3D Lineage-Specific Genome Architecture Links Enhancers and Non-coding Disease Variants to Target Gene Promoters

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Barcelona, Spain

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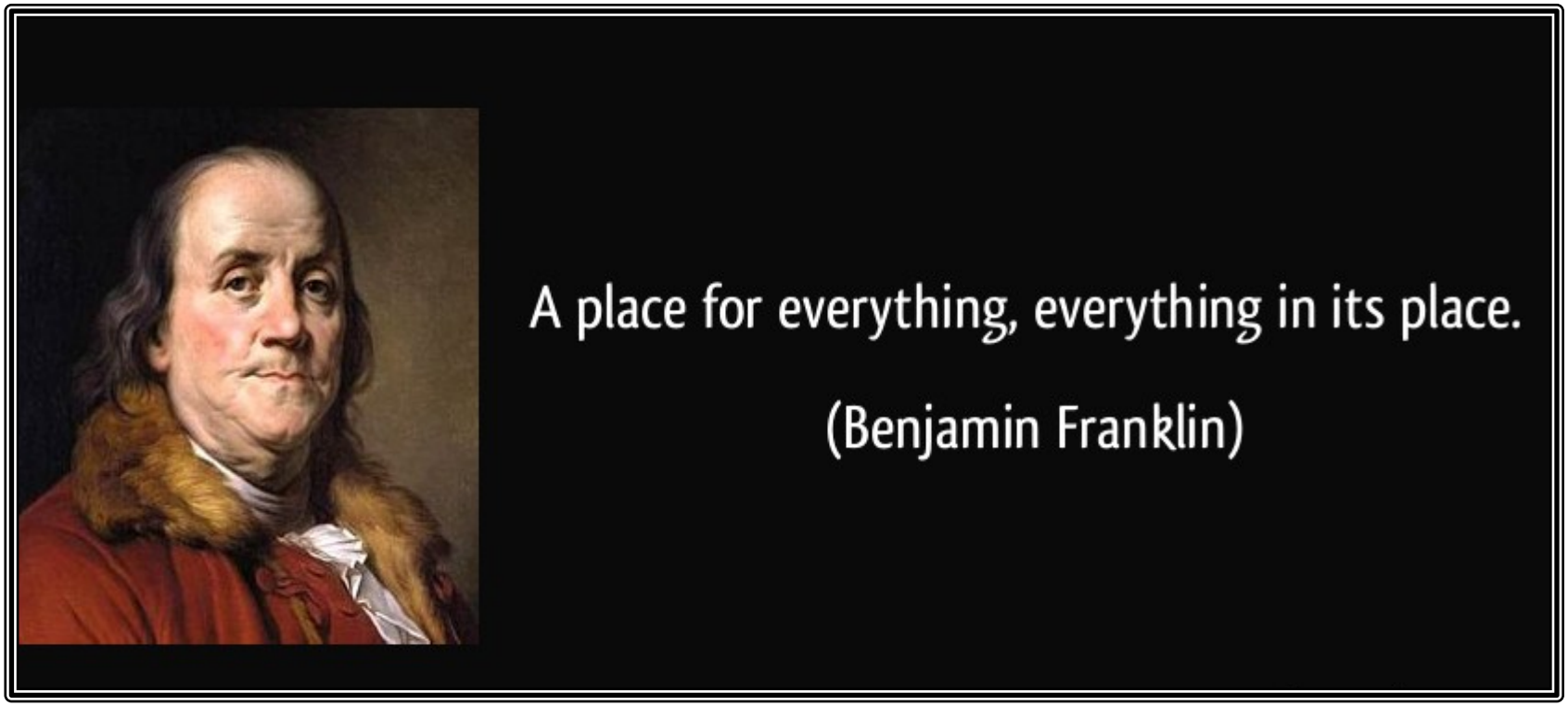
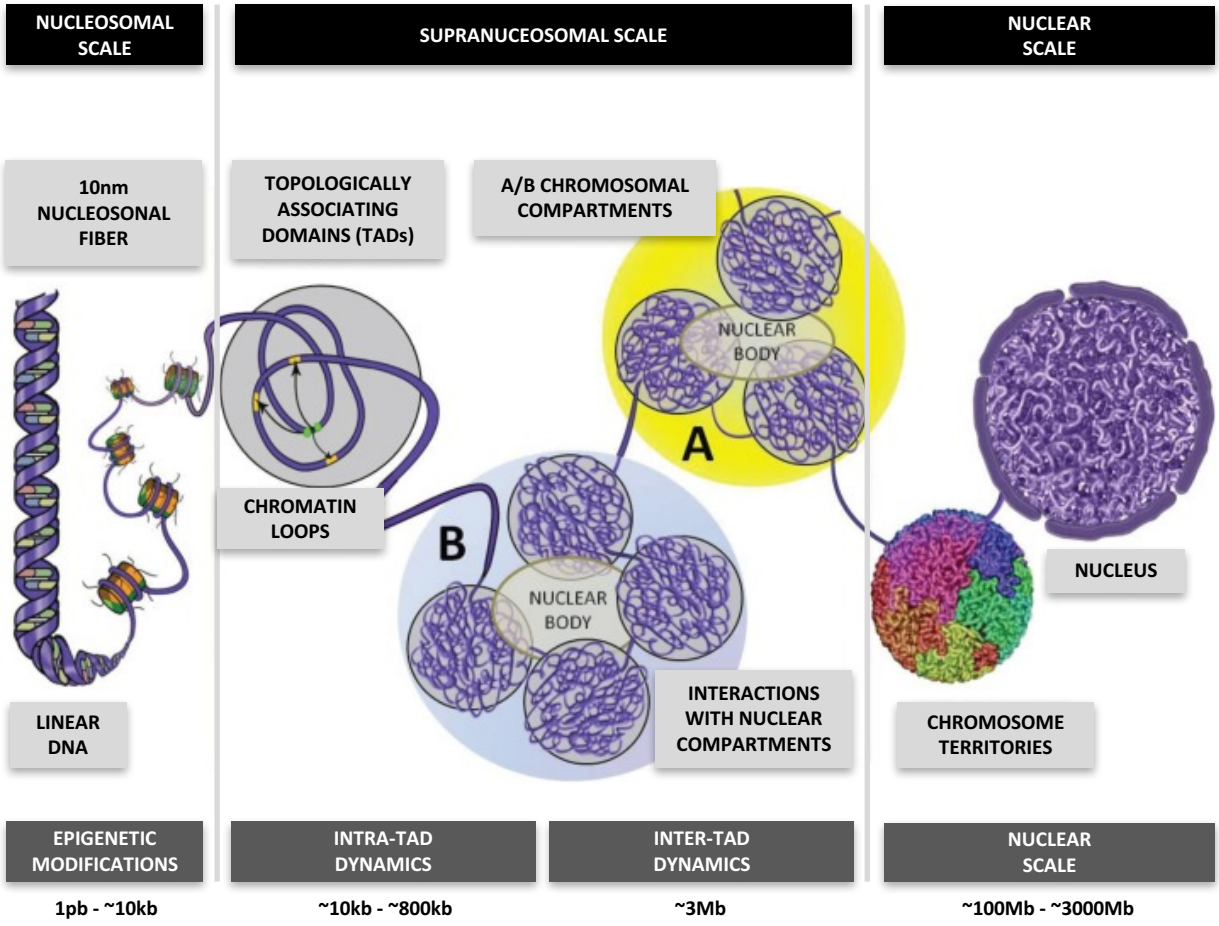
BSC


A place for everything, everything in its place.
(Benjamin Franklin)

The genomes of higher eukaryotes are packaged into exquisitely organized hierarchical structures.



From: Ea et al., Genes (2015)

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Long-range elements control genes through physical contact with promoters

Some Promoter-regulatory element interactions are cell specific

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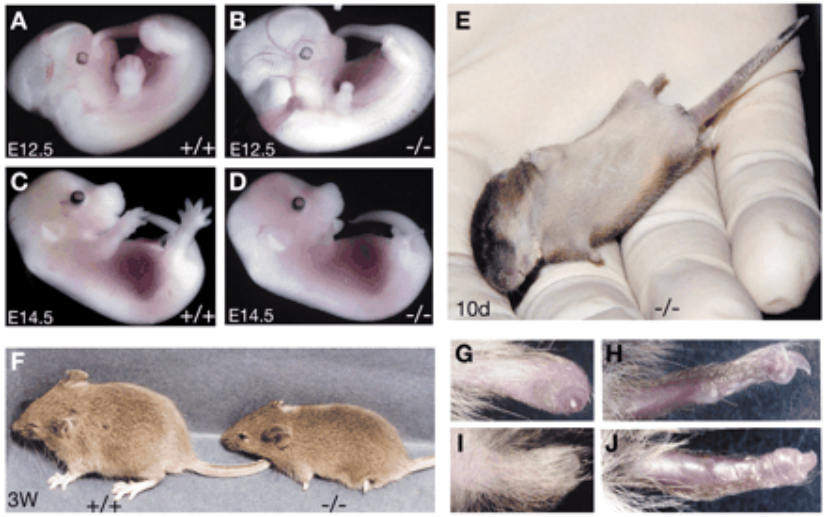
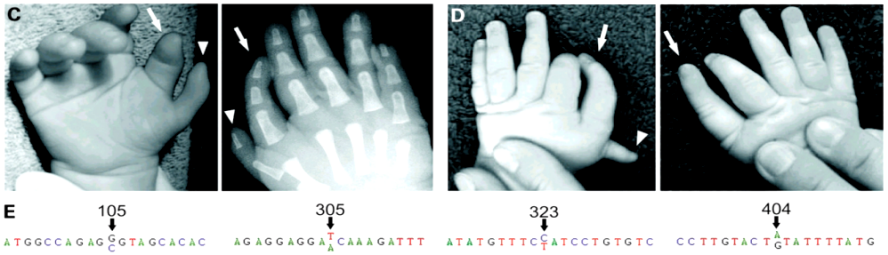


From: Lettice et al., Hum. Mol. Gen. (2003)



From: Sagai et al., Development (2005)

From: Amano et al., Dev Cell (2009)

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Difficult functional evaluation of the effect of these noncoding SNPs

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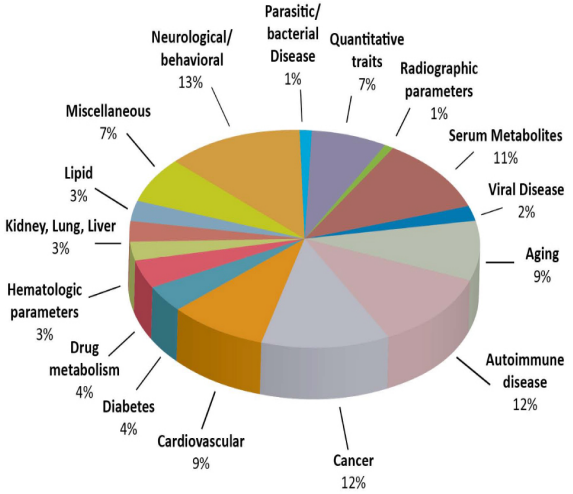
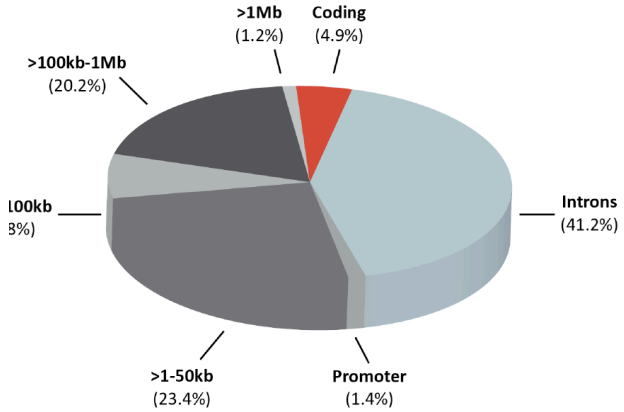
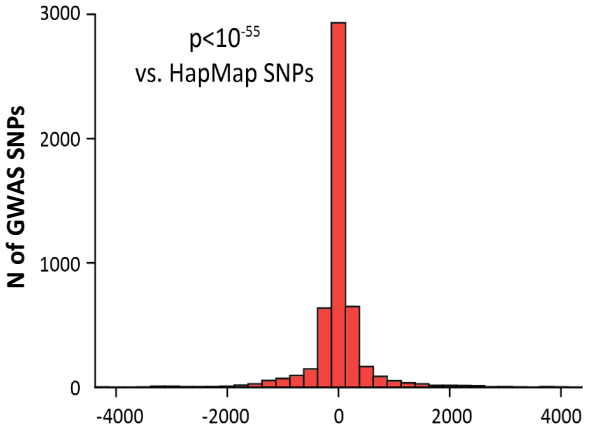


% of GWAS SNPs (6011 from 920 studies) by disease/trait class



Genomic distribution of GWAS SNPs (5386) vs. RefSeq



Distance to the nearest DHS (bp)

From: Maurano et al., Science (2012)

1. INTRODUCTION

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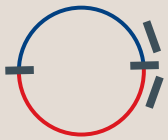
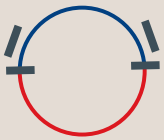
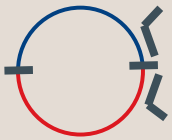
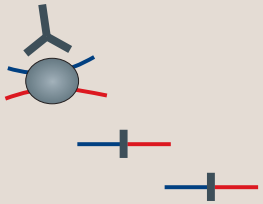
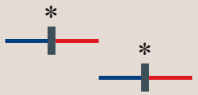
What is needed is a genome-wide systematic way to assign regulatory elements to their putative target genes in an cell specific manner in order to exploit this rich GWAS data resource

Chromatin Conformation Capture-based methods

a **3C: converting chromatin interactions into ligation products**

b **Ligation product detection methods**

3C	4C	5C	ChIA–PET	Hi-C
One-by-one All-by-all	One-by-all	Many-by-many	Many-by-many	All-by-all
			• DNA shearing • Immunoprecipitation 	• Biotin labelling of ends • DNA shearing 
PCR or sequencing	Inverse PCR sequencing	Multiplexed LMA sequencing	Sequencing	Sequencing

From: Dekker et al., Nat Rev Genet. (2013)

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What is needed is a genome-wide systematic way to assign regulatory elements to their putative target genes in an cell specific manner in order to exploit this rich GWAS data resource

Linking regulatory elements to specific promoters genome-wide is currently impeded by the limited resolution of HiC

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Economic and technical limitation: low resolution because low signal-to-noise ratios

Typical mammalian genome: $3x10^9$ bp (≈ 900,000 HindIII fragments)

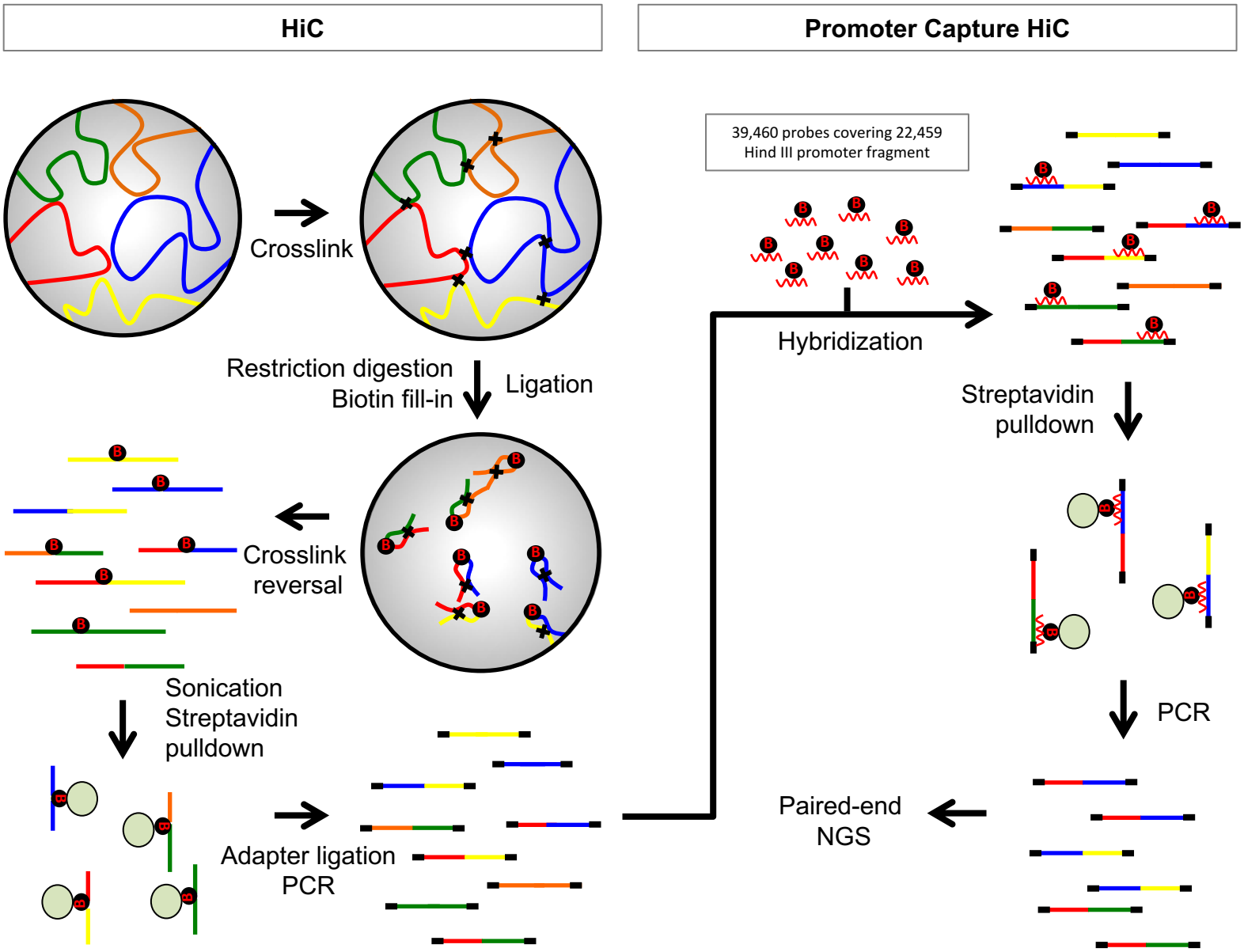
Randomly ligated: $\mathbf{10^{12}}$ different ligation junction molecules

