Occupancy patterns of 208 DNA-associated proteins in a single human cell type

Eric Mendenhall
HudsonAlpha/UAH
ENCODE Consortium Call
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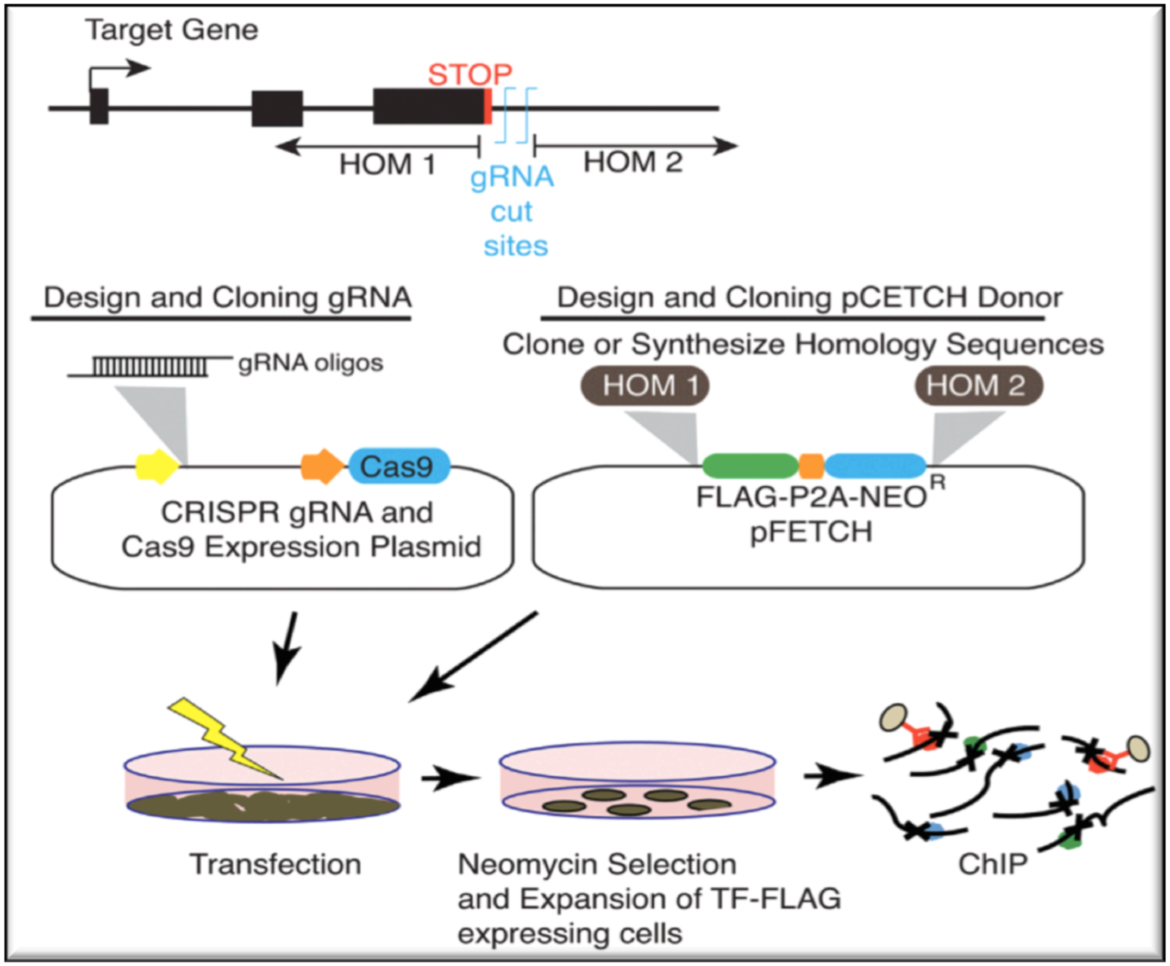
Goals of HudsonAlpha Group in ENCODE3/4

ChIP of DNA Associated Proteins (DAPs)

- -Transcription Factors
- -Transcriptional Co-Factors
- -Chromatin Regulators

Traditional Antibody based methods started showing diminishing returns

Developed CETCh-seq (CRISPR Epitope Tagging ChIP-seq) to tag endogenous TFs



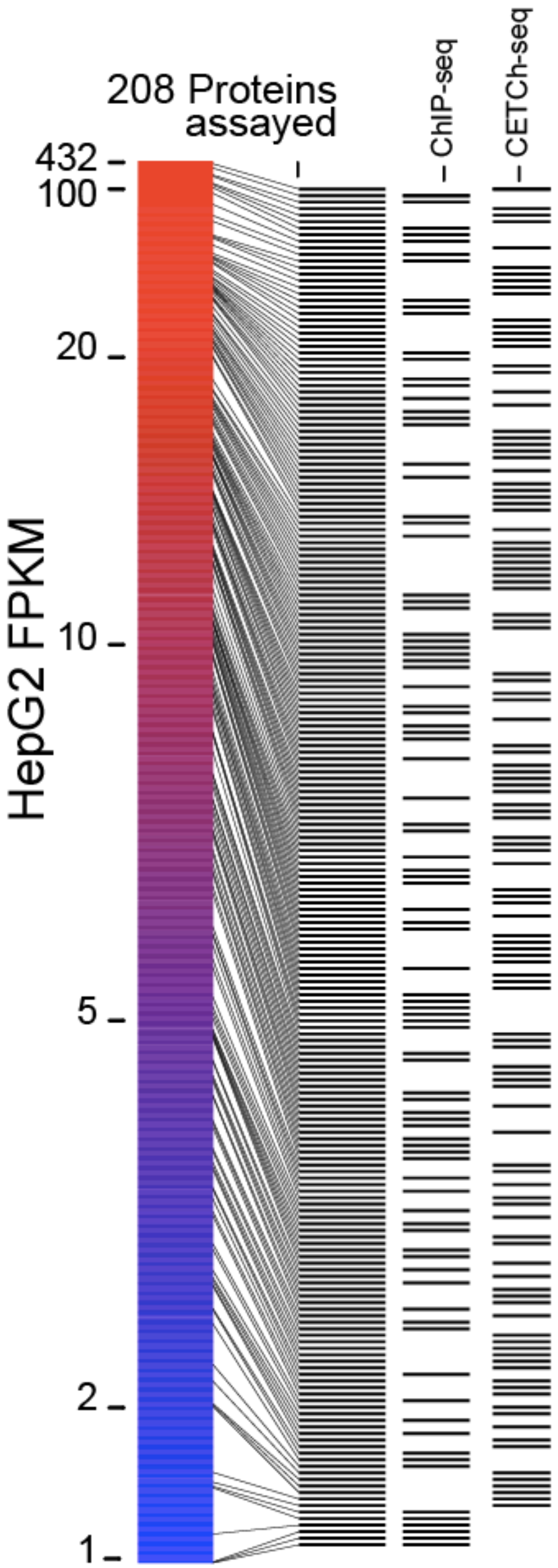
Insights from a deep dive into one cell type (HepG2)

