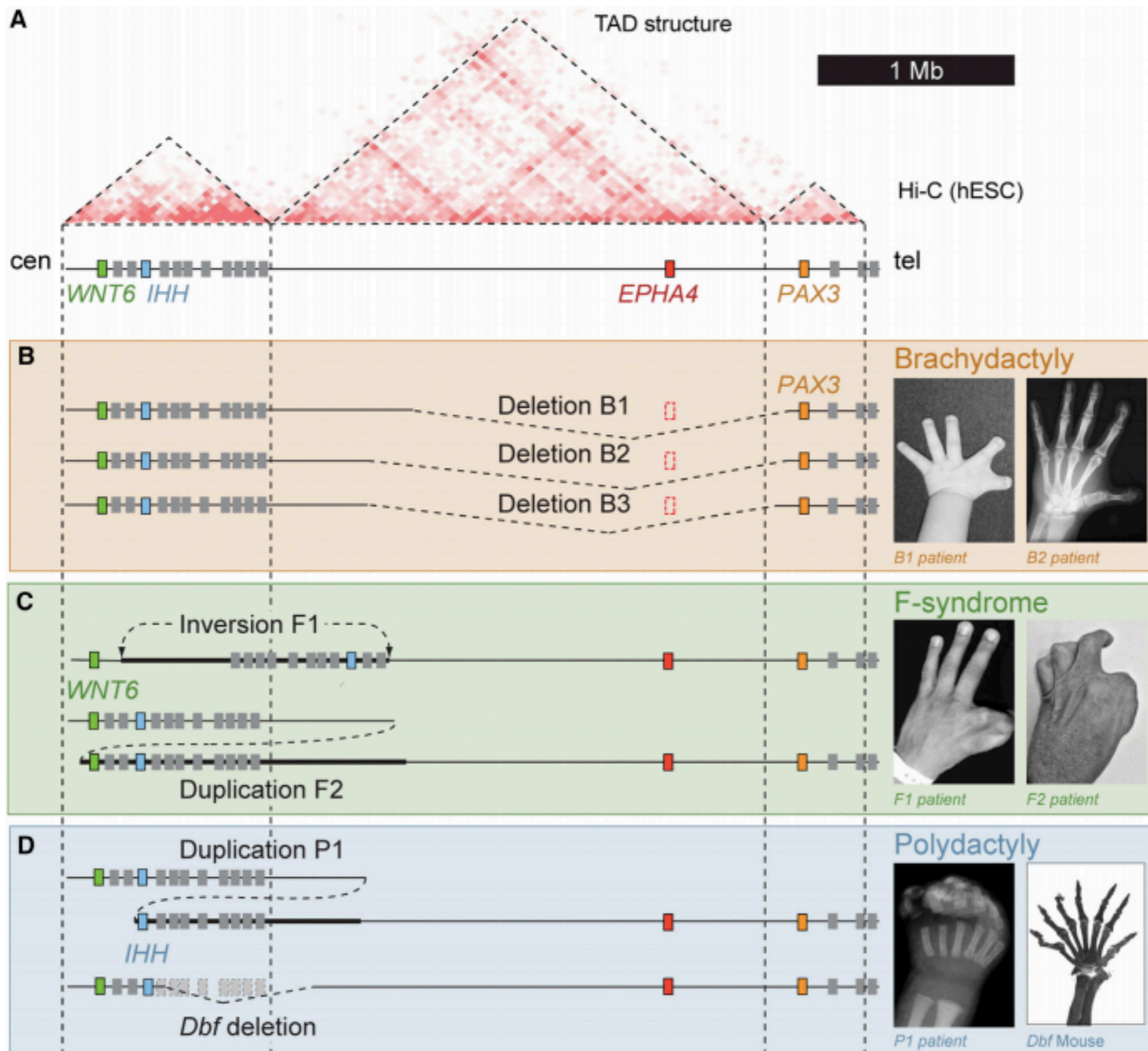
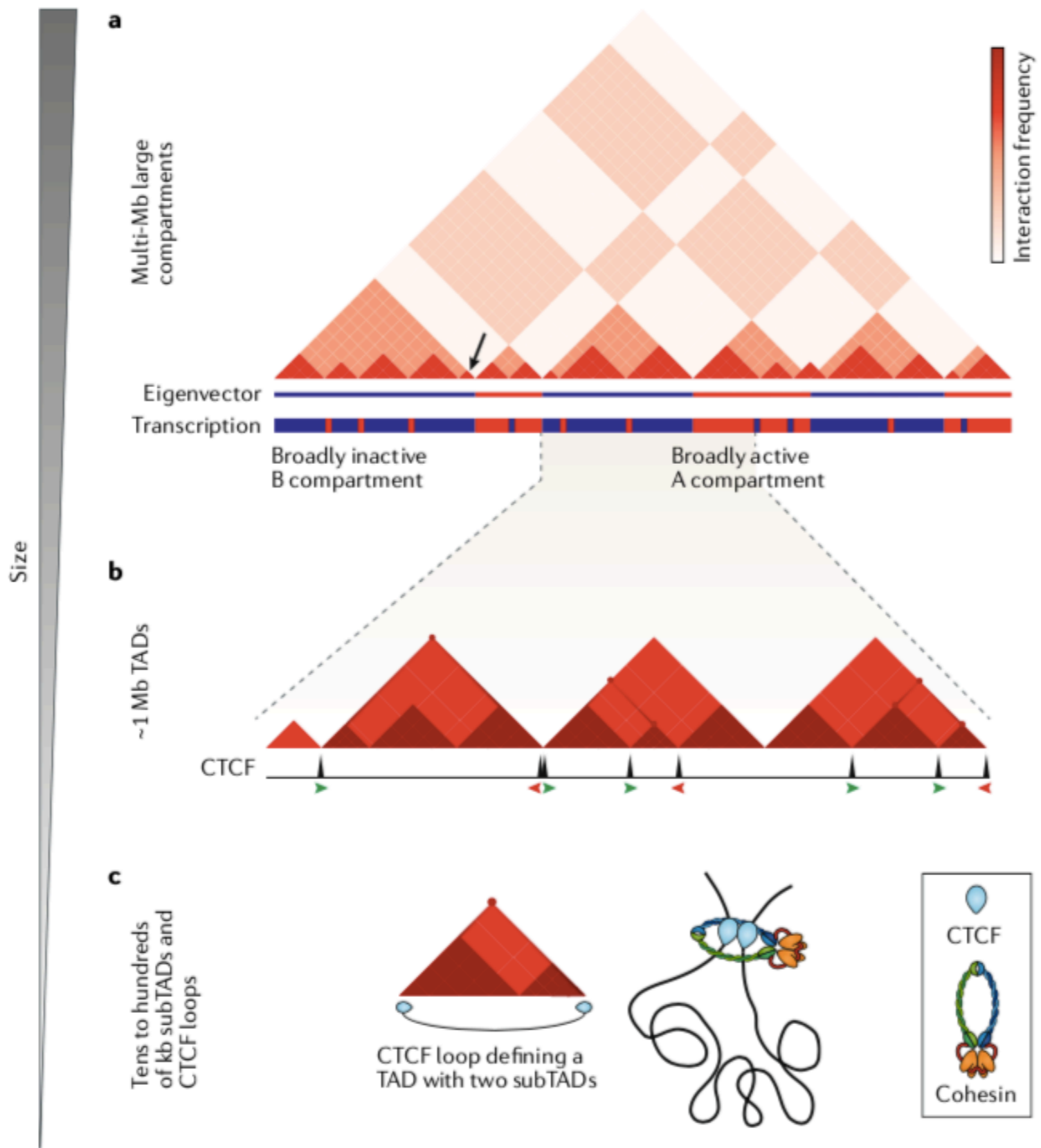