Published reports usually contain anywhere from $\mathbf{10^7}$-$\mathbf{10^9}$ mapped read pairs

What is needed is a genome-wide systematic way to assign regulatory elements to their putative target genes in an cell specific manner in order to exploit this rich GWAS data resource

It is almost impossible to identify enhancer-promoter contacts with any kind of statistical certainty from conventional Hi-C analyses

Linking regulatory elements to specific promoters genome-wide is currently impeded by the limited resolution of HiC



From: Nagano et al. Genome Biol. (2015)

From: Schoenfelder et al. Genome Res. (2015)
Javierre et al. Cell (2016)
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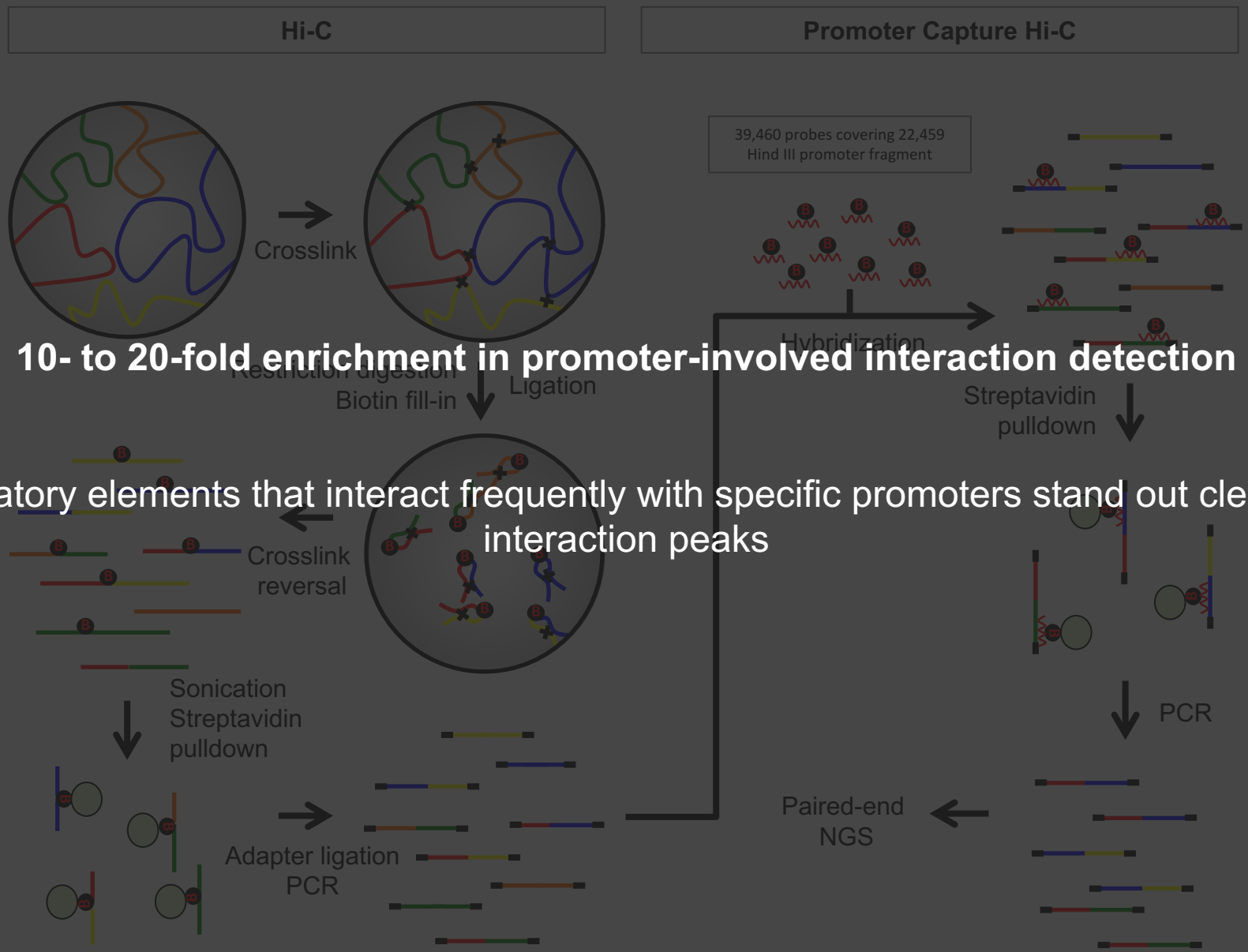

10- to 20-fold enrichment in promoter-involved interaction detection

Regulatory elements that interact frequently with specific promoters stand out clearly as interaction peaks

From: Nagano et al. Genome Biol. (2015)

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2. PCHiC: sequencing, HICUP & CHiCAGO

Cell Type	Biological Replicates	Processed Reads	Capture Unique Valid Reads	Significant Interactions
Megakaryocytes	4	2,696,317,863	653,848,788	150,203
Erythroblasts	3	2,338,677,291	588,786,672	144,771
Neutrophils	3	2,241,977,639	736,055,569	131,609
Monocytes	3	1,942,858,536	572,357,387	151,389
Macrophages M0	3	2,125,716,849	668,675,248	163,791
Macrophages M1	3	2,067,485,594	497,683,496	163,399
Macrophages M2	3	2,055,090,022	523,561,551	173,449
Naïve B	3	2,127,262,739	629,928,642	171,439
Total B	3	1,874,130,921	702,533,922	183,119
Fetal Thymus	3	2,728,388,103	776,491,344	145,577
Naïve CD4+	4	2,797,861,611	844,697,853	192,048
Total CD4+	3	2,227,386,686	836,974,777	166,668
Unstimulated Total CD4+	3	2,034,344,692	721,030,702	177,371
Stimulated Total CD4+	3	1,971,143,855	749,720,649	188,714
Naïve CD8+	3	1,910,881,702	747,834,572	187,399
Total CD8+	3	1,849,225,803	628,771,947	183,964
Endothelial Precursors	3	2,308,749,174	420,536,621	141,382
	53	**37,297,499,080**	**11,299,489,740**	**2,816,292**
			* HICUP	*CHiCAGO

- 2CCNM-BN-TN-NWFDCP

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Total unique interactions	**708,007**
Promoter-promoter	**67,781**
Promoter-other end	**640,226**
Total unique other ends	**247,962**
Promoters	**15,646**
Non-promoter	**232,316**

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Median of **4** interactions per promoter fragment and cell type

55% of PIRS interacted with a single promoter fragment

Median linear distance between interacting regions of **331 Kb**

10% of interactions were between fragments greater than 1 Mb apart

5,103 mapped across chromosomes

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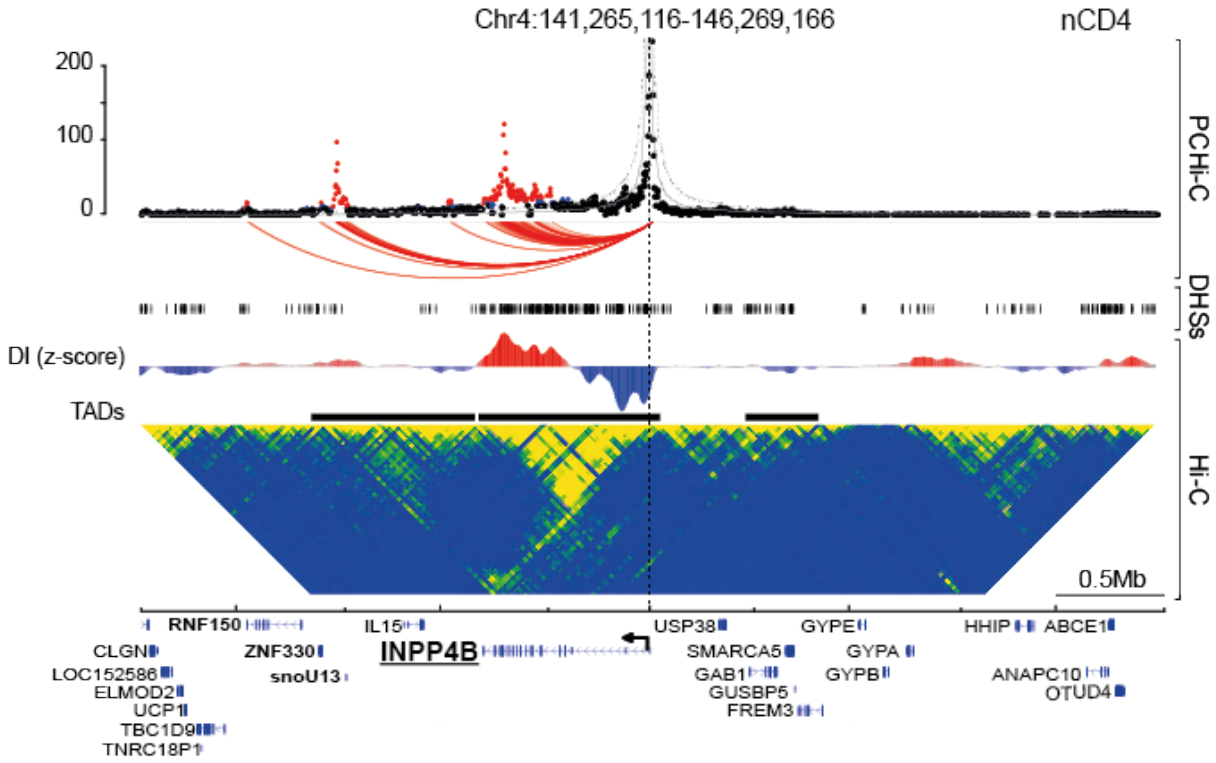

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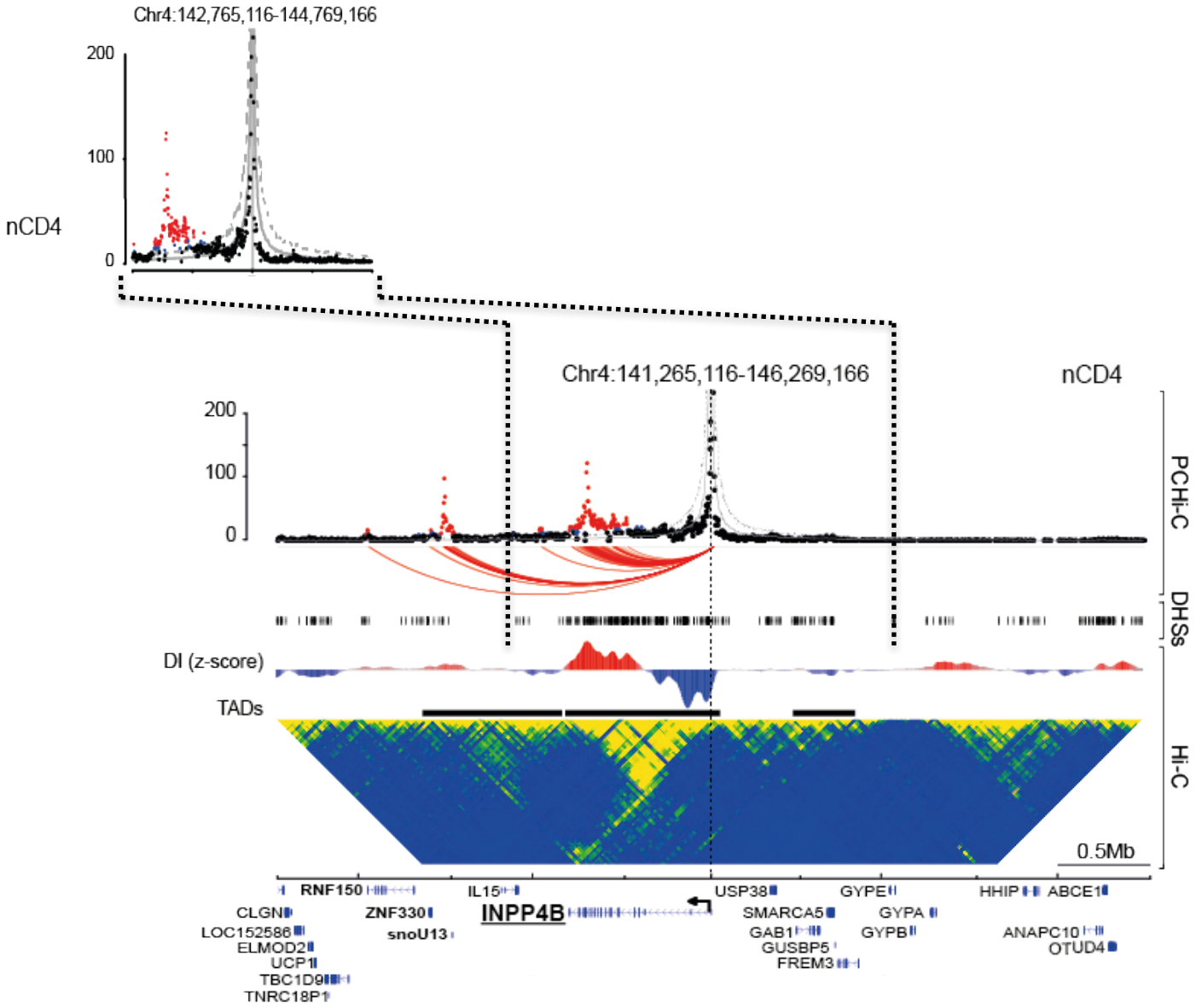

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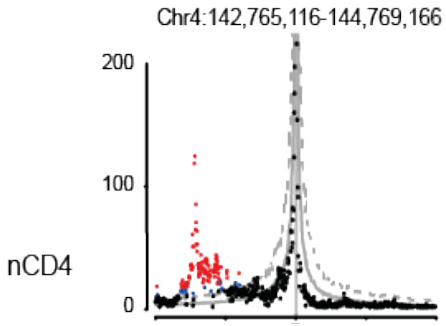

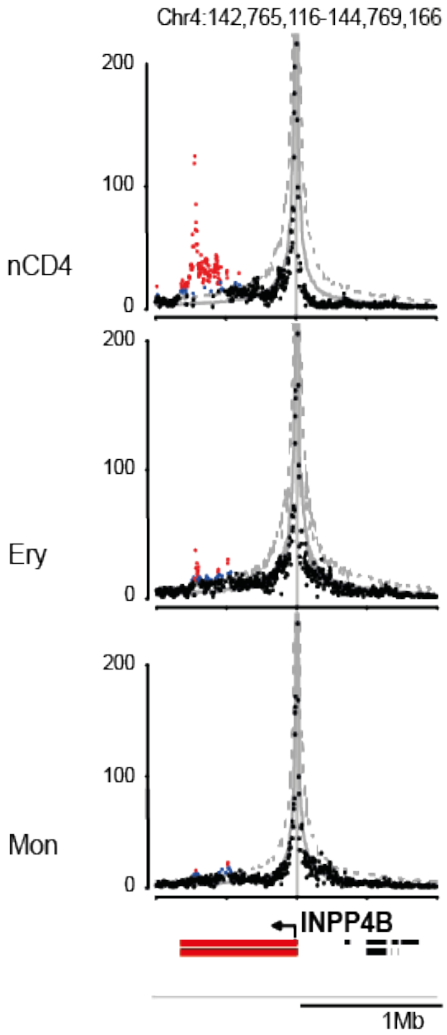
Chr4:142,765,116-144,769,166
200
100
0
nCD4
200
100
0
Ery
200
100
0
Mon
INPP4B
1Mb

