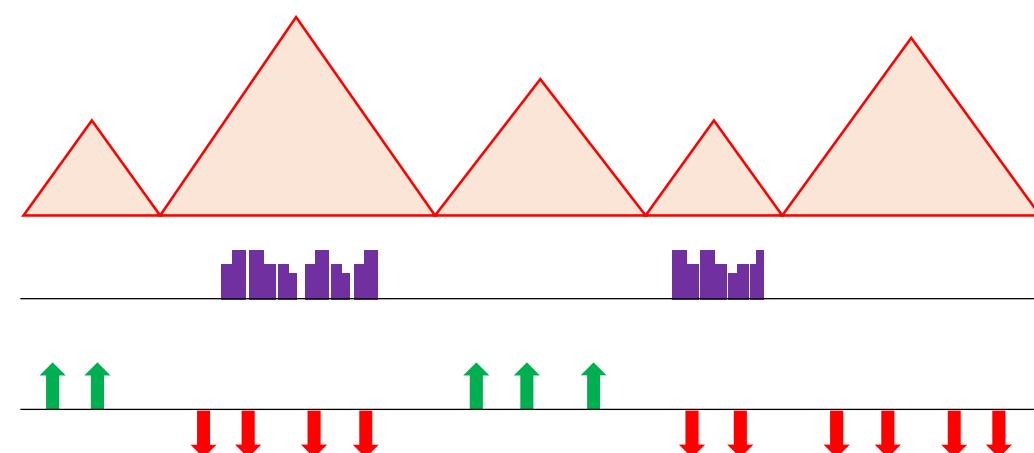


TADs

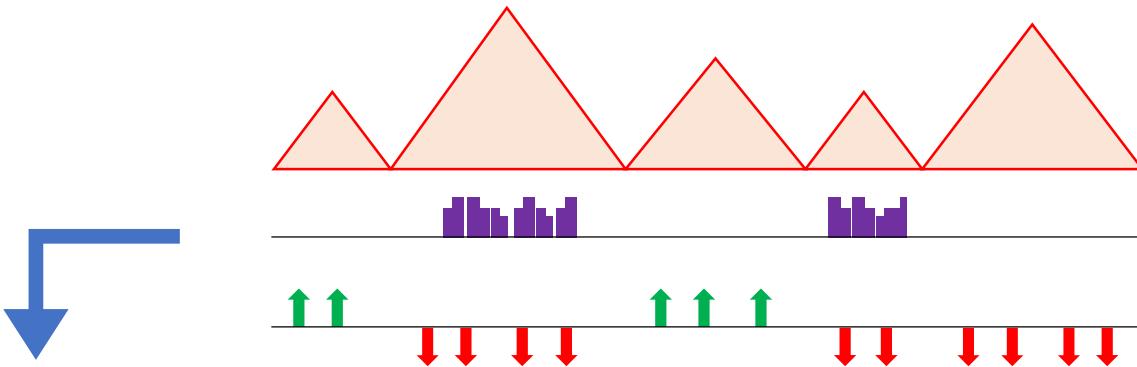
H3K27me3
fold changes

mRNA
fold changes

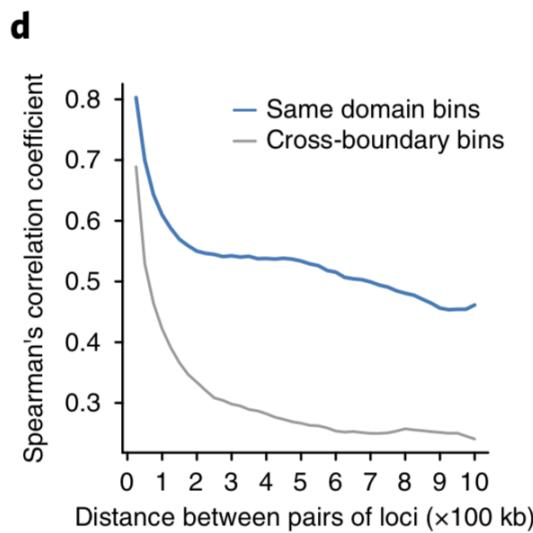
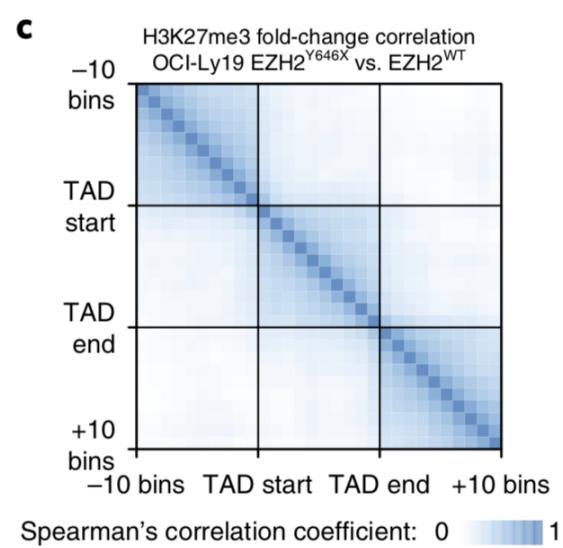
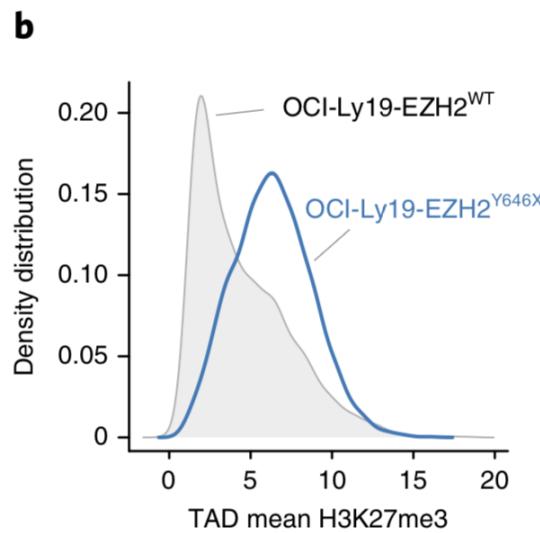
Observed Distribution