# Chromatin three-dimensional interactions mediate genetic effects on gene expression

Journal Club  
21 May 2019  
Sasha Galitsyna

# TADs and insulation are important for gene expression regulation

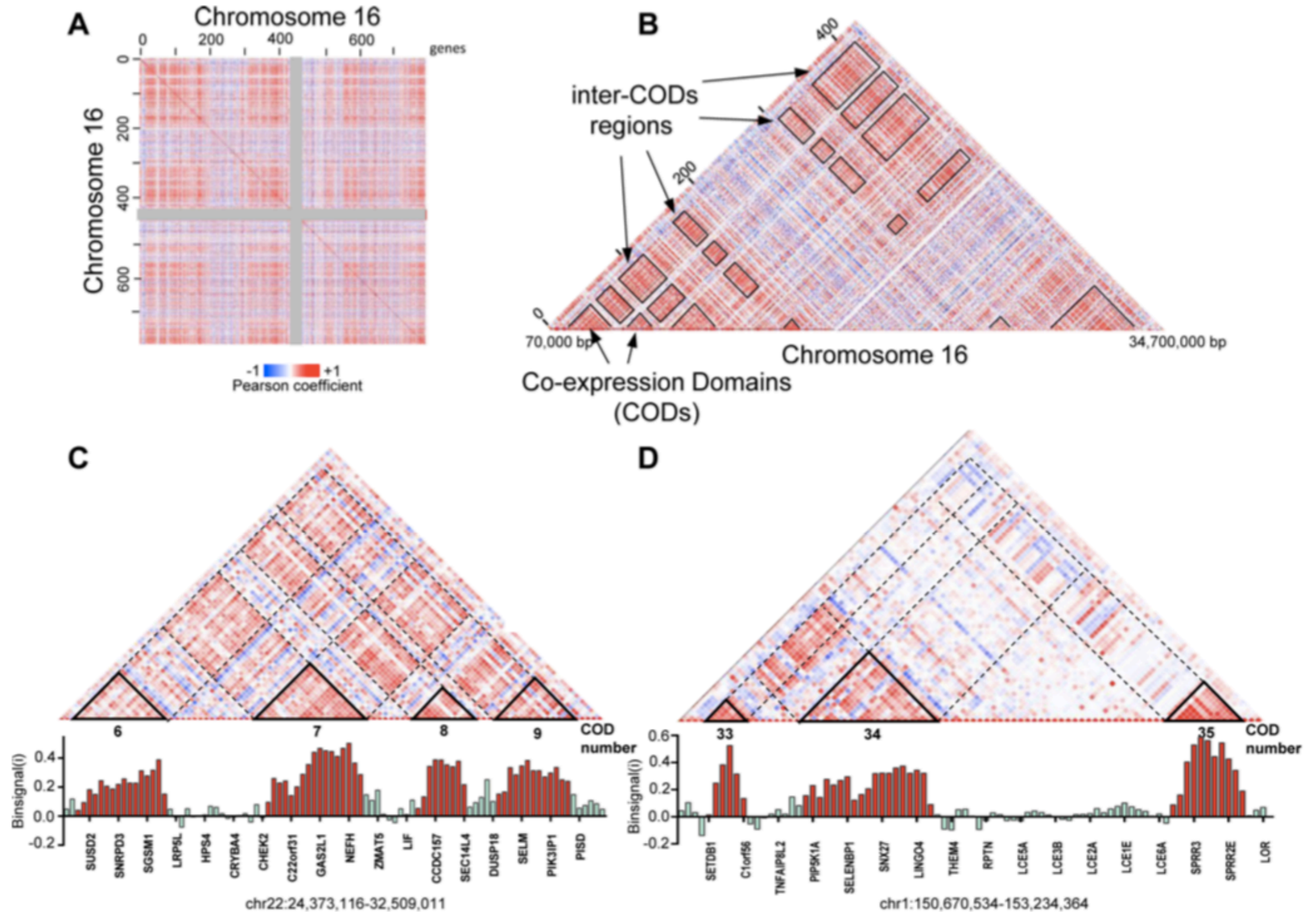




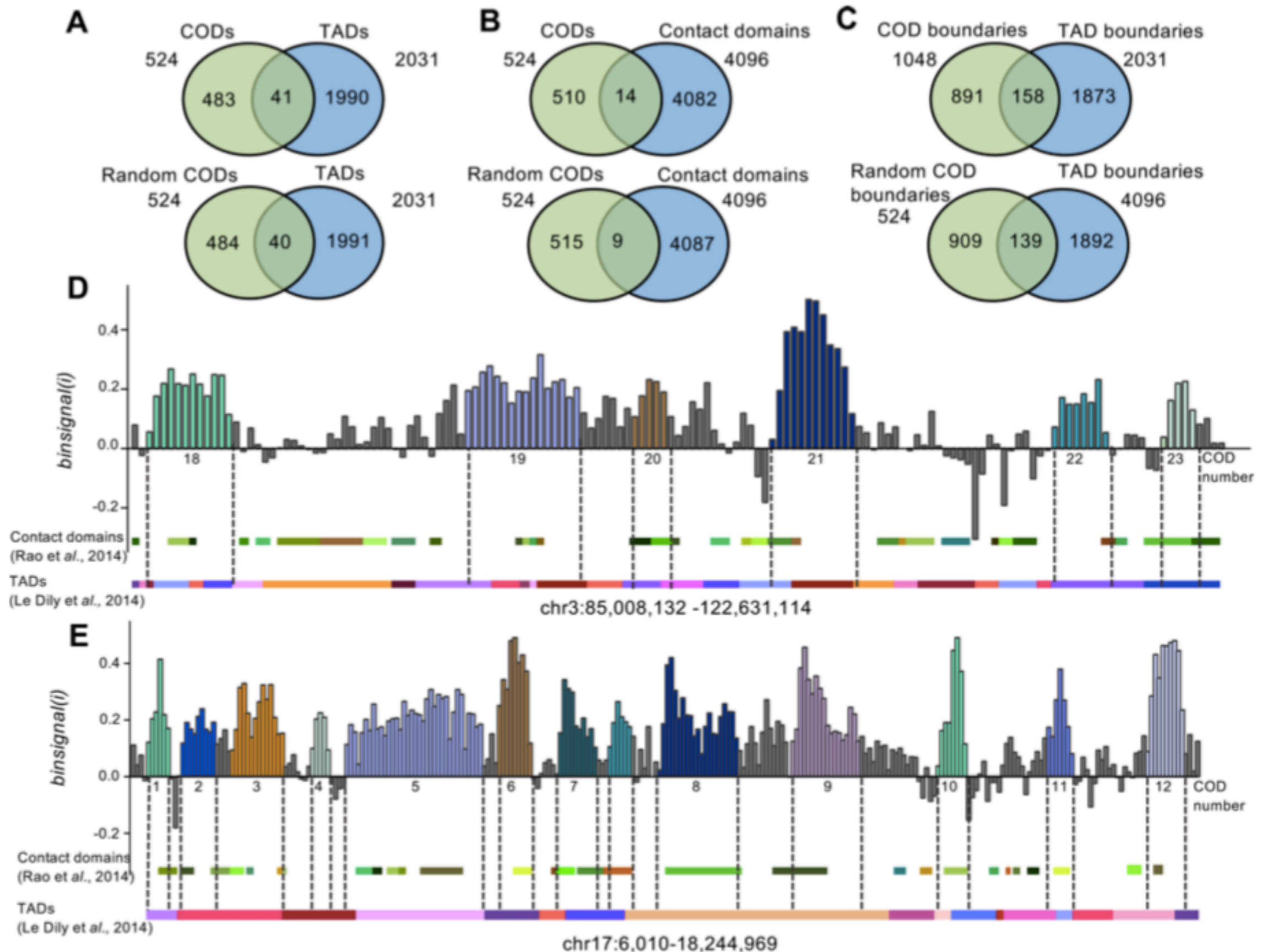
# Are genes within the same TAD co-expressed?

- "Analyzing the relationship between CODs (coexpression domains) and chromatin 3D organization using Hi-C contact data, we find that **CODs do not correspond to TADs**. In fact, intra-TAD gene coexpression is the same as random for most chromosomes." - from "Analysis of the relationship between coexpression domains and chromatin 3D organization" Soler-Oliva et al. 2017 PLOS Comput. Biology
- Based on bulk RNA-Seq expression of 20,502 genes from 100 normal breast tissue samples from The Cancer Genome Atlas (TCGA).

# Bulk RNA-Seq: no evidence?



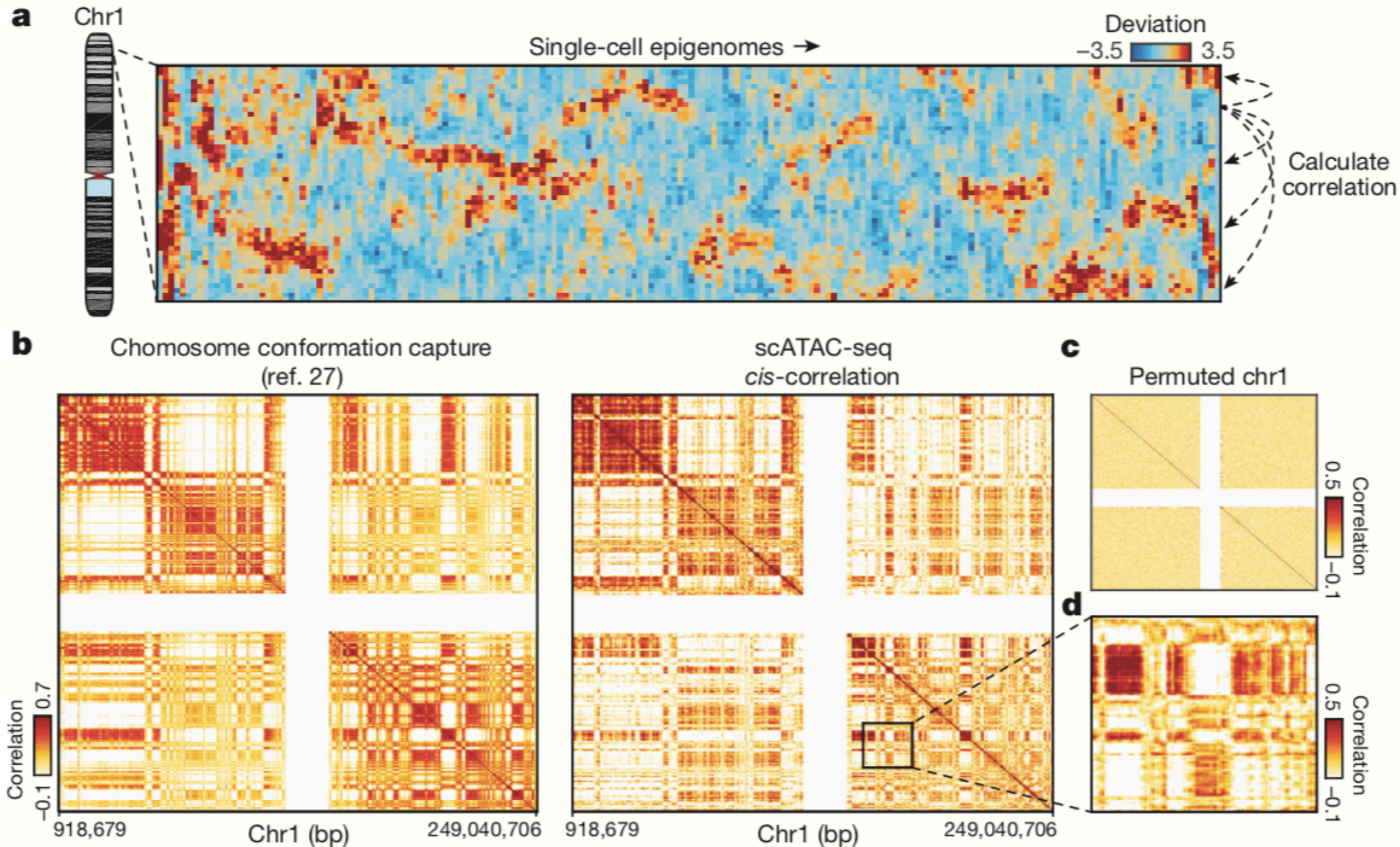
# Bulk RNA-Seq: no evidence?



# Single-cell RNA-Seq: no evidence?

- "There was no bias towards associating similar CV (coefficient of variation) value genes with same TADS. Also, tightly co-expressed High CV genes in each cluster were not specifically enriched for any biological process nor primed for specific lineage."
- Based on 63 mouse ES and 32 human ES.

# Single-cell epigenomics evidence





- Available on github since 2017:

## RESEARCH ARTICLE

### HUMAN GENOMICS

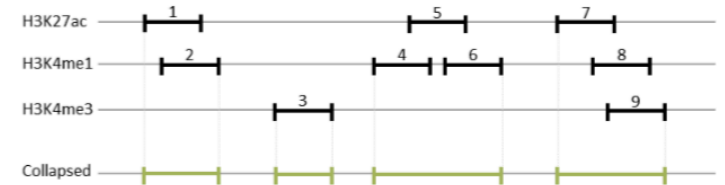
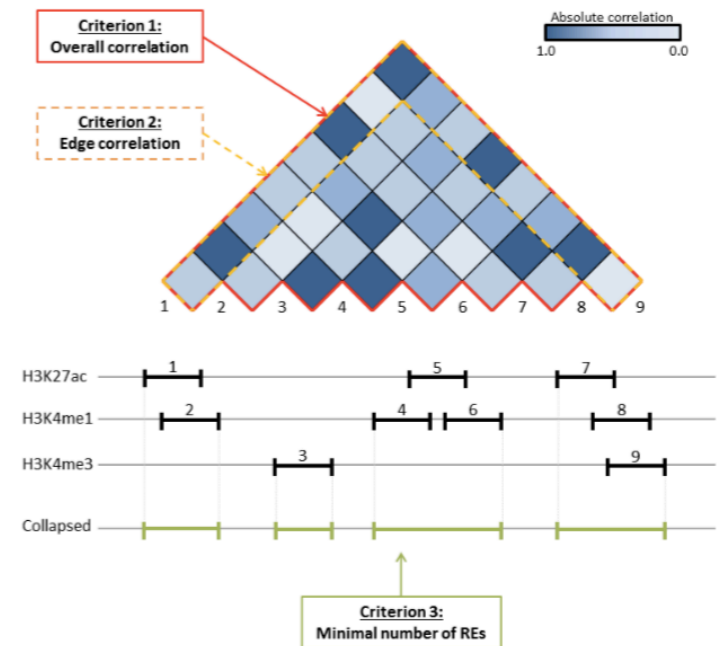
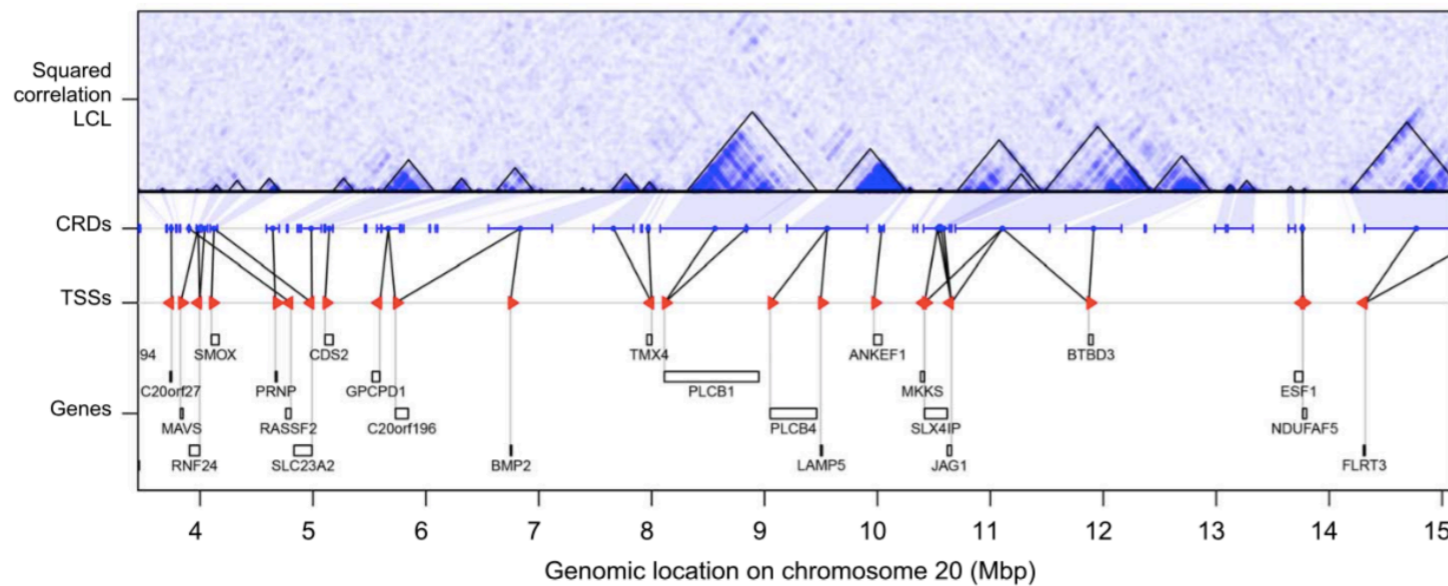
# Chromatin three-dimensional interactions mediate genetic effects on gene expression

