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Dual DNA and Protein Tagging of Open Chromatin Unveils Dynamics of Epigenomic Landscapes in Leukemia

Citation

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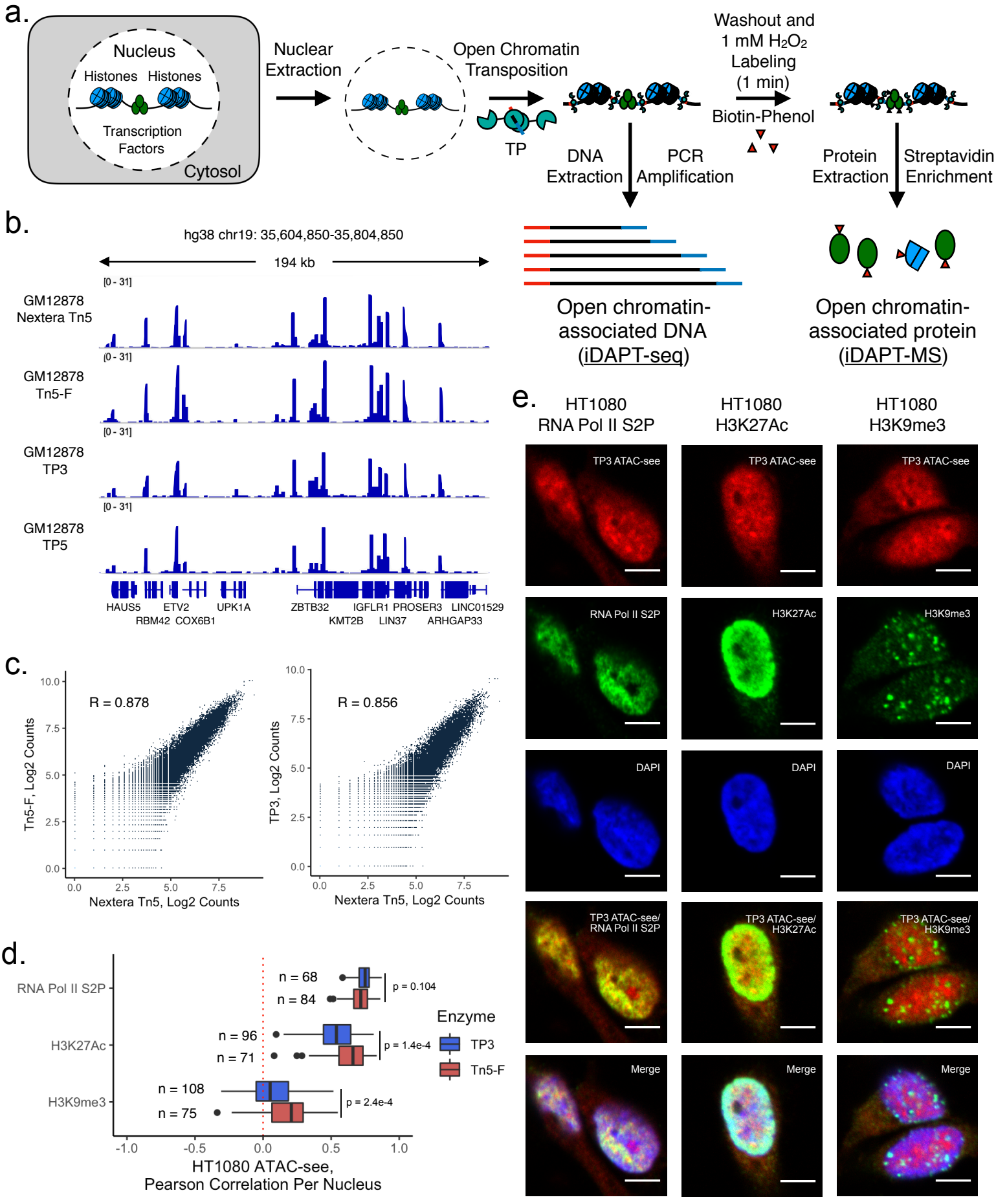
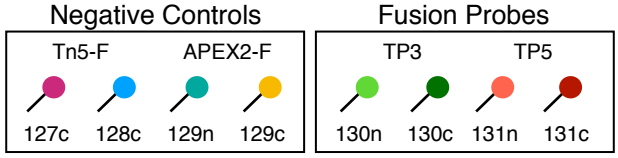
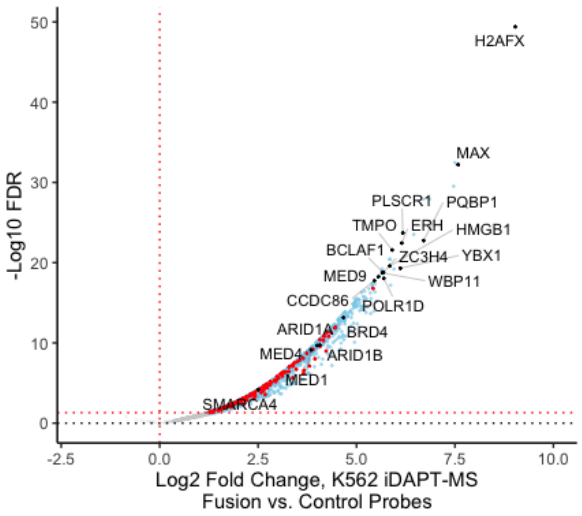