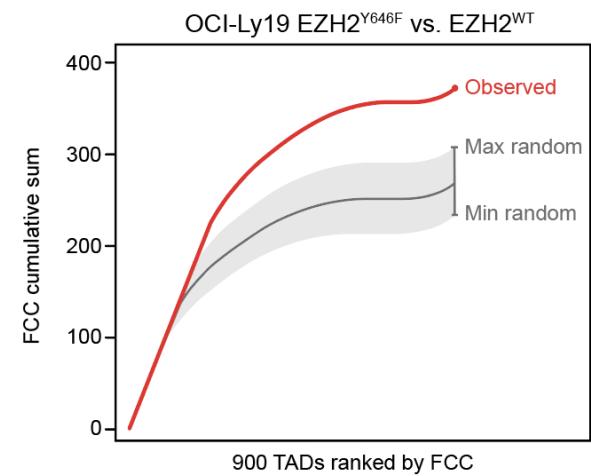
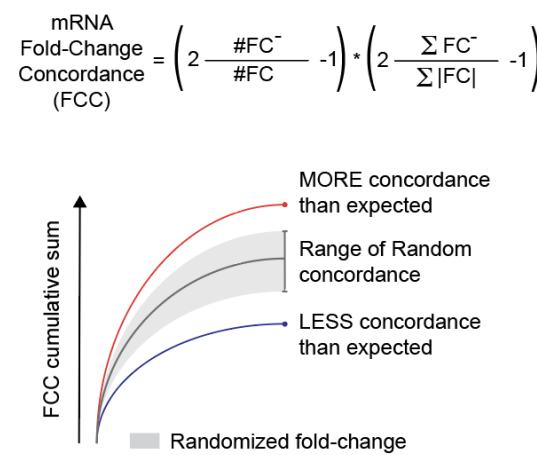
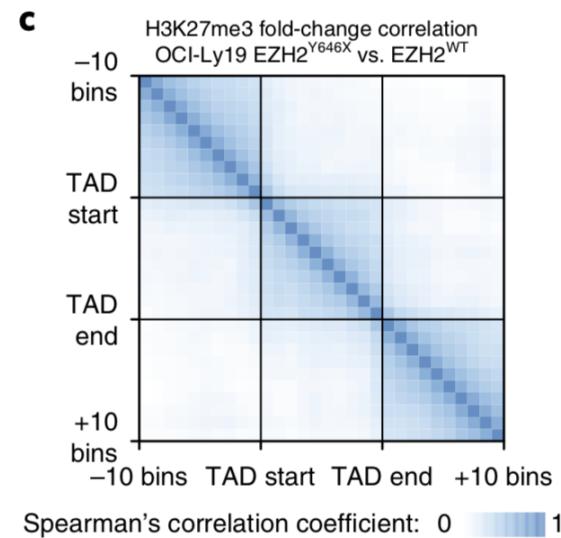
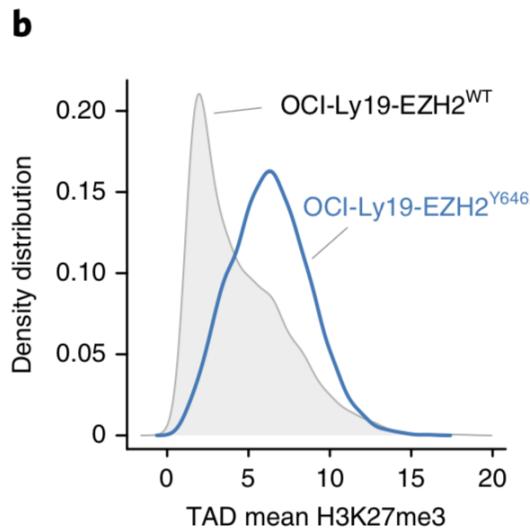
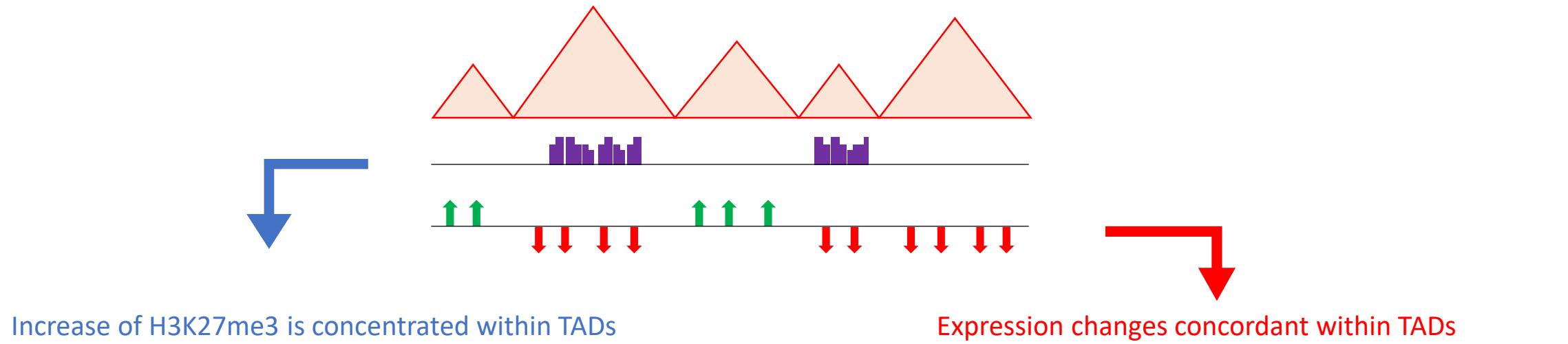
$\text{EZH2}^{\text{Y646X}}$ -driven molecular changes are more concordant within TADs than expected



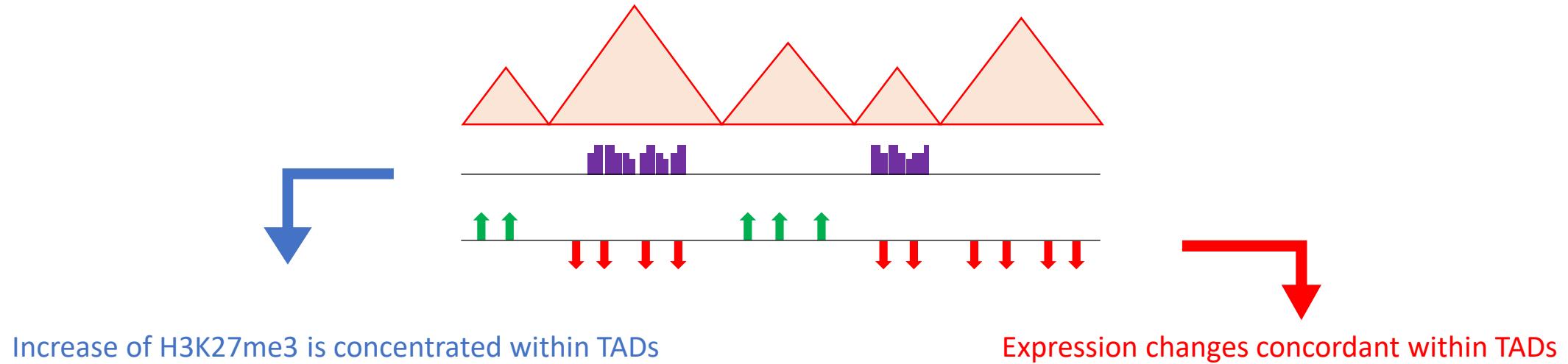
Increase of H3K27me3 is concentrated within TADs



$\text{EZH2}^{\text{Y646X}}$ -driven molecular changes are more concordant within TADs than expected

