Charting the epigenomic landscape of human transposable elements

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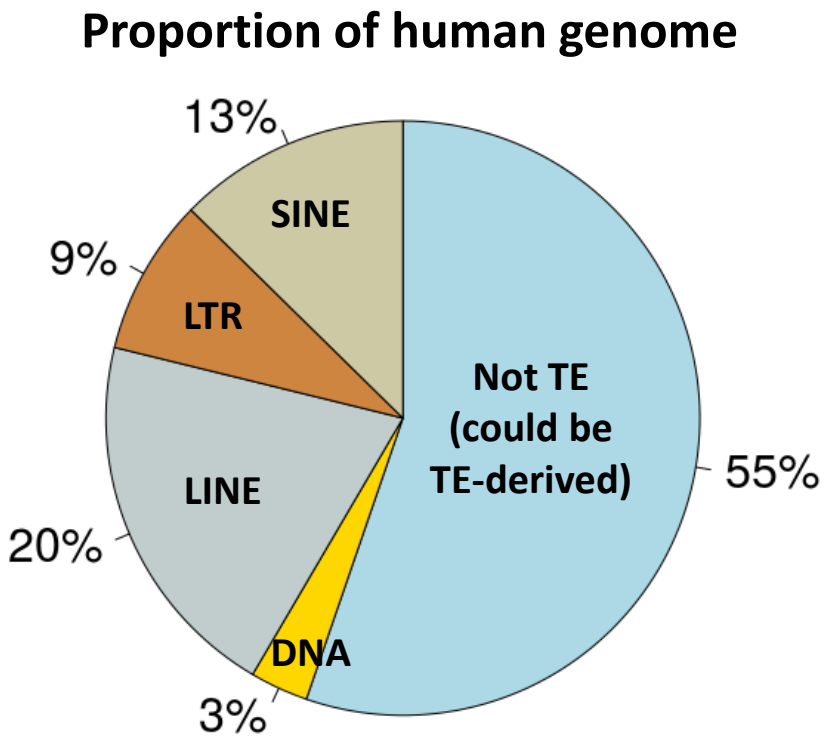
Transposable elements (TEs) encode regulatory elements



- TEs comprise ~45% of the human genome
- Can encode gene regulatory elements
- Overlap 18% of transcription start sites, 44% open chromatin regions (Djebali 2012, Jacques 2013)

TEs contributed innovations to regulatory networks

NAS

Species-specific endogenous retroviruses shape the transcriptional network of the human tumor suppressor protein p53

Ting Wang*, Jue Zeng†, Craig B. Lowe*, Robert G. Sellers*‡, Sofie R. Salama*‡, Min Yang†, Shawn M. Burgess§, Rainer K. Brachmann†¶‖, and David Haussler*‡‖

CSH PRESS GENOME RESEARCH

Evolution of the mammalian transcription factor binding repertoire via transposable elements

Guillaume Bourque, Bernard Leong, Vinsensius B. Vega, et al.

LETTERS

nature genetics

Transposable elements have rewire network of human embryonic stem

Galih Kunarso[1,2], Na-Yu Chia[3,4], Justin Jeyakani[1], Catalina Hwang[1,5], Huck-Hui Ng[3,4,6–8] & Guillaume Bourque[1]

Research

Rewirable gene regulatory networks preimplantation embryonic develop of three mammalian species

IMMUNOGENOMICS

Regulatory evolution of innate immunity through co-option of endogenous retroviruses

Edward B. Chuong, Nels C. Elde,*† Cédric Feschotte*†

szek,[2,3,4,9] Shu Xiao, Xiaoyi Cao, had Cowan,[3,4] and Sheng Zhong[1,7,8,10]

LETTERS

Transposon-mediated rewiring of gene regulatory networks contributed to the evolution of pregnancy in mammals

Vincent J Lynch, Robert D Leclerc, Gemma May & Günter P Wagner

Cell

Endogenous retroviruses function as species-spe enhancer elements in the placenta

Edward B Chuong[1], M A Karim Rumi[2], Michael J Soares[2] & Julie C Baker[1]

Waves of Retrotransposon Expansion Remodel Genome Organization and CTCF Binding in Multiple Mammalian Lineages

Dominic Schmidt,[1,2,6] Petra C. Schwalie,[3,6] Michael D. Wilson,[1,2] Benoit Ballester,[3] Ângela Gonçalves,[3] Claudia Kutter,[1,2] Gordon D. Brown,[1,2] Aileen Marshall,[1,5] Paul Flicek,[3,4,*] and Duncan T. Odom[1,2,4,*]

Impact of TEs on gene regulation and chromatin architecture – main interest/focus of our lab