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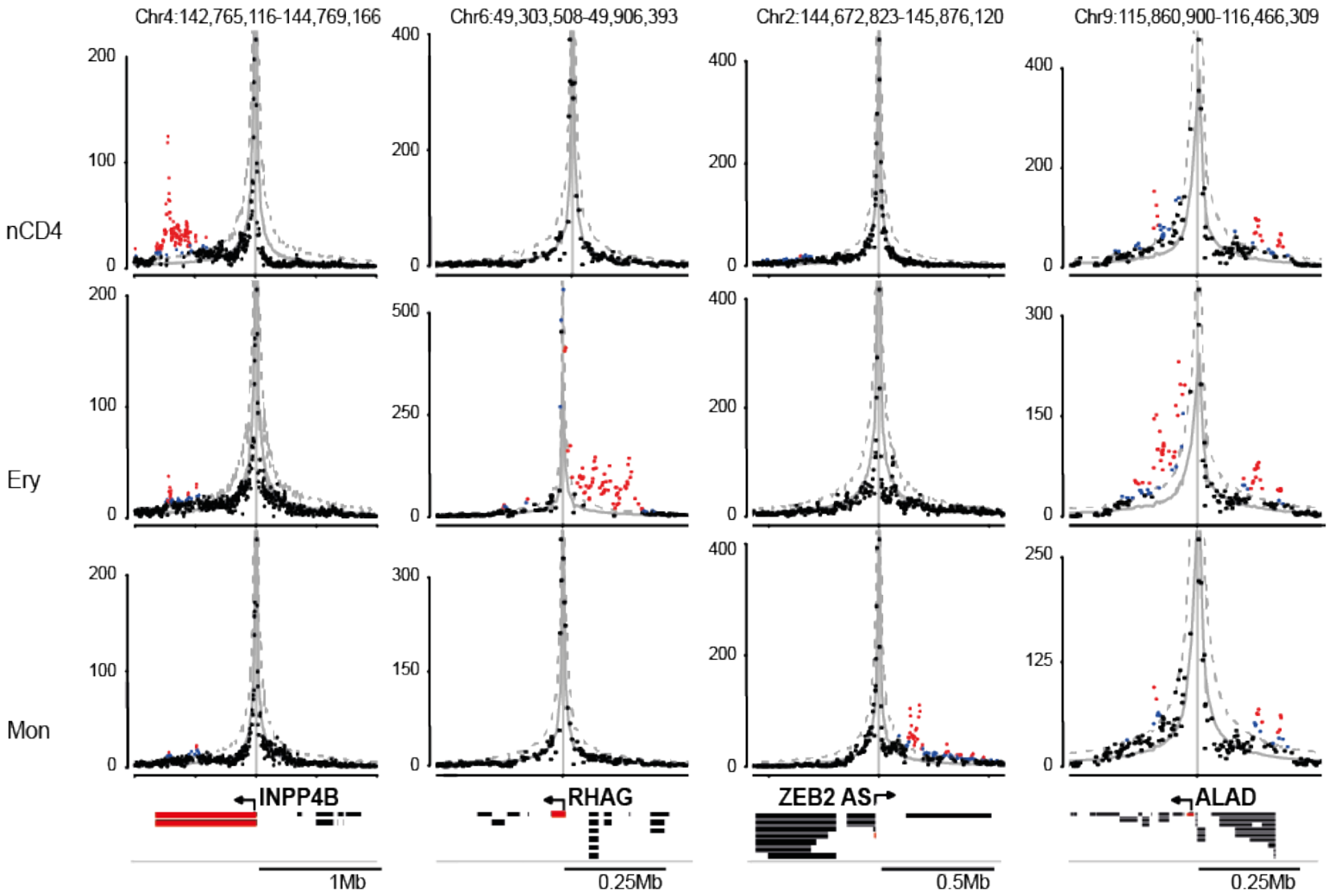

3. HiC and Reciprocal Capture System Validation

Hi-C

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Erythroblasts	2	477,032,218	191,539,678
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Monocytes	2	514,780,999	223,883,910
Macrophages M0	2	509,022,370	237,153,171
Naïve B	2	544,208,352	275,087,329
Naïve CD4+	2	507,479,090	261,813,418
Naïve CD8+	2	477,096,972	241,624,219
	16	**4,072,283,872**	**1,882,639,153**

Reciprocal Capture Validation

Cell Type	Biological Replicates	Processed Reads	Capture Unique Valid Reads
Megakaryocytes	2	893,997,658	59,026,262
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Unstimulated Total CD4+	2	782,404,919	81,037,708
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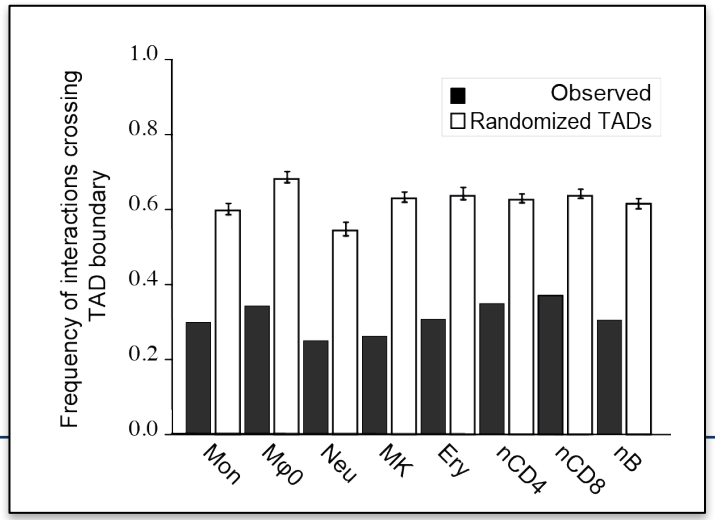

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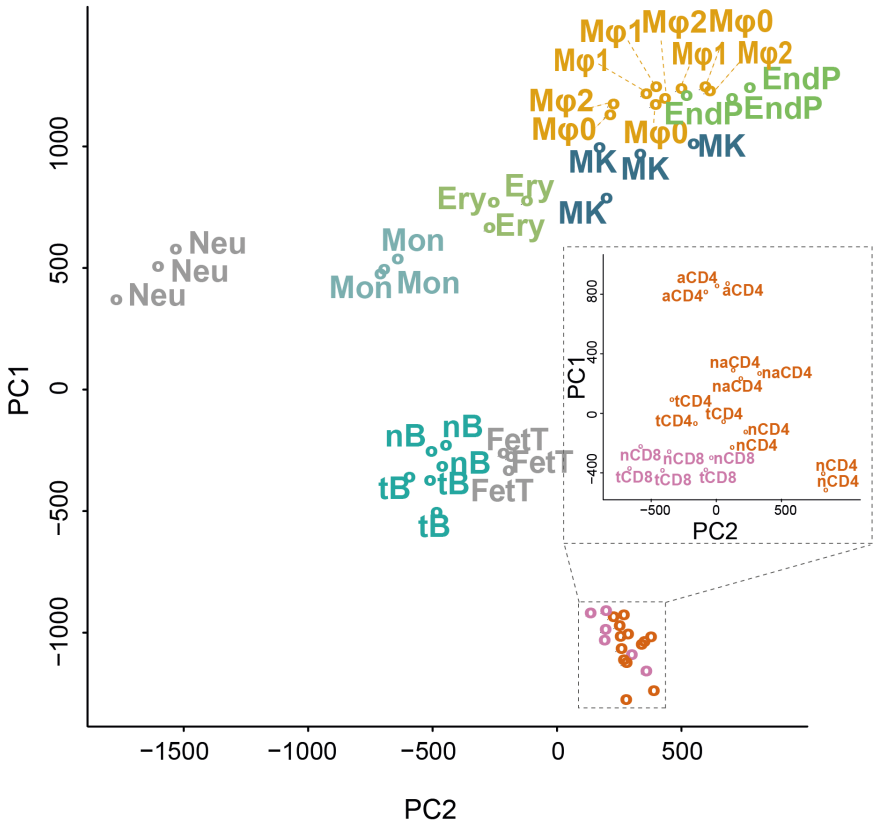
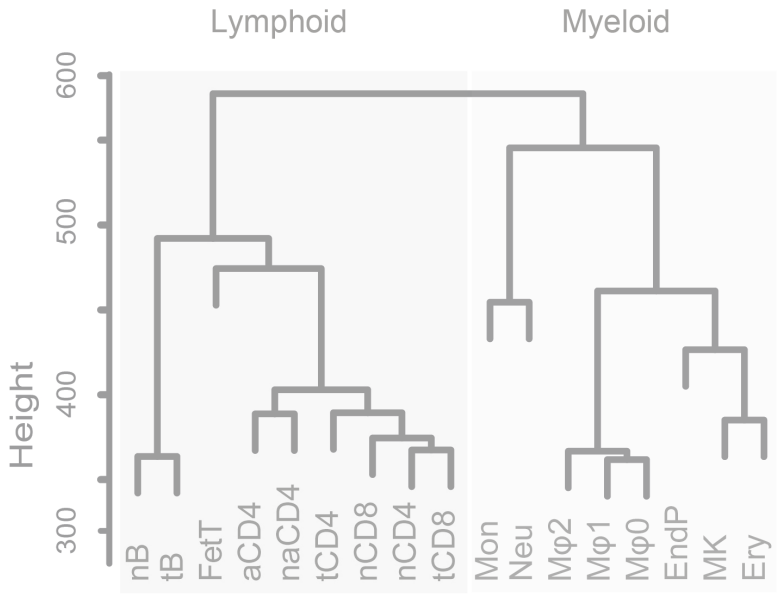
4. Promoter Interactomes Are Lineage and Cell Type Specific



PCA of CHiCAGO interaction scores across all biological replicates of the 17 cell types



Hierarchical clustering of the 17 cell types based on their CHiCAGO interaction scores

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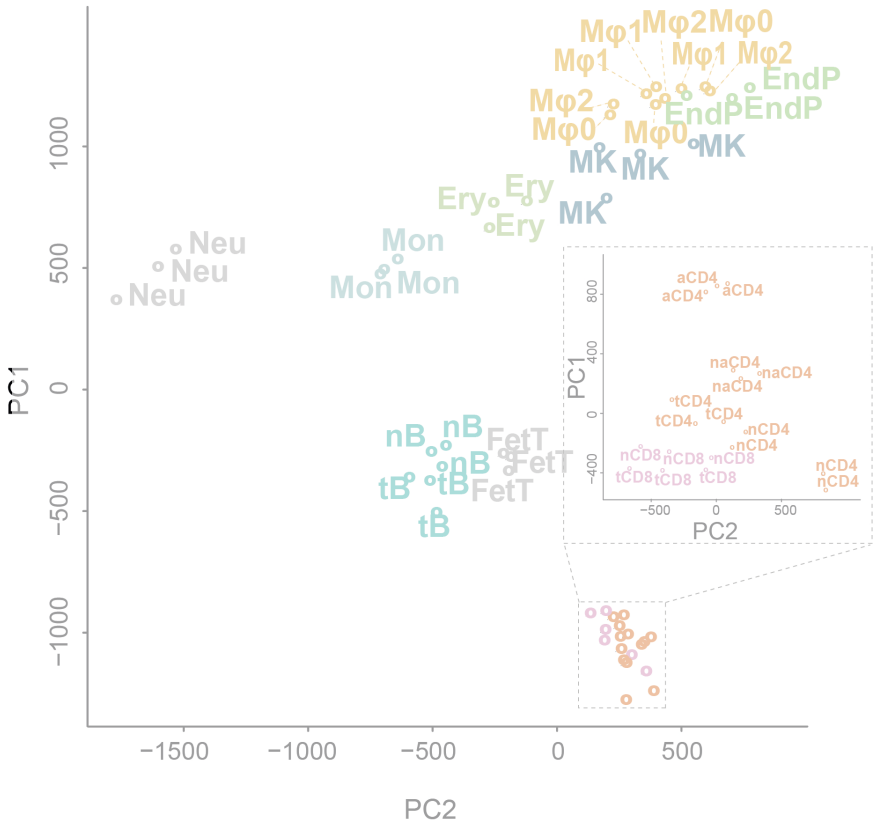

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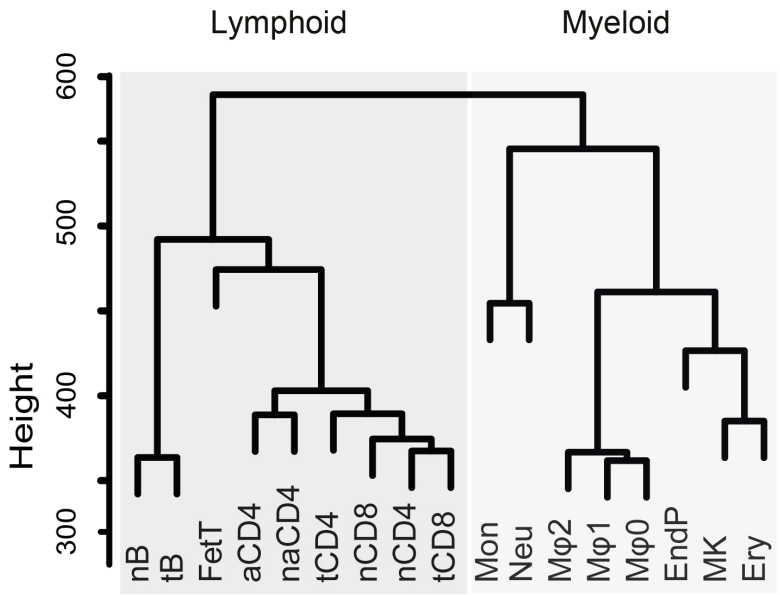

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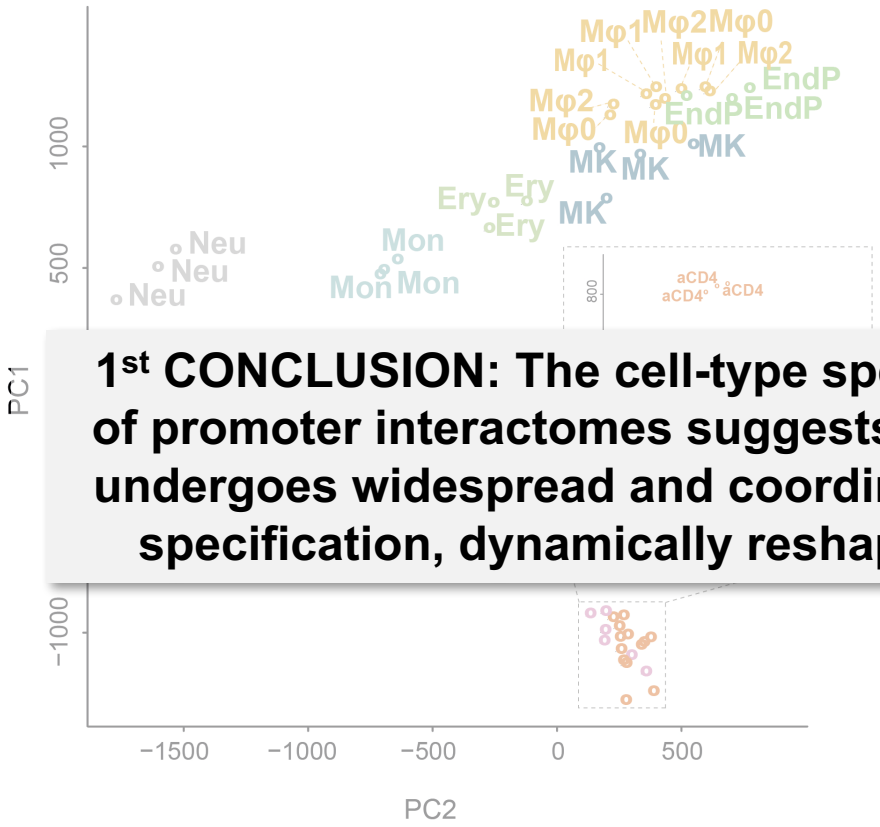