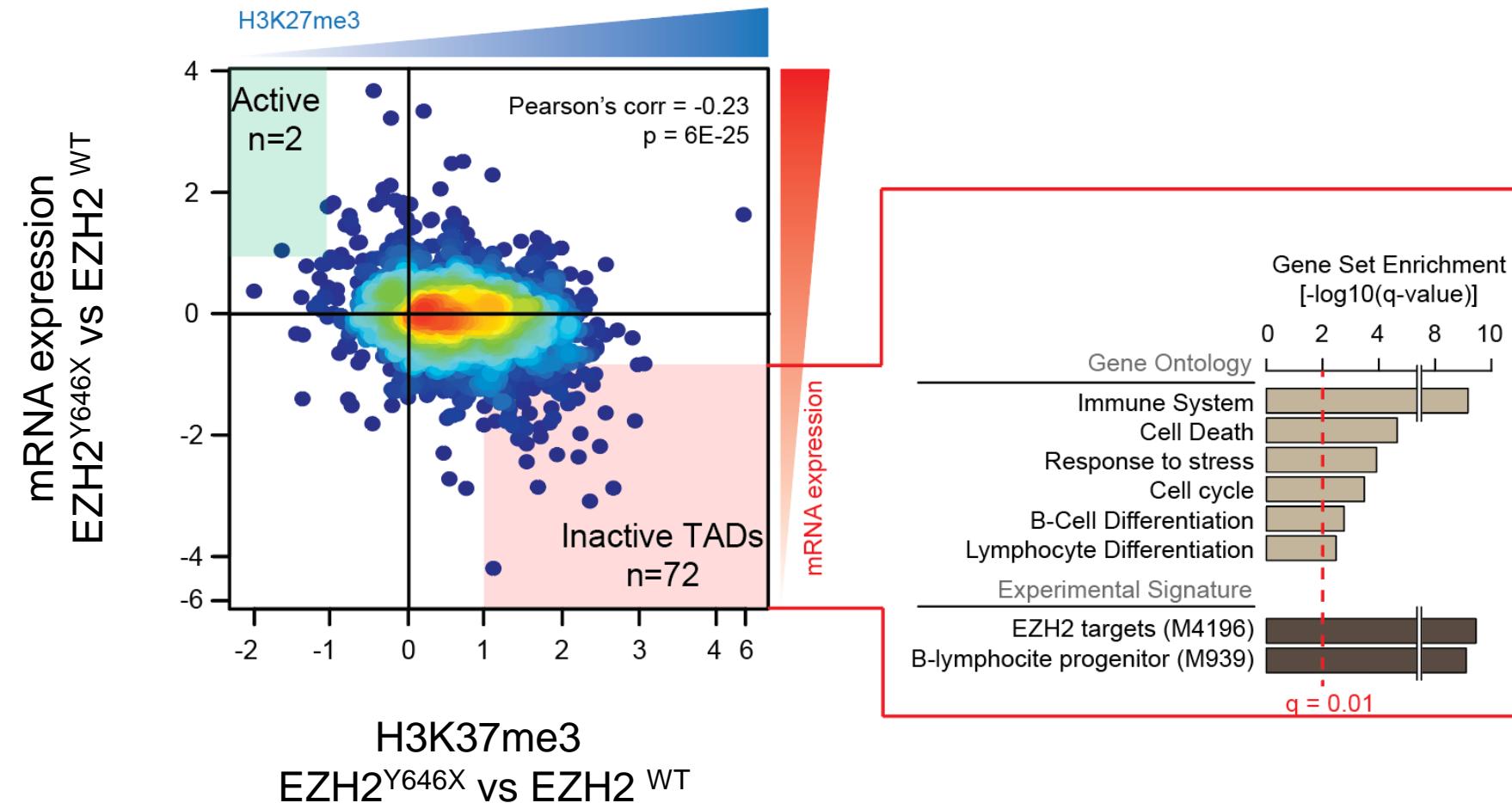


EZH2^{Y646X} -driven molecular changes are more concordant within TADs than expected

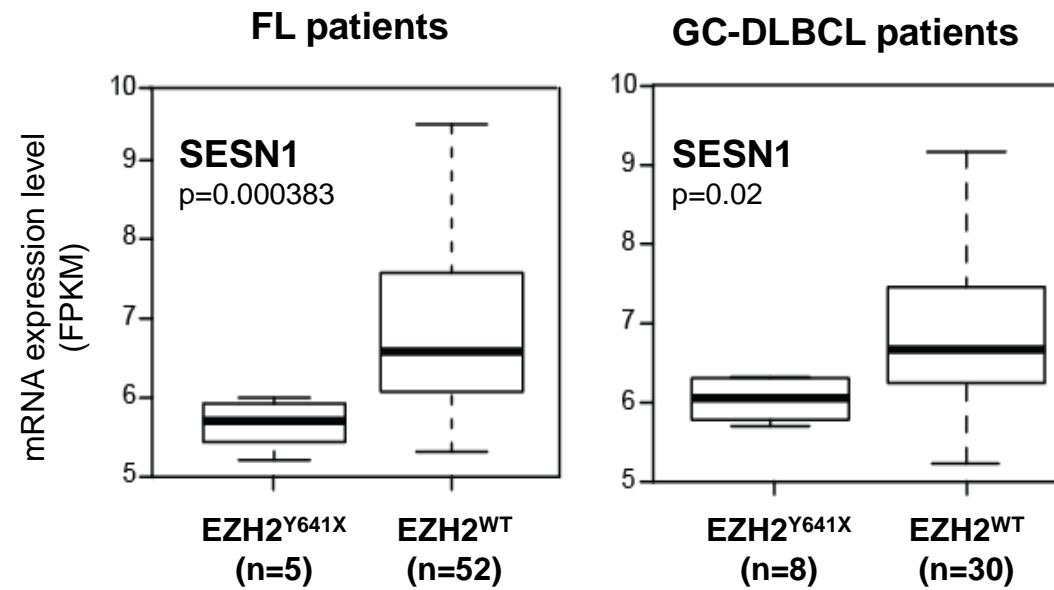
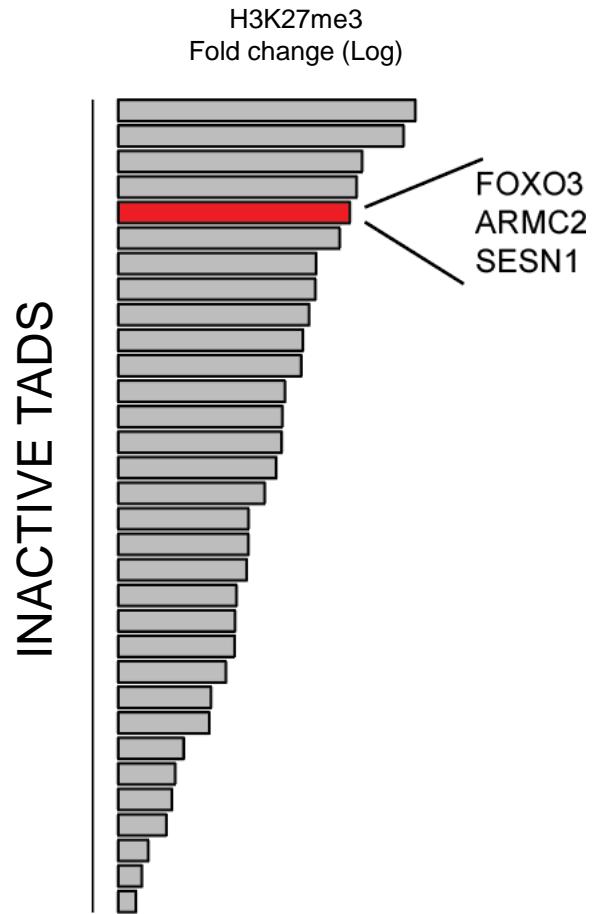


- EZH2 mutations induce genome-wide epigenetic and transcriptional changes
- Chromatin structure / TADs are overall stable
- Epigenetic and transcriptional changes are NOT randomly distributed but concordant and enriched within specific TADs

Inactive TADs are enriched in EZH2 target genes involved in B-cells differentiation and cell death