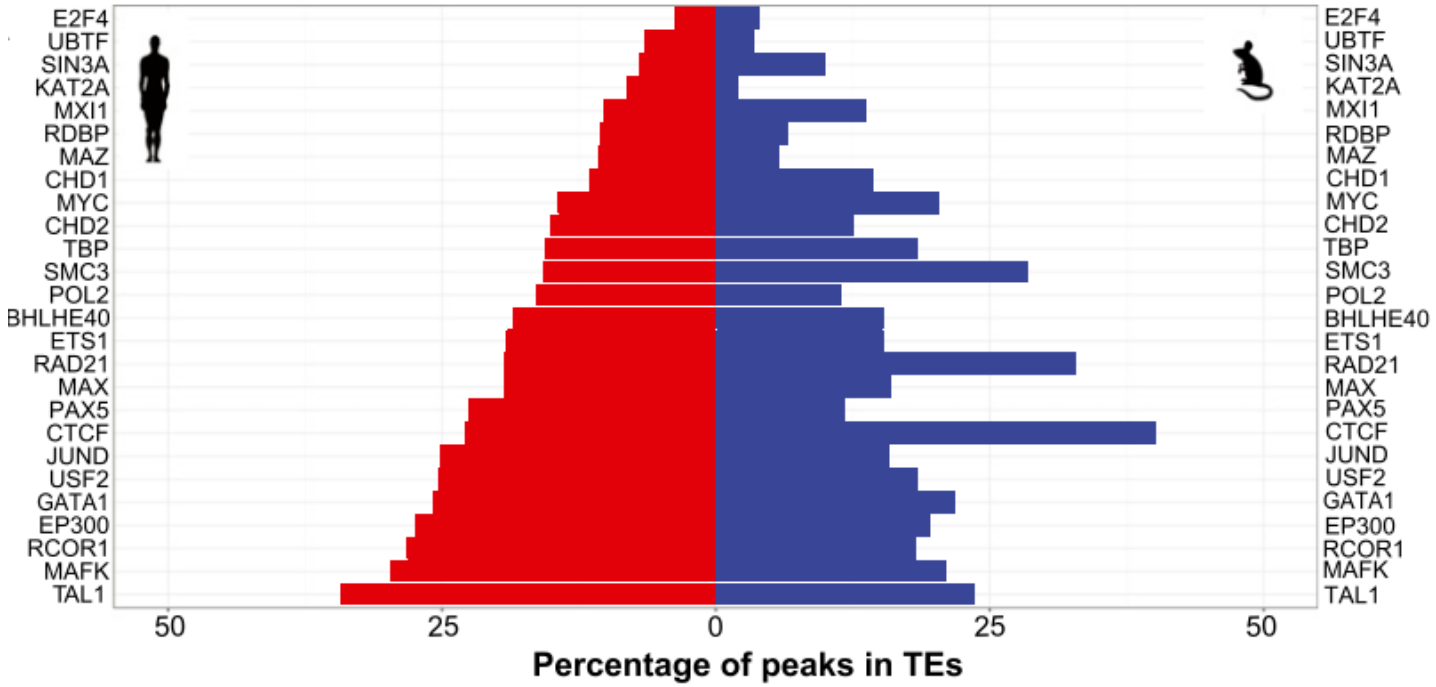
ENCODE4 U01

Goal: to develop and apply computational methods specifically designed to analyze TEs as a source of regulatory sequences using ENCODE data.

1. To quantify the contribution of TEs to gene regulatory networks
2. To better understand the role of TEs in shaping genome topology
3. To identify sequence features that control epigenetic and regulatory properties of TEs
4. To create a public resource that allows investigators to display, analyze, compare, and integrate ENCODE data and their own data on TEs

WashU: Wang, Cohen, Saccone, Zhang
Utah→ Cornell: Feschotte

TEs encode 20% of transcription factor binding sites in human and mouse

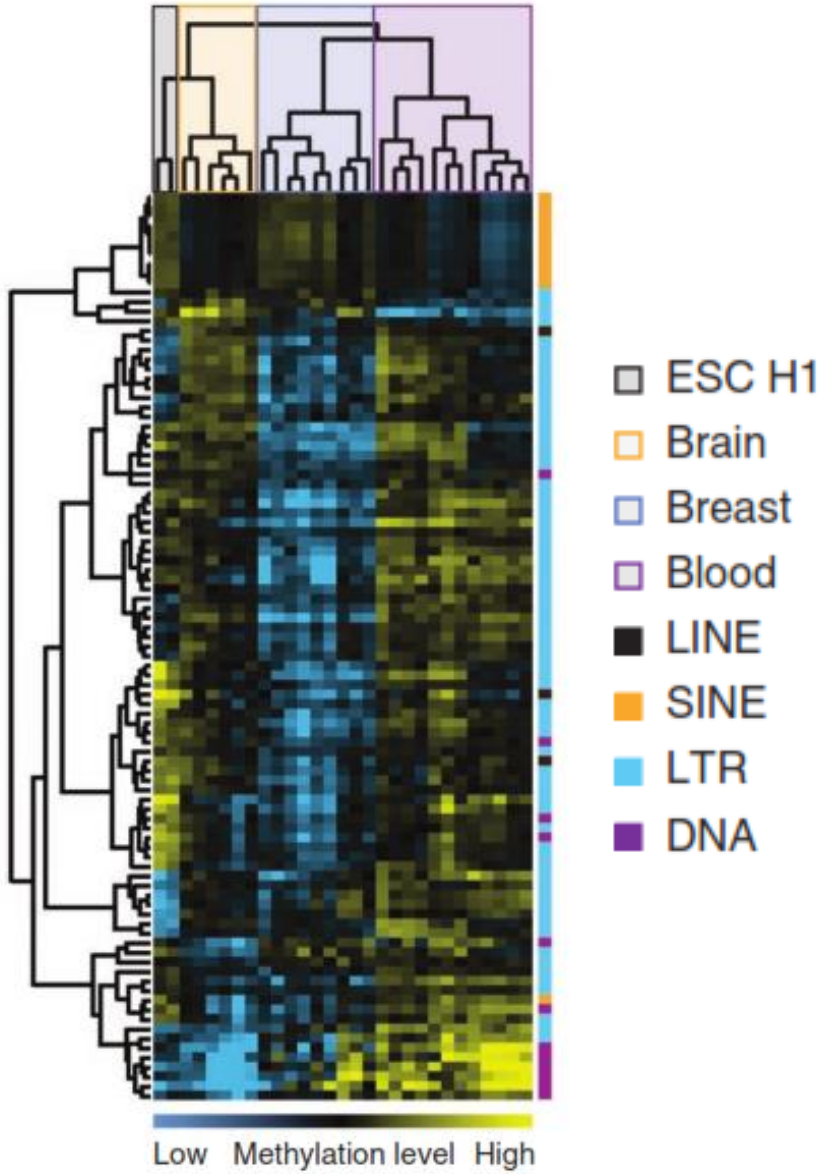


- ChIP-seq for 26 transcription factors in leukemia and lymphoblast cell lines
- 2-40% of binding sites per transcription factor are within TEs