a.
Nucleus
Histones Histones
Transcription Factors
Cytosol
Nuclear Extraction
Open Chromatin Transposition
TP
Washout and 1 mM H2O2 Labeling (1 min)
Biotin-Phenol
DNA Extraction
PCR Amplification
Protein Extraction
Streptavidin Enrichment
Open chromatin-associated DNA (iDAPT-seq)
Open chromatin-associated protein (iDAPT-MS)
b.
hg38 chr19: 35,604,850-35,804,850
194 kb
GM12878 Nextera Tn5
GM12878 Tn5-F
GM12878 TP3
GM12878 TP5
[0 - 31]
HAUS5 ETV2 UPK1A RBM42 COX6B1
ZBTB32 IGFLR1 PROSER3 LINC01529 KMT2B LIN37 ARHGAP33
c.
R = 0.878
R = 0.856
Tn5-F, Log2 Counts
TP3, Log2 Counts
Nextera Tn5, Log2 Counts
d.
RNA Pol II S2P
H3K27Ac
H3K9me3
n = 68
n = 84
p = 0.104
n = 96
n = 71
p = 1.4e-4
n = 108
n = 75
p = 2.4e-4
Enzyme
TP3
Tn5-F
HT1080 ATAC-see, Pearson Correlation Per Nucleus
e.
HT1080 RNA Pol II S2P
HT1080 H3K27Ac
HT1080 H3K9me3
TP3 ATAC-see
RNA Pol II S2P
H3K27Ac
H3K9me3
DAPI
TP3 ATAC-see/ RNA Pol II S2P
TP3 ATAC-see/ H3K27Ac
TP3 ATAC-see/ H3K9me3
Merge

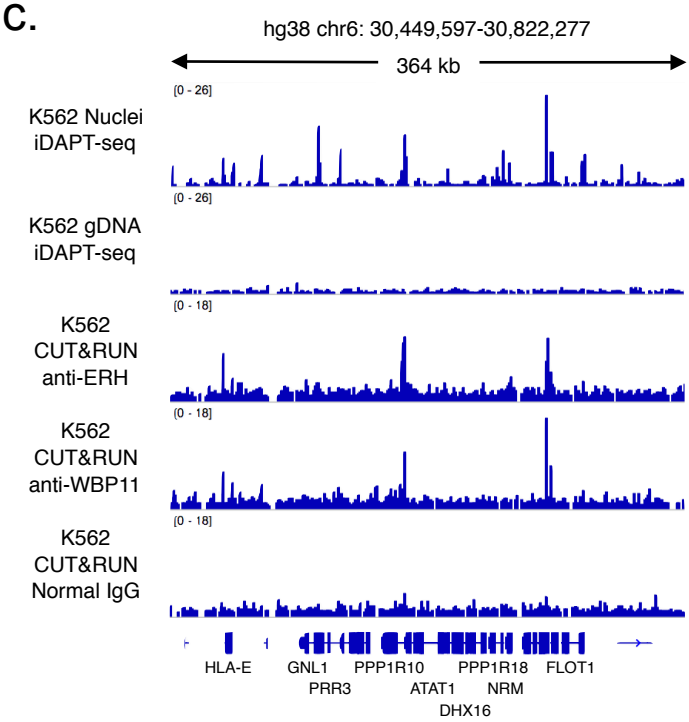
a.