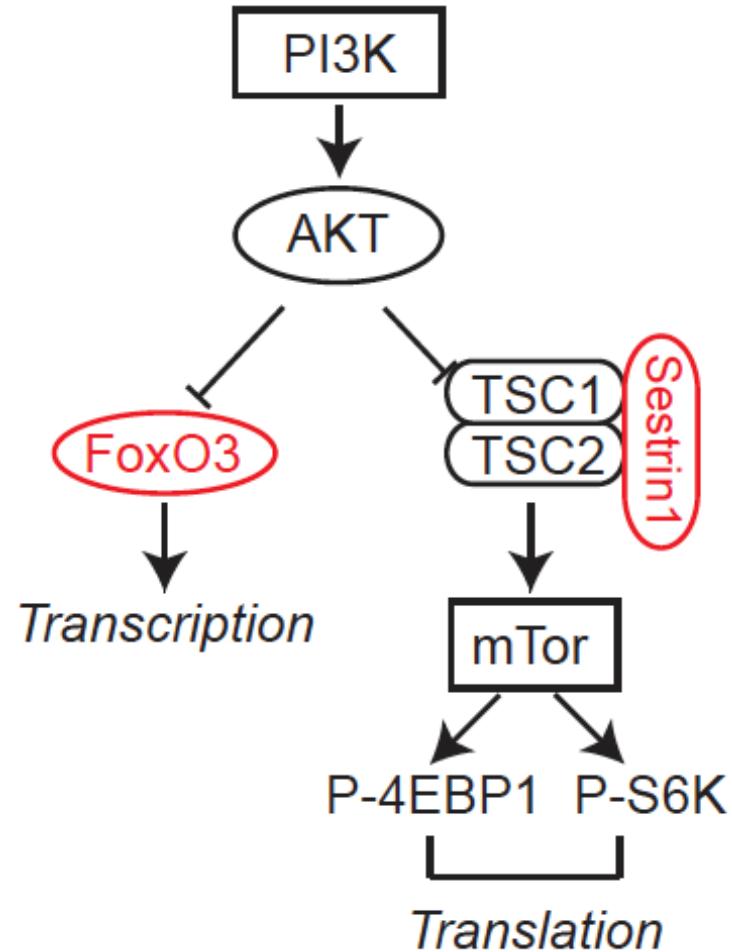
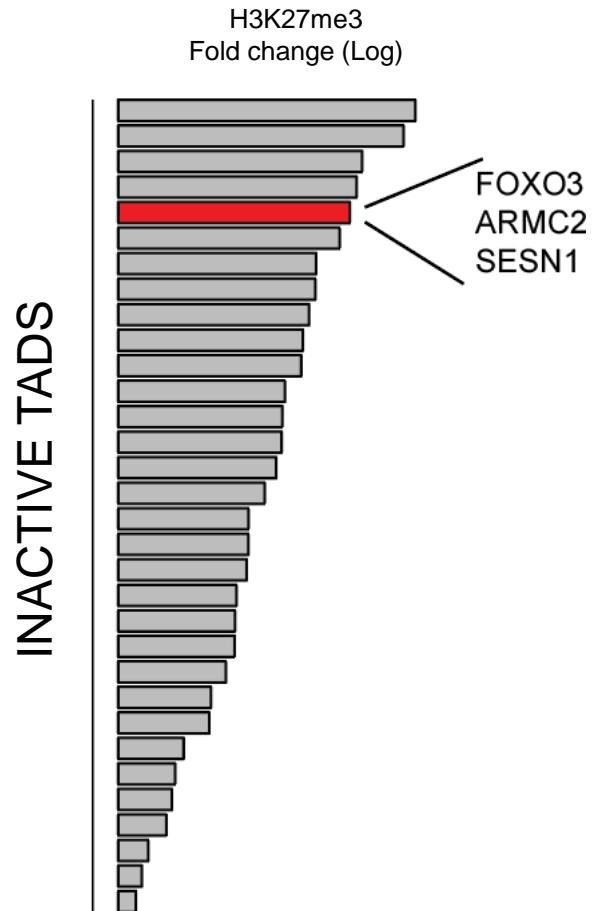


Inactive TADs concurrently repress multiple tumor suppressors

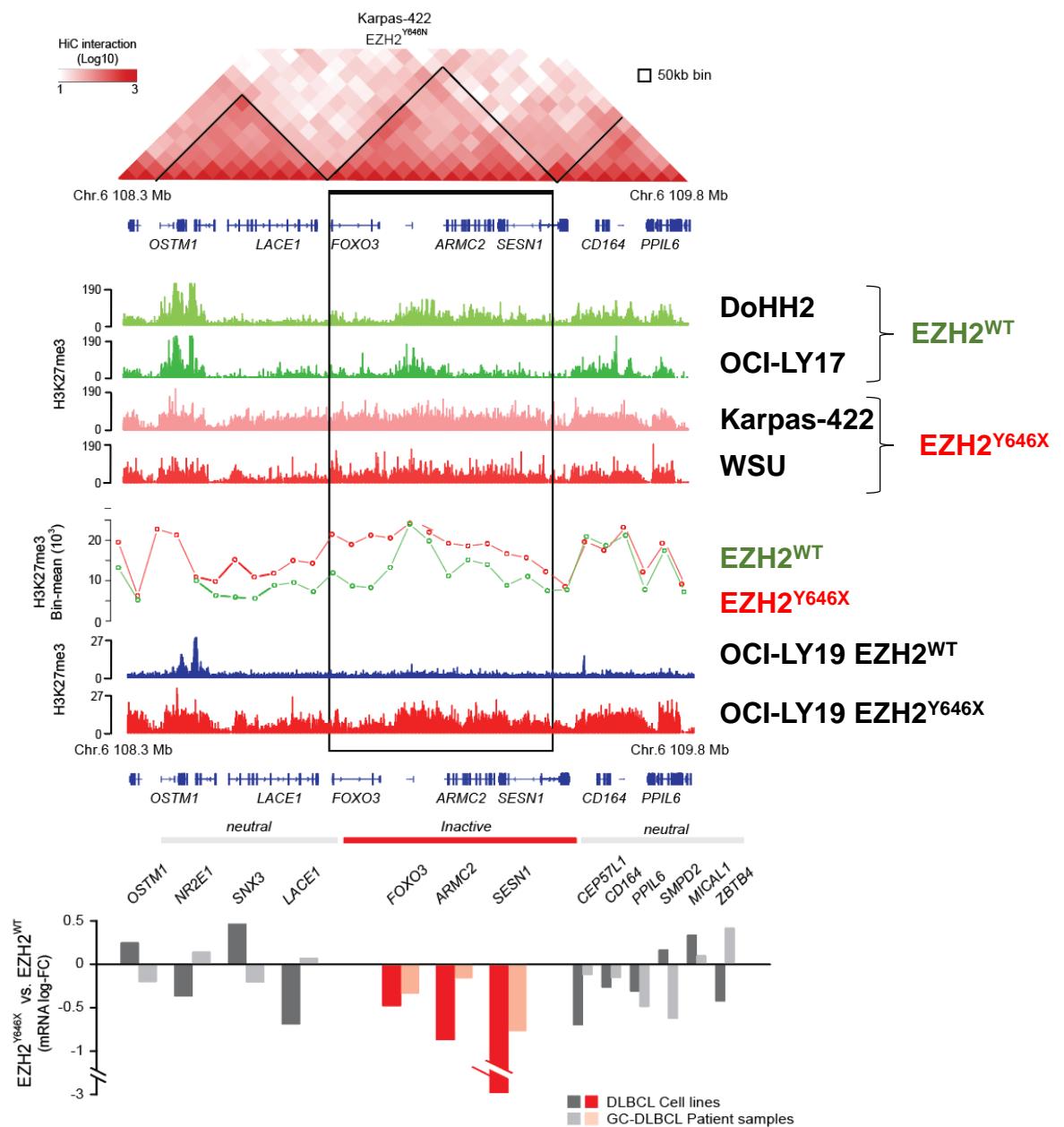
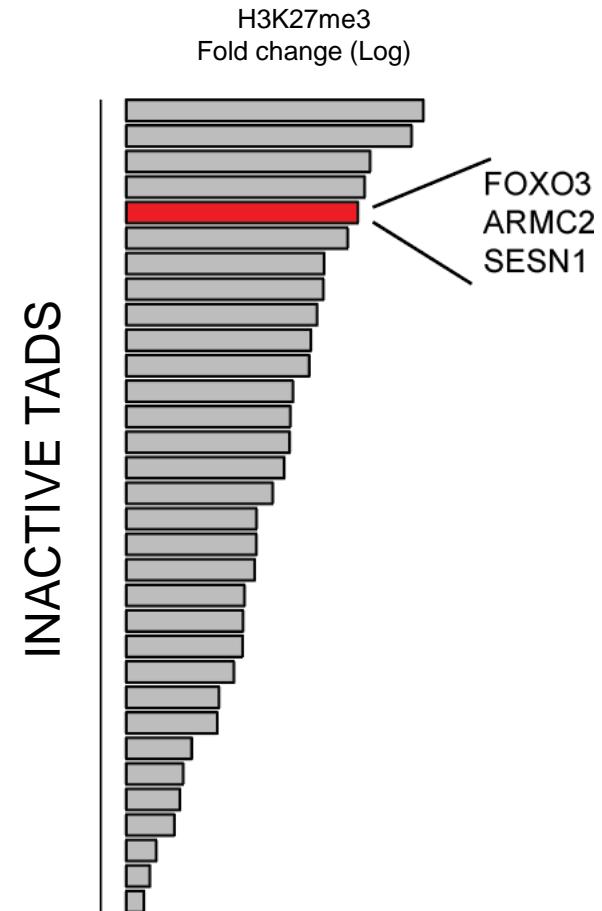


