

Regulator	Motif analysis	Regulator	Motif analysis	Regulator	Motif analysis
ATF3	1	HDAC8	0	SETDB1	0
BATF	0	HMG3	0	SIN3A	0
BCL11A	0	HNF4A	1	SIRT6	0
BCL3	0	HNF4G	1	SIX5	1
BCLAF1	0	HSF1	1	SMARCA4	0
BDP1	0	IRF1	1	SMARCB1	0
BHLHE40	1	IRF3	1	SMARCC1	0
BRCA1	1	IRF4	1	SMARCC2	0
BRF1	0	JUN	1	SMC3	0
BRF2	0	JUNB	1	SP1	1
CCNT2	0	JUND	1	SP2	0
CEBPB	1	MAFF	1	SPI1	0
CHD2	0	MAFK	1	SREBF1	1
CTBP2	0	MAX	1	SRF	1
CTCF	1	MEF2A	1	STAT1	1
CTCF1	0	MEF2C	1	STAT2	1
E2F1	1	MXI1	1	STAT3	1
E2F4	1	MYC	1	SUZ12	0
E2F6	1	NANOG	1	TAF1	1
EBF1	1	NFE2	1	TAF7	1
EGR1	1	NFKB1	1	TAL1	1
ELF1	1	NFYA	1	TBP	1
ELK4	1	NFYB	1	TCF12	1
EP300	1	NR2C2	0	TCF7L2	1
ESR1	0	NR3C1	1	TFAP2A	1
ESRRA	1	NRF1	1	TFAP2C	1
ETS1	1	PAX5	1	THAP1	0
FOS	1	PBX3	1	TRIM28	0
FOSL1	1	POLR2A	0	USF1	1
FOSL2	1	POLR3A	0	USF2	1
FOXA1	1	POLR3G	0	WRNIP1	0
FOXA2	1	POU2F2	1	YY1	1
GABPA	1	POU5F1	1	ZBTB33	1
GATA1	1	PPARGC1A	1	ZBTB7A	1
GATA2	1	PRDM1	1	ZEB1	1
GATA3	0	RAD21	0	ZNF143	1
GTF2B	1	RDBP	0	ZNF263	0
GTF2F1	1	REST	1	ZNF274	0
GTF3C2	0	RFX5	1	ZZZ3	0
HDAC2	0	RXRA	1		

Supplementary Table 1: Table of Regulators. The table lists the regulators included in the analysis in **Figure 2**, and further specifies which regulators were included in the motif analysis in **Figure 3**, denoted by 1. A regulator was included in the motif analysis if instances for a known motif were available from (Kheradpour et al, in preparation).

ATP-dependent chromatin complexes	Cyclin Kinase associated with transcription	DNA repair	general Pol II associated factor, not site-specific	histone acetylation complexes	histone deacetylation complexes
CHD2	CCNT2	RAD21	GTF2B	EP300	HDAC2
SMARCA4		SMC3	GTF2F1		HDAC8
SMARCB1		WRNIP1	RDBP		SIN3A
SMARCC1			TAF1		SIRT6
SMARCC2			TAF7		
			TBP		
histone methylation complexes	Pol II subunit	Pol II co-repressor/co-activator	Pol II TF; DNA repair	Pol III associated	
SETDB1	POLR2A	CTBP2	BRCA1	BDP1	
SUZ12		HMGN3		BRF1	
TRIM28				BRF2	
				GTF3C2	
				POLR3A	
				POLR3G	
Pol II TF					
ATF3	ETS1	HSF1	NFE2	RXRA	THAP1
BATF	E2F1	IRF1	NFKB1	SIX5	USF1
BCLAF1	E2F4	IRF3	NFYA	SPI1	USF2
BCL3	E2F6	IRF4	NFYB	SP1	YY1
BCL11A	FOS	JUN	NRF1	SP2	ZBTB7A
BHLHE40	FOSL1	JUNB	NR2C2	SREBF1	ZBTB33
CEBPB	FOSL2	JUND	NR3C1	SRF	ZEB1
CTCF	FOXA1	MAFF	PAX5	STAT1	ZNF143
CTCFL	FOXA2	MAFK	PBX3	STAT2	ZNF263
EBF1	GABPA	MAX	POU2F2	STAT3	ZNF274
EGR1	GATA1	MEF2A	POU5F1	TAL1	ZZZ3
ELF1	GATA2	MEF2C	PPARGC1A	TCF7L2	
ELK4	GATA3	MXI1	PRDM1	TCF12	
ESRRA	HNF4A	MYC	REST	TFAP2A	
ESR1	HNF4G	NANOG	RFX5	TFAP2C	

Supplementary Table 2: Annotation of Regulators. The annotation of the type of regulator as provided by (ENCODE Project Consortium, 2012)

Cluster	Interaction	Cluster	Interaction
C1	BRCA1--E2F4	C5	SMARCA4--SMARCC2
C1	BRCA1--ELK4	C5	SMARCA4--SP1
C1	BRCA1--ETS1	C5	SMARCA4--STAT1
C1	BRCA1--GTF2F1	C5	SMARCA4--STAT2
C1	E2F1--E2F4	C5	SMARCB1--SMARCC1
C1	E2F1--SP2	C5	SMARCB1--SMARCC2
C1	E2F1--TBP	C5	SMARCC1--SMARCC2
C1	E2F4--SIN3A	C5	SMARCC1--SP1
C1	GTF2B--GTF2F1	C5	SMARCC1--STAT2
C1	GTF2B--TBP	C5	SMARCC2--SP1
C1	GTF2F1--TAF1	C5	SMARCC2--STAT2
C1	GTF2F1--TBP	C5	STAT1--STAT2
C1	NR3C1--TBP	C6	EP300--GATA1
C1	SIN3A--TAF1	C6	EP300--GATA2
C1	SIN3A--TBP	C6	EP300--JUN
C1	SREBF1--YY1	C6	EP300--MEF2C
C1	TAF1--TAF7	C6	EP300--NFKB1
C1	TAF1--TBP	C6	EP300--STAT3
C1	TAF7--TBP	C6	EP300--TCF12
C2	ELF1--NFYA	C6	GATA2--JUN
C2	NFYA--NFYB	C6	HDAC2--NFKB1
C4	GTF3C2--MYC	C6	HDAC2--STAT3
C4	MAX--MYC	C6	JUN--STAT3
C4	USF1--USF2	C6	NFKB1--STAT3
C5	BCL3--CTBP2	C7	BATF--IRF4
C5	BCL3--RXRA	C7	BATF--JUNB
C5	BCL3--STAT1	C7	CEBPB--SPI1
C5	ESRRA--PPARGC1A	C7	FOS--JUND
C5	ESRRA--SP1	C7	FOSL1--JUNB
C5	PPARGC1A--RXRA	C7	FOS--SPI1
C5	RXRA--SMARCA4	C7	IRF4--SPI1
C5	RXRA--SP1	C8	RAD21--SMC3
C5	SMARCA4--SMARCB1	C9	SETDB1--TRIM28
C5	SMARCA4--SMARCC1		

Supplementary Table 3: Co-clustering Regulators Supported by Protein-Protein Interaction Data. The table lists all known protein-protein interactions involving regulators that fell into the same cluster in **Figure 1**.

(a) Forward sites peaks without motifs significantly interacting with reverse sites peaks with motifs

Experiment	Cell	Regulator
BroadHistoneK562CtcfStdAlnRep0	K562	CTCF
OpenChromChipHelas3CtcfAlnRep0	HeLa-S3	CTCF
UwTfbsK562CtcfStdAlnRep0	K562	CTCF
SydhTfbsHelas3JundlggrabAlnRep0	HeLa-S3	JUND
SydhTfbsHelas3CjunlggrabAlnRep0	HeLa-S3	JUN
SydhTfbsHelas3CfosStdAlnRep0	HeLa-S3	FOS
OpenChromChipK562CtcfAlnRep0	K562	CTCF
SydhTfbsHelas3Ap2alphaStdAlnRep0	HeLa-S3	TFAP2A
SydhTfbsK562CebpblggrabAlnRep0	K562	CEBPB
HaibTfbsH1hescSp1Pcr1xAlnRep0	H1hesc	SP1

(b) Reverse sites peaks without motifs significantly interacting with forward sites peaks with motifs

Experiment	Cell	Regulator
BroadHistoneK562CtcfStdAlnRep0	K562	CTCF
OpenChromChipK562CtcfAlnRep0	K562	CTCF
HaibTfbsH1hescCtcfsc5916V0416102AlnRep0	H1hesc	CTCF
OpenChromChipHelas3CtcfAlnRep0	HeLa-S3	CTCF
UwTfbsK562CtcfStdAlnRep0	K562	CTCF
SydhTfbsGm12878Ctcf20StdAlnRep0	GM12878	CTCF
BroadHistoneHelas3CtcfStdAlnRep0	HeLa-S3	CTCF
OpenChromChipGm12878CtcfAlnRep0	GM12878	CTCF
BroadHistoneGm12878CtcfStdAlnRep0	GM12878	CTCF
SydhTfbsHelas3CebpblggrabAlnRep0	HeLa-S3	CEBPB
HaibTfbsH1hescUsf1Pcr1xAlnRep0	H1hesc	USF1
SydhTfbsGm12878NfkbllggrabAlnRep0	GM12878	NFKB1
BroadHistoneH1hescCtcfStdAlnRep0	H1hesc	CTCF
UwTfbsGm12878CtcfStdAlnRep0	GM12878	CTCF
HaibTfbsH1hescJundV0416102AlnRep0	H1hesc	JUND
SydhTfbsHelas3JundlggrabAlnRep0	HeLa-S3	JUND
UwTfbsHelas3CtcfStdAlnRep0	HeLa-S3	CTCF
UchicagoTfbsK562EjundControlAlnRep0	K562	JUND
HaibTfbsGm12878Elf1sc631V0416101AlnRep0	GM12878	ELF1

Supplementary Table 4: Experiments for significant interactions of peaks without motif for peaks with a motif. (a) The tables lists the 10 experiments in which peaks without a motif significantly enriched for interacting with peaks with a motif at an uncorrected p-value of 0.01 (based on randomization see methods) out of 56 experiments considered which had at least 10 possible interactions that could be measured. (b) The tables lists the 19 experiments in which peaks without a motif significantly enriched for interacting for peaks with a motif at an uncorrected p-value of 0.01 (based on randomization see methods) out of 54 experiments considered which had at least 10 possible interactions that could be measured. For both (a) and (b) no experiment had a significant depletion for interactions at the 0.01 significance level.