(Sundaram, *Genome Research*, 2014)
Collaboration with Mike Snyder

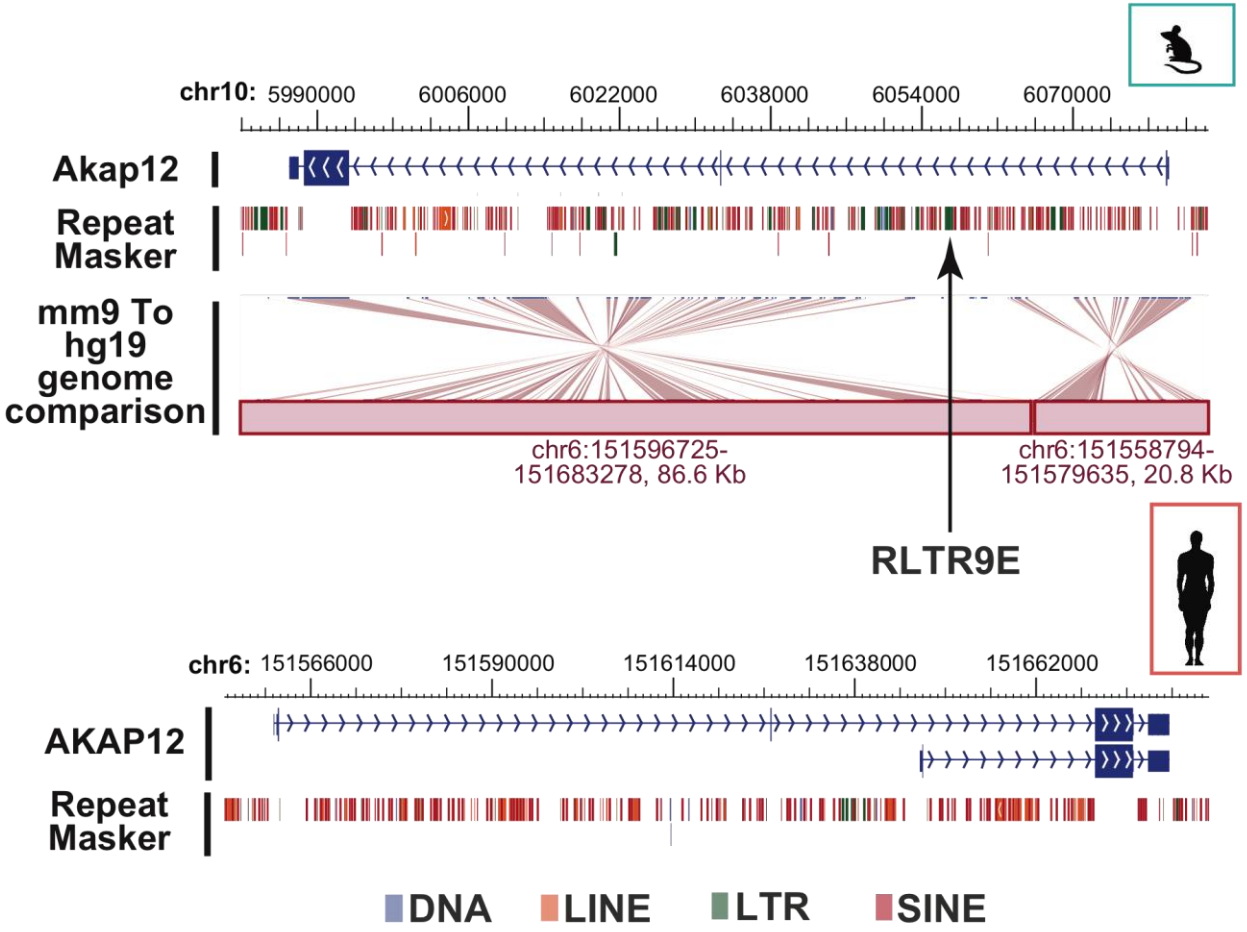
TEs encode tissue-specific enhancers in normal tissue

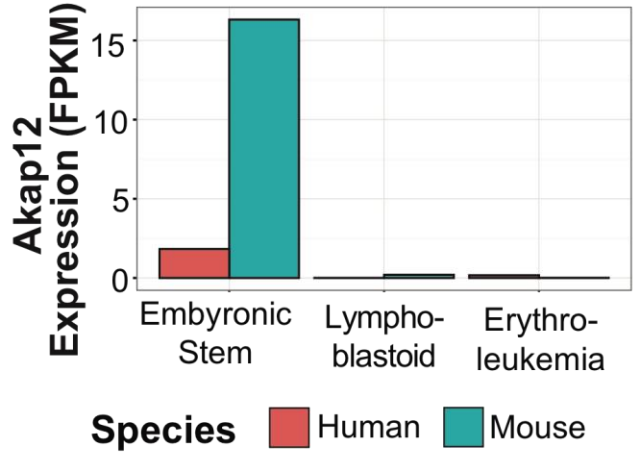
- TE subfamilies exhibit tissue-specific DNA hypomethylation
- Correlates with enhancer epigenetic marks, transcription factor binding sites
- Enriched near tissue-specific genes
- Examples
  - LFSINE (brain)
  - LTR77 (blood)

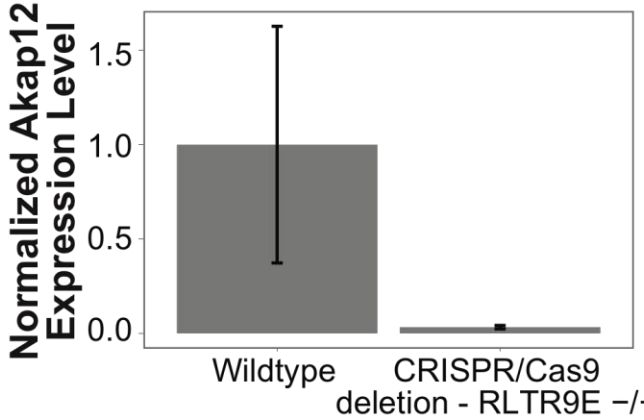


(Xie, *Nature Genetics*, 2013)