Oricchio et al. 2017

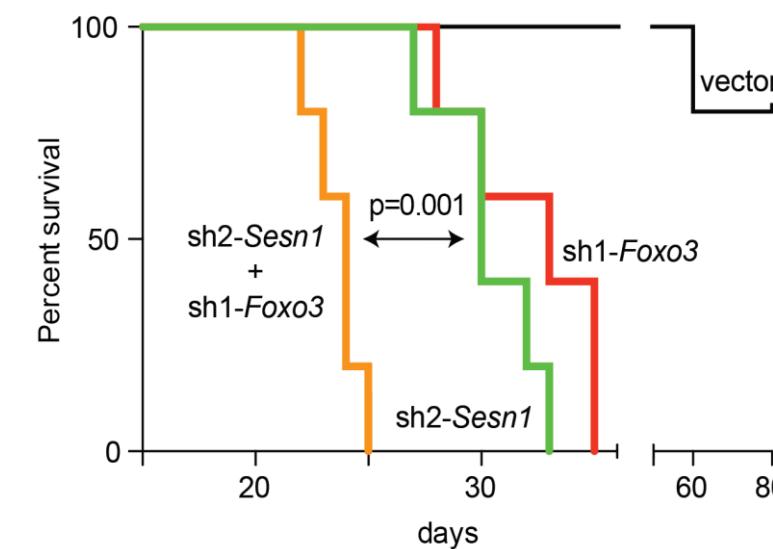
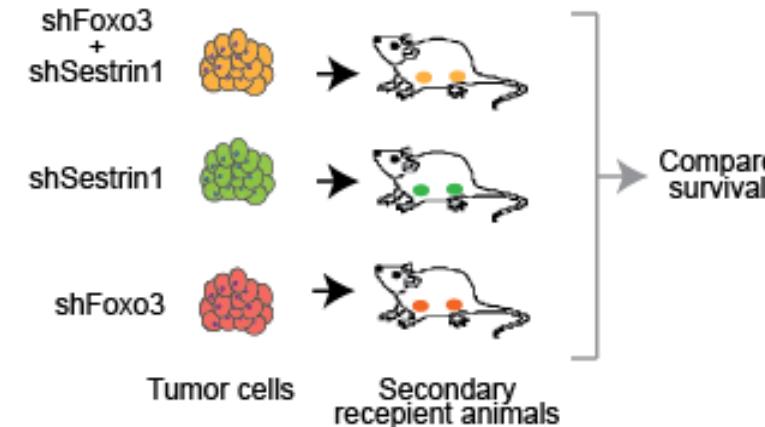
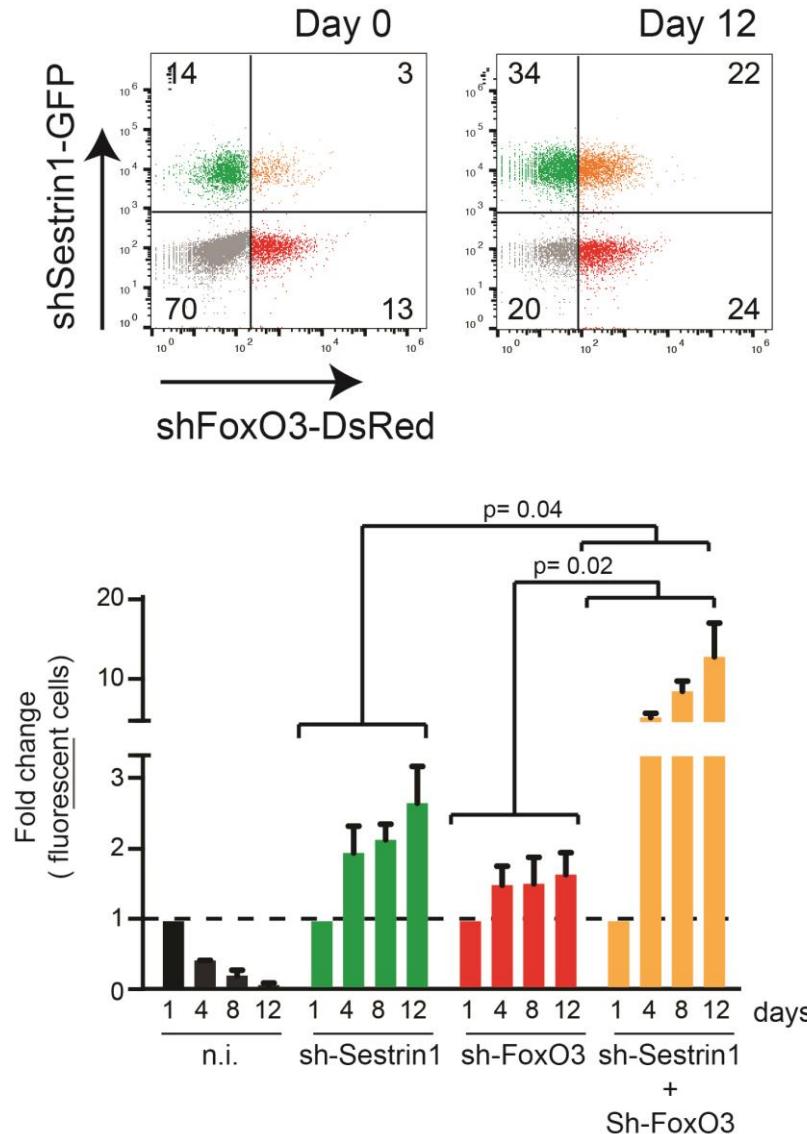
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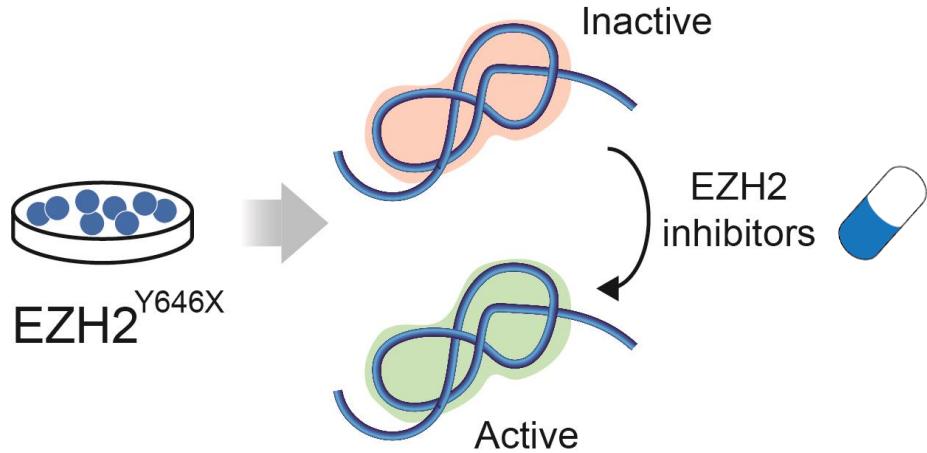