O. Delaneau<sup>1,2,3\*</sup>, M. Zazhytska<sup>4</sup>, C. Borel<sup>1,3</sup>, G. Giannuzzi<sup>4</sup>, G. Rey<sup>1,2,3</sup>, C. Howald<sup>1,2,3</sup>, S. Kumar<sup>5,6</sup>, H. Ongen<sup>1,2,3</sup>, K. Popadin<sup>4,6,7</sup>, D. Marbach<sup>8,6</sup>, G. Ambrosini<sup>5,6</sup>, D. Bielser<sup>1</sup>, D. Hacker<sup>9</sup>, L. Romano<sup>1</sup>, P. Ribaux<sup>1</sup>, M. Wiederkehr<sup>4</sup>, E. Falconnet<sup>1</sup>, P. Bucher<sup>5,6</sup>, S. Bergmann<sup>8,6†</sup>, S. E. Antonarakis<sup>1,3‡</sup>, A. Reymond<sup>4‡§</sup>, E. T. Dermitzakis<sup>1,2,3‡§</sup>

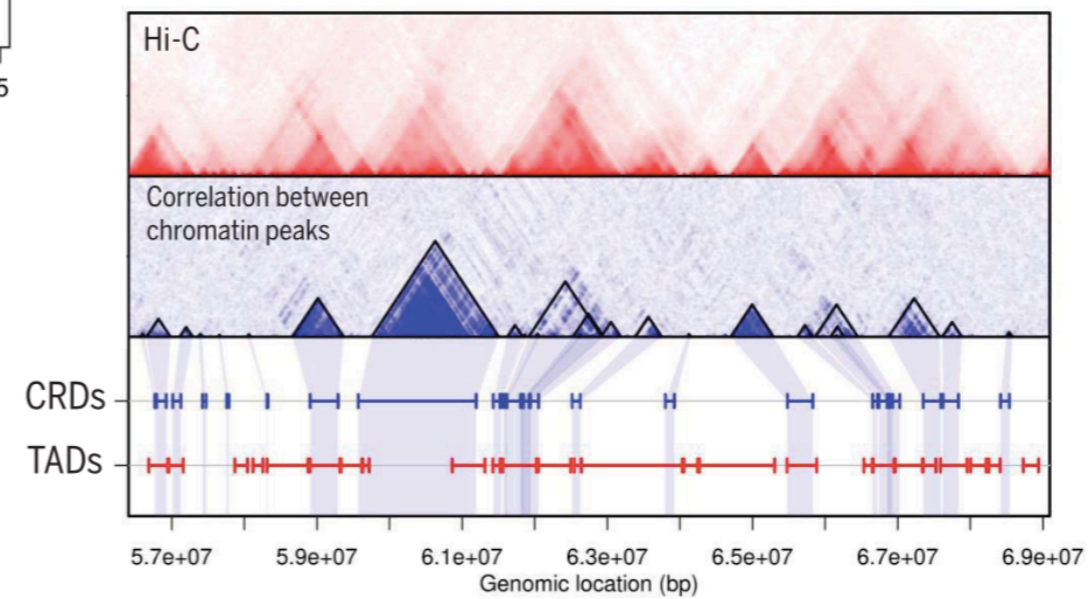
# Experimental setup:

- Based on:
  - CHIP-Seq for 271 LCLs (lymphoblastoid cell line, GM12878) and 78 primary fibroblast lines: H3K27ac, H3K4me1 and H3K4me3
  - RNA-Seq for the same lines

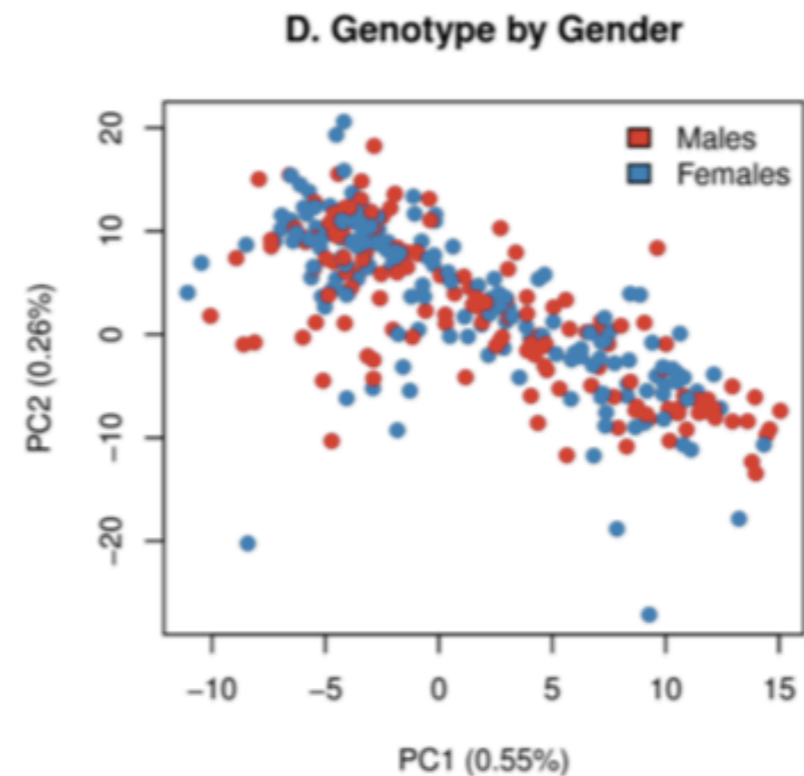
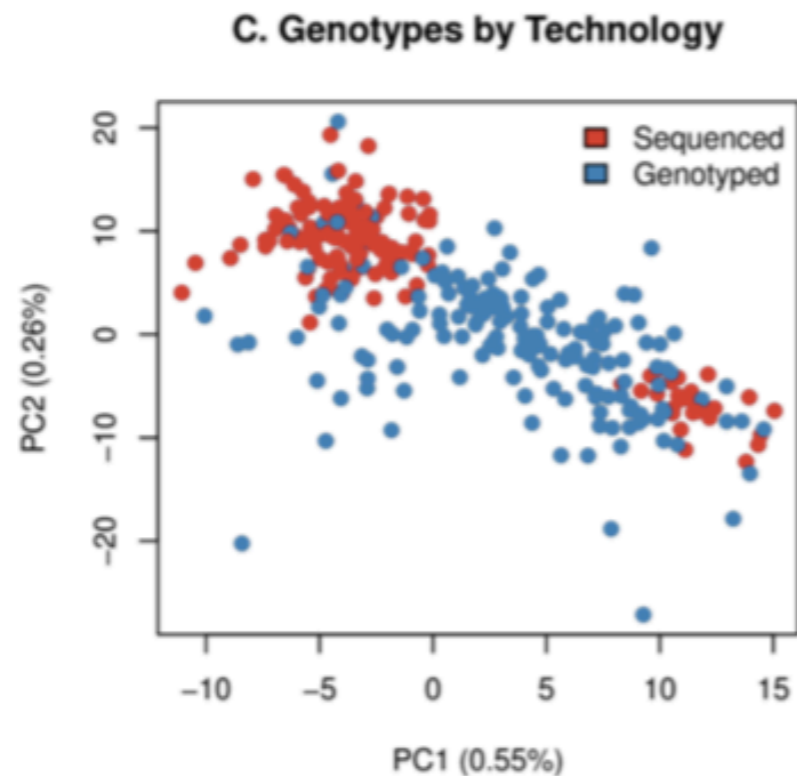
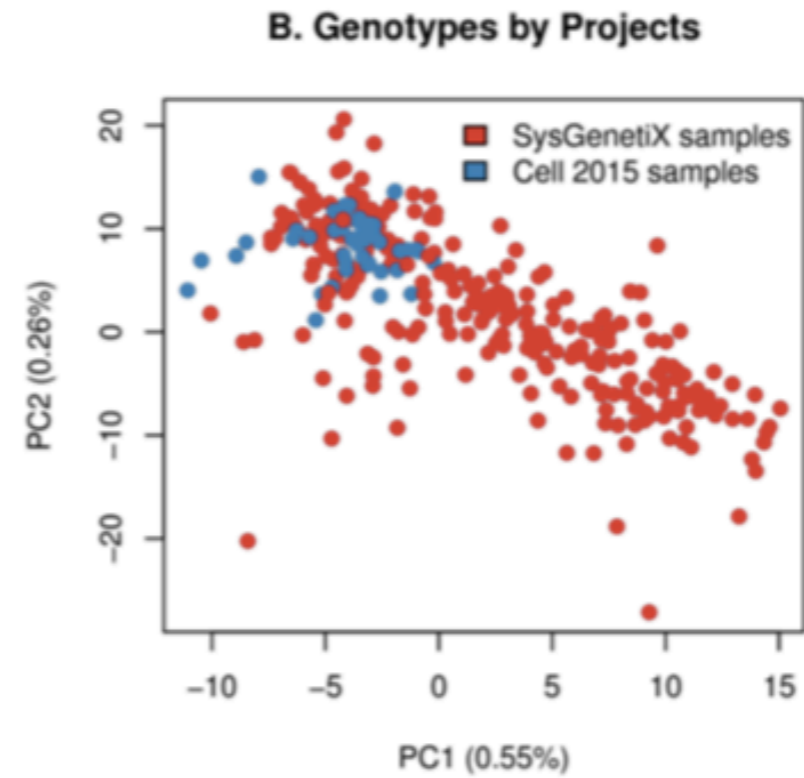
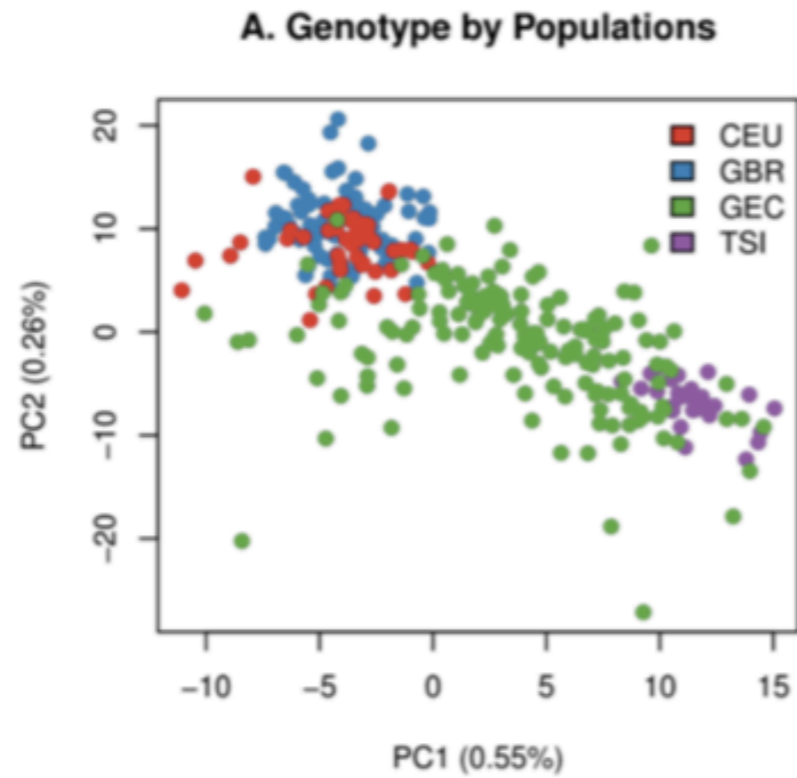
1. Identify CHIP-Seq peaks and correlation of activity:
2. Identify cis-regulatory domains (CRDs):
3. Associate genes with CRDs:



4. Compare with Hi-C:

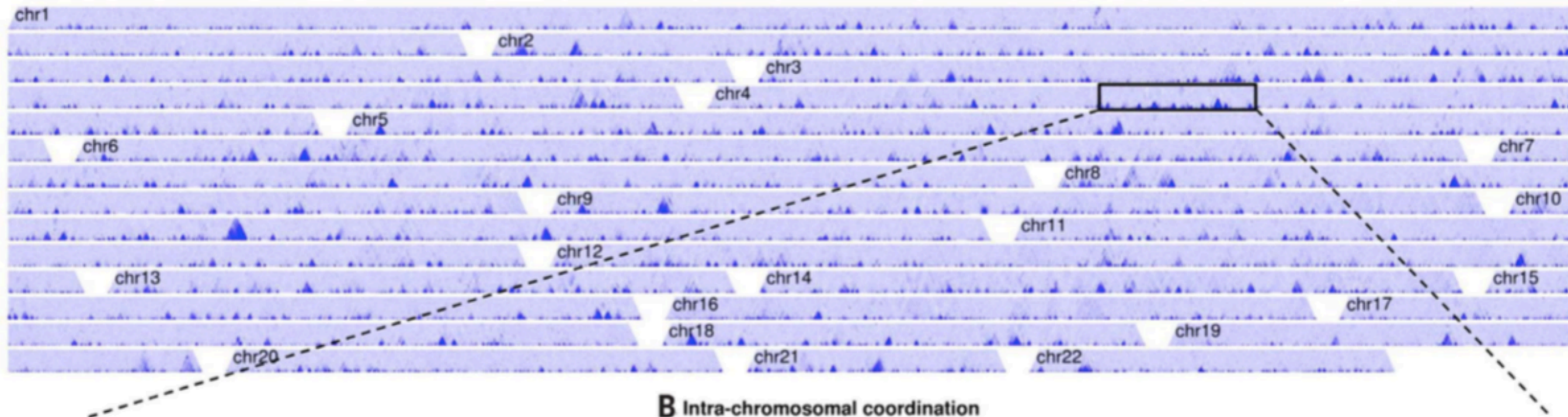


# Accounting for technical and biological variability:

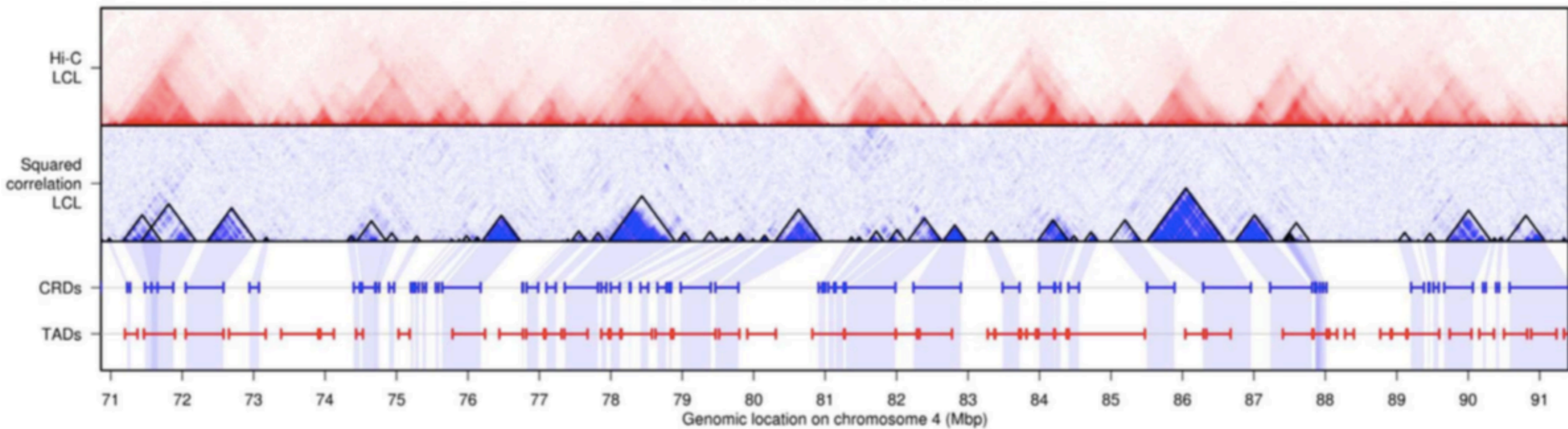


# Map of ChIP-Seq peaks correlations:

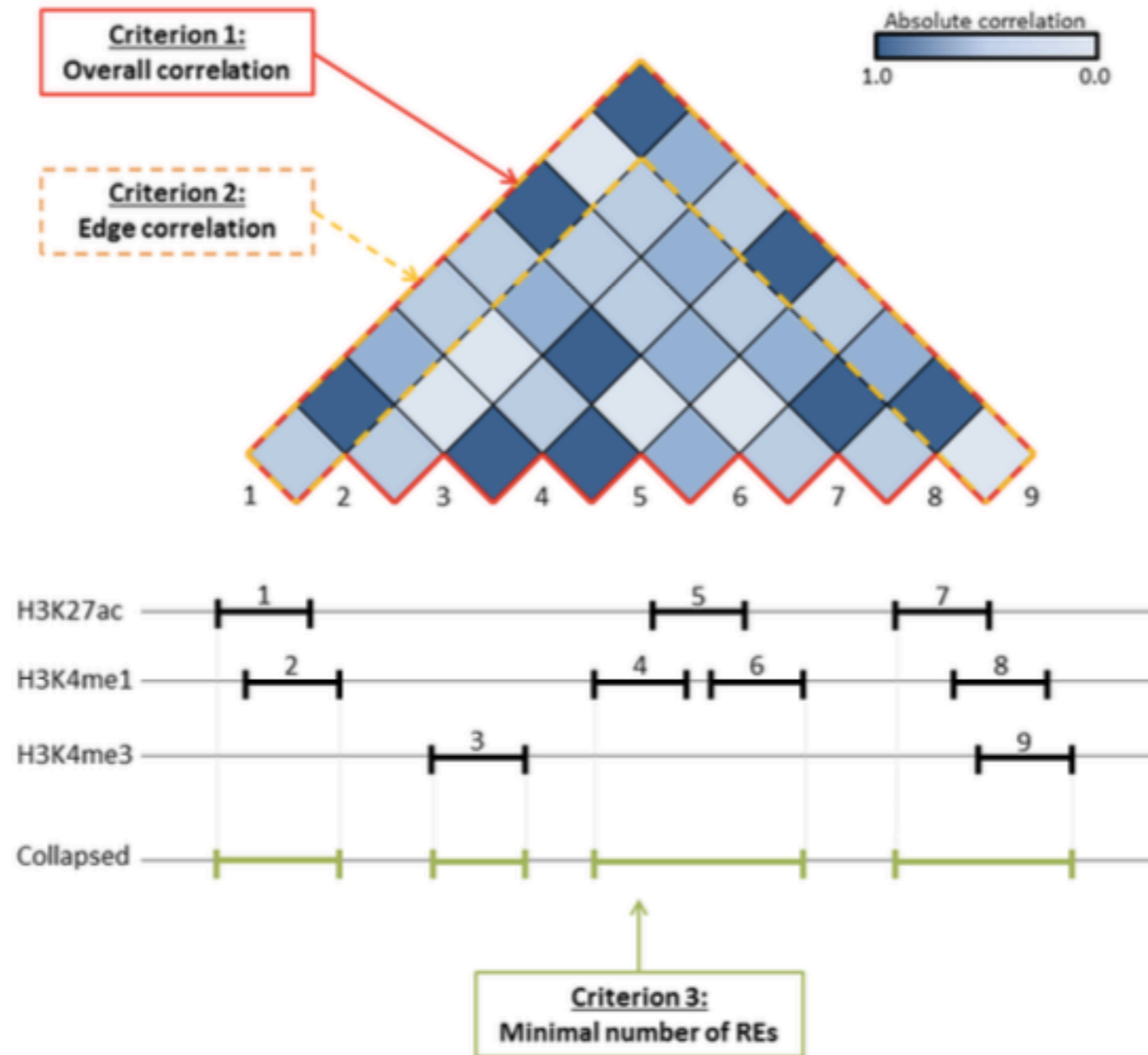
**A** Genome-wide map of correlation between chromatin peaks