TEs encode complex *cis*-regulatory modules – a battery of cooperating TFBSs





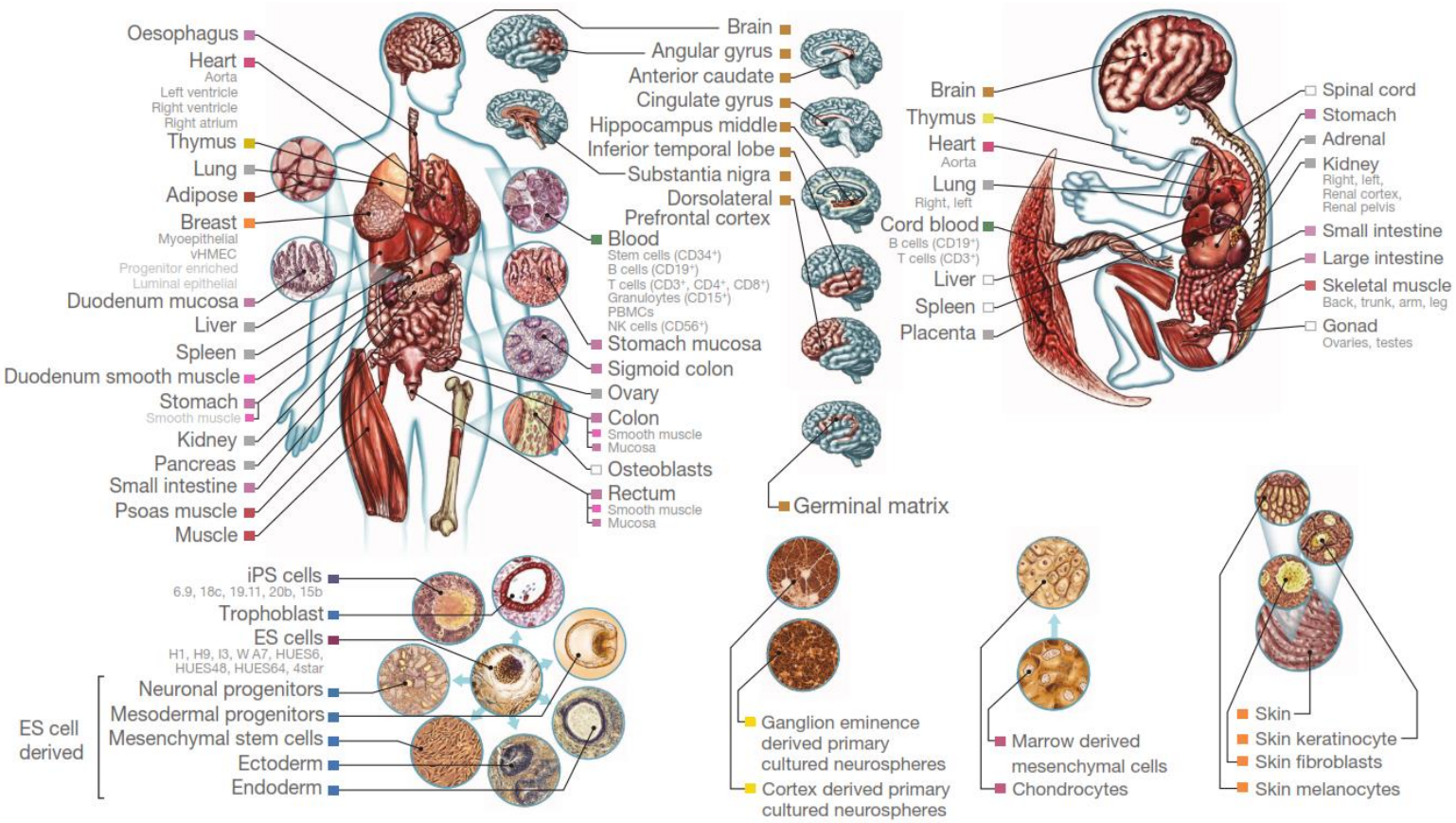


(Sundaram, *Nat Comms,* 2017)

Outstanding questions

1. What is the overall contribution of TEs to gene regulation?
2. How many TEs possess the potential to be regulatory?
3. How specific is TE activity to tissues or cell types?
4. Which TEs perform regulatory roles?
5. How do TEs evolve – obtain or lose – their regulatory capacity?
6. Are regulatory functions conserved between species?

Profiling regulatory role of TEs using Roadmap Epigenomics Project data



- **Histone modification ChIP-seq:**
  - H3K4me3 (promoter)
  - H3K4me1 (enhancer)
  - H3K36me3 (transcribed)
  - H3K27me3 (Polycomb repression)
  - H3K9me3 (heterochromatin)
- **Additional:**
  - H3K27ac/H3K9ac ChIP-seq (enhancer/promoter increased activation)
  - DNase hypersensitivity (accessible chromatin)
  - DNA methylation
  - Expression

(Roadmap Epigenomics Project, *Nature* 2015)