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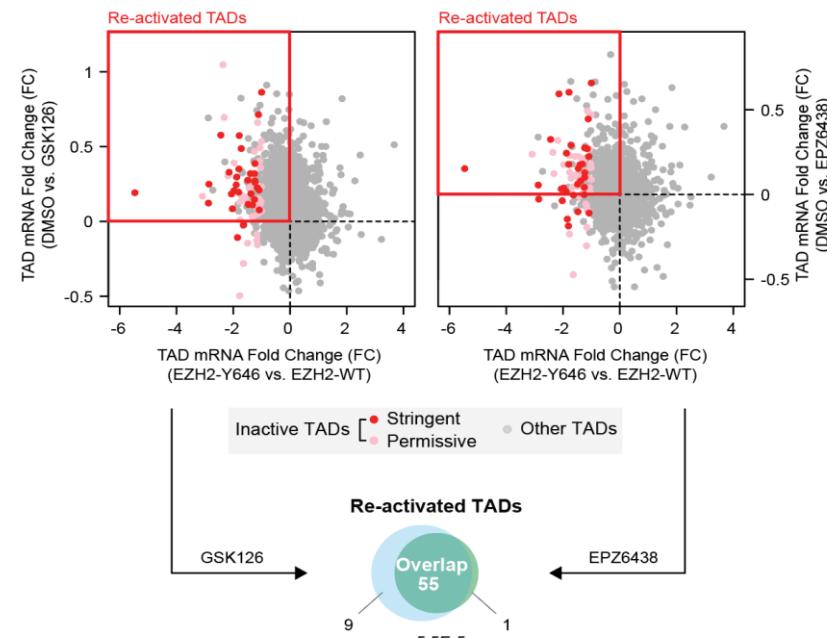
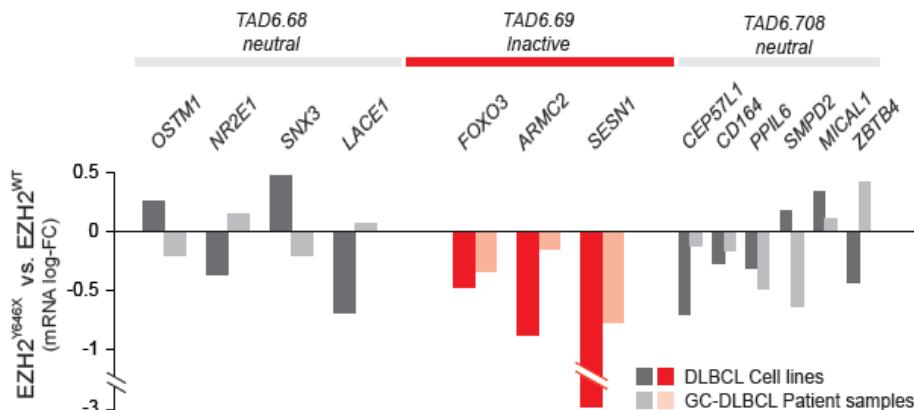
Silencing of Tumor Suppressive TADs accelerates tumorigenesis