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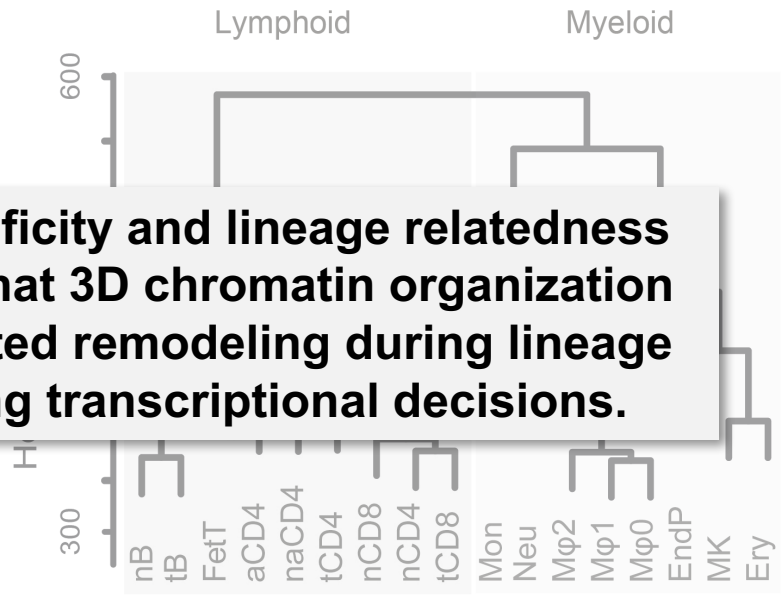

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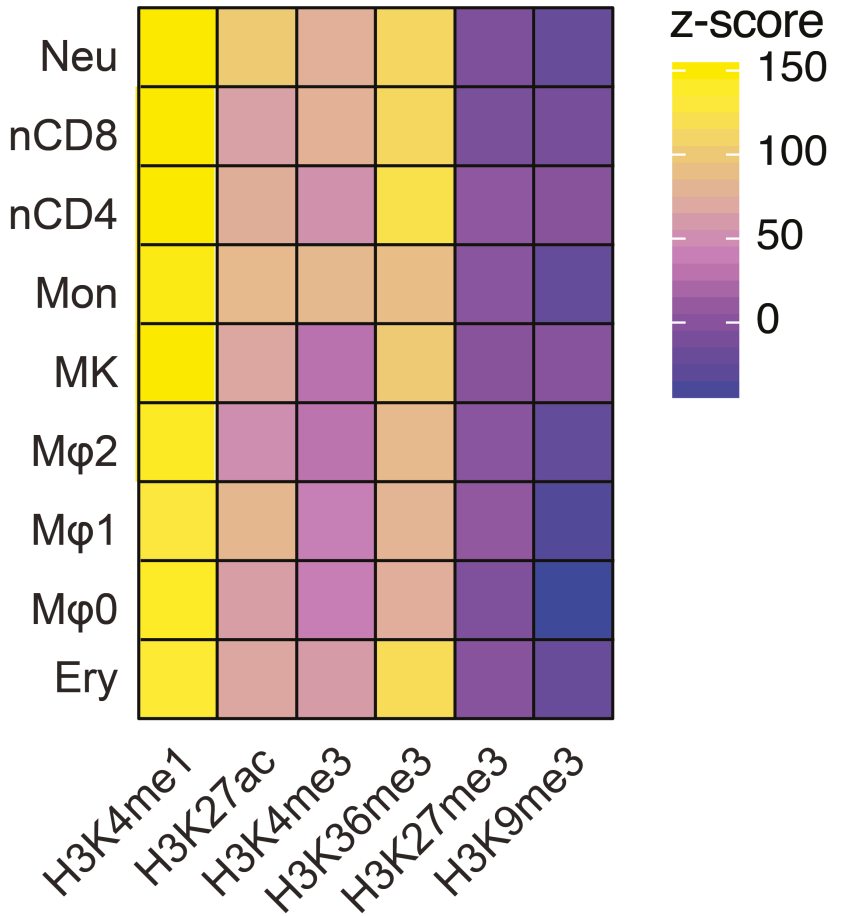
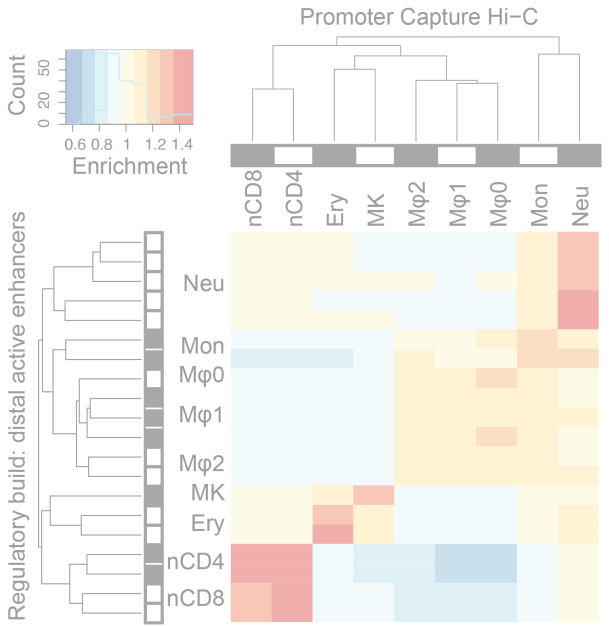
1st CONCLUSION: The cell-type specificity and lineage relatedness of promoter interactomes suggests that 3D chromatin organization undergoes widespread and coordinated remodeling during lineage specification, dynamically reshaping transcriptional decisions.

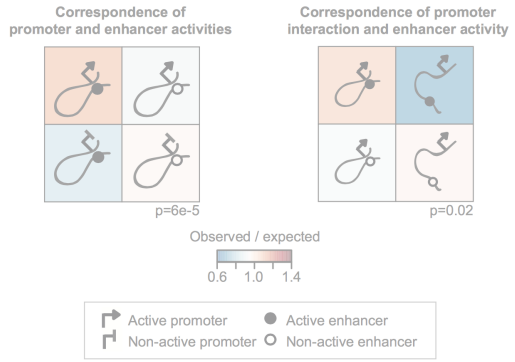
5. Promoter-Interacting Regions Are Enriched for Regulatory Chromatin Features



Significance of PIR enrichment for histone marks expressed in terms of Z scores

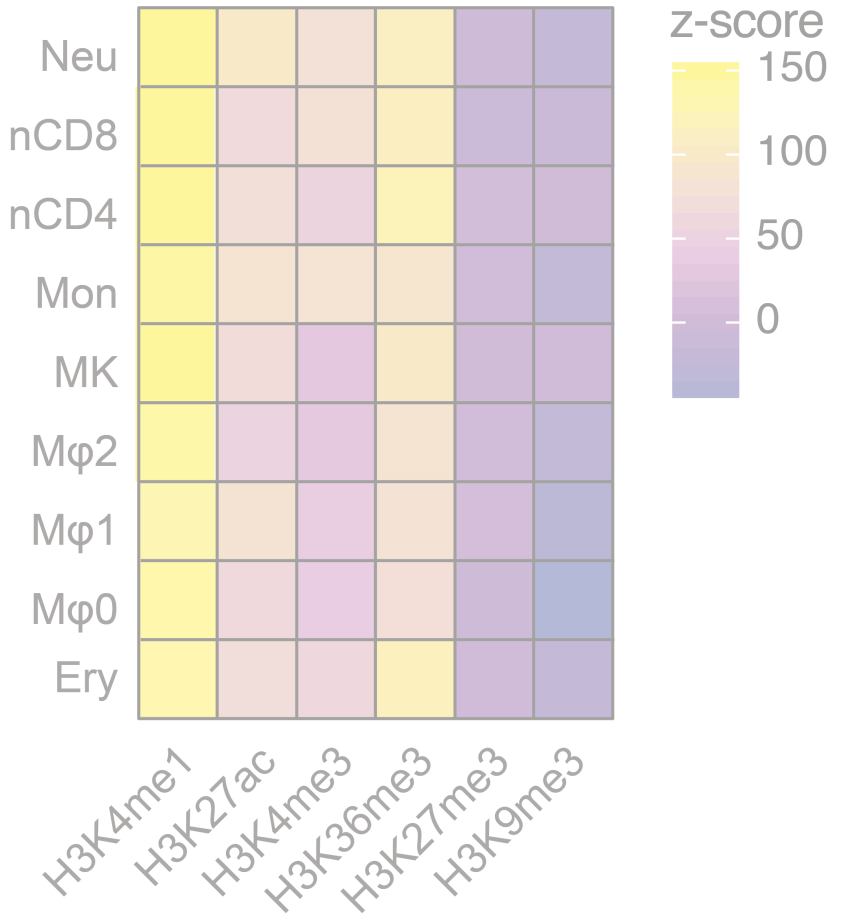


Enrichment of PIRs for active distal enhancers

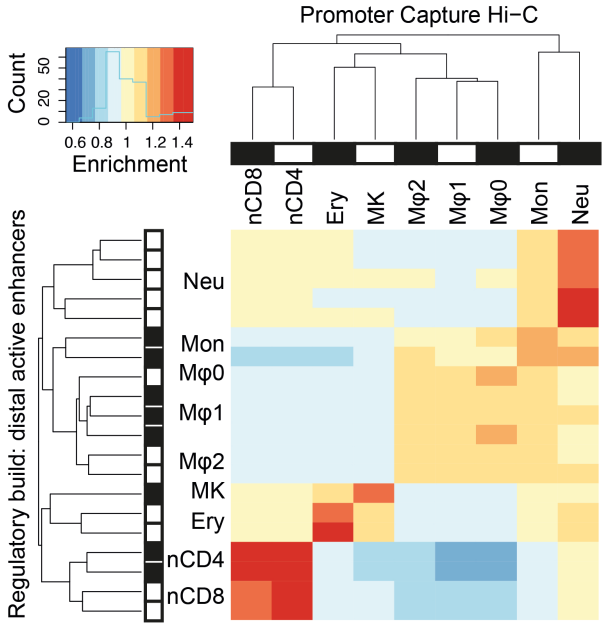


Observed to expected ratios for each combination of enhancer activity and the presence or absence of interaction

5. Promoter-Interacting Regions Are Enriched for Regulatory Chromatin Features



Significance of PIR enrichment for histone marks expressed in terms of Z scores



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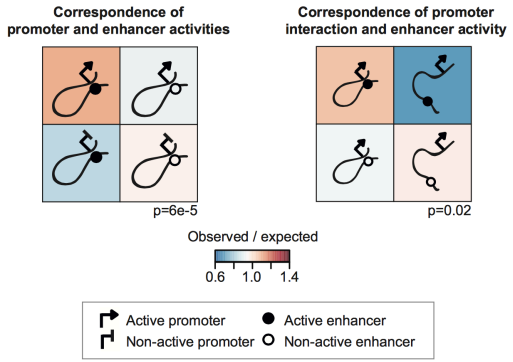

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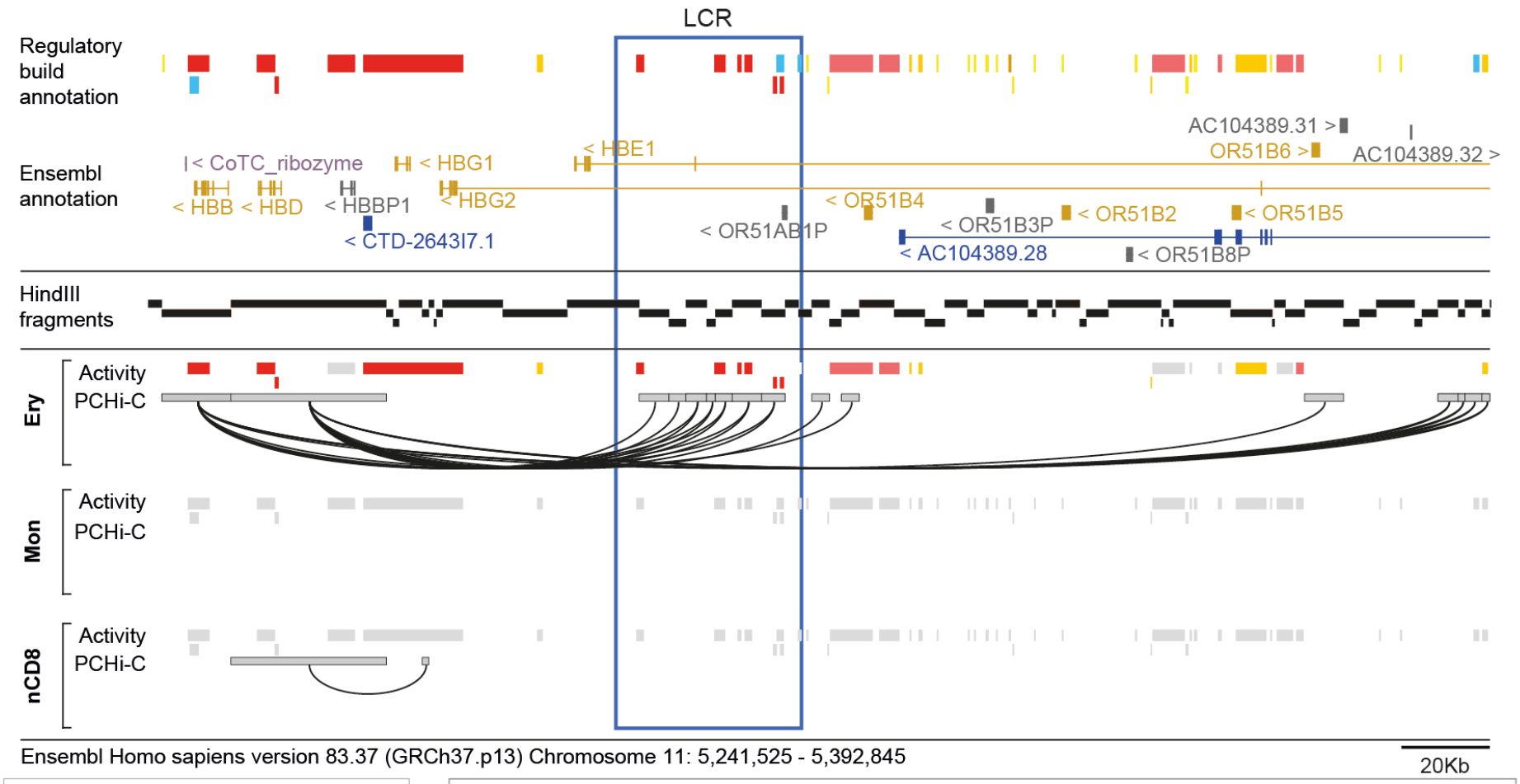