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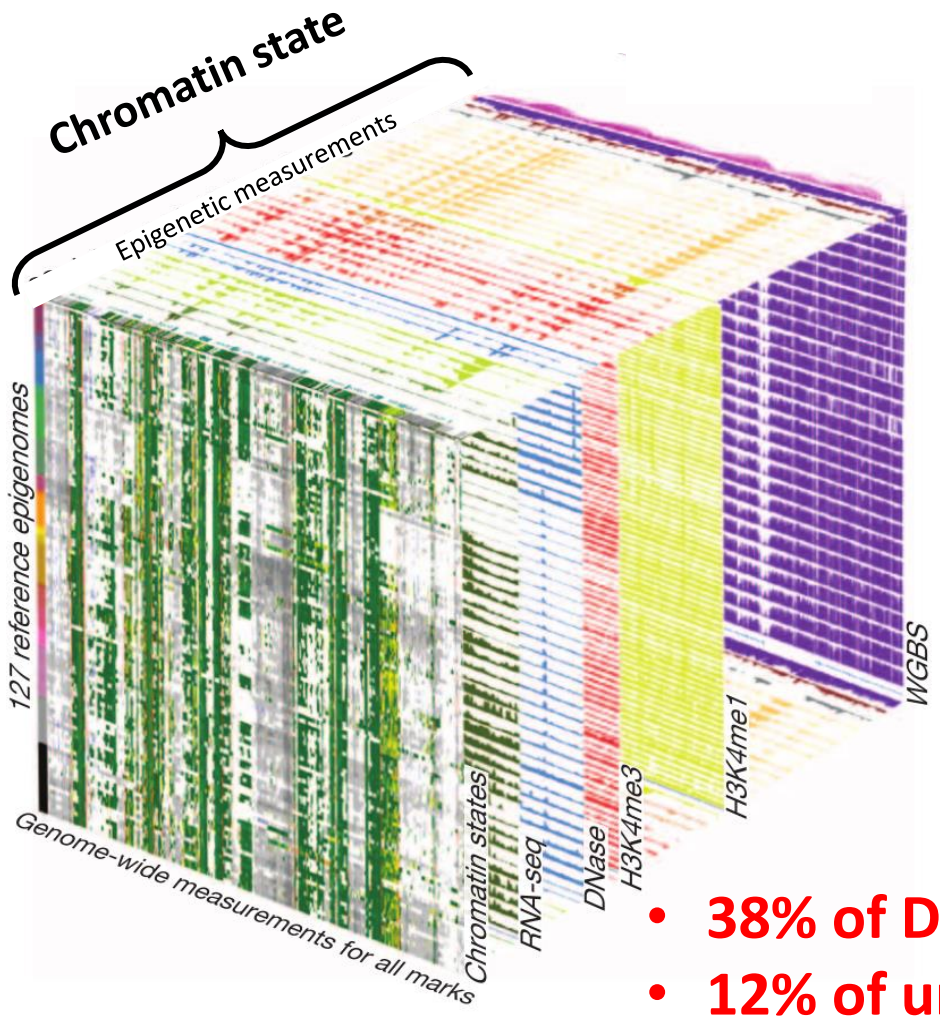
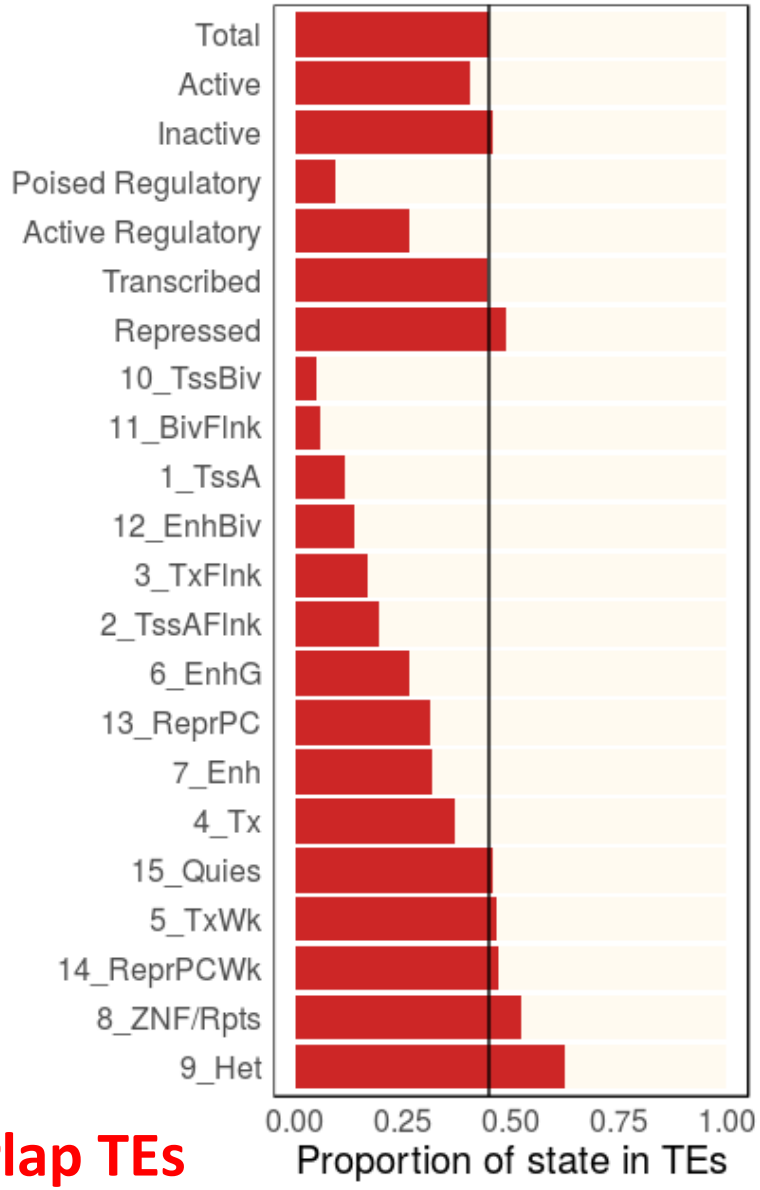
TEs have a large contribution to active and regulatory chromatin states