208 ChIP-seq Maps of DAPs
    171 Sequence Specific Transcription Factors
    10 Transcriptional Co-Factors
    27 Chromatin Regulators

92 Done by Ab based ChIP-Seq
116 Done by CETCh-seq

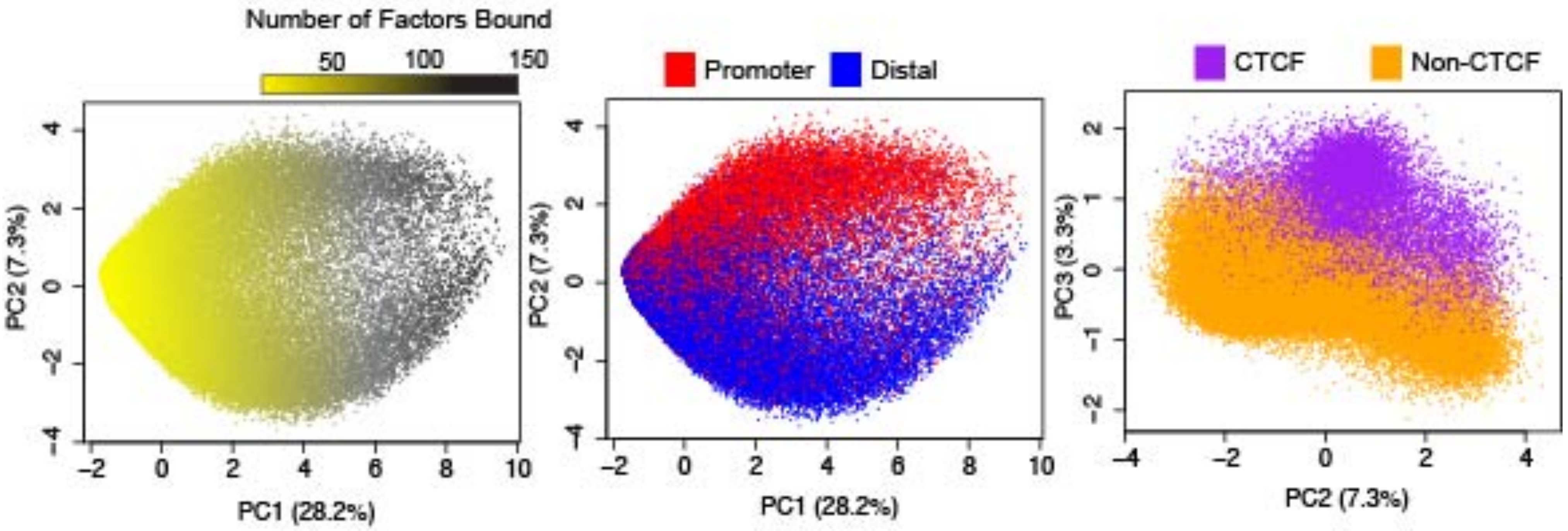
From Myers, Snyder, Bernstein, Farnham Labs

How much of the cis and trans gene regulatory network can be captured and understood in this cell type?



Global patterns of ChIP-seq peaks based on presence/ absence of bound Factors

PCA Analysis of Genomic Loci with 2-158 DAPs bound



Conclusions: The DAPs bound at an element can distinguish Promoter/Distal or CTCF bound loci

Where in the genome are individual DAPs binding?

IDEAS States

Promoter Associated
- 1 TSS
- 2 TSS F
- 3 TSS Ctcf
- 4 PromCtcf
- 5 PromF1
- 6 PromF2
- 7 TSS W
- 8 PromP

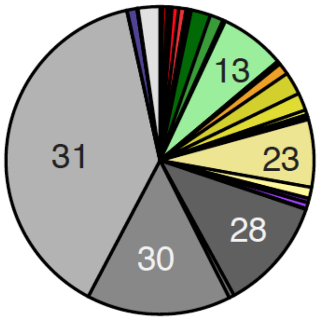
Gene Body
- 9 Pol2
- 10 Gen5
- 11 Gen3
- 12 Gen3Ctcf
- 13 Elon
- 14 Elon W

Enhancer Associated
- 15 Enh
- 16 Enh F
- 17 Enh WF1
- 18 Enh WF2
- 19 Enh WF3
- 20 Enh W