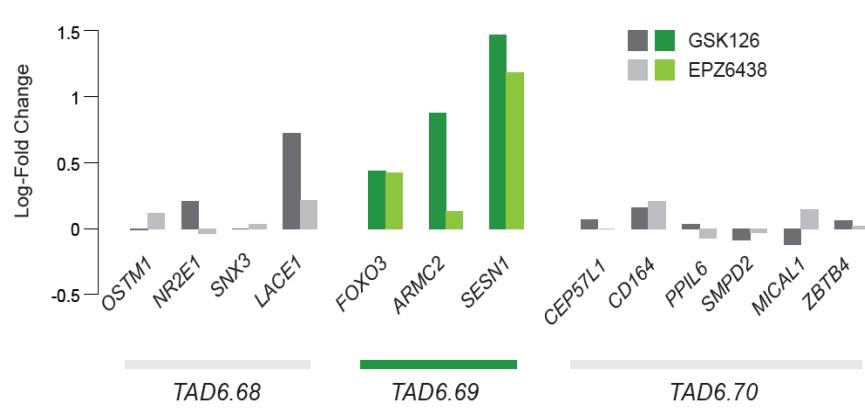
EZH2 inhibitors reactivate tumor suppressive TADs



Increase in H3K27me3 down-regulates tumor suppressive TADs

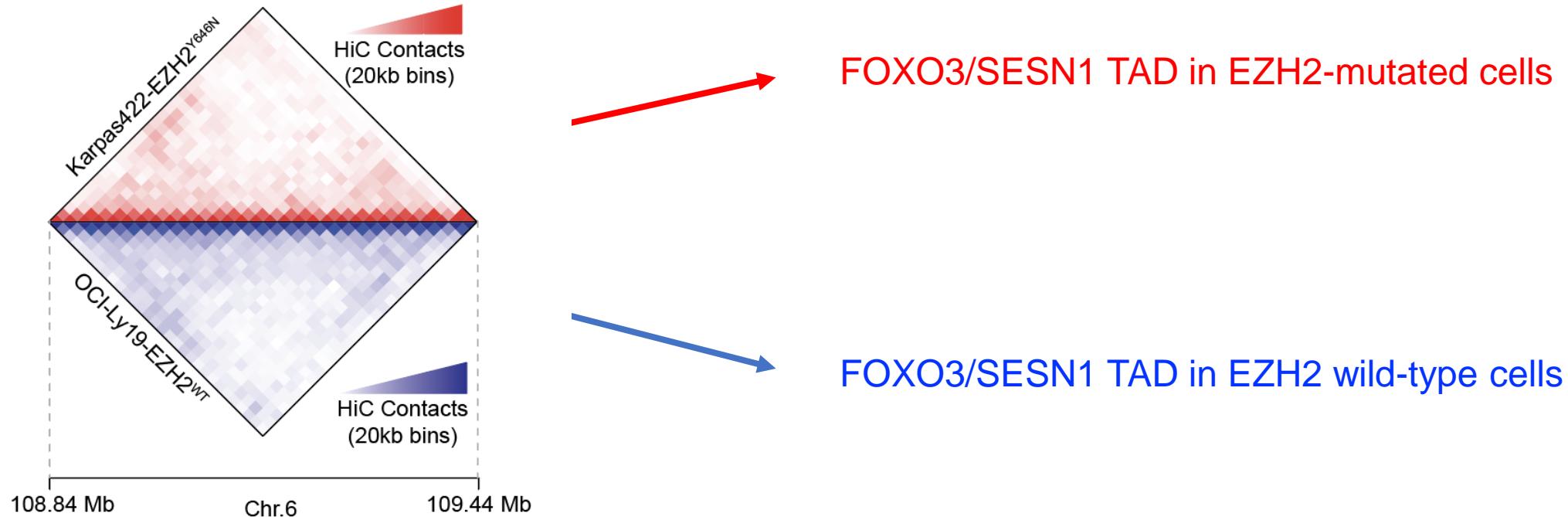


H3K27me3 depletion reactivates tumor suppressive TADs

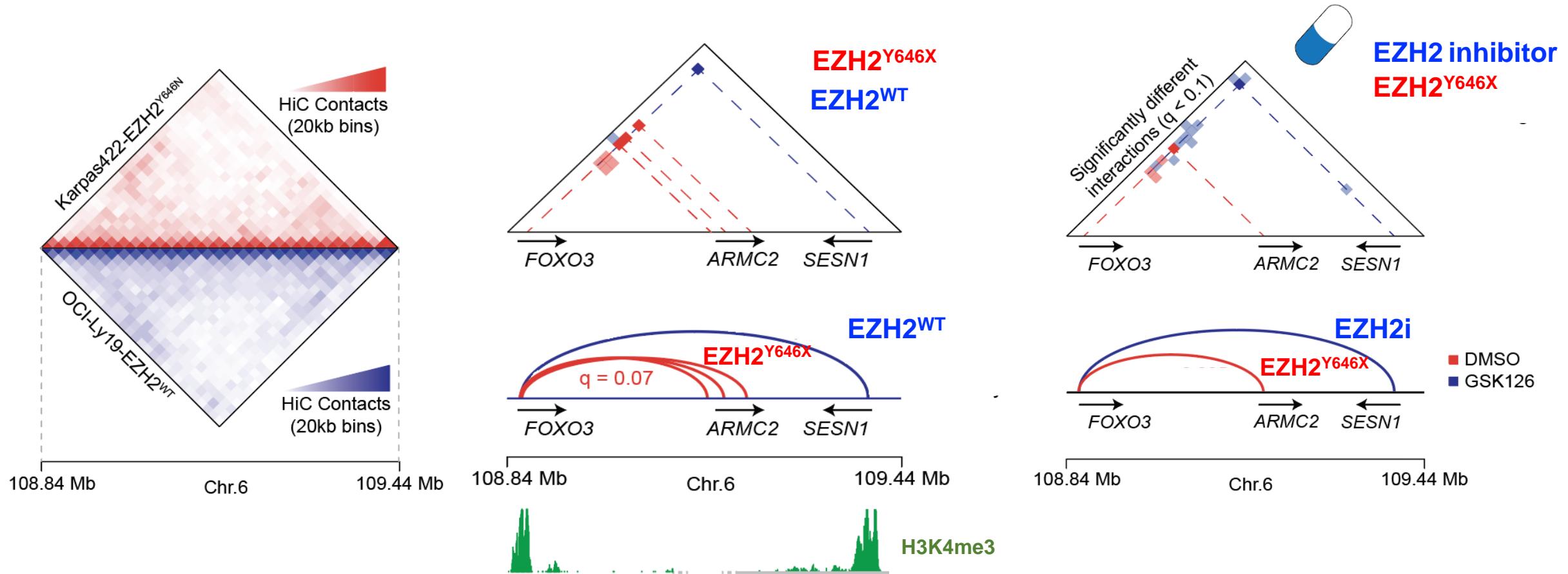


Are the transcriptional and epigenetic changes in inactive TADs
coupled with intra-TAD structural changes?

Compare intra-TAD structure of EZH2 wild-type and mutated cells



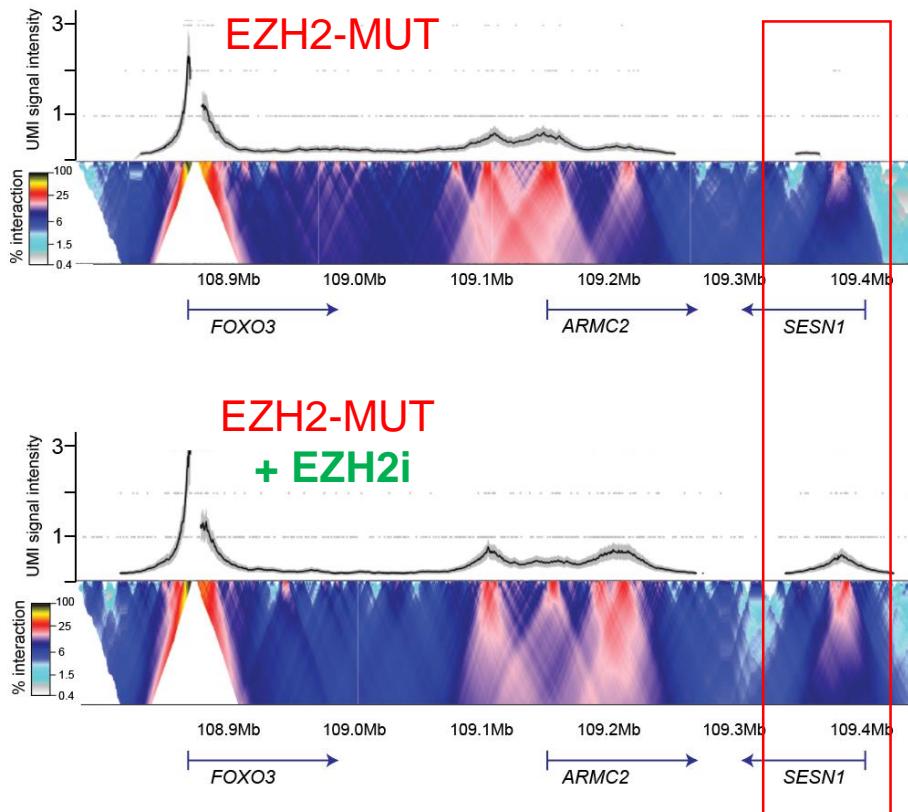
Comparing the strength of the interactions