- **38% of DHS peaks overlap TEs**
- **12% of unmethylated CpGs overlap TEs**

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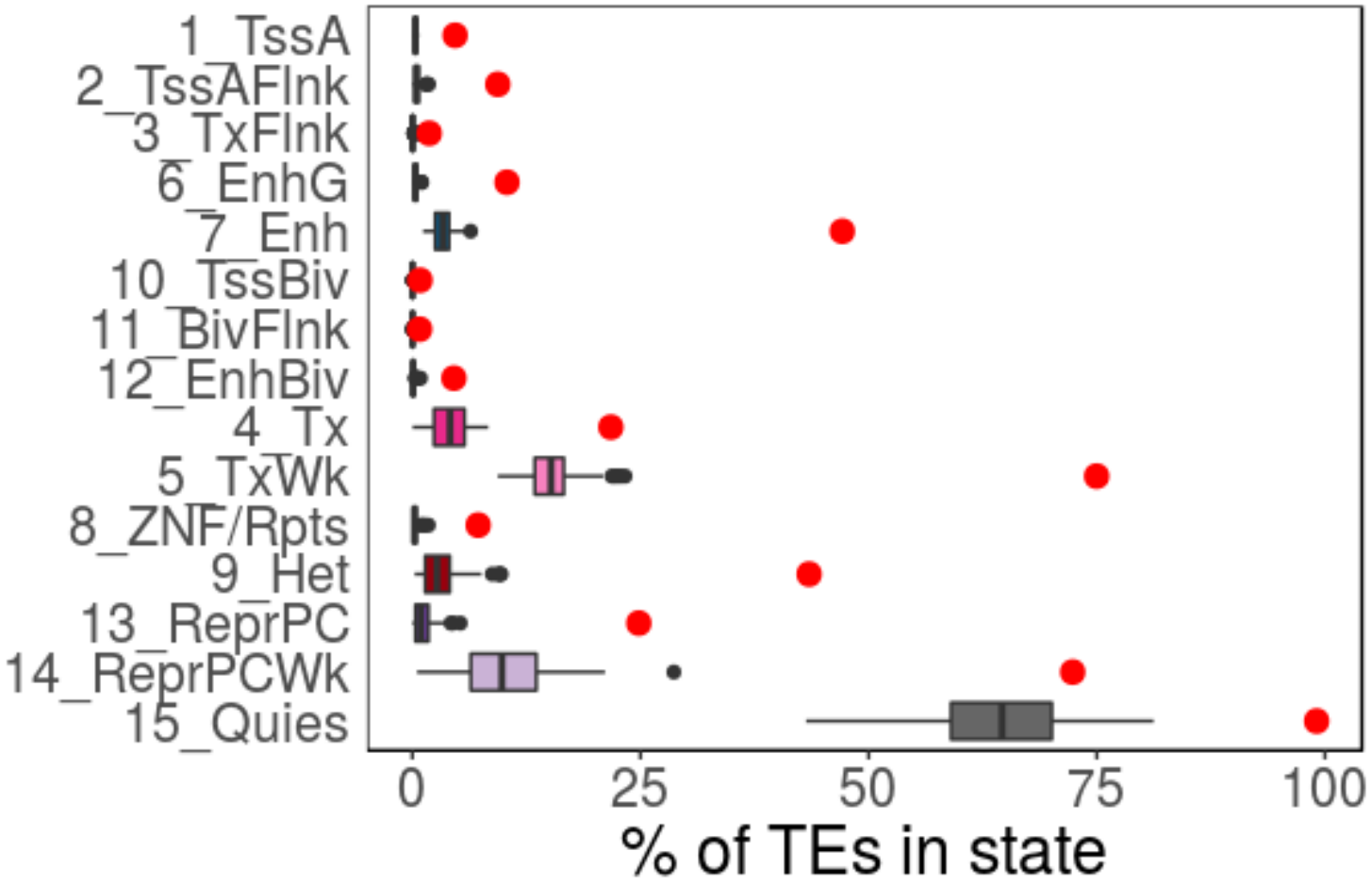
50% of TEs can be in an active regulatory state