**B** Intra-chromosomal coordination

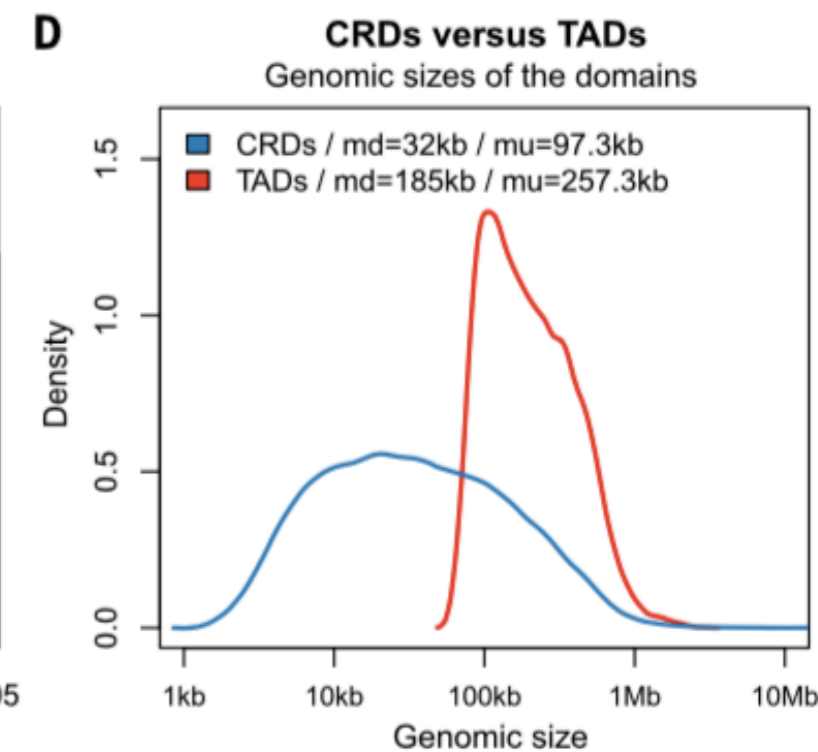
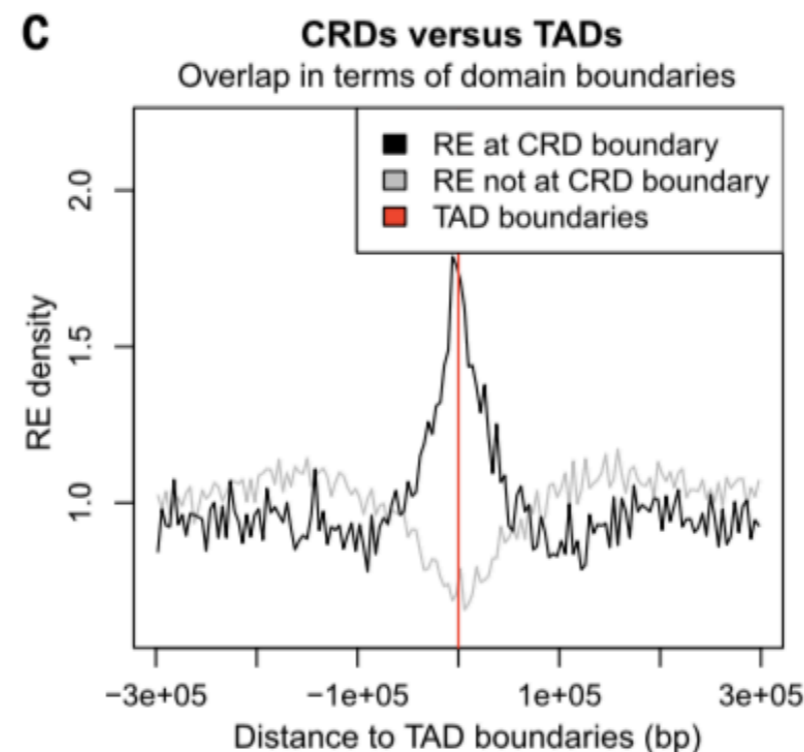
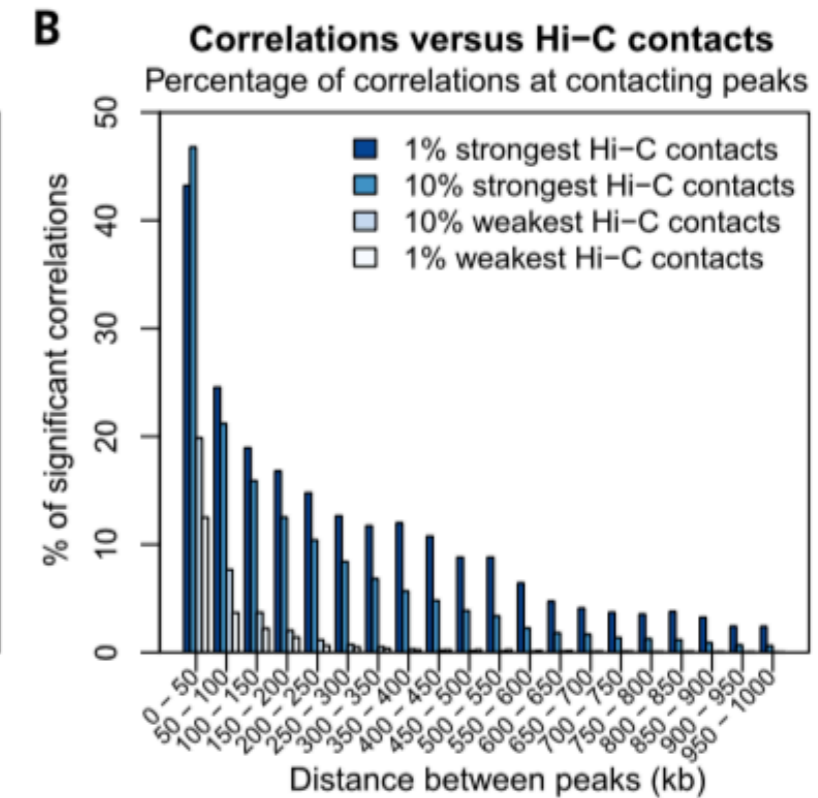
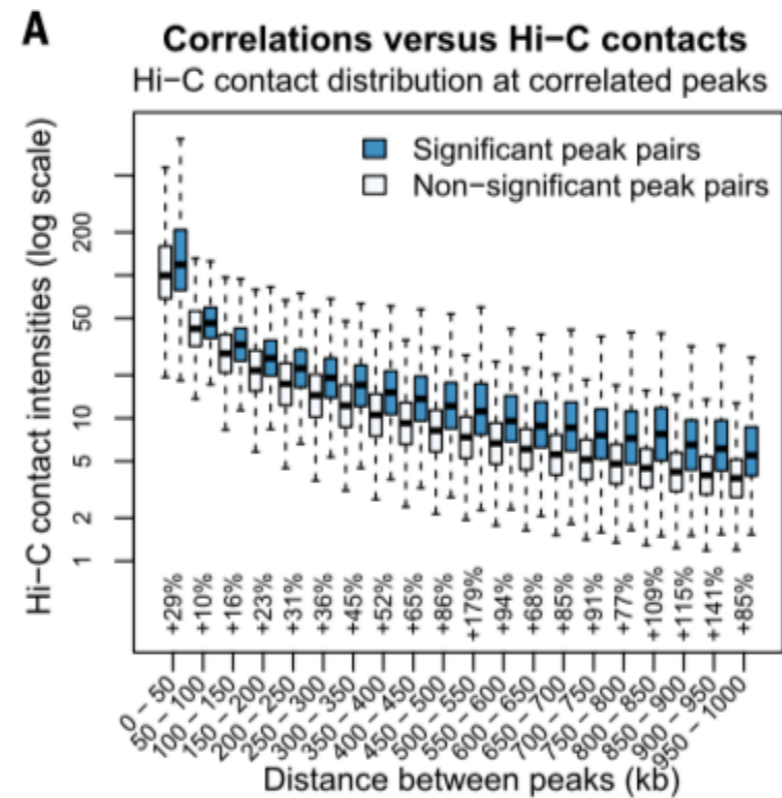


# Identification of cis-regulatory domains (CRDs):



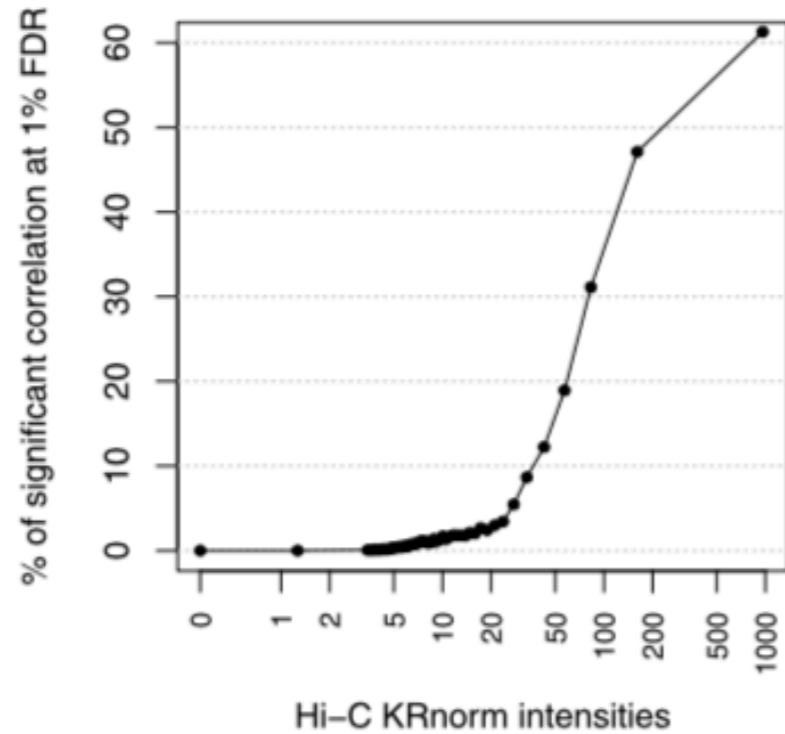
# Comparison of CRDs with Hi-C

- ChIP-Seq correlations are associated with Hi-C contacts
- CRDs are generally smaller than TADs
- Regulatory elements (REs) tend to be located at the CRD and TAD boundaries