Negative Controls
Tn5-F
APEX2-F
127c
128c
129n
129c
Fusion Probes
TP3
TP5
130n
130c
131n
131c

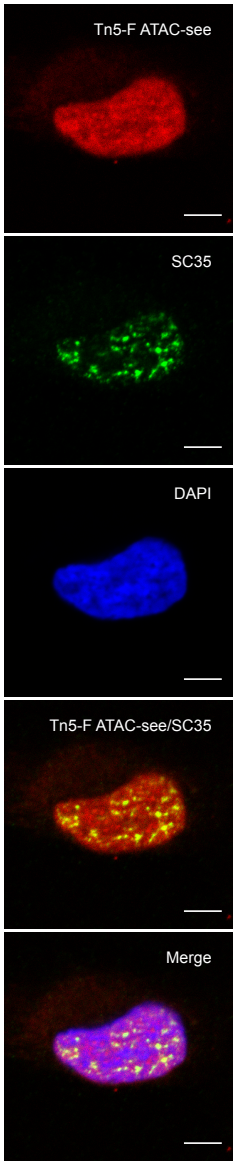
b.


H2AFX
MAX
PLSCR1
PQBP1
TMPO
ERH
HMGB1
BCLAF1
ZC3H4
YBX1
MED9
WBP11
CCDC86
POLR1D
ARID1A
BRD4
MED4
ARID1B
MED1
SMARCA4
-Log10 FDR
Log2 Fold Change, K562 iDAPT-MS
Fusion vs. Control Probes

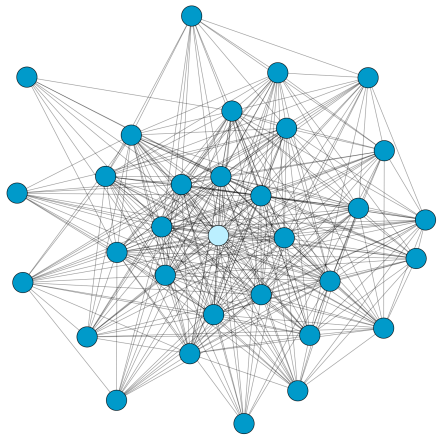
c.


hg38 chr6: 30,449,597-30,822,277
364 kb
K562 Nuclei iDAPT-seq
K562 gDNA iDAPT-seq
K562 CUT&RUN anti-ERH
K562 CUT&RUN anti-WBP11
K562 CUT&RUN Normal IgG
HLA-E
GNL1
PPP1R10
PPP1R18
FLOT1
PRR3
ATAT1
NRM
DHX16

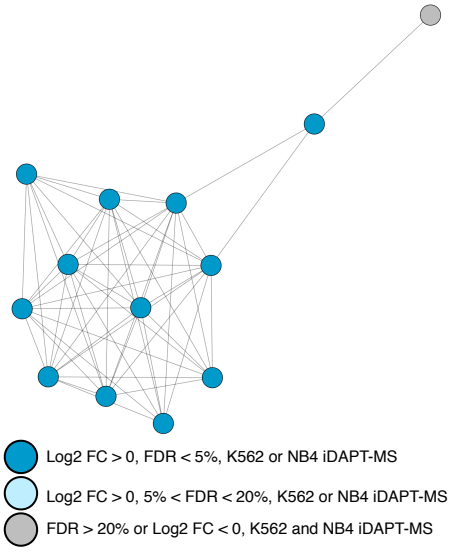
d.


HT1080
SC35
Tn5-F ATAC-see
SC35
DAPI
Tn5-F ATAC-see/SC35
Merge

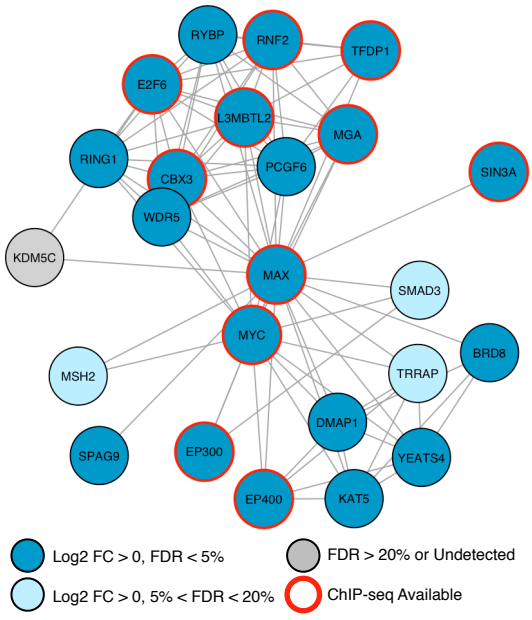
e.