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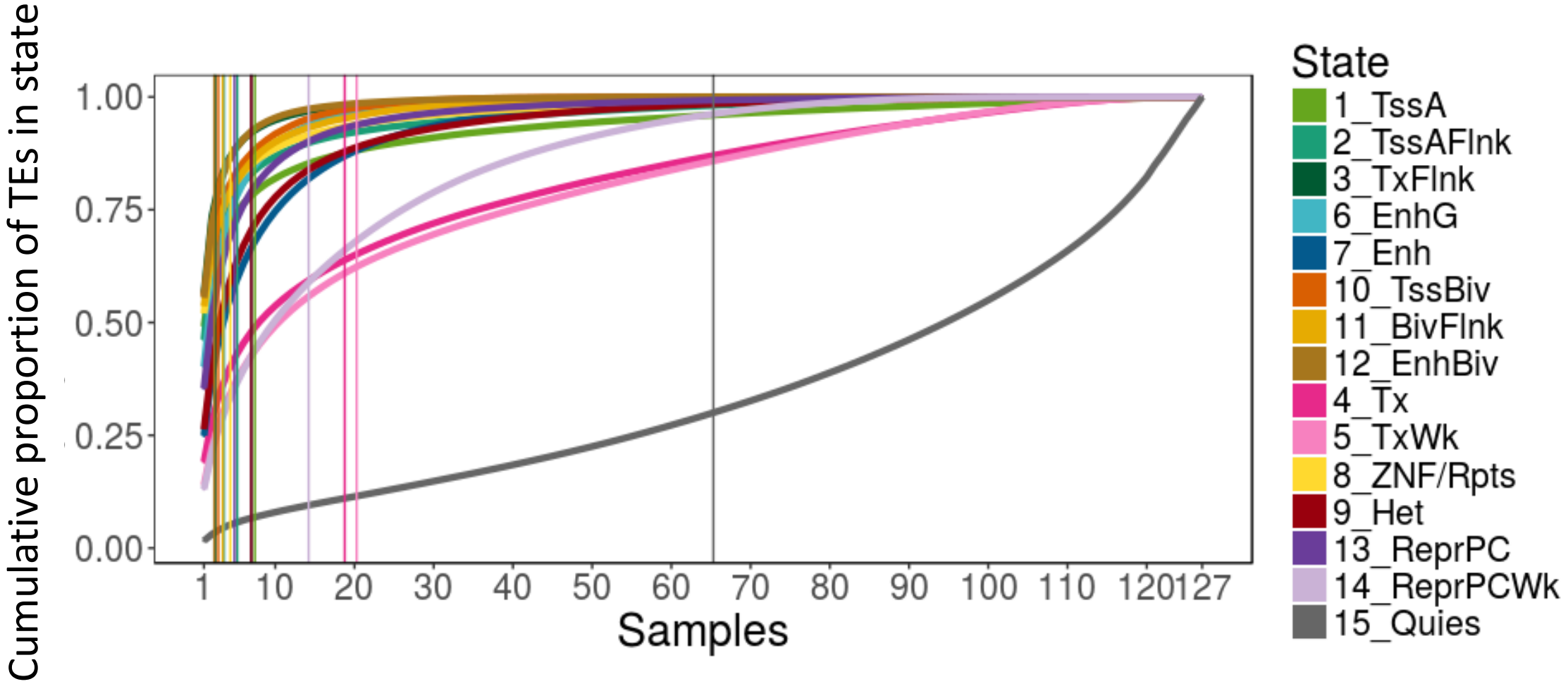
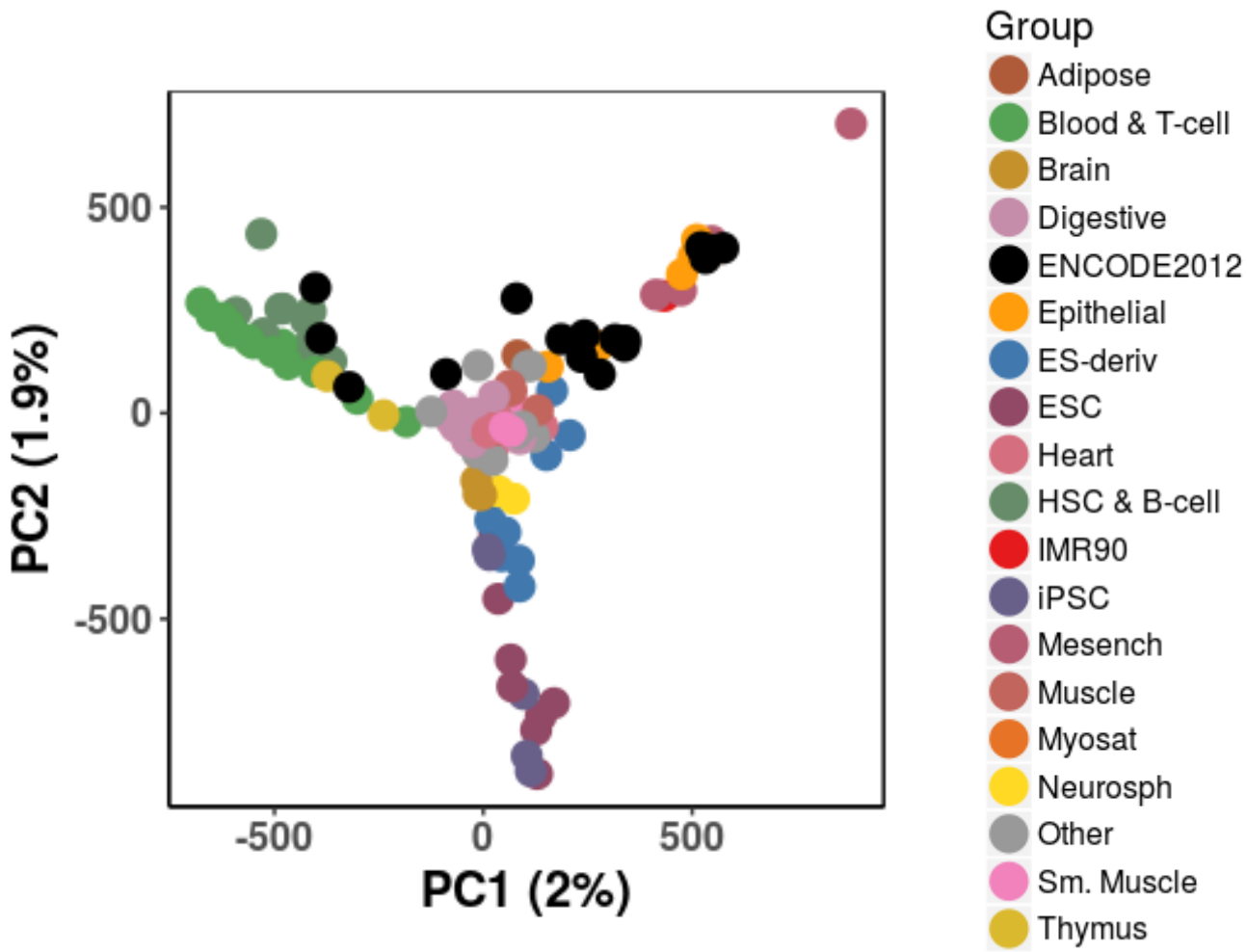
TE activity is cell type-specific



Enhancer activity differs by sample type



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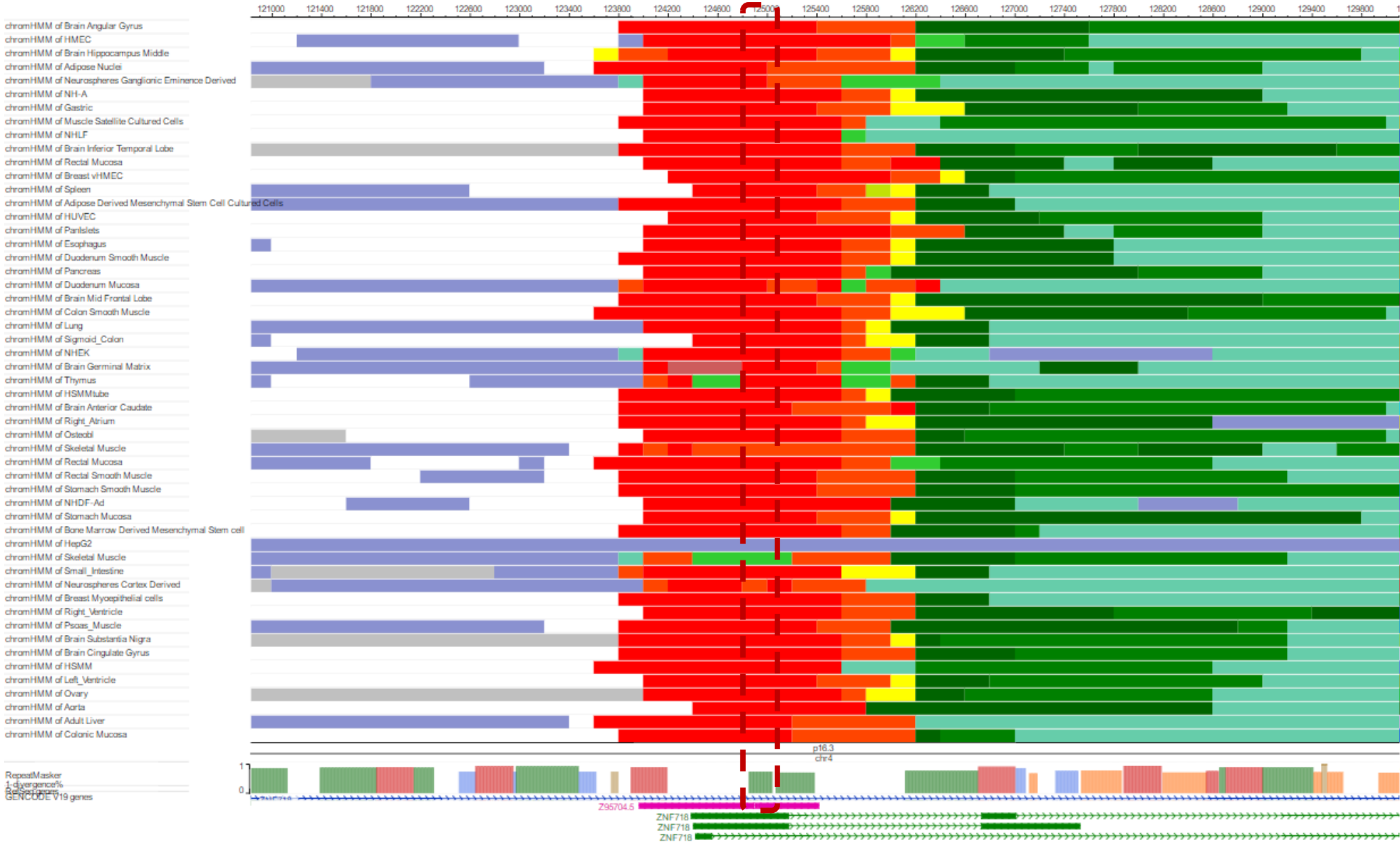
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chromHMM of Brain Angular Gyrus
chromHMM of HMEC
chromHMM of Brain Hippocampus Middle
chromHMM of Adipose Nuclei
chromHMM of Neurospheres Ganglionic Eminence Derived
chromHMM of NH-A
chromHMM of Gastric
chromHMM of Muscle Satellite Cultured Cells
chromHMM of NHLF
chromHMM of Brain Inferior Temporal Lobe
chromHMM of Rectal Mucosa
chromHMM of Breast vHMEC
chromHMM of Spleen
chromHMM of Adipose Derived Mesenchymal Stem Cell Cultured Cells
chromHMM of HUVEC
chromHMM of Panlslets
chromHMM of Esophagus
chromHMM of Duodenum Smooth Muscle
chromHMM of Pancreas
chromHMM of Duodenum Mucosa
chromHMM of Brain Mid Frontal Lobe
chromHMM of Colon Smooth Muscle
chromHMM of Lung
chromHMM of Sigmoid_Colon
chromHMM of NHEK
chromHMM of Brain Germinal Matrix
chromHMM of Thymus
chromHMM of HSMMtube
chromHMM of Brain Anterior Caudate
chromHMM of Right_Atrium
chromHMM of Osteobl
chromHMM of Skeletal Muscle
chromHMM of Rectal Mucosa
chromHMM of Rectal Smooth Muscle
chromHMM of Stomach Smooth Muscle
chromHMM of NHDF-Ad
chromHMM of Stomach Mucosa
chromHMM of Bone Marrow Derived Mesenchymal Stem cell
chromHMM of HepG2
chromHMM of Skeletal Muscle
chromHMM of Small_Intestine
chromHMM of Neurospheres Cortex Derived
chromHMM of Breast Myoepithelial cells
chromHMM of Right_Ventricle
chromHMM of Psoas_Muscle
chromHMM of Brain Substantia Nigra
chromHMM of Brain Cingulate Gyrus
chromHMM of HSMM
chromHMM of Left_Ventricle
chromHMM of Ovary
chromHMM of Aorta
chromHMM of Adult Liver
chromHMM of Colonic Mucosa
p16.3
chr4
RepeatMasker
1-divergence%
GENCODE V19 genes
Z95704.5
ZNF718
ZNF718
ZNF718

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