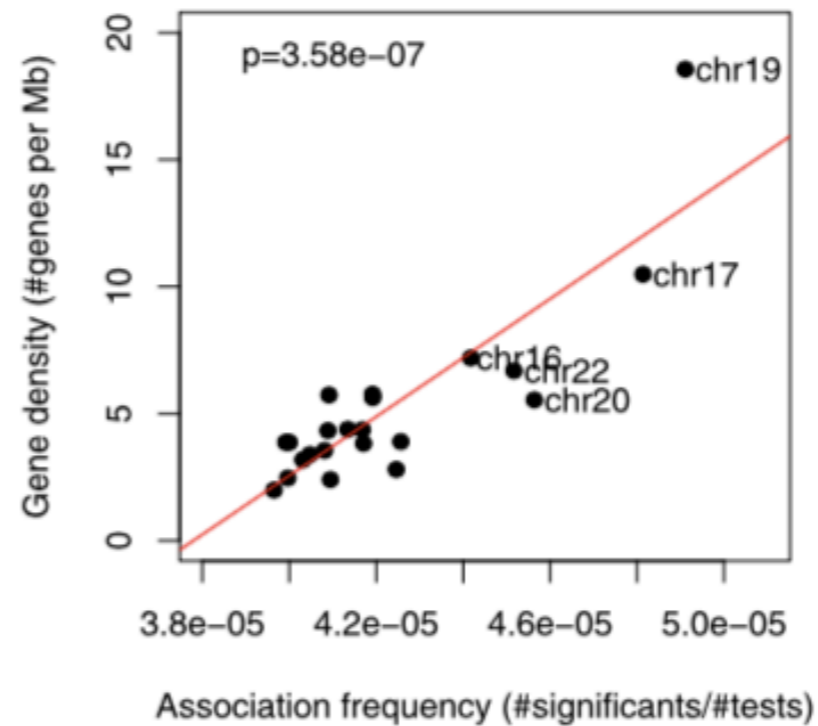


# Interchromosomal coordination

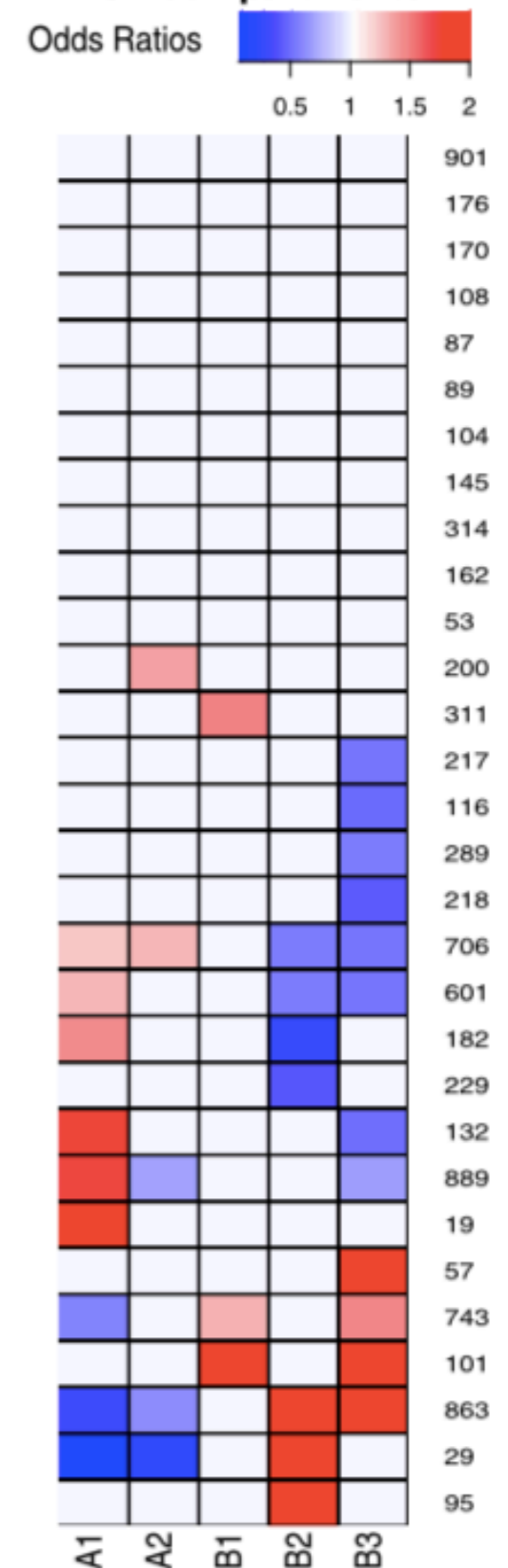
**A** Concordance with Hi-C contacts



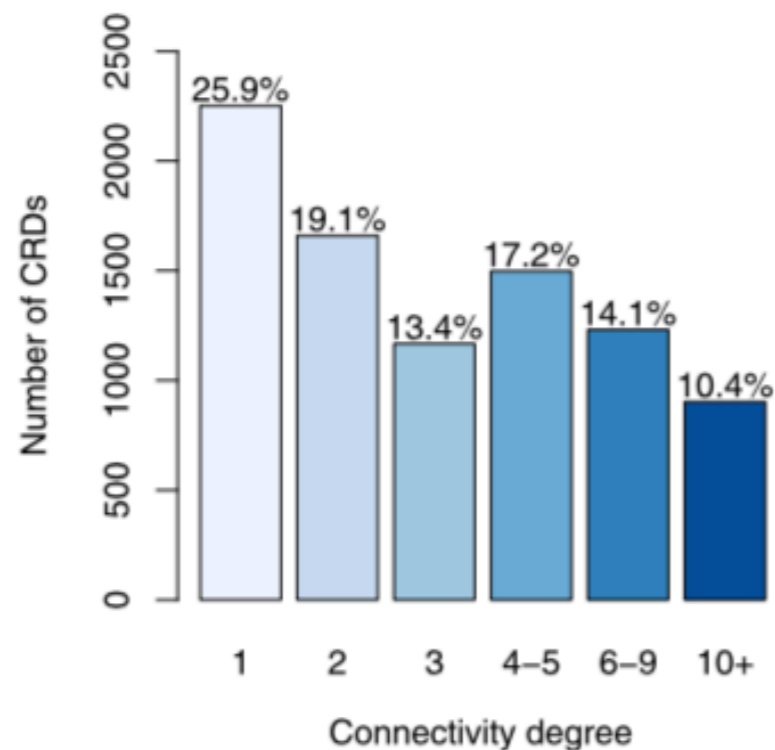
**B** Correlation with gene density



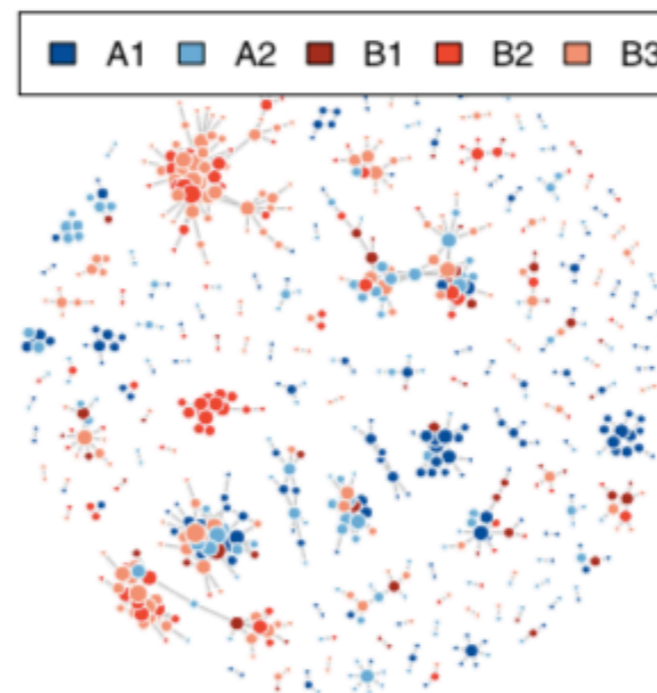
**E** Enrichment of TRHs in A/B compartments



**C** Connectivity degrees of CRDs

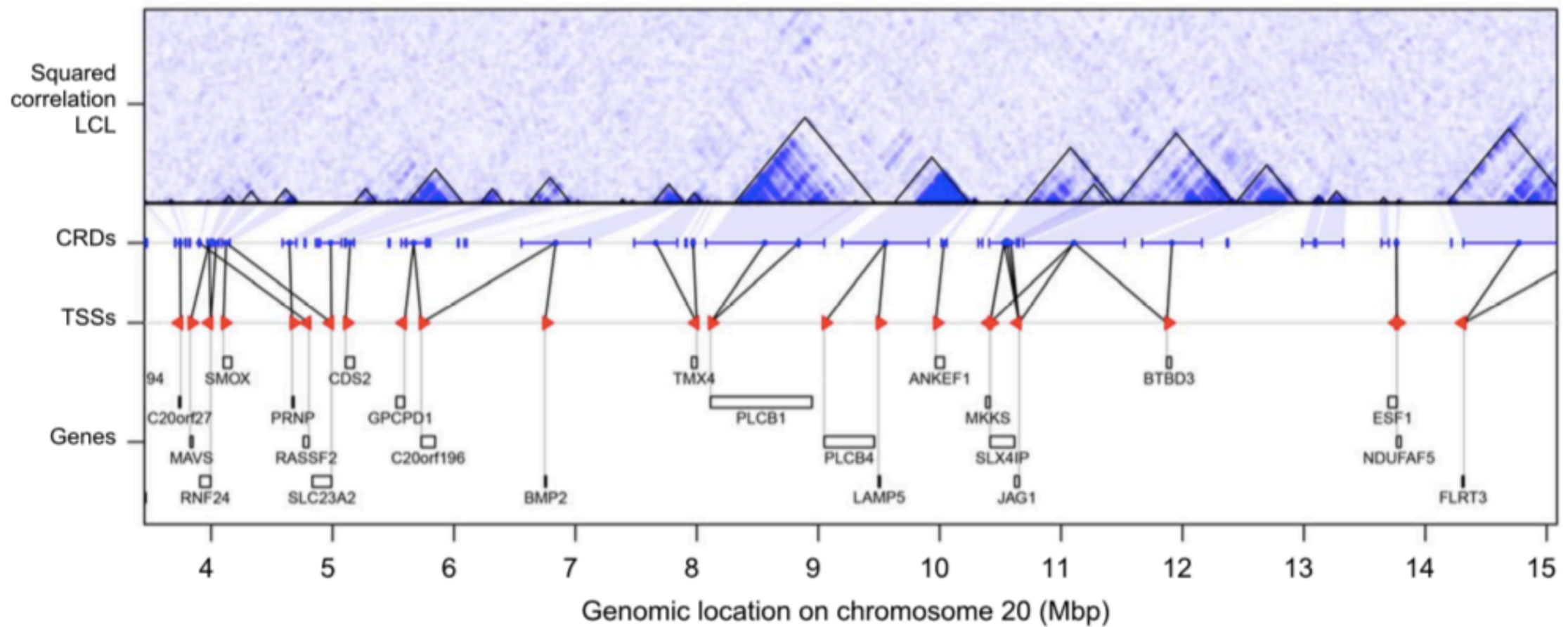


**D** Trans Regulatory Hub (TRH) examples

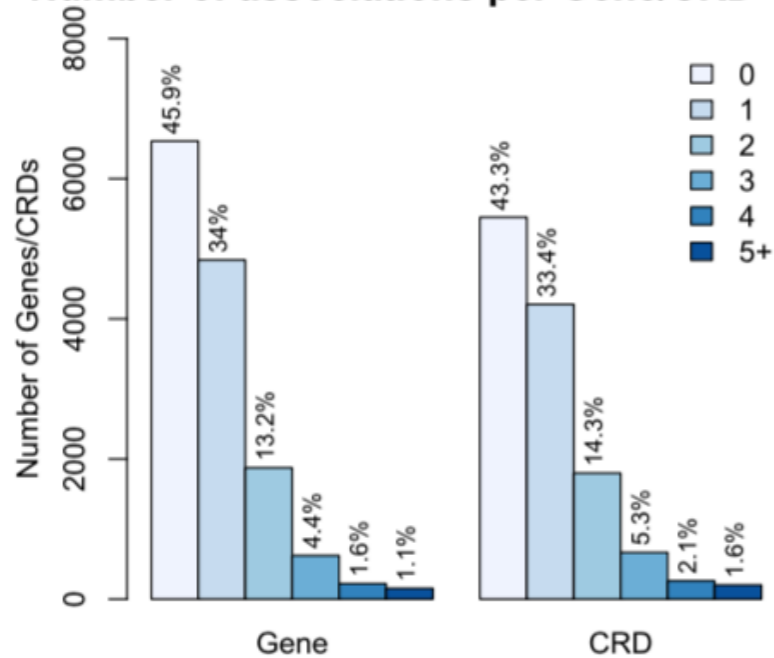


# Genes-CRD association

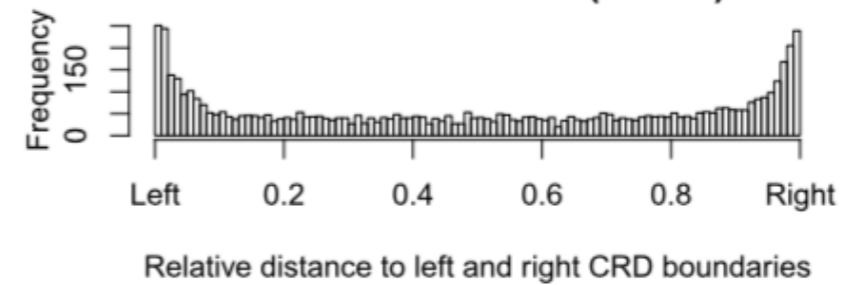
Example of gene-CRD associations



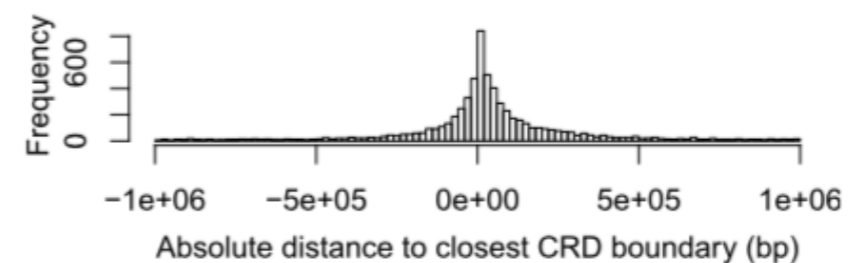
Number of associations per Gene/CRD



Genes inside CRDs (53.2%)