Promoter interactions and chromatin features in the b-globin locus

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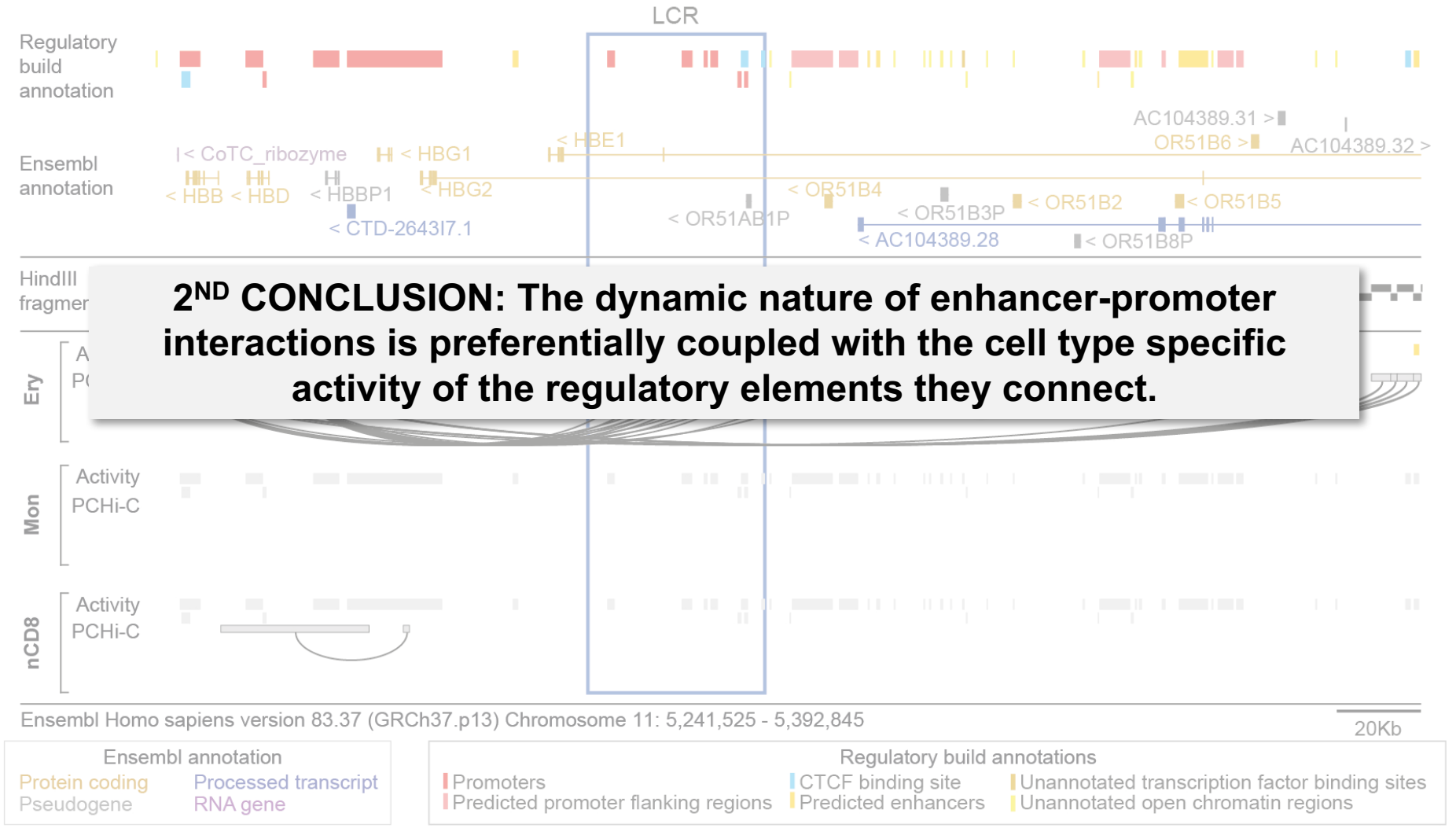
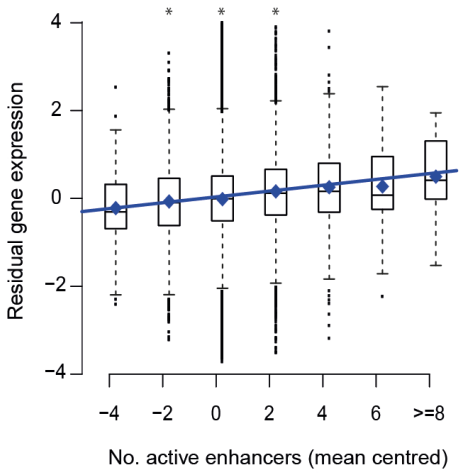


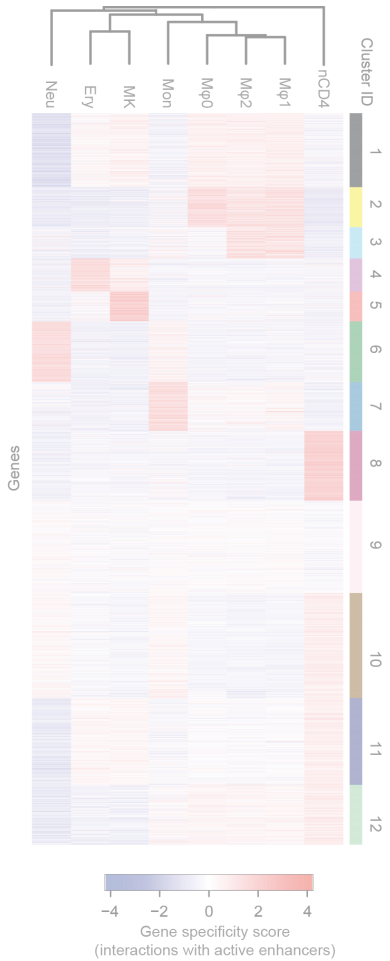
2ND CONCLUSION: The dynamic nature of enhancer-promoter interactions is preferentially coupled with the cell type specific activity of the regulatory elements they connect.

Promoter interactions and chromatin features in the b-globin locus

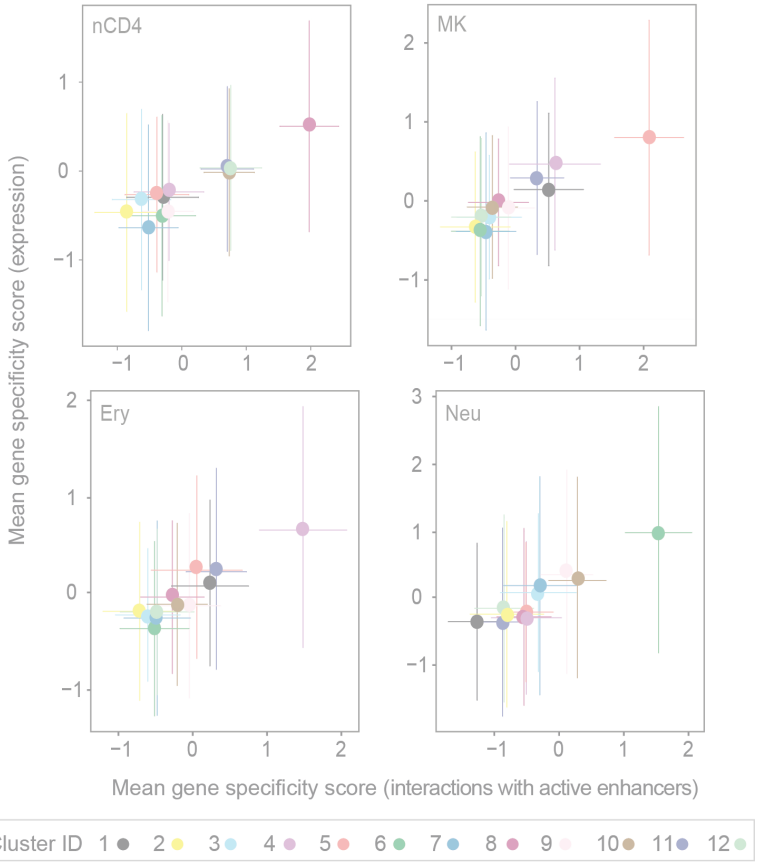
6. Enhancer Activity Associates with Lineage-Specific Gene Expression



Plot of log2-gene expression as a function of the number of interacting active enhancers where the promoter is active



k-means clustering of of "gene specificity scores" for genes based on the cell-type specificity of their interactions with active enhancers



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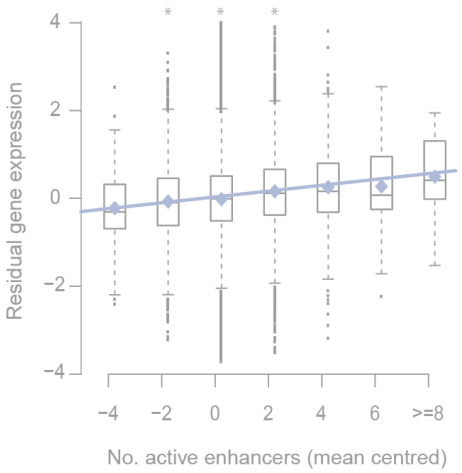

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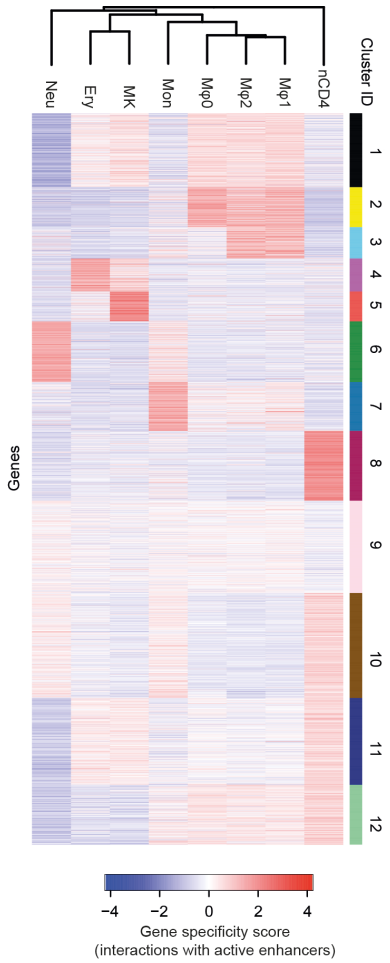

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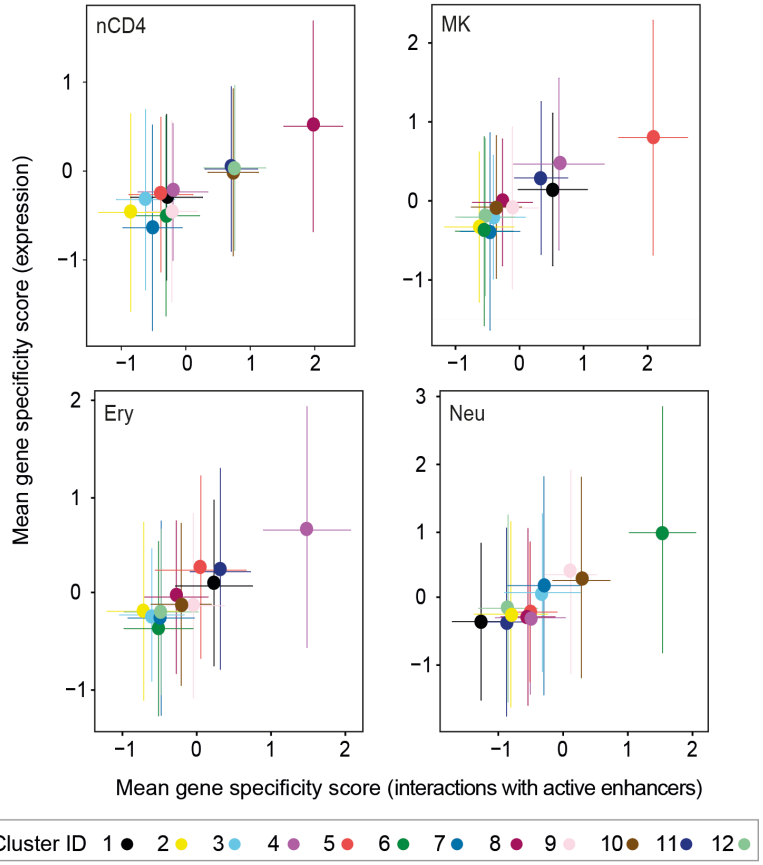

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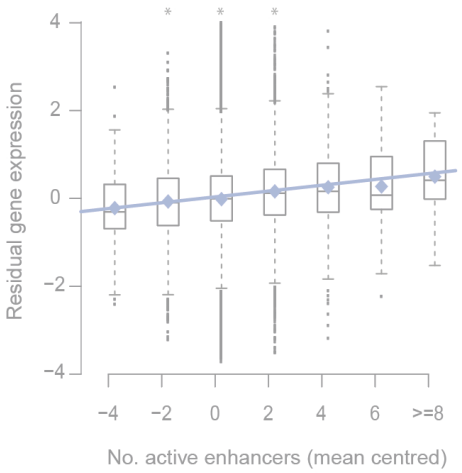

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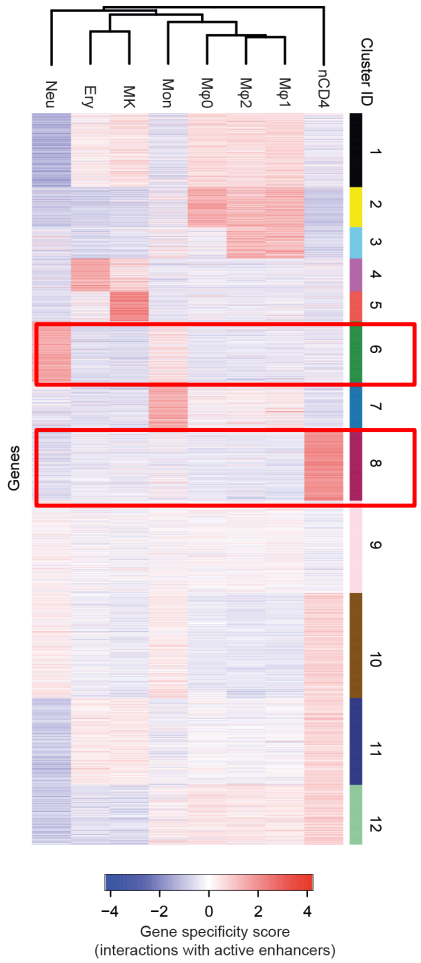

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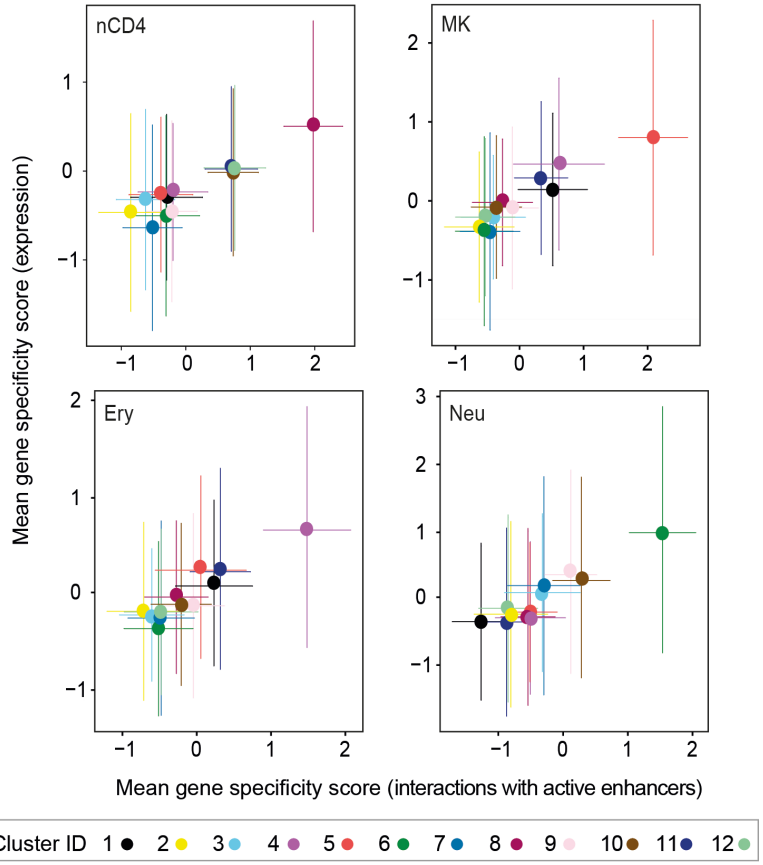

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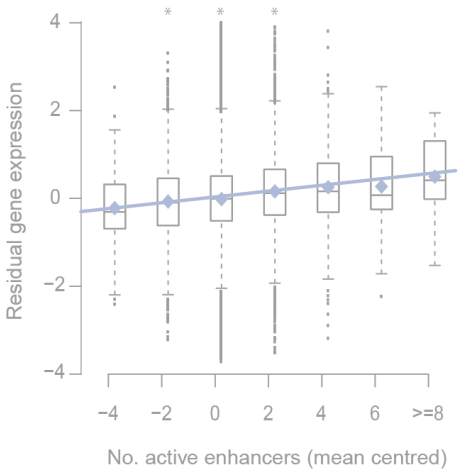

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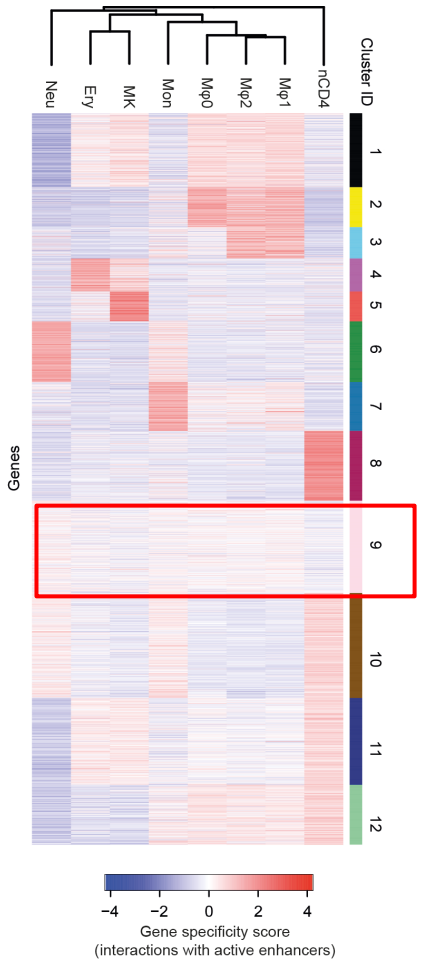