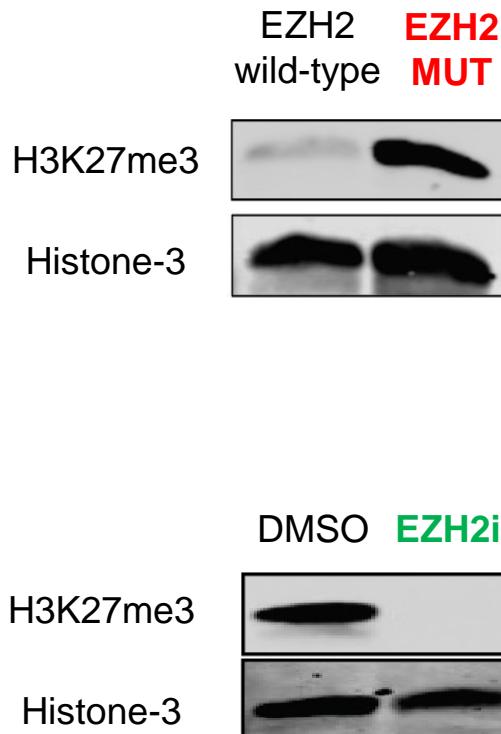
EZH2 inhibition re-establishes promoter-promoter interactions between FOXO3 and SESN1

Inhibition of EZH2^{Y646X} restores promoter-promoter interactions and re-activation of gene expression

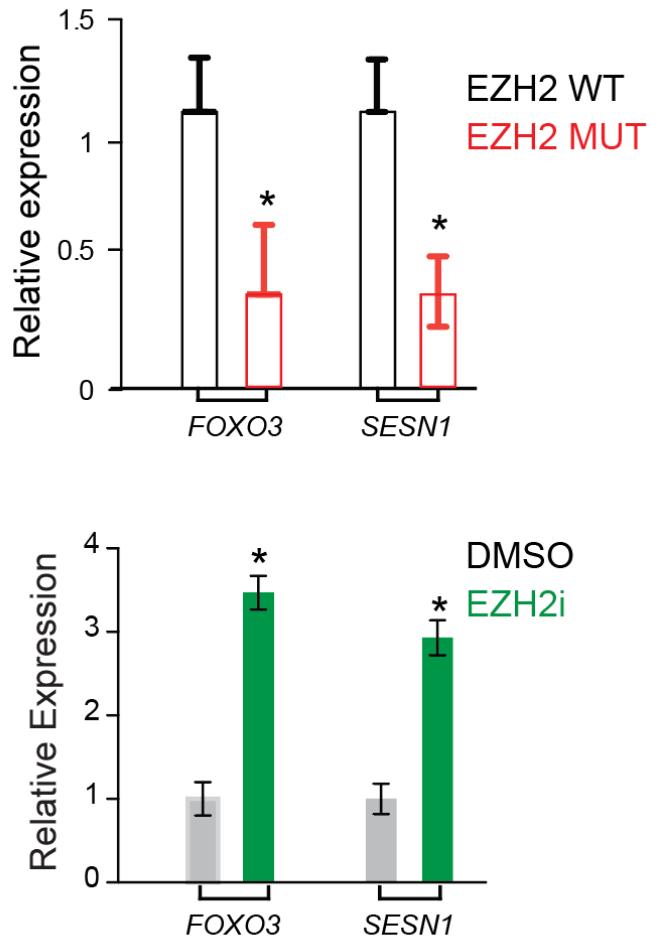
1. STRUCTURE

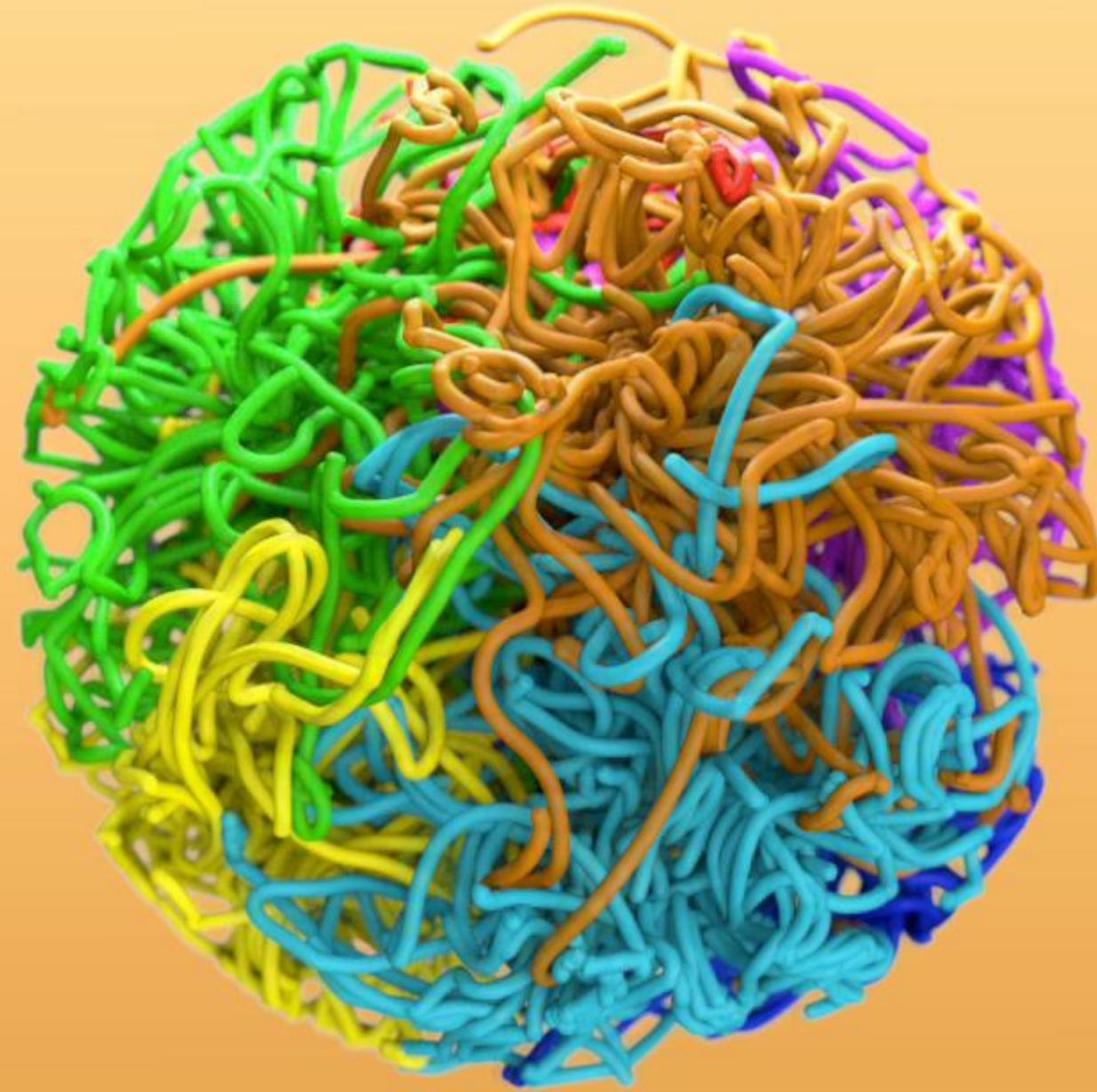


2. EPIGENETIC



3. EXPRESSION





Thanks to.....

Oricchio's Lab

*Maria Donaldson-Collier
Stephanie Sungalee
Ruxandra Lambuta*

Ciriello's Lab

*Maria Zufferey
Daniele Tavernari
Yuanlong Liu*