Mediator complex (CORUM, 32 Proteins)
K562: NES = 1.681, p-value = 0.0055
NB4: NES = 1.763, p-value = 0.0020

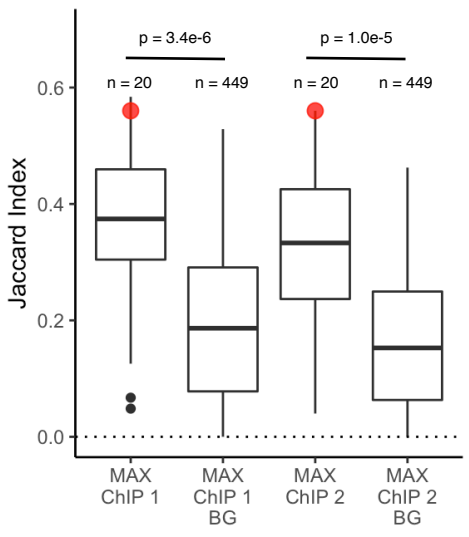
f.


BAF complex (CORUM, 13 Proteins)
K562: NES = 1.717, p-value = 0.0072
NB4: NES = 1.725 p-value = 0.0081
Log2 FC > 0, FDR < 5%, K562 or NB4 iDAPT-MS
Log2 FC > 0, 5% < FDR < 20%, K562 or NB4 iDAPT-MS
FDR > 20% or Log2 FC < 0, K562 and NB4 iDAPT-MS

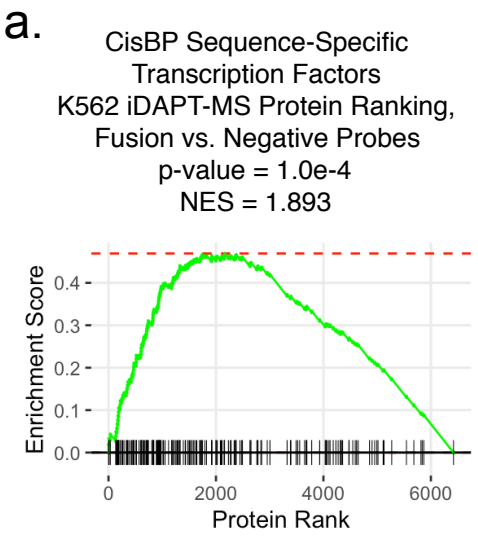
g.


MAX Network (BioGrid)
K562 NES = 1.617, p-value = 0.0130
RYBP
RNF2
TFDP1
E2F6
L3MBTL2
MGA
RING1
CBX3
PCGF6
SIN3A
WDR5
KDM5C
MAX
SMAD3
MYC
BRD8
MSH2
TRRAP
DMAP1
SPAG9
EP300
YEATS4
EP400
KAT5
Log2 FC > 0, FDR < 5%
FDR > 20% or Undetected
Log2 FC > 0, 5% < FDR < 20%
ChIP-seq Available

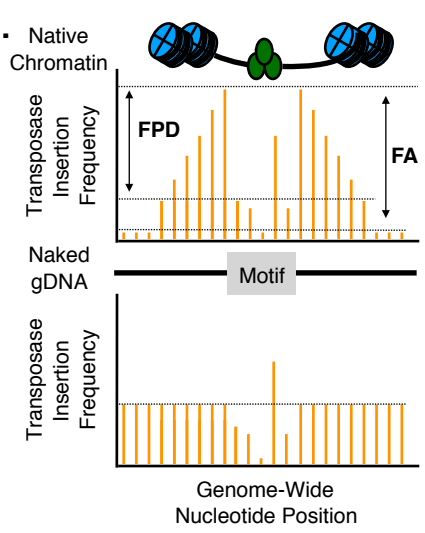
h.


p = 3.4e-6
p = 1.0e-5
n = 20
n = 449
n = 20
n = 449
Jaccard Index
MAX ChIP 1
MAX ChIP 1 BG
MAX ChIP 2
MAX ChIP 2 BG