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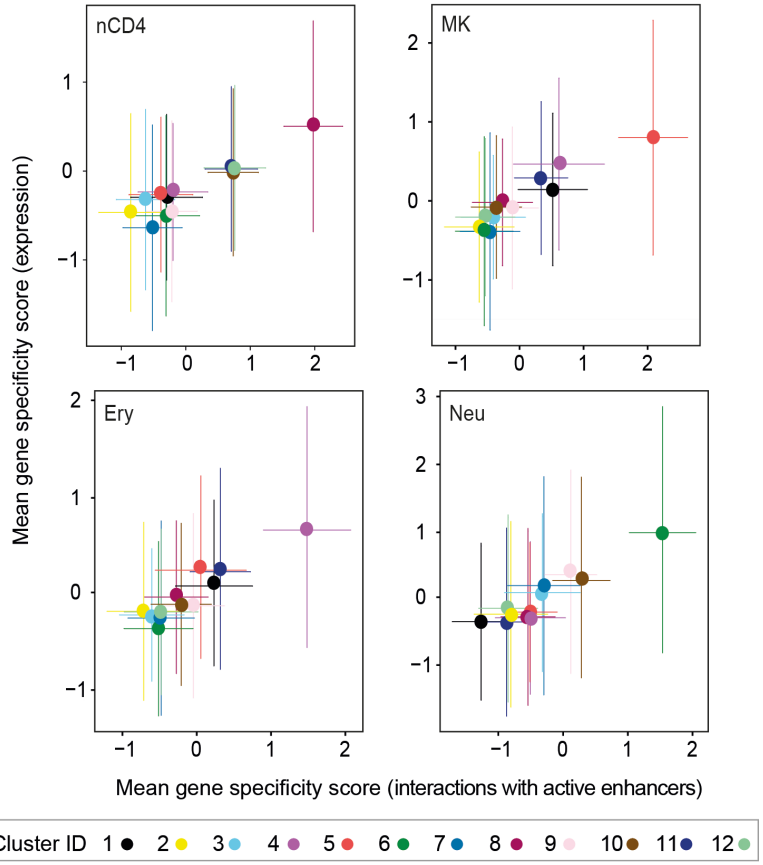

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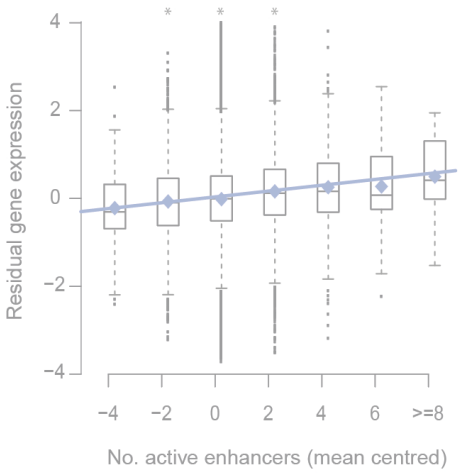

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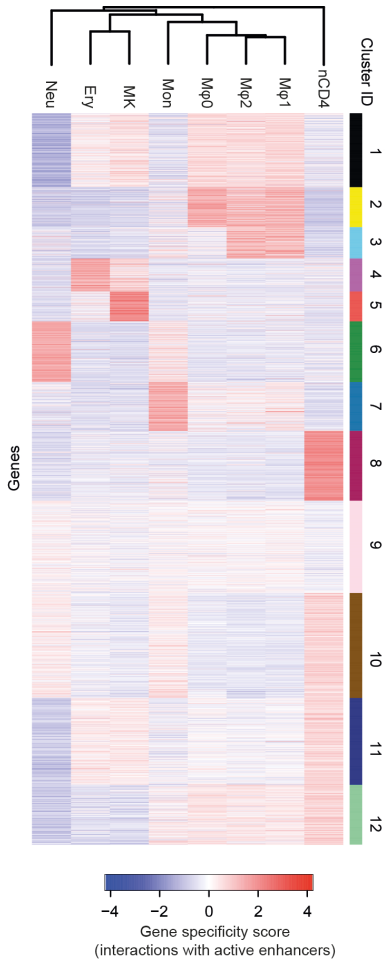

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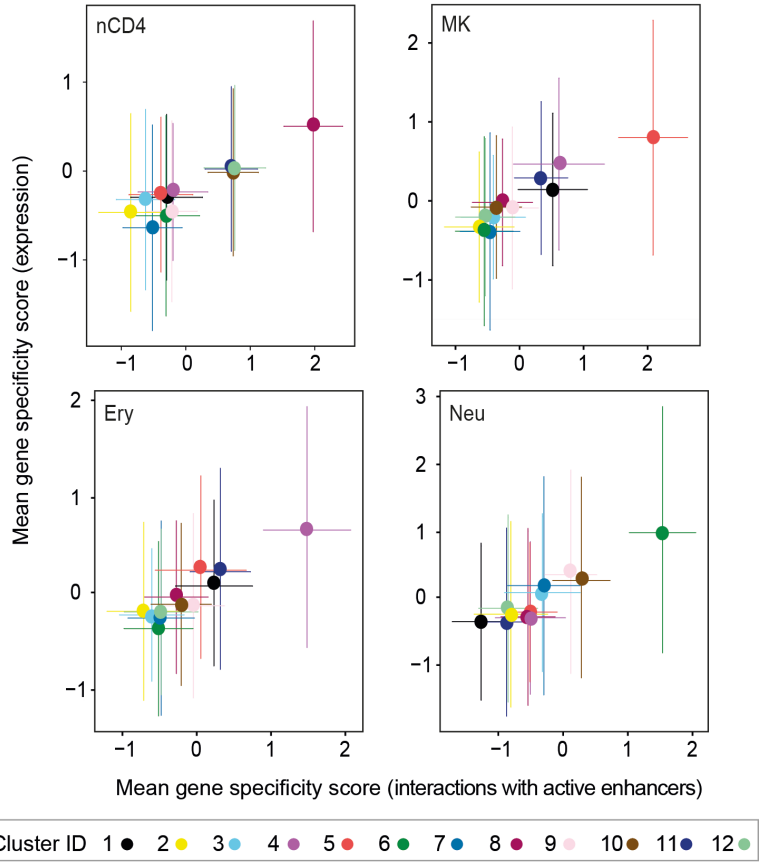

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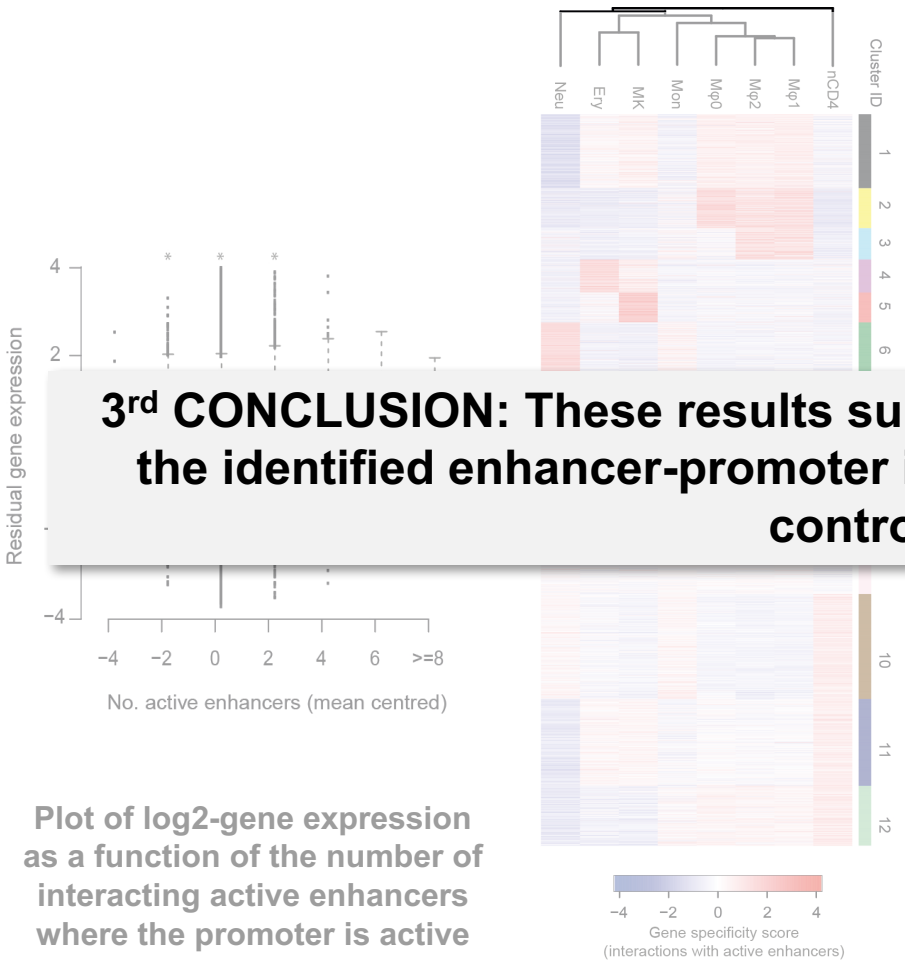

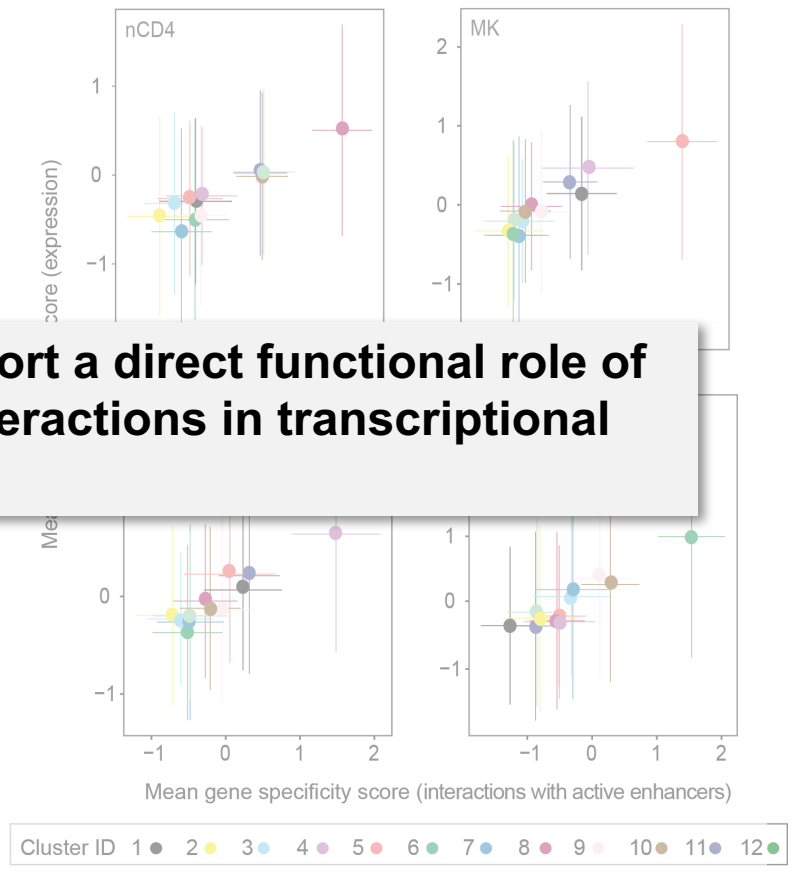

3rd CONCLUSION: These results support a direct functional role of the identified enhancer-promoter interactions in transcriptional control.

Plot of log2-gene expression as a function of the number of interacting active enhancers where the promoter is active

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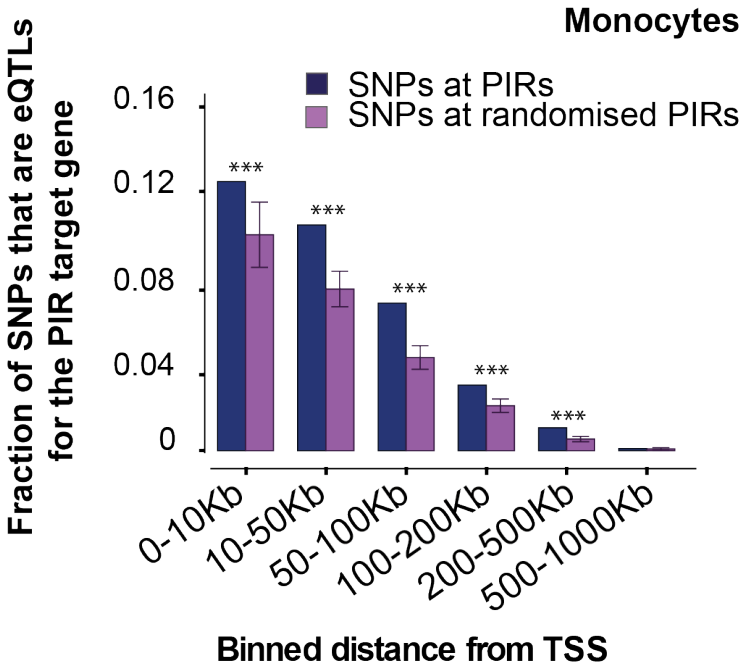
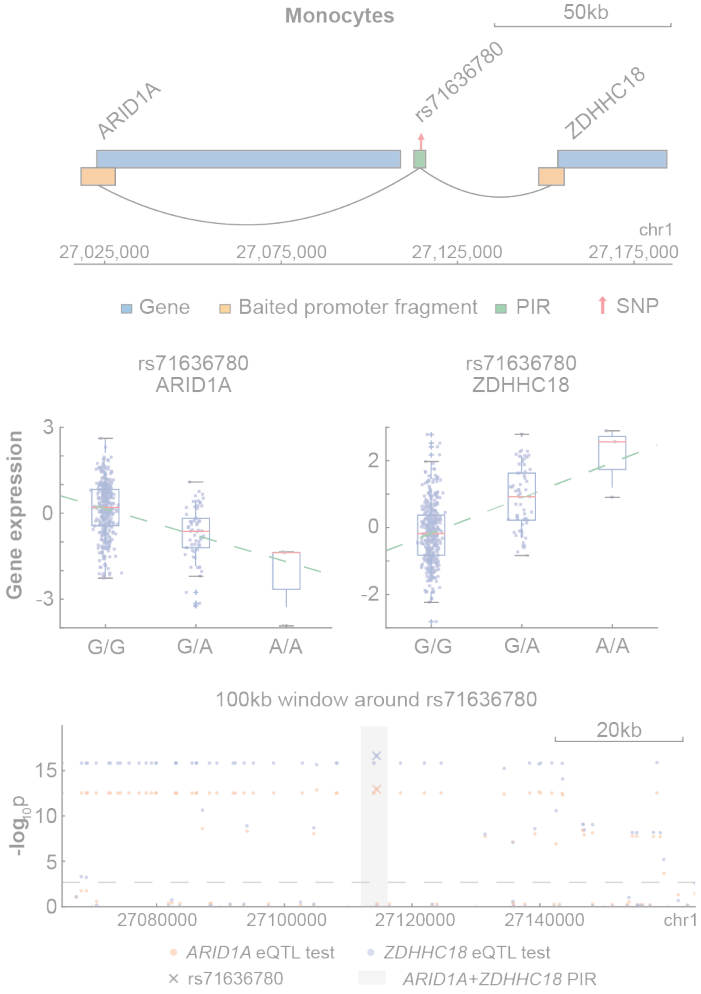
7. Expression Quantitative Trait Loci Provide Evidence for PIR Regulatory Function



The proportion of SNPs that are eQTLs for the PIR-connected gene compared with the equivalent proportion at matched random regions in Monocytes



Example of a single common eQTL SNP identified for two genes (*ARID1A* and *ZDHHC18*) with the opposite directionality of effect.

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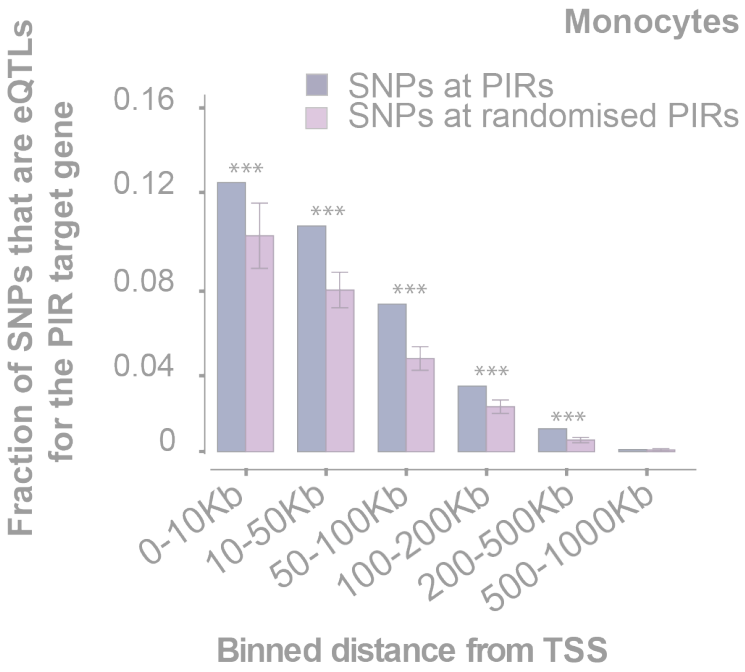

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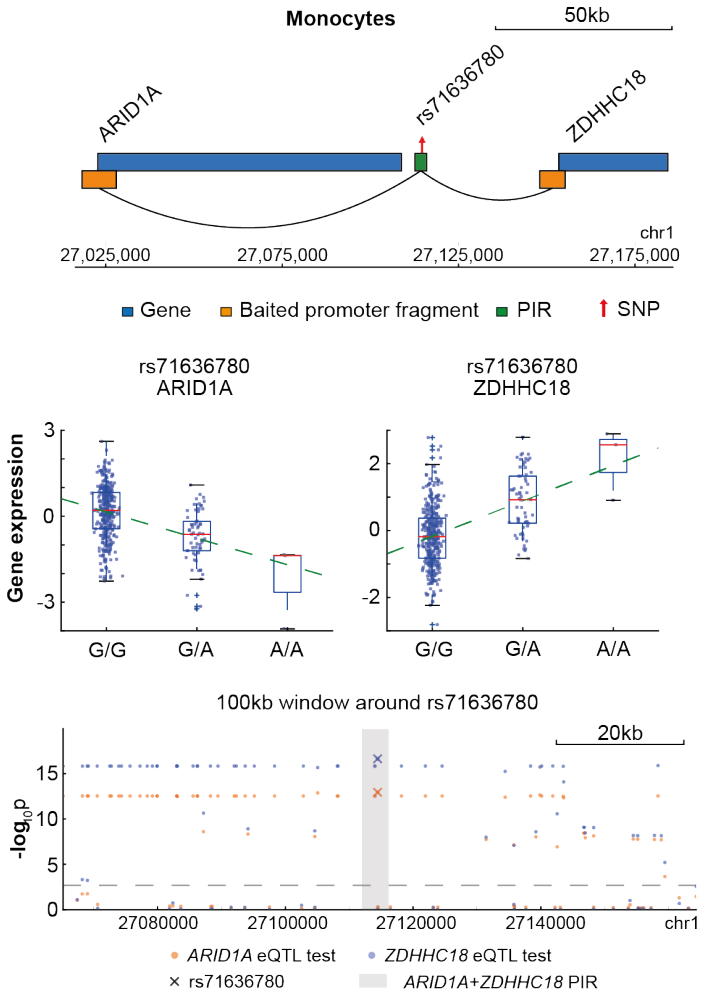

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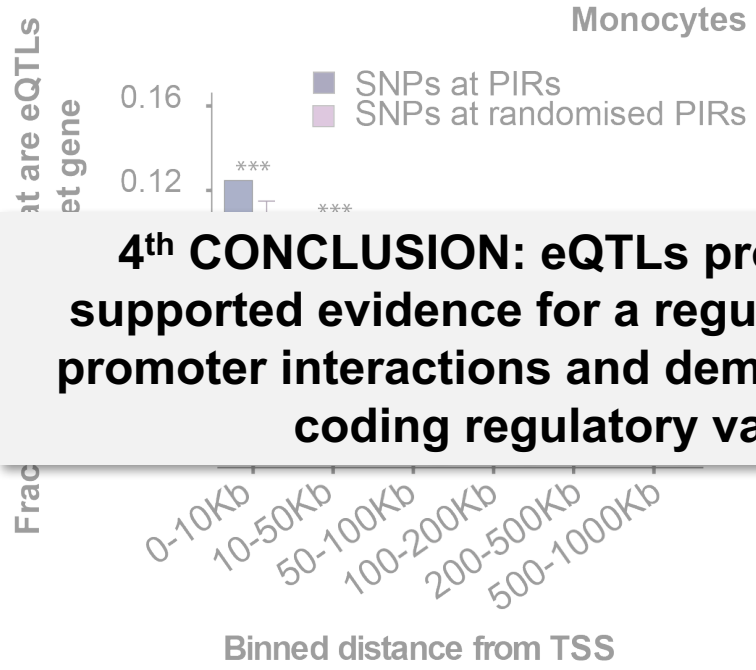

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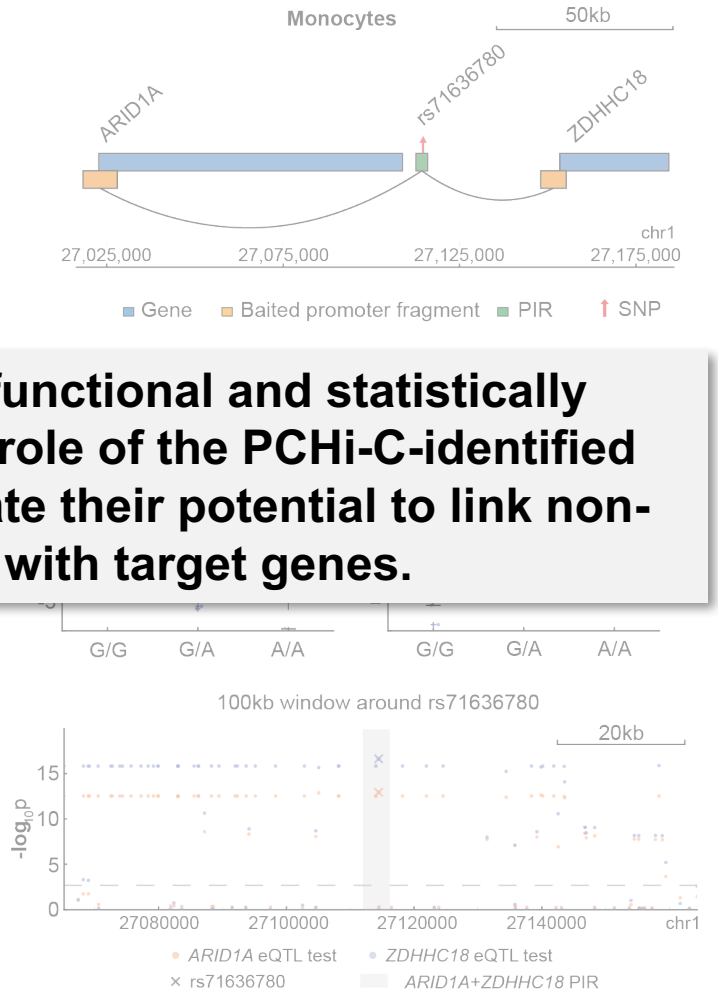

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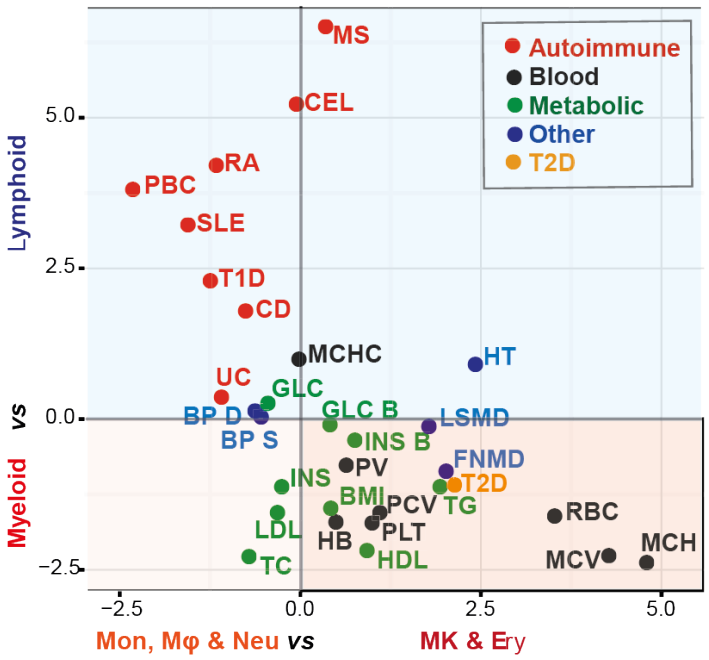
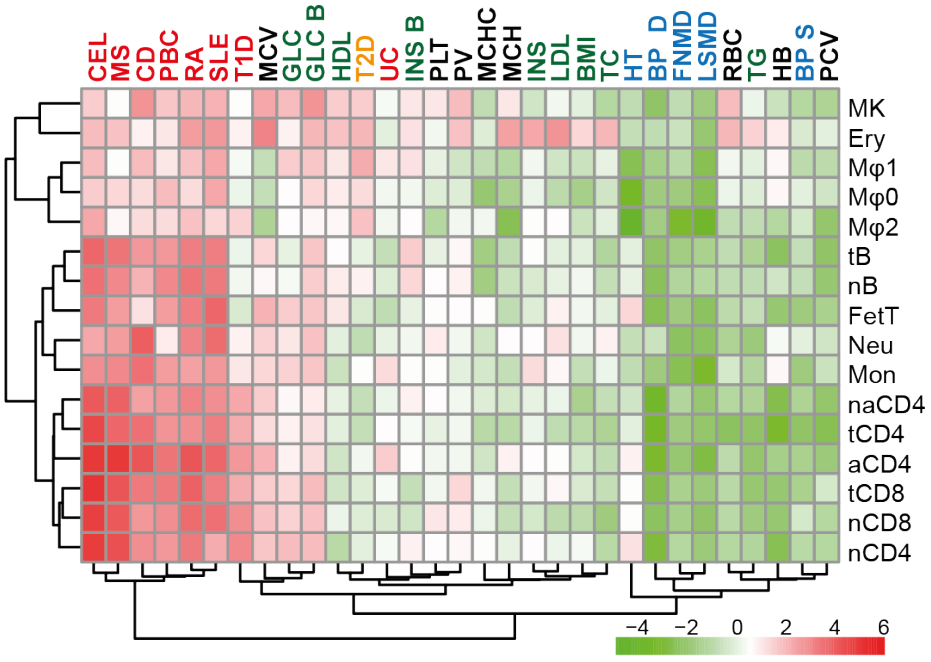
4th CONCLUSION: eQTLs provide functional and statistically supported evidence for a regulatory role of the PCHi-C-identified promoter interactions and demonstrate their potential to link non-coding regulatory variants with target genes.

8. Promoter Interactions Prioritize Target Genes of Disease-Associated SNPs



Enrichment of GWAS summary statistics at PIRs by tissue type. Axes reflect blockshifter Z scores for two different tissue group comparisons



Blockshifter enrichment Z scores of GWAS summary statistics in PIRs by individual tissue type using endothelial cells as a control.

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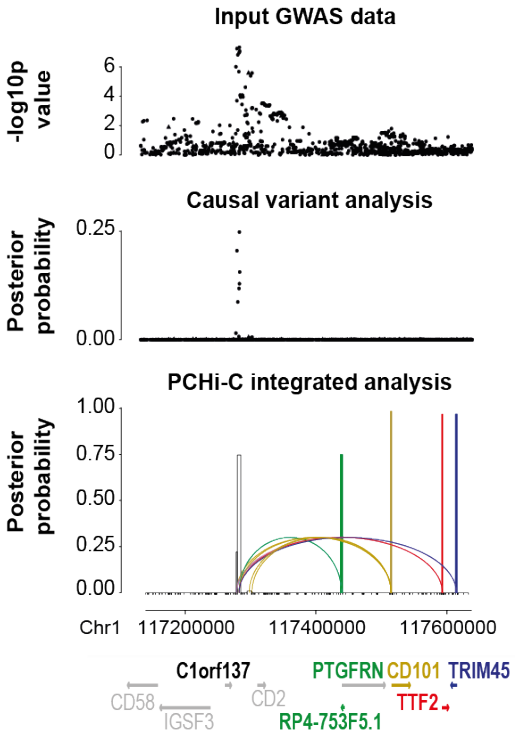
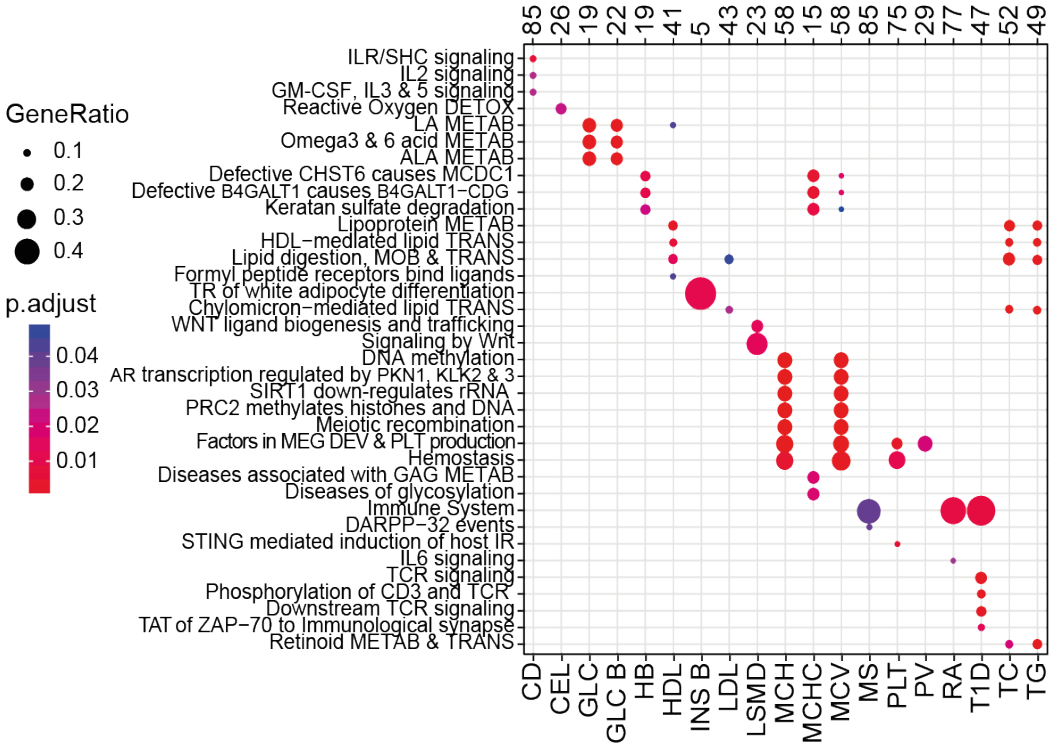
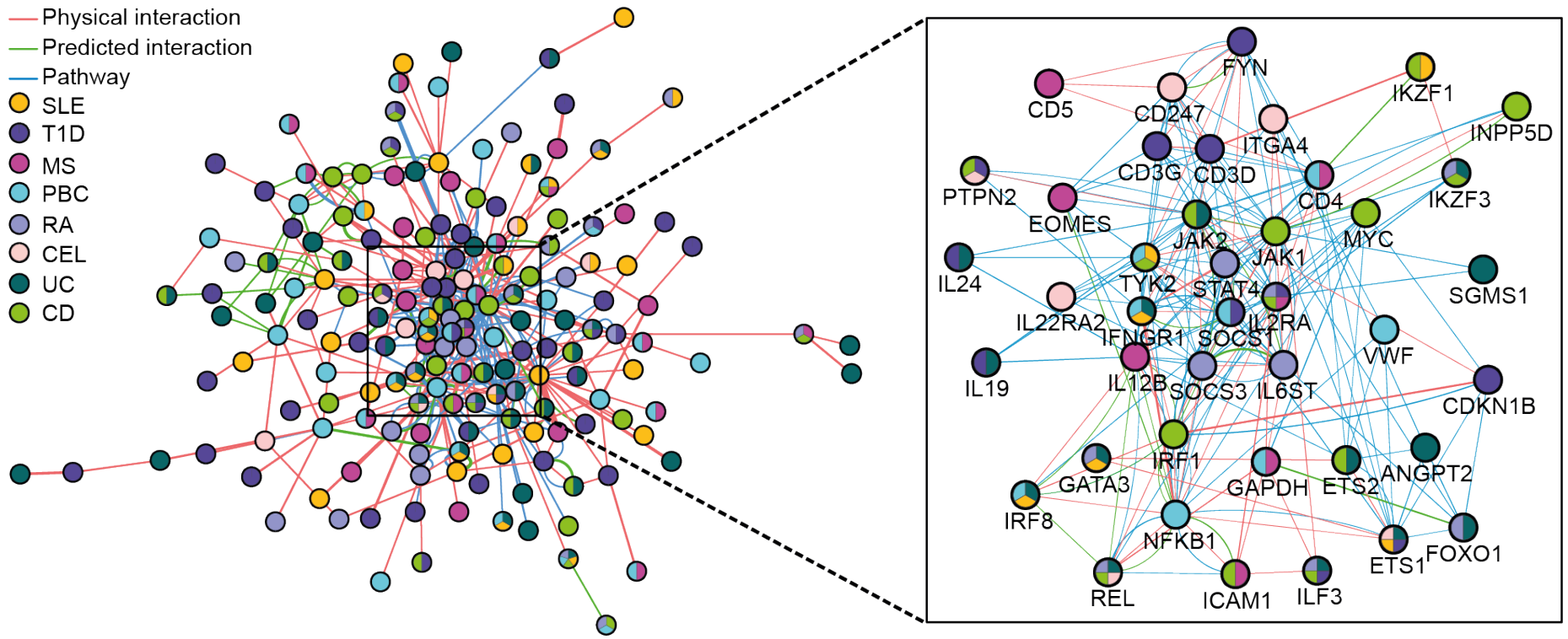


Example of the COGS gene prioritization method in 1p13.1 RA susceptibility region



Bubble plot of traits with significant enrichment (p.adj < 0.05) in one or more pathways from the Reactome pathway database.

8. Promoter Interactions Prioritize Target Genes of Disease-Associated SNPs



The "core autoimmune disease network" containing the 421 highest-scoring genes prioritized for autoimmune disease obtained from GeneMania

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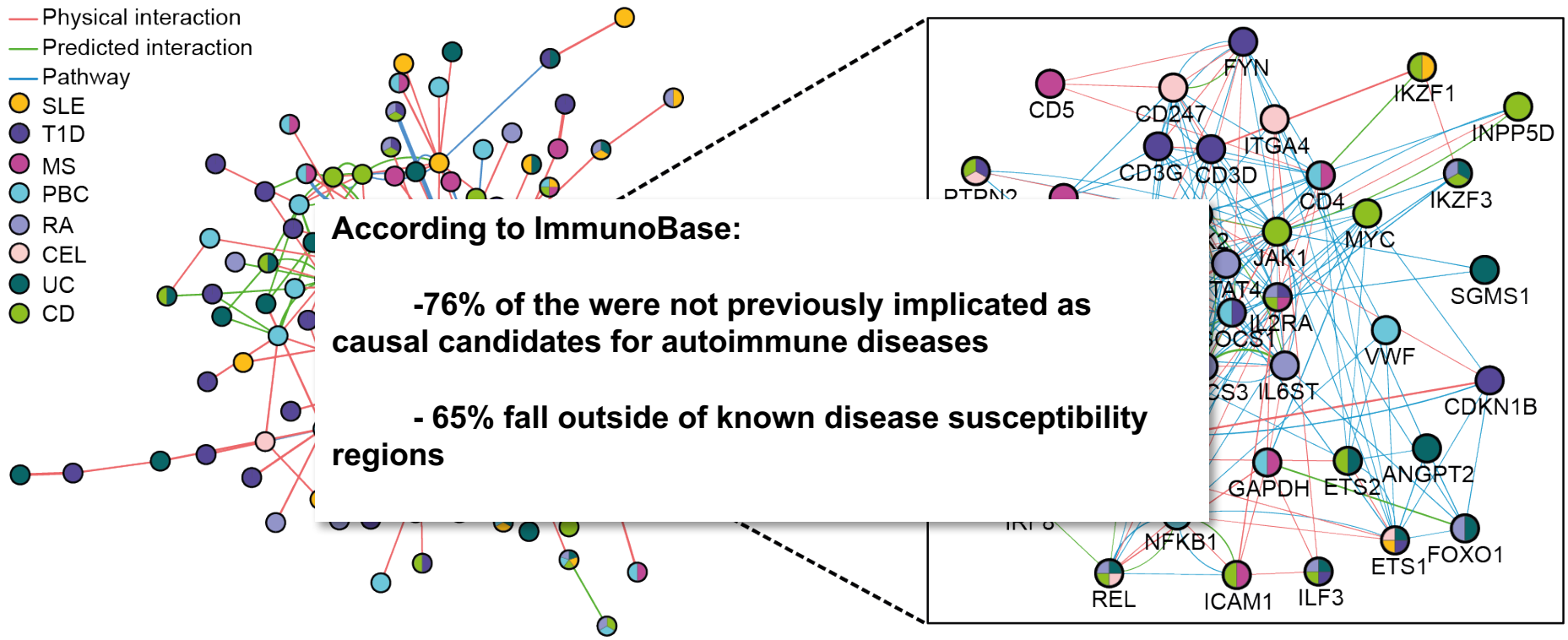

According to ImmunoBase:

-76% of the were not previously implicated as causal candidates for autoimmune diseases

- 65% fall outside of known disease susceptibility regions

The "core autoimmune disease network" containing the 421 highest-scoring genes prioritized for autoimmune disease obtained from GeneMania

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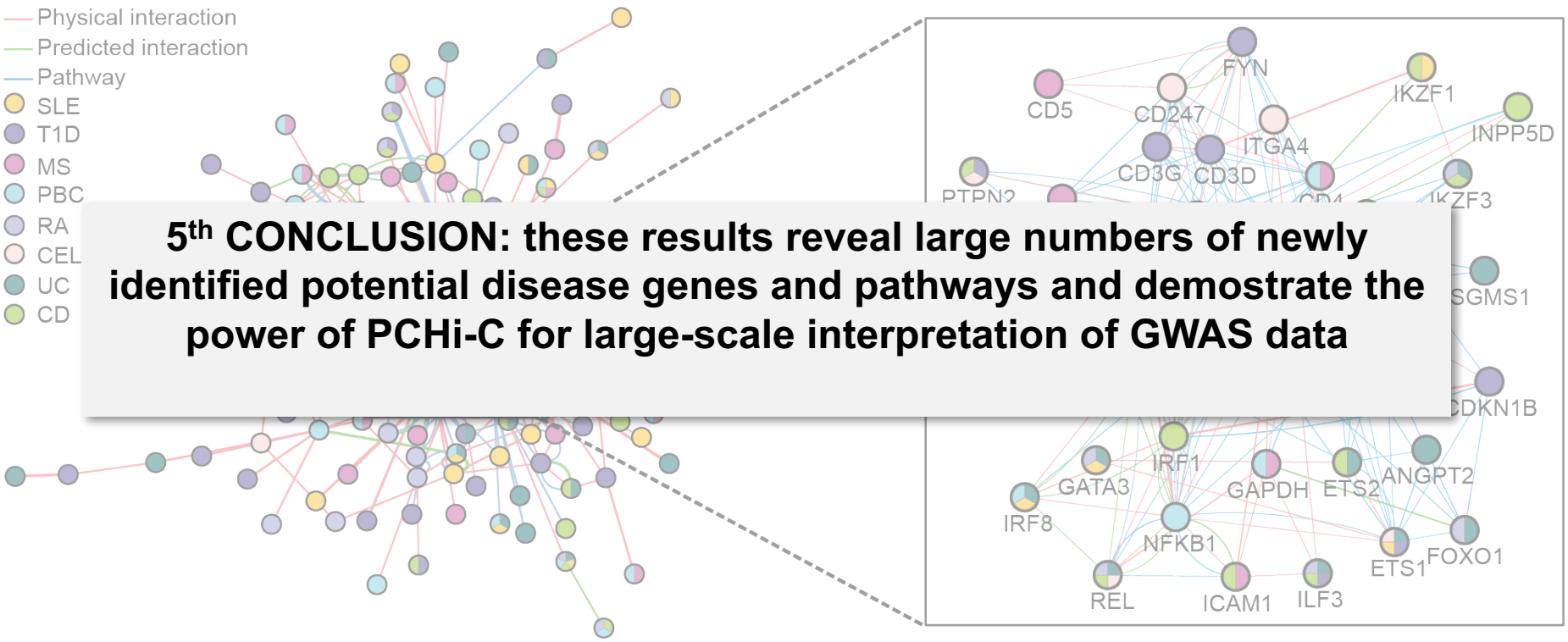


5th CONCLUSION: these results reveal large numbers of newly identified potential disease genes and pathways and demostrate the power of PCHi-C for large-scale interpretation of GWAS data

The "core autoimmune disease network" containing the 421 highest-scoring genes prioritized for autoimmune disease obtained from GeneMania

9. Take Home Messages

- We have combined HiC technology with sequence capture to enrich HiC material for interactions involving ~22,000 known promoters in primary human cells.

- Using a peak-calling algorithm (CHiCAGO), we have detected 2.816.292 putative regulatory interactions across 17 primary human cell types (708,007 unique interactions) at a single-restriction fragment resolution.

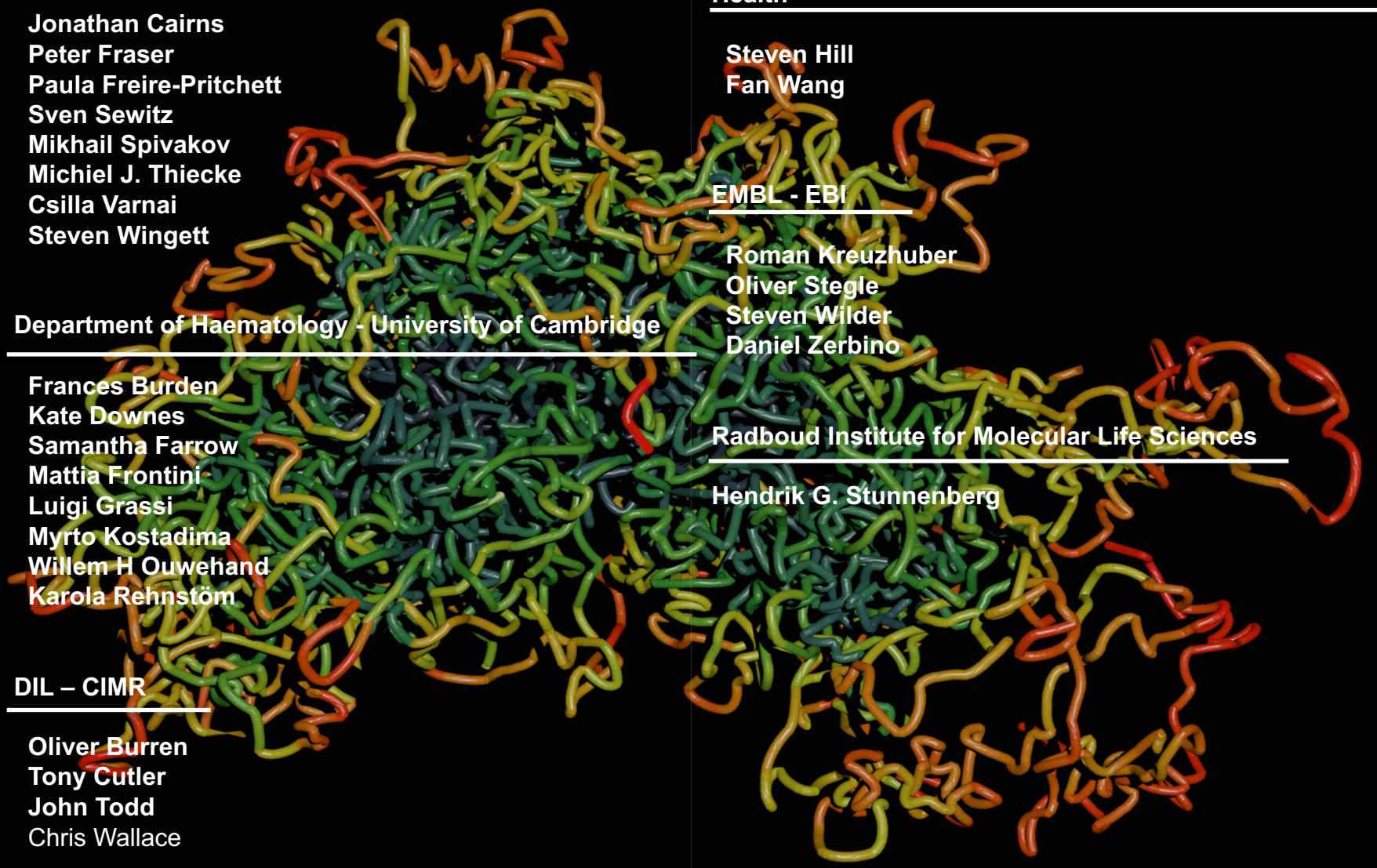
- Long-range promoter interactions preferentially link active promoters and enhancers, and are highly cell-type specific while preserving the lineage relationships between cell types.

- Patterns of promoter interactions recapitulate the haematopoieitic lineage tree, consistent with a robust and dynamic nuclear architecture.

- There's a strong and cell-specific enrichment of eQTLs and GWAS SNPs at promoter-interacting regions, affirming the potential of PCHi-C data to connect non-coding regulatory variants with their putative target genes.

- We have connected non-coding disease-associated variants to their target promoters, identifying dozens of new disease-candidate genes and/or gene pathways.

- Taken together, this work presents the first large-scale resource of promoter interactomes from primary cells and demonstrates its power to reveal insights into global genomic regulatory mechanisms and gene pathways underlying disease pathologies.



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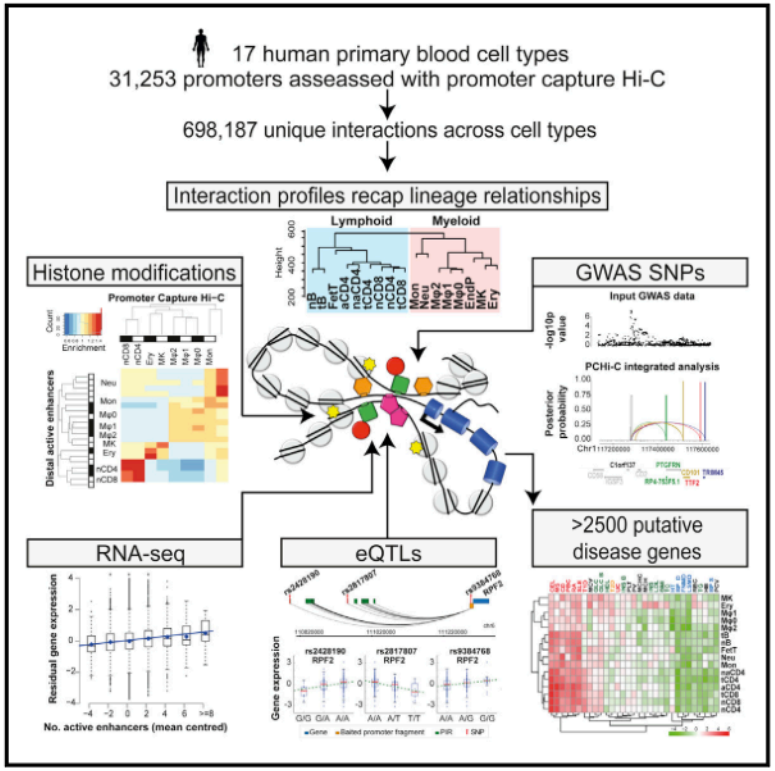
Resource

Cell

Lineage-Specific Genome Architecture Links Enhancers and Non-coding Disease Variants to Target Gene Promoters

Graphical Abstract



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In Brief

This study deploys a promoter capture Hi-C approach in 17 primary blood cell types to match collaborating regulatory regions and identify genes regulated by noncoding disease-associated variants. Explore this and other papers at the Cell Press IHEC webportal at http://www.cell.com/consortium/IHEC.

Institut de Recerca
CONTRA LA LEUCÈMIA
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Hunting for enthusiastic PhD students and postdocs!