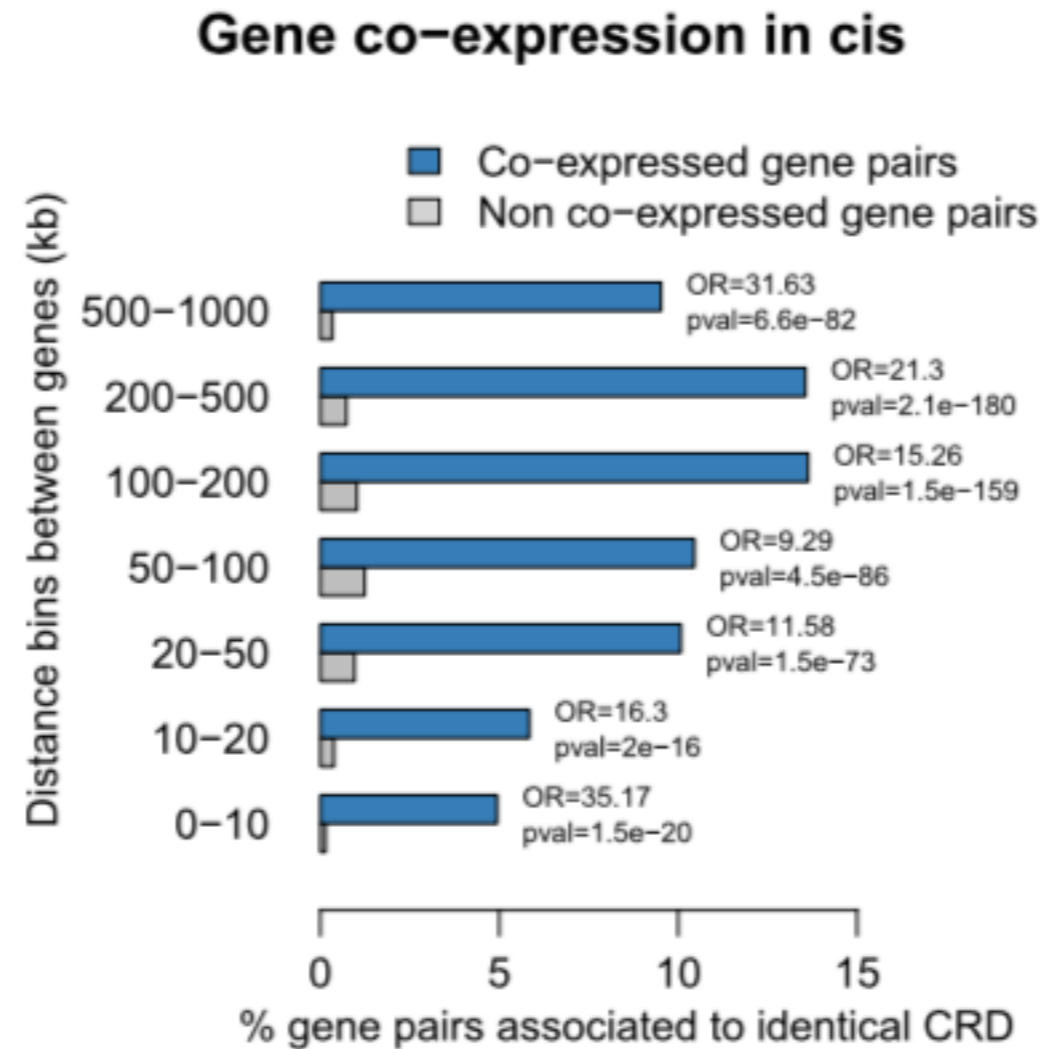


Genes outside CRDs (46.8%)