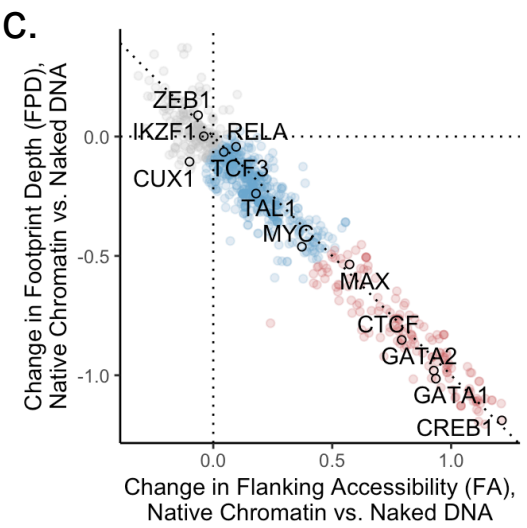
a.



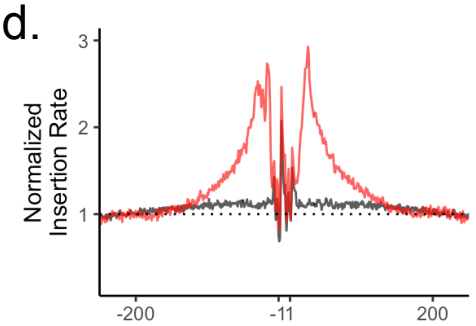
b.



c.

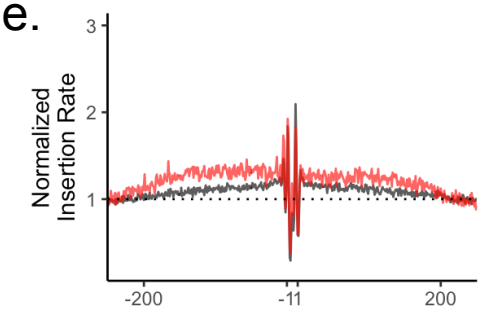


d.



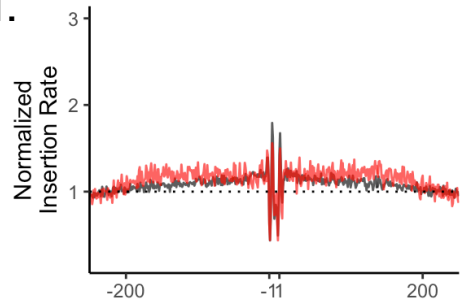
iDAPT-MS: LFC = 4.07, FDR = 4.1e-11
ChIP-seq (ENCFF519CXF): NES = 3.28, p = 1e-4, 25,977 peaks
ChIP-seq (ENCFF843VHC): NES = 3.32, p = 1e-4, 25,271 peaks
ChIP-seq (ENCFF396BZQ): NES = 3.36, p = 1e-4, 29,858 peaks
ChIP-seq (ENCFF119XFJ): NES = 3.35, p = 1e-4, 28,054 peaks

e.



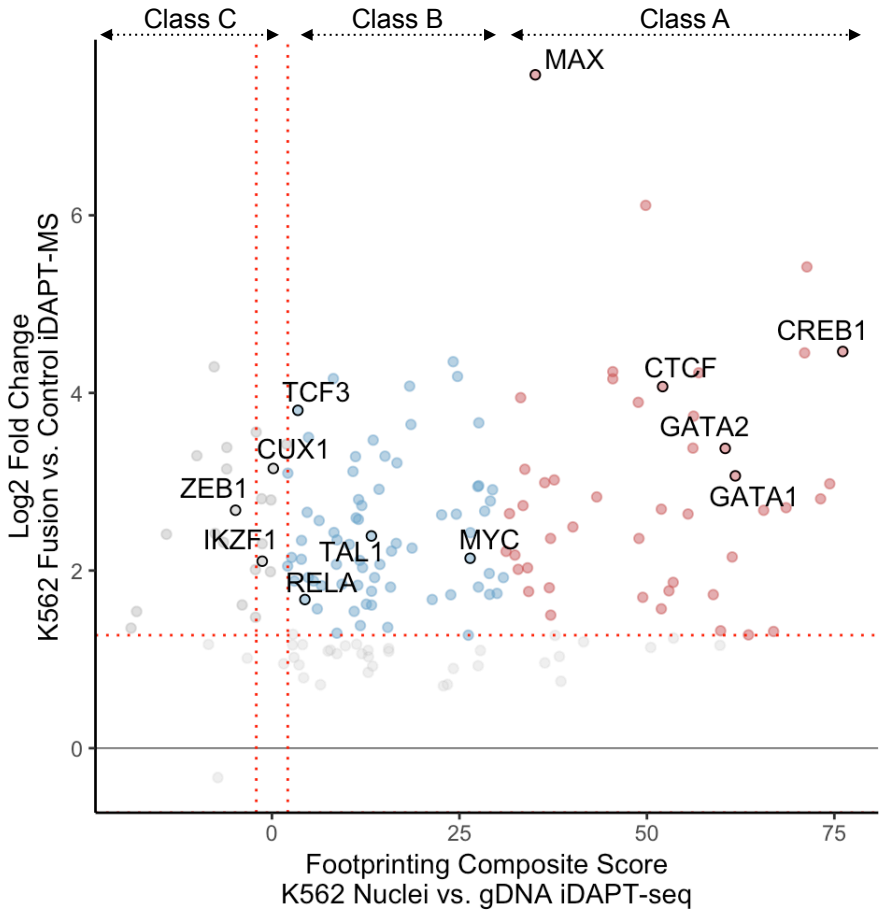
iDAPT-MS: LFC = 1.67, FDR = 0.011
ChIP-seq (ENCFF931SVP): NES = 3.61, p = 1e-4, 6,465 peaks

f.



iDAPT-MS: LFC = 2.11, FDR = 9.1e-4
ChIP-seq (ENCFF9940QH): NES = 3.63, p = 1e-4, 28,290 peaks
ChIP-seq (ENCFF785BTP): NES = 3.71, p = 1e-4, 28,233 peaks

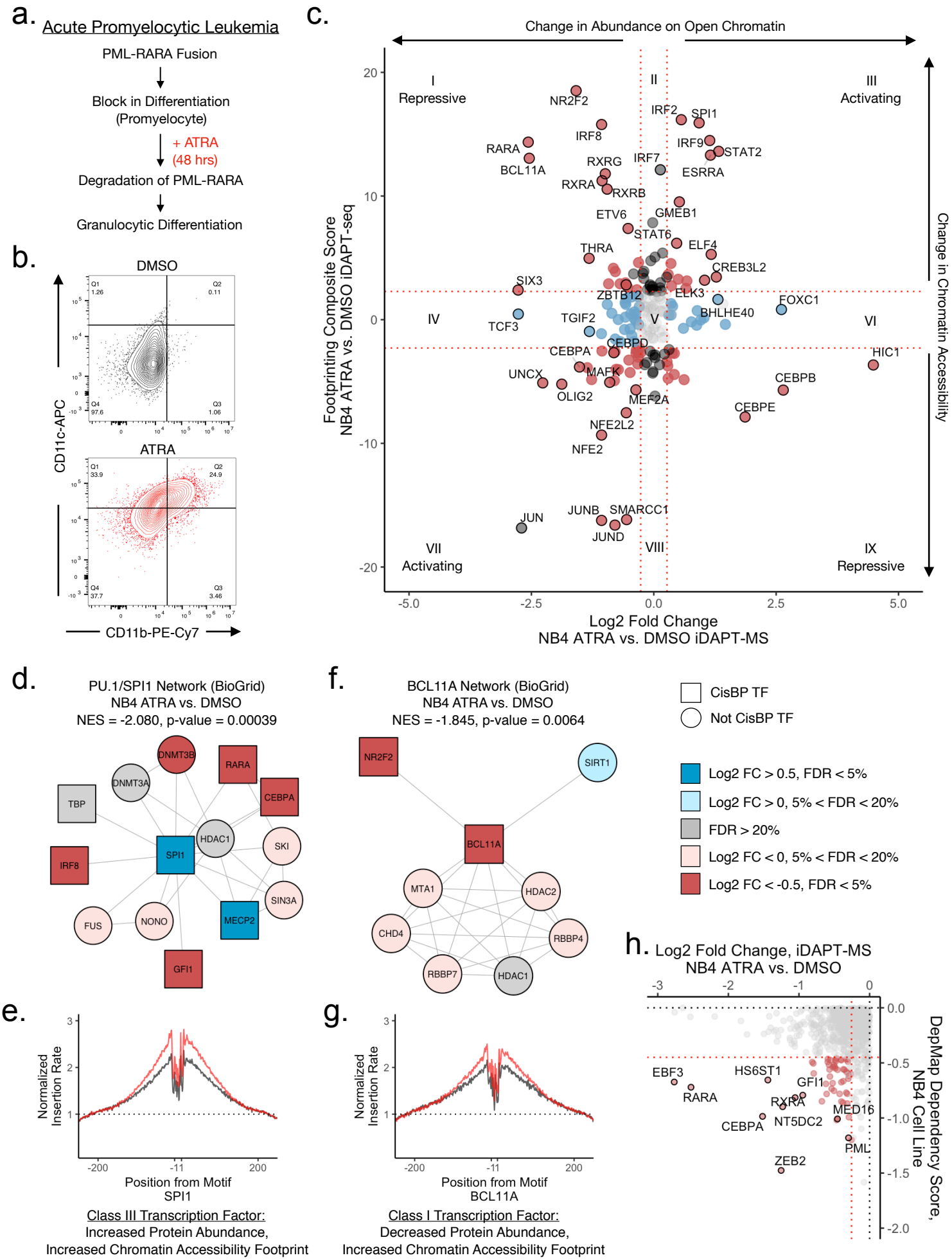
g.



h.

K562 CisBP Transcription Factors

	iDAPT-seq	iDAPT-MS	ChIP-seq (ENCODE)
Strong Footprinting (Class A)	145	45	58
Weak Footprinting (Class B)	444	70	65
No/Negative Footprinting (Class C)	175	21	11
Total	764	136	134


a.
Acute Promyelocytic Leukemia
PML-RARA Fusion
Block in Differentiation (Promyelocyte)
+ ATRA (48 hrs)
Degradation of PML-RARA
Granulocytic Differentiation
b.
DMSO
ATRA
CD11c-APC
CD11b-PE-Cy7
c.
Change in Abundance on Open Chromatin
Change in Chromatin Accessibility
Footprinting Composite Score NB4 ATRA vs. DMSO iDAPT-seq
Log2 Fold Change NB4 ATRA vs. DMSO iDAPT-MS
I Repressive
II
III Activating
IV
V
VI
VII Activating
VIII
IX Repressive
NR2F2
IRF2
SPI1
IRF8
IRF9
STAT2
RARA
BCL11A
IRF7
ESRRA
RXRG
RXRA
RXRB
ETV6
GMEB1
STAT6
ELF4
THRA
CREB3L2
SIX3
ZBTB12
ELK3
FOXC1
TCF3
TGIF2
BHLHE40
CEBPD
CEBPA
HIC1
UNCX
MAFK
CEBPB
OLIG2
MEF2A
CEBPE
NFE2L2
NFE2
JUN
JUNB
SMARCC1
JUND
d.
PU.1/SPI1 Network (BioGrid)
NB4 ATRA vs. DMSO
NES = -2.080, p-value = 0.00039
DNMT3B
RARA
DNMT3A
CEBPA
TBP
HDAC1
SKI
SPI1
IRF8
SIN3A
FUS
NONO
MECP2
GFI1
f.
BCL11A Network (BioGrid)
NB4 ATRA vs. DMSO
NES = -1.845, p-value = 0.0064
NR2F2
SIRT1
BCL11A
MTA1
HDAC2
CHD4
RBBP4
RBBP7
HDAC1
CisBP TF
Not CisBP TF
Log2 FC > 0.5, FDR < 5%
Log2 FC > 0, 5% < FDR < 20%
FDR > 20%
Log2 FC < 0, 5% < FDR < 20%
Log2 FC < -0.5, FDR < 5%
e.
Normalized Insertion Rate
Position from Motif SPI1
Class III Transcription Factor:
Increased Protein Abundance,
Increased Chromatin Accessibility Footprint
g.
Normalized Insertion Rate
Position from Motif BCL11A
Class I Transcription Factor:
Decreased Protein Abundance,
Increased Chromatin Accessibility Footprint
h.
Log2 Fold Change, iDAPT-MS
NB4 ATRA vs. DMSO
DepMap Dependency Score, NB4 Cell Line
EBF3
HS6ST1
GFI1
RARA
RXRA
MED16
CEBPA
NT5DC2
PML
ZEB2