Euchromatin
- 21 DNase D1
- 22 DNase D2
- 23 FAIRE W1
- 24 FAIRE W2

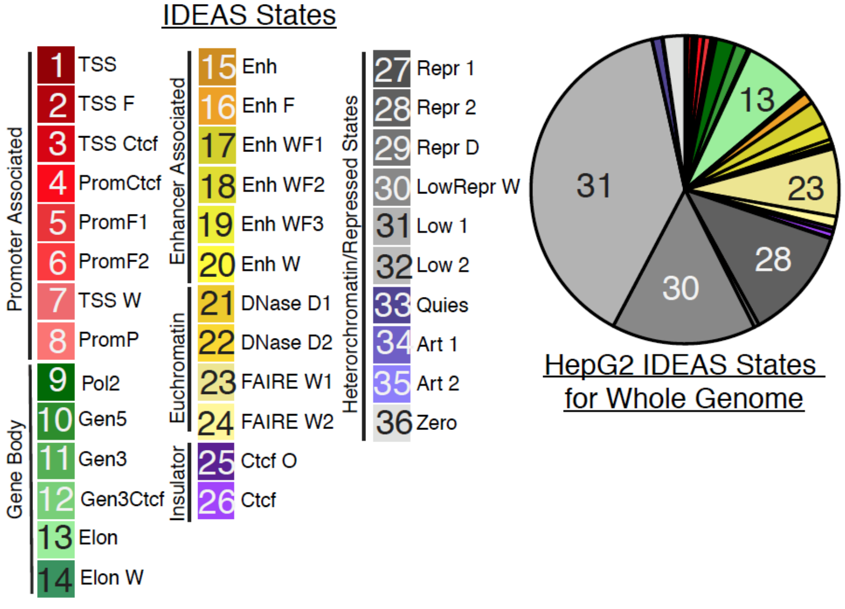
Insulator
- 25 Ctcf O
- 26 Ctcf

Heterorchromatin/Repressed States
- 27 Repr 1
- 28 Repr 2
- 29 Repr D
- 30 LowRepr W
- 31 Low 1
- 32 Low 2
- 33 Quies
- 34 Art 1
- 35 Art 2
- 36 Zero

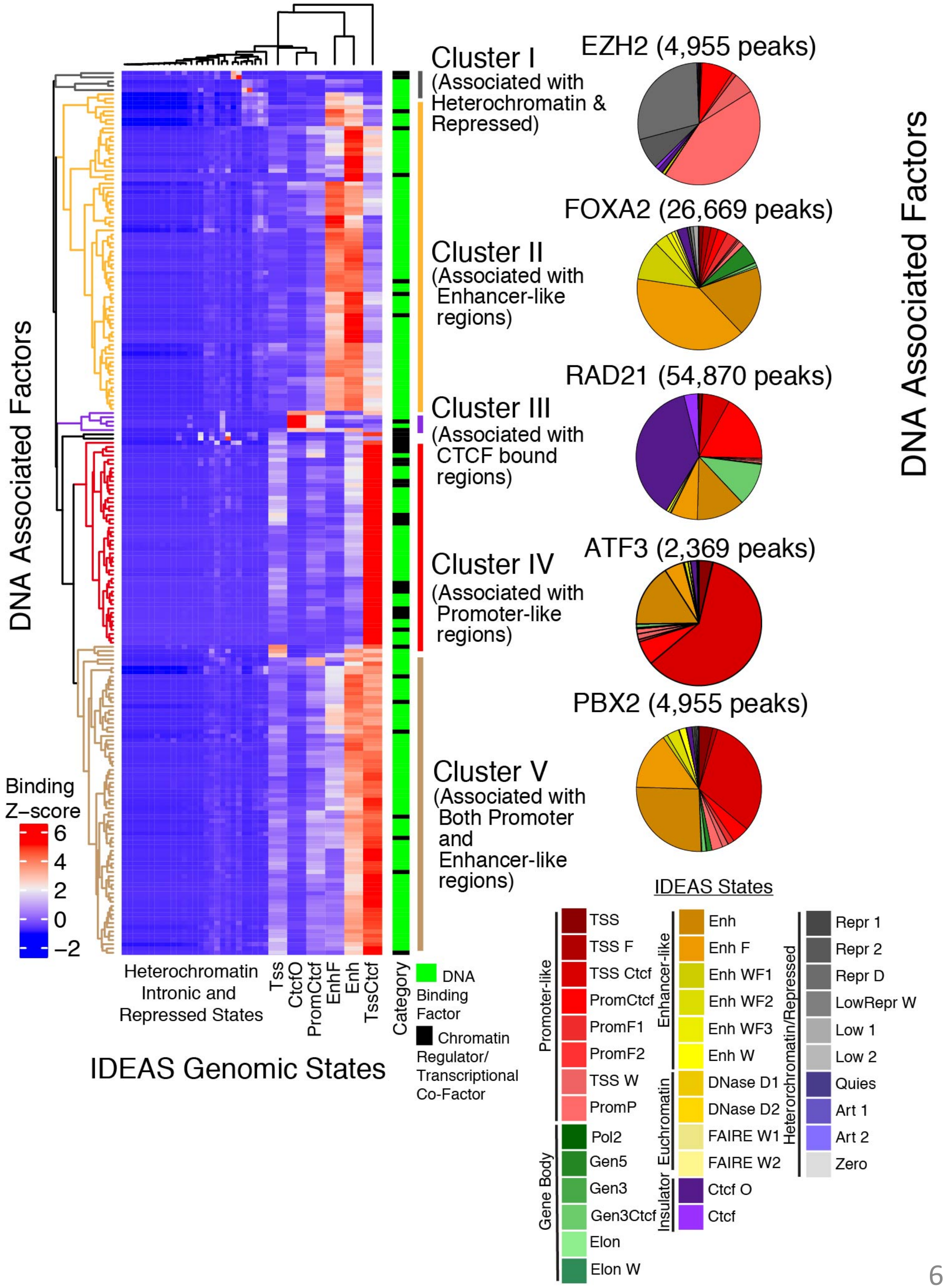


HepG2 IDEAS States for Whole Genome

Where in the genome are individual DAPs binding?



HepG2 IDEAS States for Whole Genome

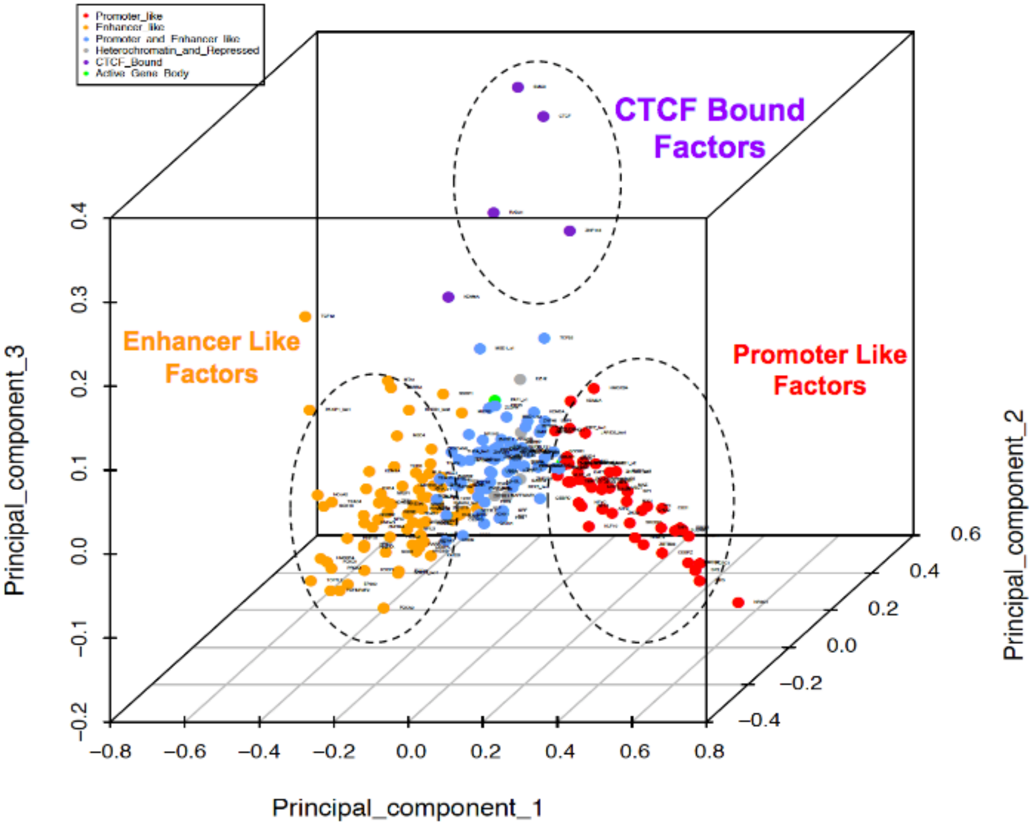


DAPs cluster into three major groups:

1. Enhancer Enriched
2. Promoter Enriched
3. Both

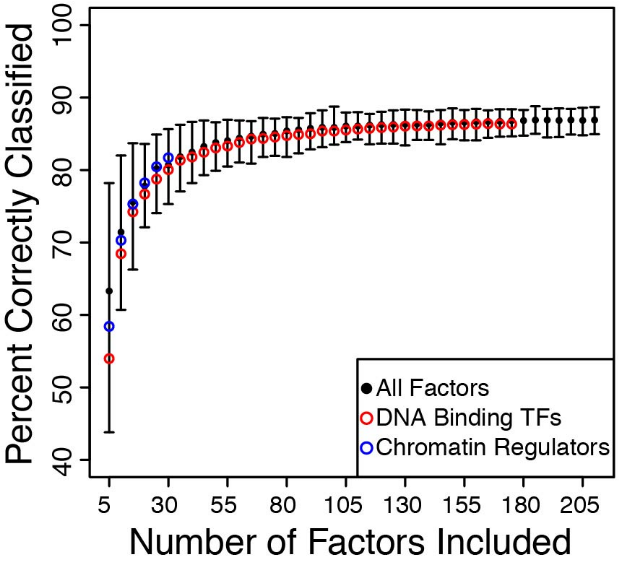
Similar results found with PCA of Factors based on IDEAS state binding profiles

- 🟥 Promoter_like
- 🟧 Enhancer_like
- 🟦 Promoter_and_Enhancer_like
- ⬜ Heterochromatin_and_Repressed
- 🟪 CTCF_Bound
- 🟩 Active_Gene_Body

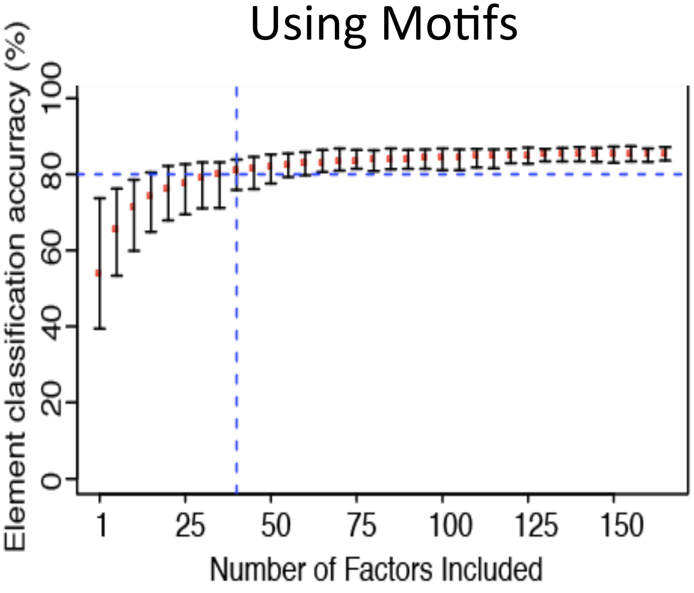


This skewed association with epigenomic states allows prediction of Promoters with TF binding information

Using bound factors



Using Motifs

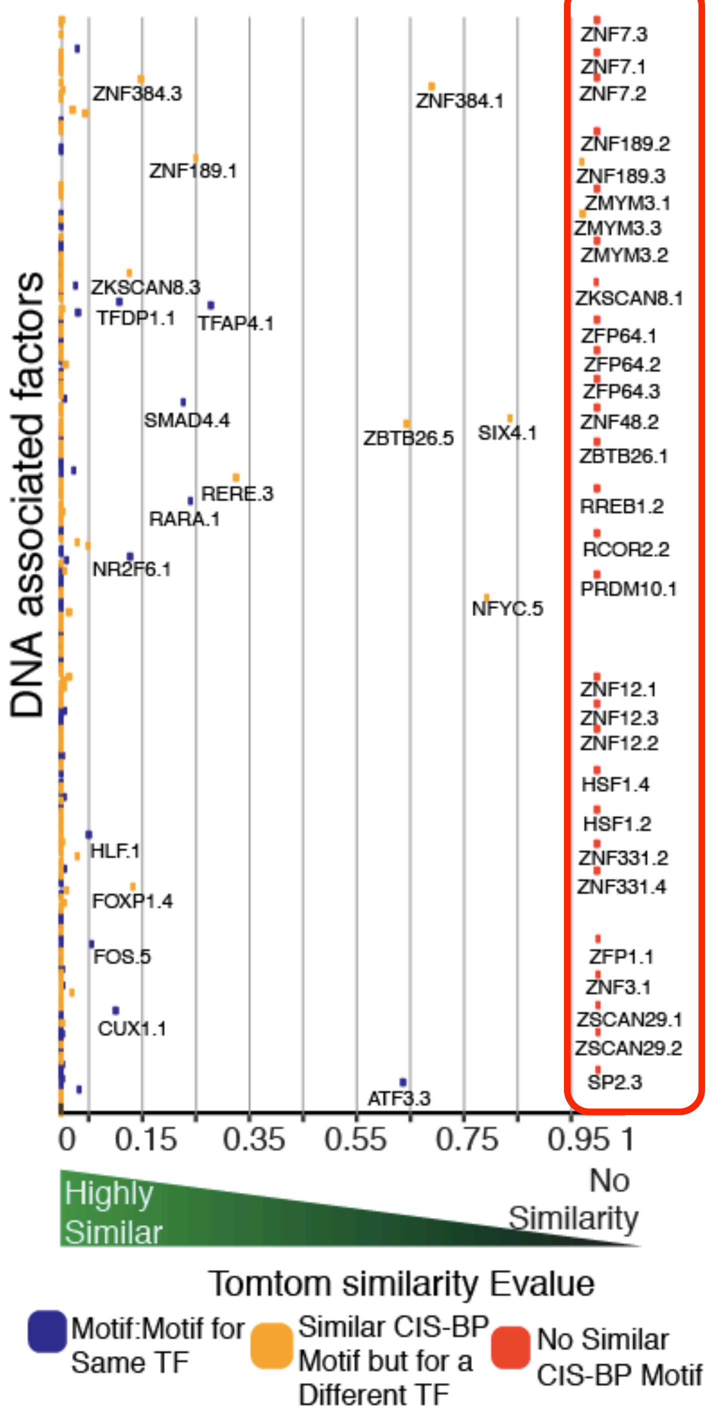


Motif Calling and Comparison to ID Putative Novel Motifs

ChIP-seq maps produced 293 High Confidence motifs for 160 TFs

Compared these 293 motifs to 733 Cis-BP Motifs for these 160 factors

Similarity of Called ChIP-Seq Motif to CisBP Motif Catalogue



Putative Novel Motifs

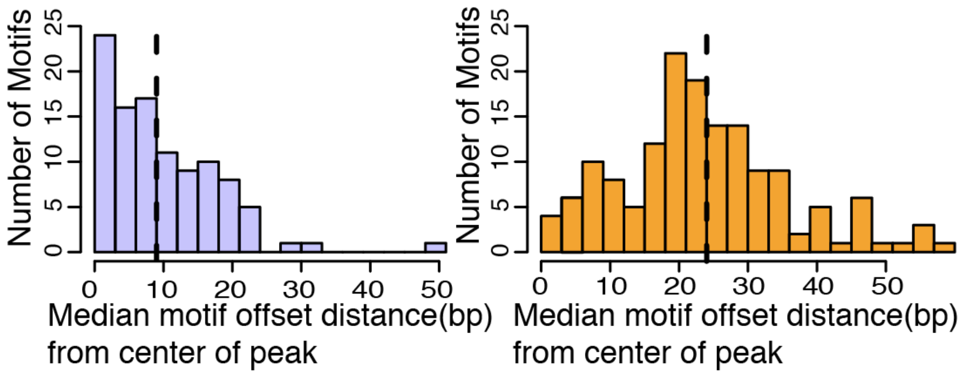
Motifs for a Different TF called in ChIP-seq Datasets

● **Concordant**

TF1 $\xrightarrow[\text{call}]{\text{Motif}}$ TF1

● **Discordant**

TF1 $\xrightarrow[\text{call}]{\text{Motif}}$ TF2



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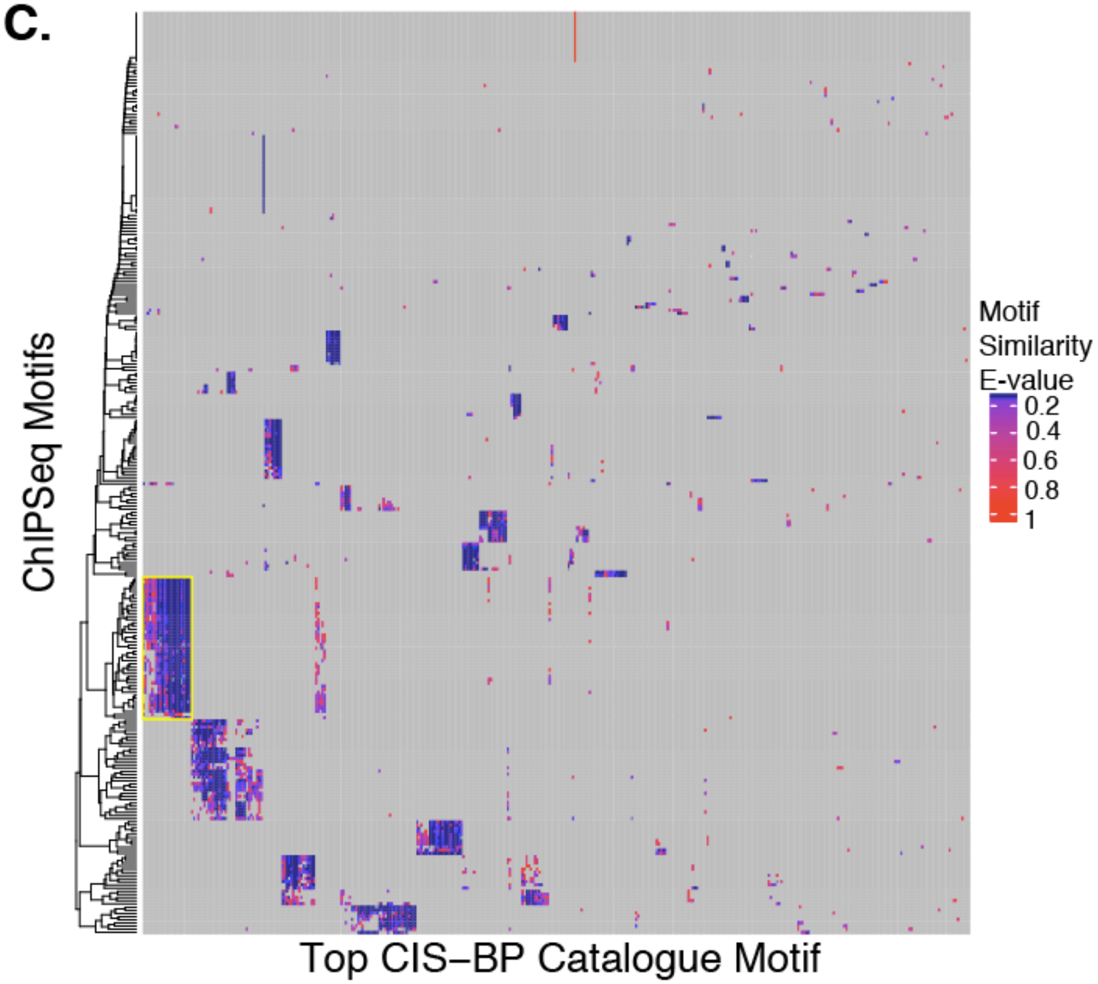
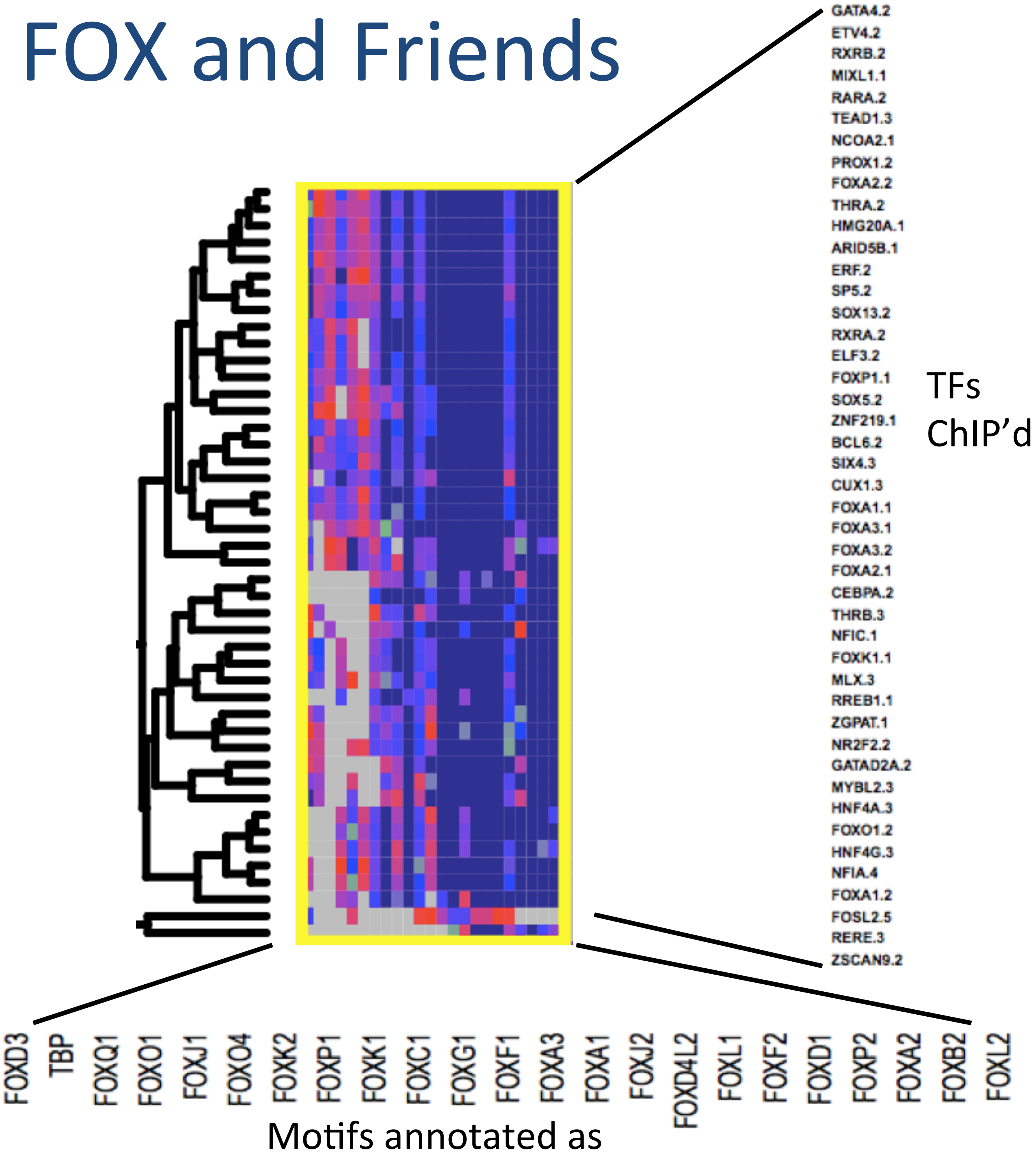


Numerous ChIP-seq maps call motif for a limited set of secondary co-localized factors, using this big dataset we can see patterns of motifs/factors

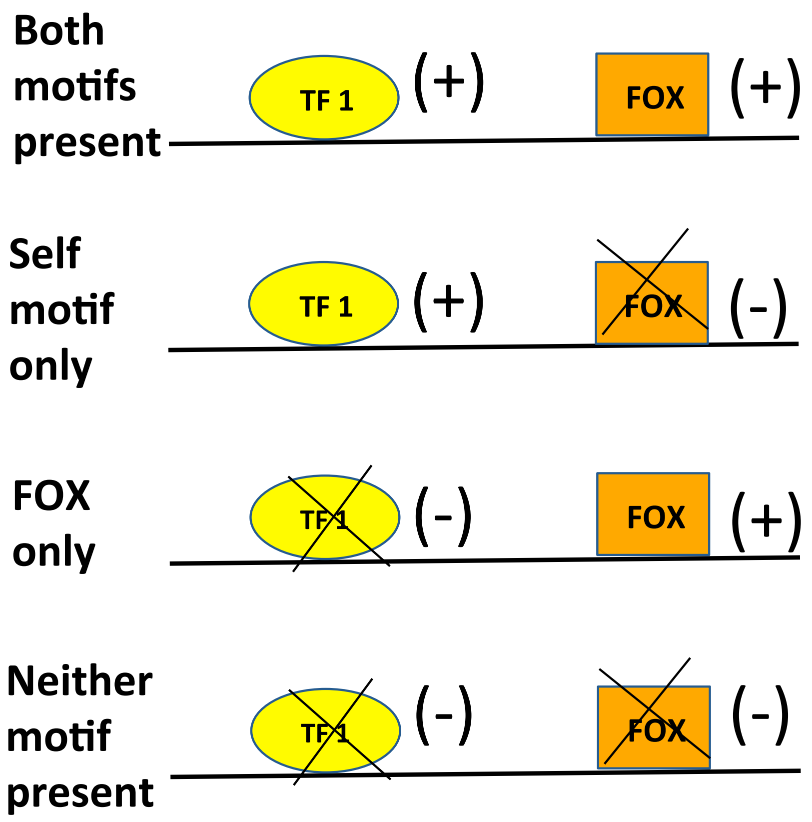
FOX and Friends

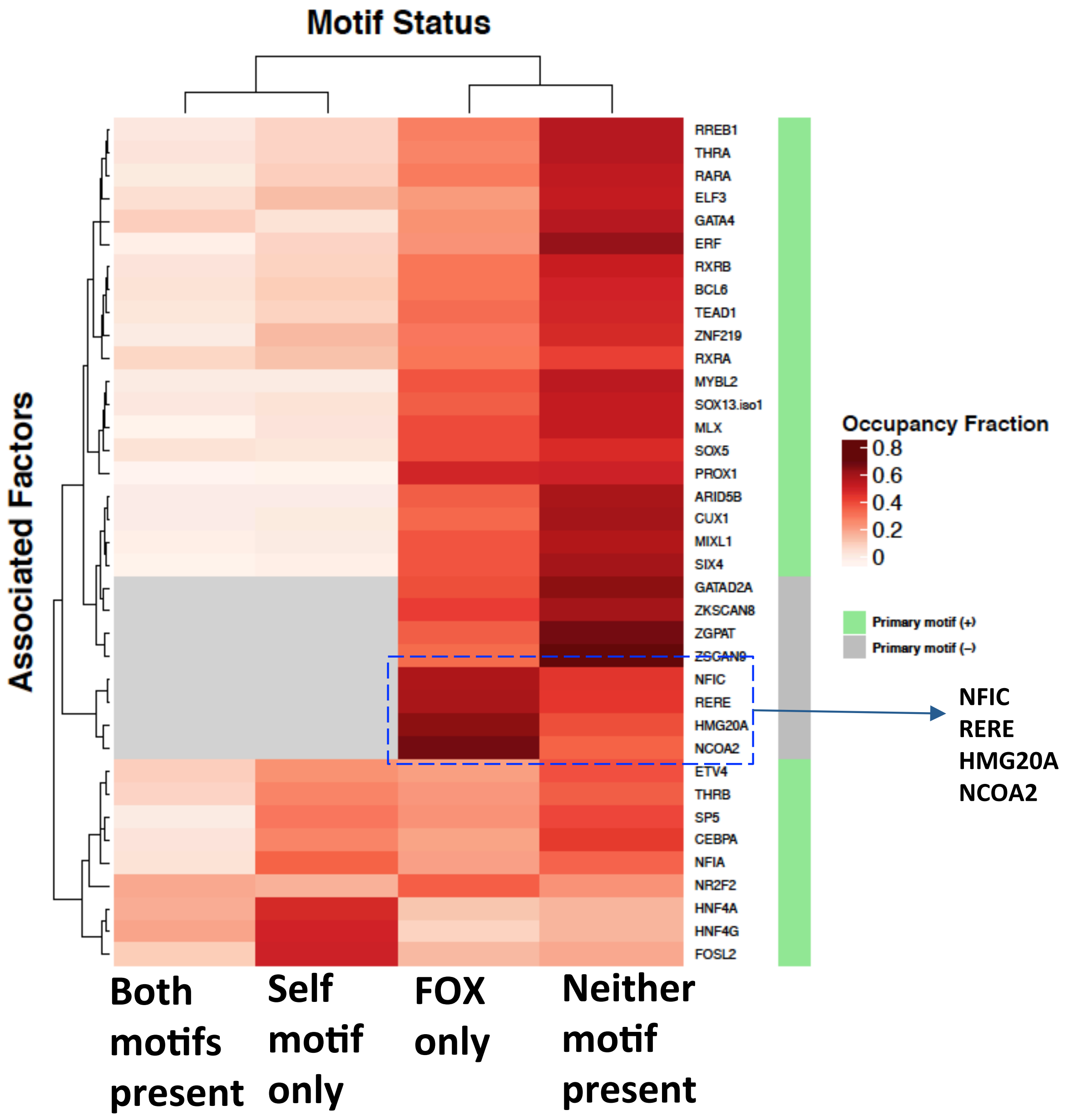


37 DAPs had a Forkhead motif called as significant from their ChIP-seq data.

Do these factors binding depend on FOX factors for “anchoring”?

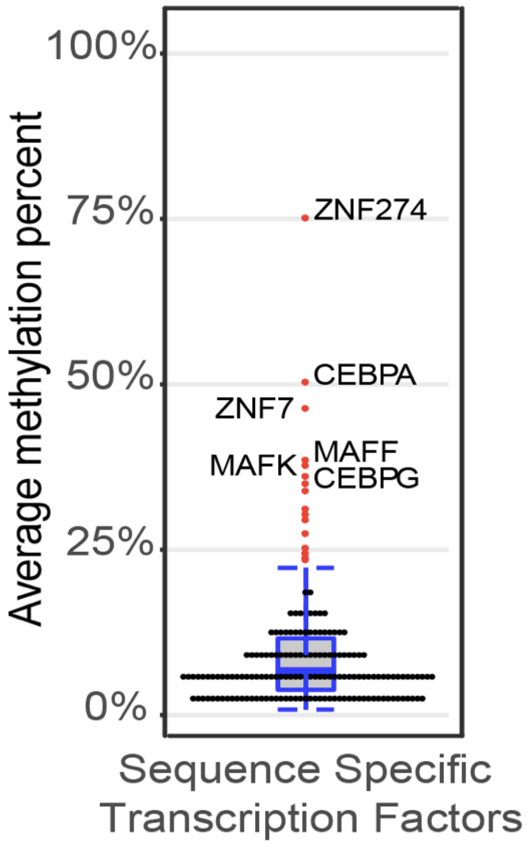
Motif status at All Peaks of Friends of FOX





Most of the “FOX partner” factors’ loci doesn’t contain a primary motif, highlighting potential protein:protein interactions or looping events in these peaks.

CEBPA Motif and Co-occupancy different at Methylated vs. Unmethylated loci



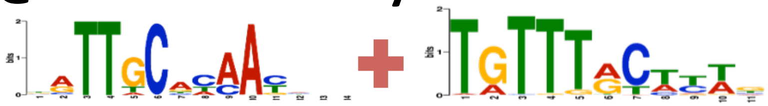
Most of the TF binding occurs on unmethylated DNA; however, a subset of TFs recognize both methylated and unmethylated DNA Sequence motifs

CEBPA

@ High DNA Methylation

CEBPA motif

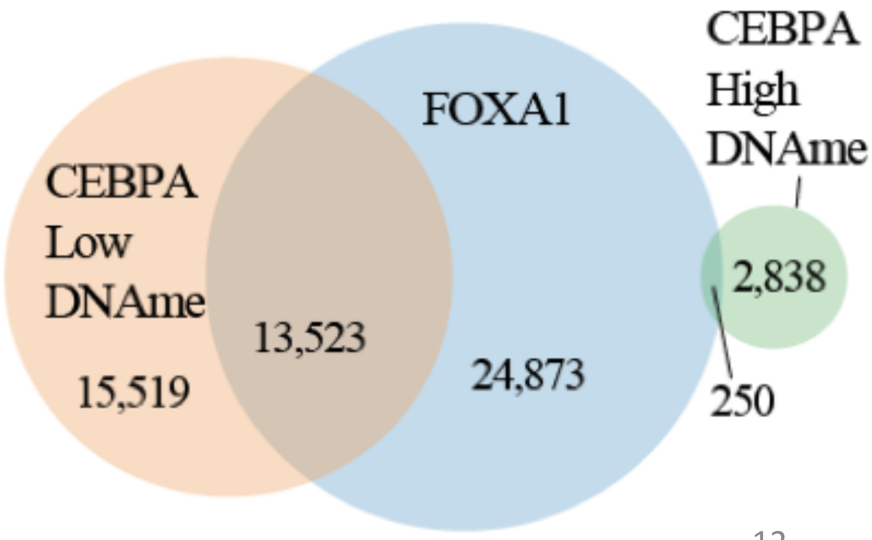
@ Low DNA methylation



CEBPA motif

FOXA1 motif

Overlap b/w FOXA1 and CEBPA ChIP-seq peaks



Summary

1. Over half of DNA associated proteins show predominant binding to Promoters or Enhancers

2. Novel and Indirect Motifs identified from ChIP-seq data

3. Integrated analysis with DNA Methylation datasets highlights potential mechanistic insights of TF:DNAme binding

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