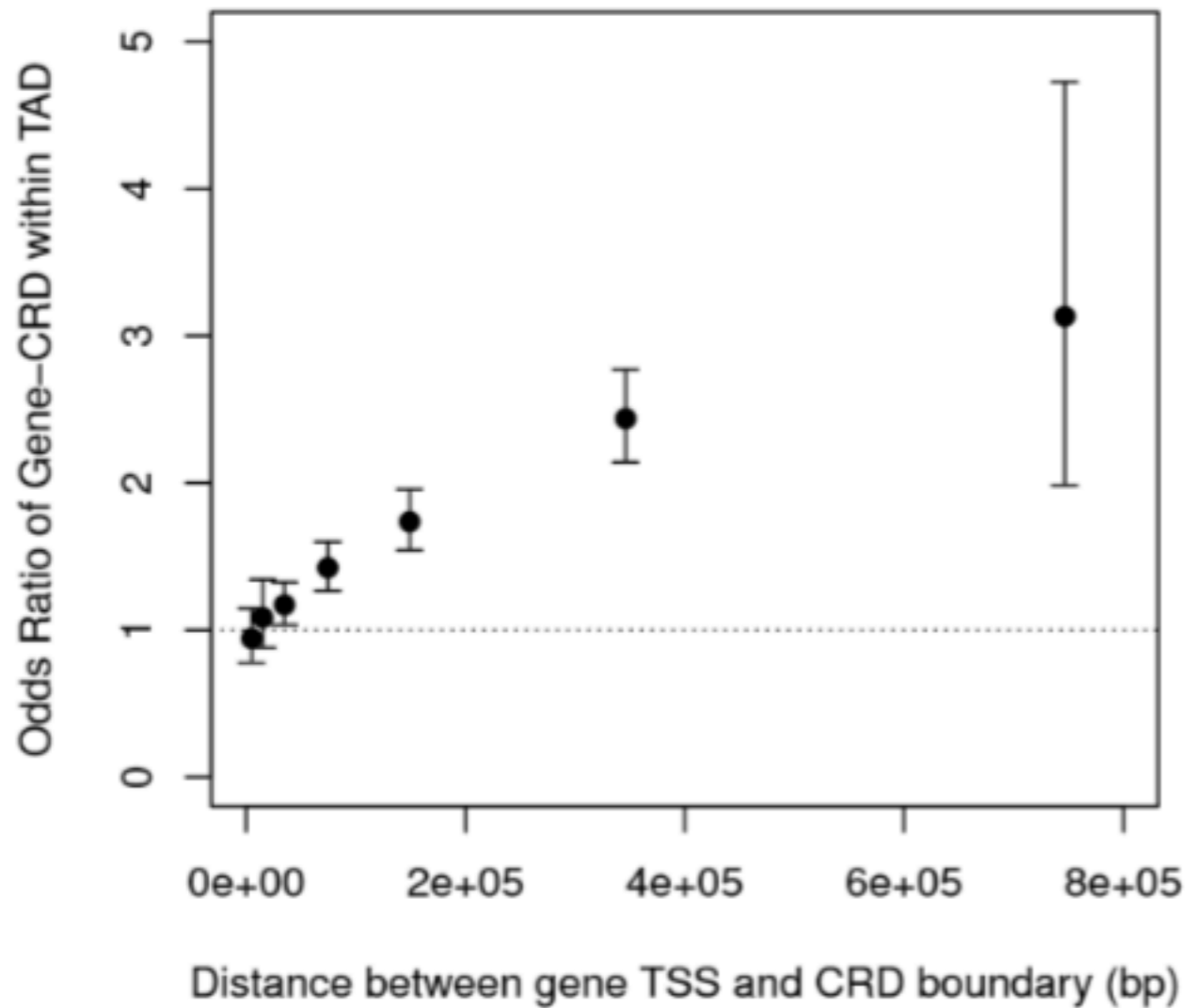


# Genes associated with the same CRD are co-expressed:

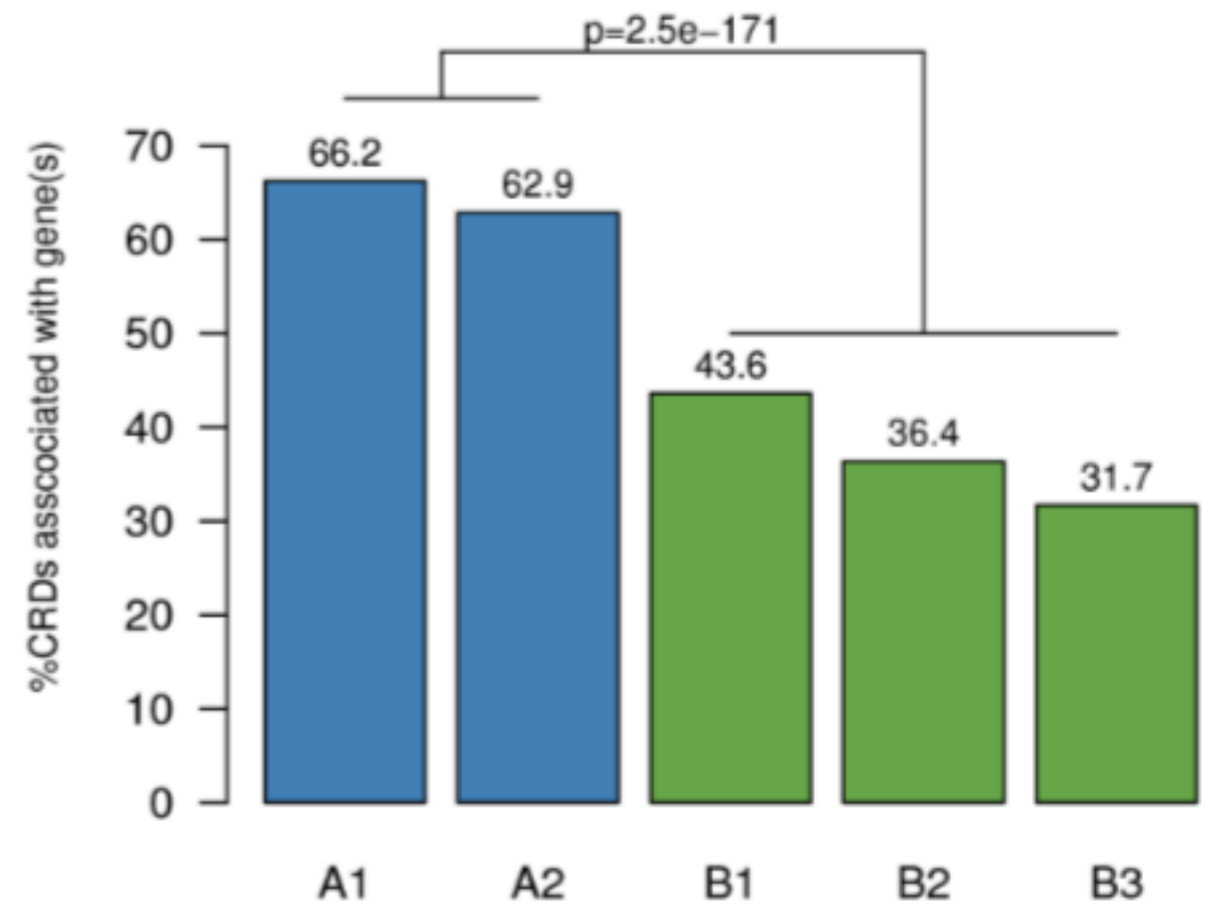


# Association of genes with Hi-C:

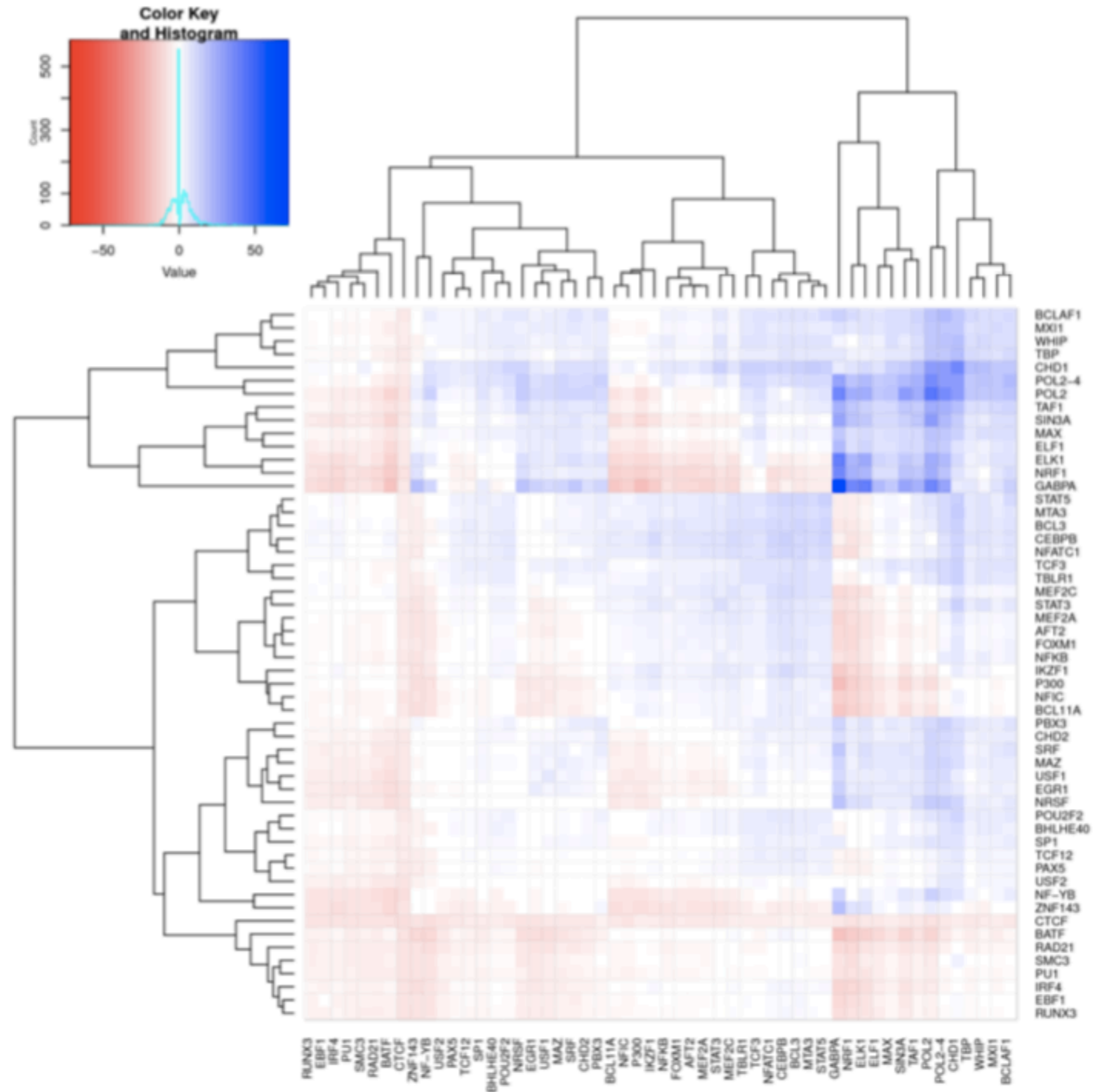
## A. Associations within TADs



## B. Associations by A/B compartments



# TFs that can explain trans-hubs



# Conclusion:

- Coexpressed genes are associated with TADs only if mediated by the same regulatory unit?

# Other papers:


- 2018:

ARTICLE

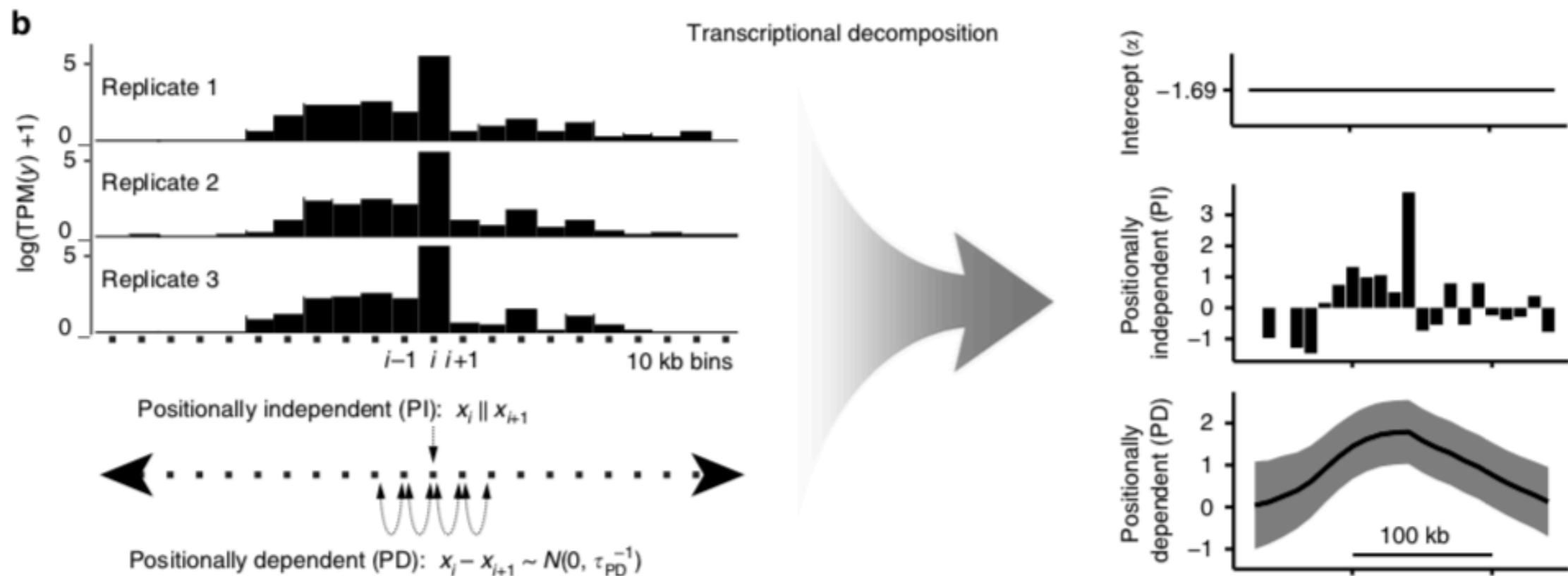
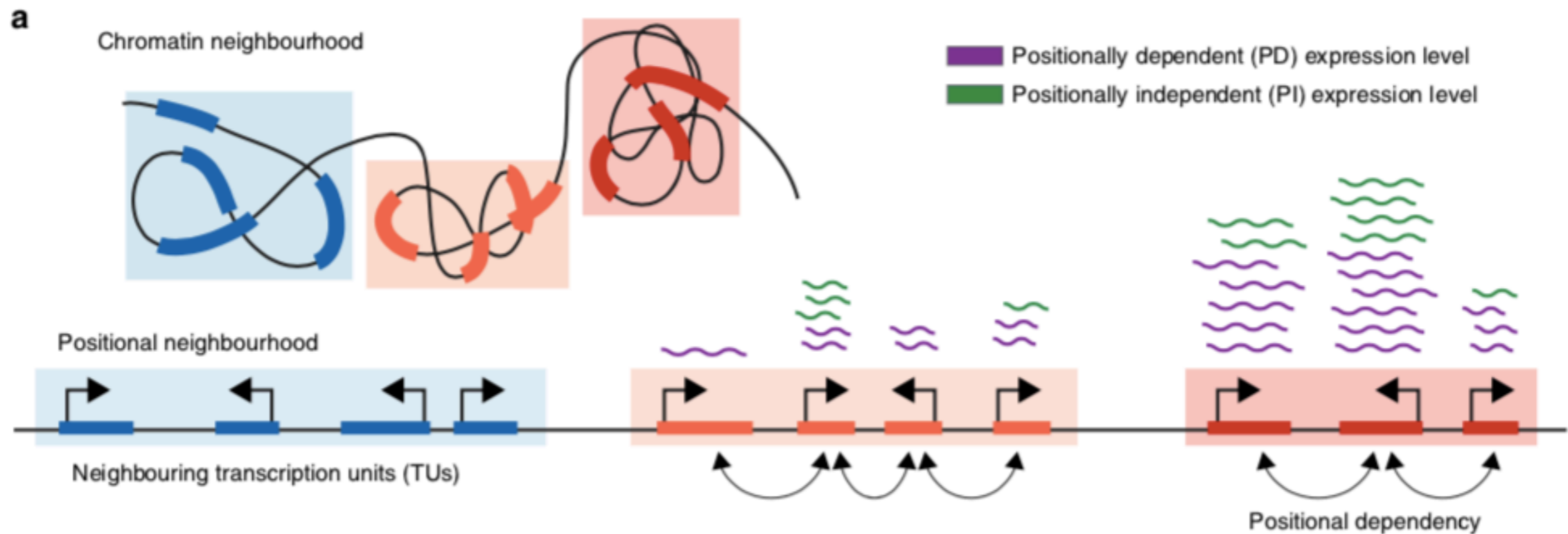
DOI: [10.1038/s41467-017-02798-1](https://doi.org/10.1038/s41467-017-02798-1)

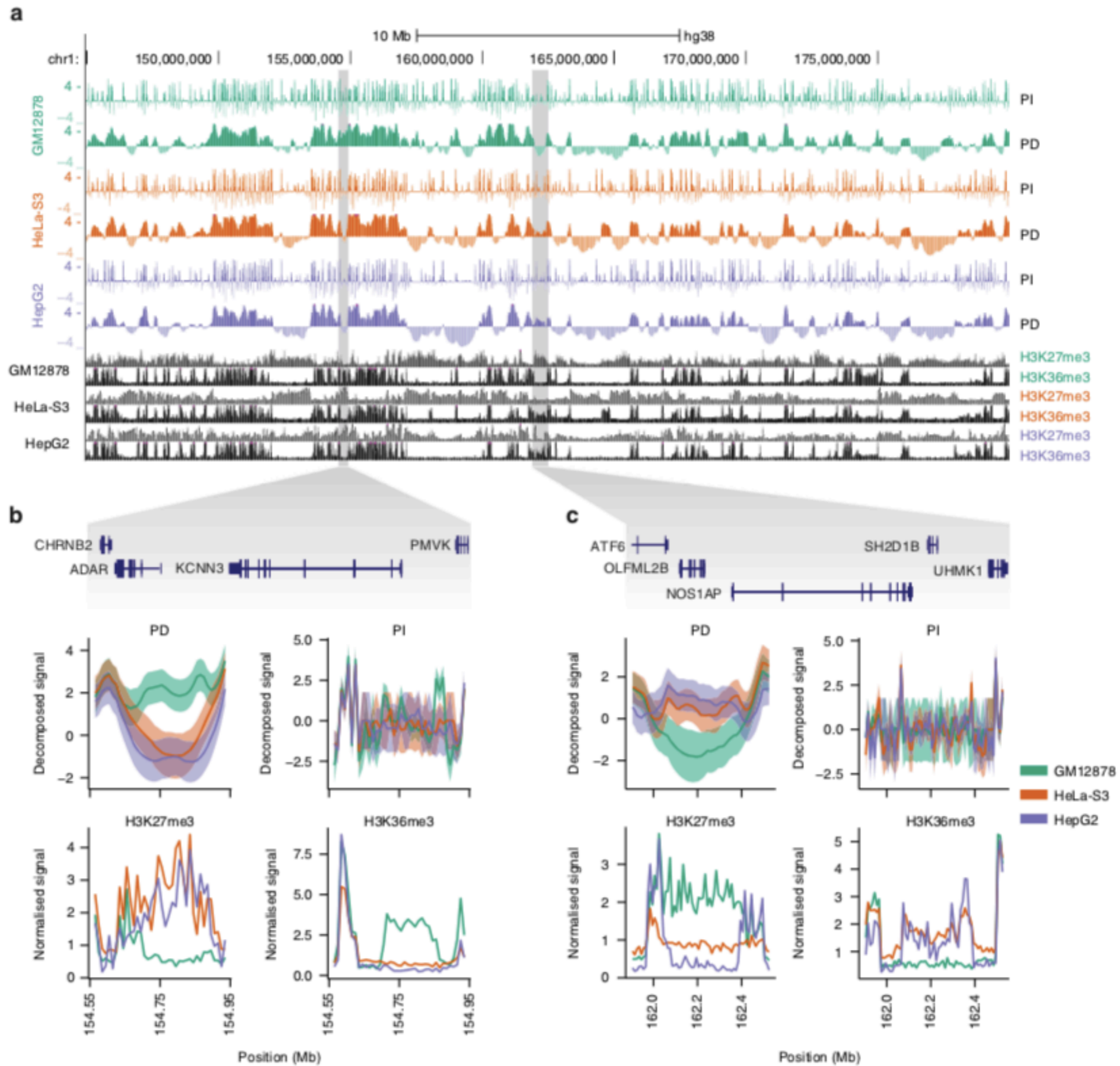
OPEN

## Transcriptional decomposition reveals active chromatin architectures and cell specific regulatory interactions

Sarah Rennie<sup>1</sup>, Maria Dalby<sup>1</sup>, Lucas van Duin<sup>1</sup> & Robin Andersson <sup>1</sup>

# Transcriptional decomposition:





- Association of XADs (expression-associated domains) with Hi-C:

