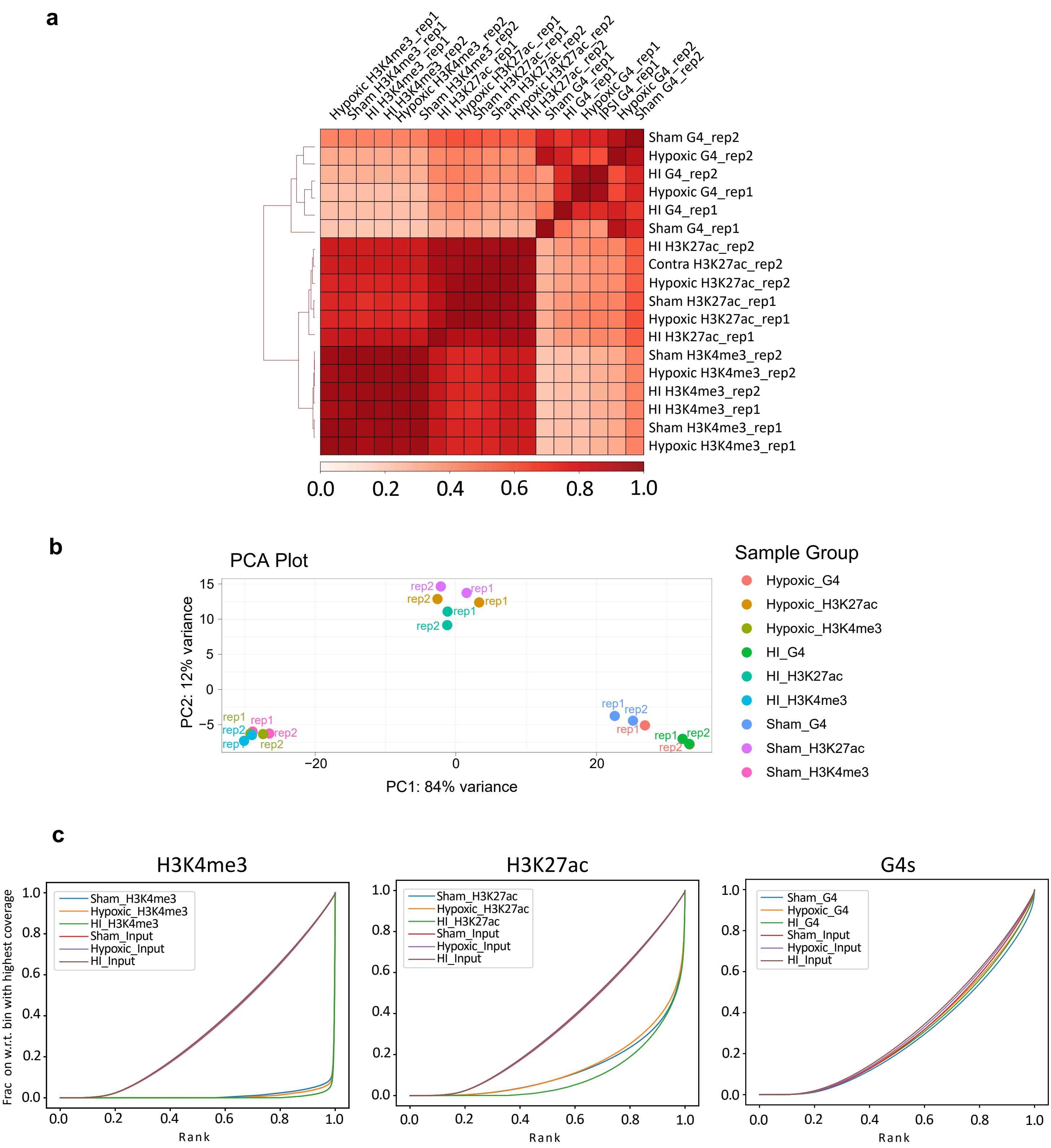
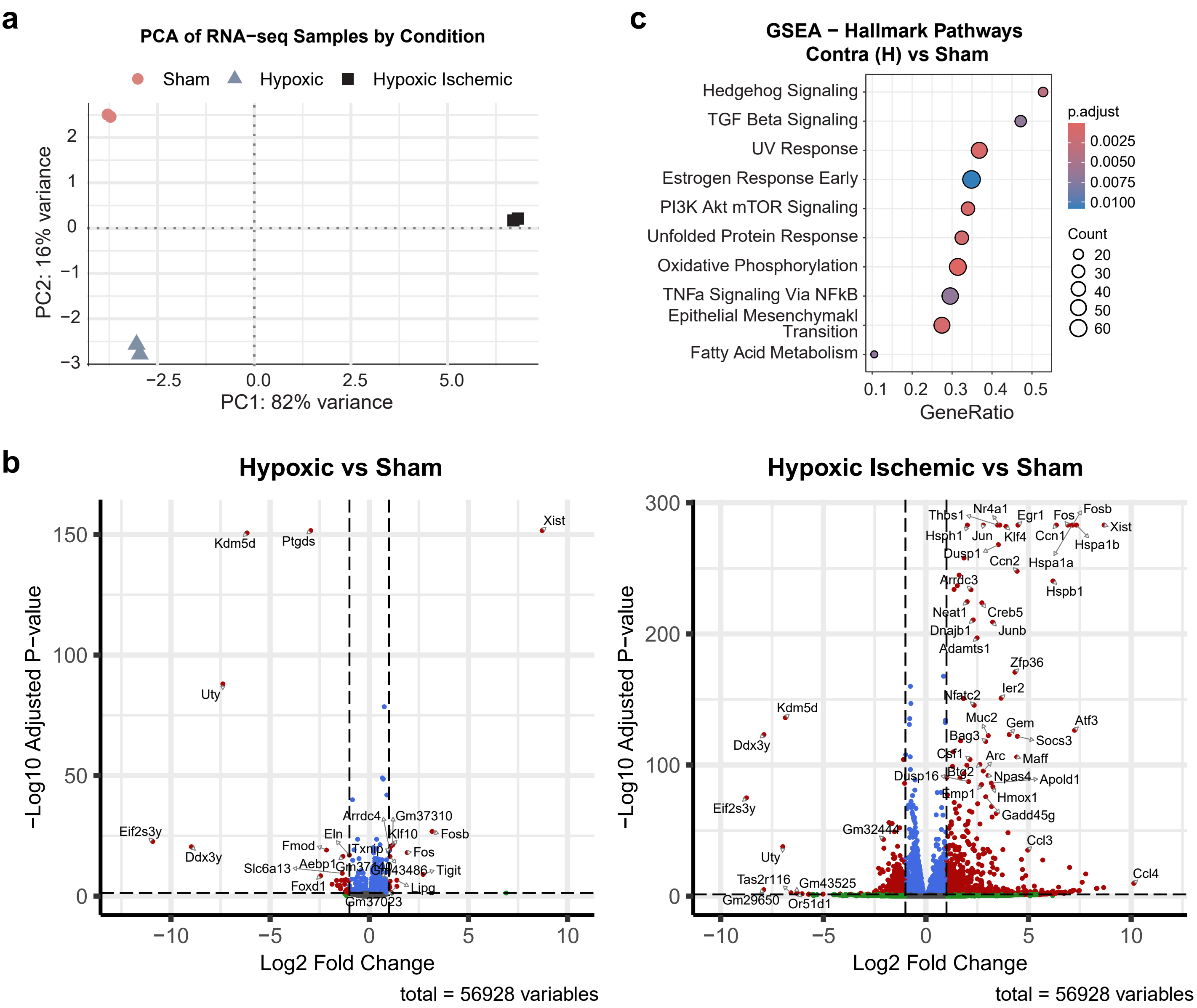


Supplementary Figure 1. a. Correlation heatmaps with Pearson correlation scores are shown for all biological replicates of ChIP-seq samples. For each chromatin mark and condition, two different biological replicates are listed, named “rep1” and “rep2. **b.** PCA plot is shown for H3K4me3, H3K27ac, and G4s for the variability among the biological replicates for three different conditions analyzed by ChIP-seq. **c.** Fingerprint plots showing the enrichment over the input signal in the three sample groups analyzed by ChIP-seq.



Supplementary Figure 2. a. PCA plot for clustering of technical replicates in the three different sample groups analyzed by RNA-seq. **b.** Volcano plots were created using the EnhancedVolcano package in R. For each comparison (IPSI vs Sham and CONTRA vs Sham), the log2 fold-change values (log2FoldChange) were plotted on the x-axis, and the -log10 adjusted p-values (-log10(padj)) on the y-axis. Genes meeting the criteria of padj < 0.05 and |log2FoldChange| > 1 were classified as significantly differentially expressed and highlighted in distinct colors to indicate upregulation or downregulation. Gene labels were added to significant genes, with connector lines drawn for clarity. **c.** GSEA analysis revealed hallmark pathways induced by hypoxia.

a

G4 – known motifs

Sham

Rank	Motif	Name	P-value	log P-pvalue	q-value (Benjamini)	# Target Sequences with Motif	% of Targets Sequences with Motif	# Background Sequences with Motif	% of Background Sequences with Motif
1		Sp1(Zf)/Promoter/Homer	1e-10	-2.498e+01	0.0000	241.0	2.09%	509.3	1.32%
2		NRF(NRF)/Promoter/Homer	1e-5	-1.375e+01	0.0002	196.0	1.70%	458.2	1.19%
3		ZNF143|STAF(Zf)/CUTLL-ZNF143-ChIP-Seq(GSE29600)/Homer	1e-4	-1.107e+01	0.0022	524.0	4.55%	1457.7	3.79%

Hypoxic

Rank	Motif	Name	P-value	log P-pvalue	q-value (Benjamini)	# Target Sequences with Motif	% of Targets Sequences with Motif	# Background Sequences with Motif	% of Background Sequences with Motif
1		FOXA1(Forkhead)/MCF7-FOXA1-ChIP-Seq(GSE26831)/Homer	1e-4	-9.904e+00	0.0214	982.0	13.48%	5110.4	11.97%
2		c-Myc(bHLH)/mES-cMyc-ChIP-Seq(GSE11431)/Homer	1e-3	-8.355e+00	0.0503	423.0	5.81%	2089.7	4.89%
3		GFY-Staf(?,Zf)/Promoter/Homer	1e-3	-8.157e+00	0.0503	61.0	0.84%	221.3	0.52%

HI

Rank	Motif	Name	P-value	log P-pvalue	q-value (Benjamini)	# Target Sequences with Motif	% of Targets Sequences with Motif	# Background Sequences with Motif	% of Background Sequences with Motif
1		Six1(Homeobox)/Myoblast-Six1-ChIP-Chip(GSE20150)/Homer	1e-3	-7.339e+00	0.2780	193.0	2.59%	867.5	2.04%
2		THRb(NR)/Liver-NR1A2-ChIP-Seq(GSE52613)/Homer	1e-2	-6.355e+00	0.3720	3356.0	45.07%	18447.8	43.38%
3		HIF-1b(HLH)/T47D-HIF1b-ChIP-Seq(GSE59937)/Homer	1e-2	-6.351e+00	0.3720	744.0	9.99%	3828.6	9.00%

b

G4 – de novo motifs

Sham

Rank	Motif	P-value	log P-pvalue	% of Targets	% of Background	STD(Bg STD)	Best Match/Details
1		1e-20	-4.629e+01	0.13%	0.00%	57.7bp (0.0bp)	GLI3(Zf)/Limb-GLI3-ChIP-Chip(GSE11077)/Homer(0.745) More Information | Similar Motifs Found
2		1e-19	-4.415e+01	0.38%	0.07%	58.9bp (62.4bp)	Smad4/MA1153.1/Jaspar(0.658) More Information | Similar Motifs Found
3		1e-16	-3.796e+01	9.20%	7.11%	53.8bp (57.5bp)	PB0200.1_Zfp187_2/Jaspar(0.609) More Information | Similar Motifs Found

Hypoxic

Rank	Motif	P-value	log P-pvalue	% of Targets	% of Background	STD(Bg STD)	Best Match/Details
1		1e-19	-4.472e+01	13.60%	10.22%	56.6bp (56.0bp)	Nkx2-5(var.2)/MA0503.1/Jaspar(0.688) More Information | Similar Motifs Found
2		1e-17	-3.989e+01	0.26%	0.02%	49.5bp (42.8bp)	Tcf21(bHLH)/ArterySmoothMuscle-Tcf21-ChIP-Seq(GSE61369)/Homer(0.635) More Information | Similar Motifs Found
3		1e-17	-3.962e+01	3.60%	2.03%	54.1bp (52.8bp)	RARa(NR)/K562-RARa-ChIP-Seq(Encode)/Homer(0.739) More Information | Similar Motifs Found

HI

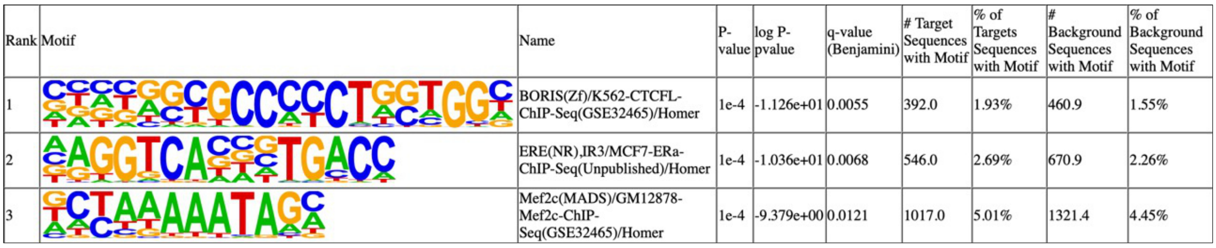
Rank	Motif	P-value	log P-pvalue	% of Targets	% of Background	STD(Bg STD)	Best Match/Details
1		1e-16	-3.785e+01	9.47%	6.89%	55.5bp (55.7bp)	PB0159.1_Rfx4_2/Jaspar(0.622) More Information | Similar Motifs Found
2		1e-13	-3.142e+01	0.17%	0.01%	46.3bp (53.4bp)	SD0002.1_at_AC_acceptor/Jaspar(0.725) More Information | Similar Motifs Found
3 *		1e-11	-2.572e+01	0.68%	0.22%	56.8bp (54.1bp)	MF0002.1_bZIP_CREB/G-box-like_subclass/Jaspar(0.689) More Information | Similar Motifs Found

Supplementary Figure 3. Motif analysis results show the top three enriched known and de novo motifs for G4s.

a

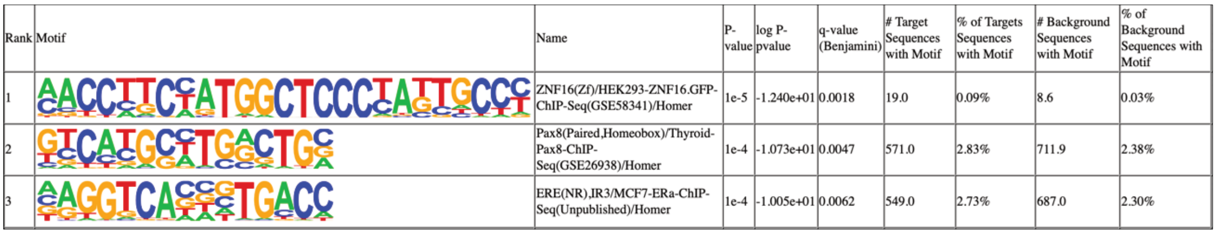
H3K4me3 – known motifs

Sham



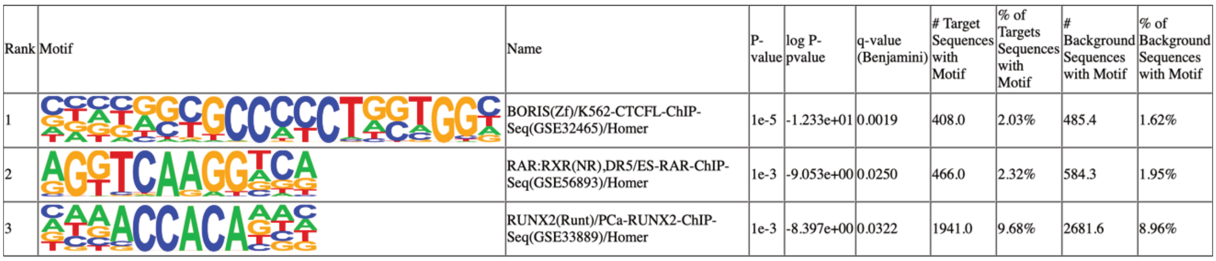
Rank	Motif	Name	P-value	log P-pvalue	q-value (Benjamini)	# Target Sequences with Motif	% of Targets Sequences with Motif	# Background Sequences with Motif	% of Background Sequences with Motif
1		BORIS(Zf)/K562-CTCFL-ChIP-Seq(GSE32465)/Homer	1e-4	-1.126e+01	0.0055	392.0	1.93%	460.9	1.55%
2		ERE(NR),IR3/MCF7-ERa-ChIP-Seq(Unpublished)/Homer	1e-4	-1.036e+01	0.0068	546.0	2.69%	670.9	2.26%
3		Mef2c(MADS)/GM12878-Mef2c-ChIP-Seq(GSE32465)/Homer	1e-4	-9.379e+00	0.0121	1017.0	5.01%	1321.4	4.45%

Hypoxic



Rank	Motif	Name	P-value	log P-pvalue	q-value (Benjamini)	# Target Sequences with Motif	% of Targets Sequences with Motif	# Background Sequences with Motif	% of Background Sequences with Motif
1		ZNF16(Zf)/HEK293-ZNF16.GFP-ChIP-Seq(GSE58341)/Homer	1e-5	-1.240e+01	0.0018	19.0	0.09%	8.6	0.03%
2		Pax8(Paired,Homeobox)/Thyroid-Pax8-ChIP-Seq(GSE26938)/Homer	1e-4	-1.073e+01	0.0047	571.0	2.83%	711.9	2.38%
3		ERE(NR),IR3/MCF7-ERa-ChIP-Seq(Unpublished)/Homer	1e-4	-1.005e+01	0.0062	549.0	2.73%	687.0	2.30%

HI

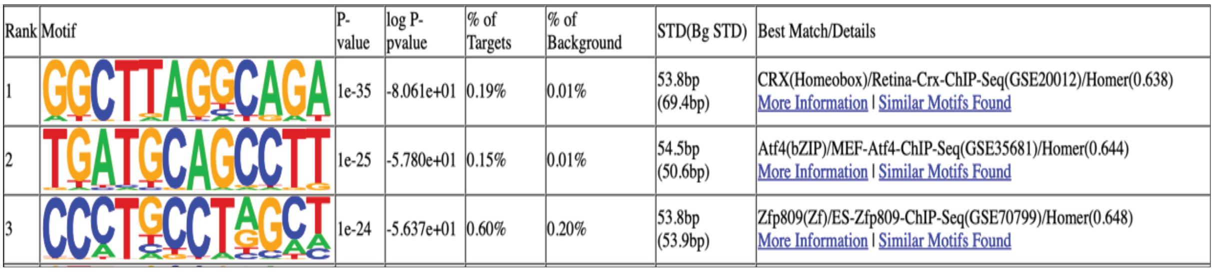


Rank	Motif	Name	P-value	log P-pvalue	q-value (Benjamini)	# Target Sequences with Motif	% of Targets Sequences with Motif	# Background Sequences with Motif	% of Background Sequences with Motif
1		BORIS(Zf)/K562-CTCFL-ChIP-Seq(GSE32465)/Homer	1e-5	-1.233e+01	0.0019	408.0	2.03%	485.4	1.62%
2		RAR:RXR(NR),DR5/ES-RAR-ChIP-Seq(GSE56893)/Homer	1e-3	-9.053e+00	0.0250	466.0	2.32%	584.3	1.95%
3		RUNX2(Runt)/PCa-RUNX2-ChIP-Seq(GSE33889)/Homer	1e-3	-8.397e+00	0.0322	1941.0	9.68%	2681.6	8.96%

b

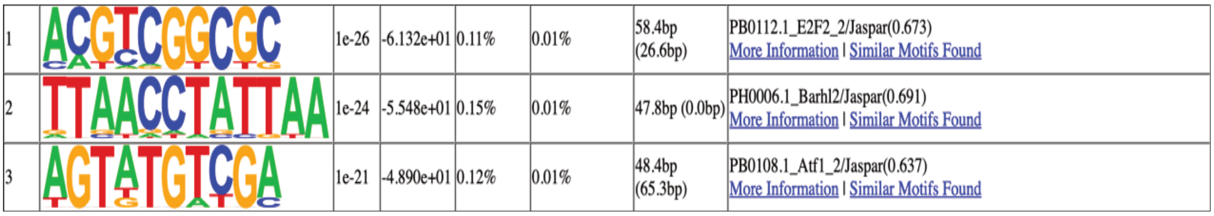
H3K4me3 – de novo motifs

Sham



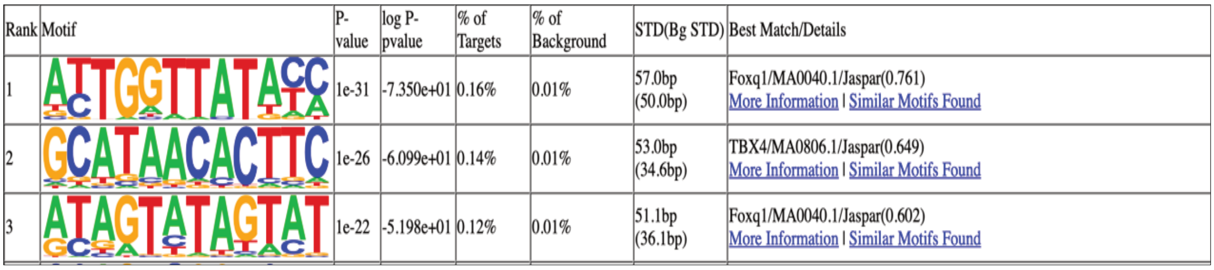
Rank	Motif	P-value	log P-pvalue	% of Targets	% of Background	STD(Bg STD)	Best Match/Details
1		1e-35	-8.061e+01	0.19%	0.01%	53.8bp (69.4bp)	CRX(Homeobox)/Retina-Crx-ChIP-Seq(GSE20012)/Homer(0.638) More Information | Similar Motifs Found
2		1e-25	-5.780e+01	0.15%	0.01%	54.5bp (50.6bp)	Atf4(bZIP)/MEF-Atf4-ChIP-Seq(GSE35681)/Homer(0.644) More Information | Similar Motifs Found
3		1e-24	-5.637e+01	0.60%	0.20%	53.8bp (53.9bp)	Zfp809(Zf)/ES-Zfp809-ChIP-Seq(GSE70799)/Homer(0.648) More Information | Similar Motifs Found

Hypoxic



1		1e-26	-6.132e+01	0.11%	0.01%	58.4bp (26.6bp)	PB0112.1_E2F2_2/Jaspar(0.673) More Information | Similar Motifs Found
2		1e-24	-5.548e+01	0.15%	0.01%	47.8bp (0.0bp)	PH0006.1_Barhl2/Jaspar(0.691) More Information | Similar Motifs Found
3		1e-21	-4.890e+01	0.12%	0.01%	48.4bp (65.3bp)	PB0108.1_Atf1_2/Jaspar(0.637) More Information | Similar Motifs Found

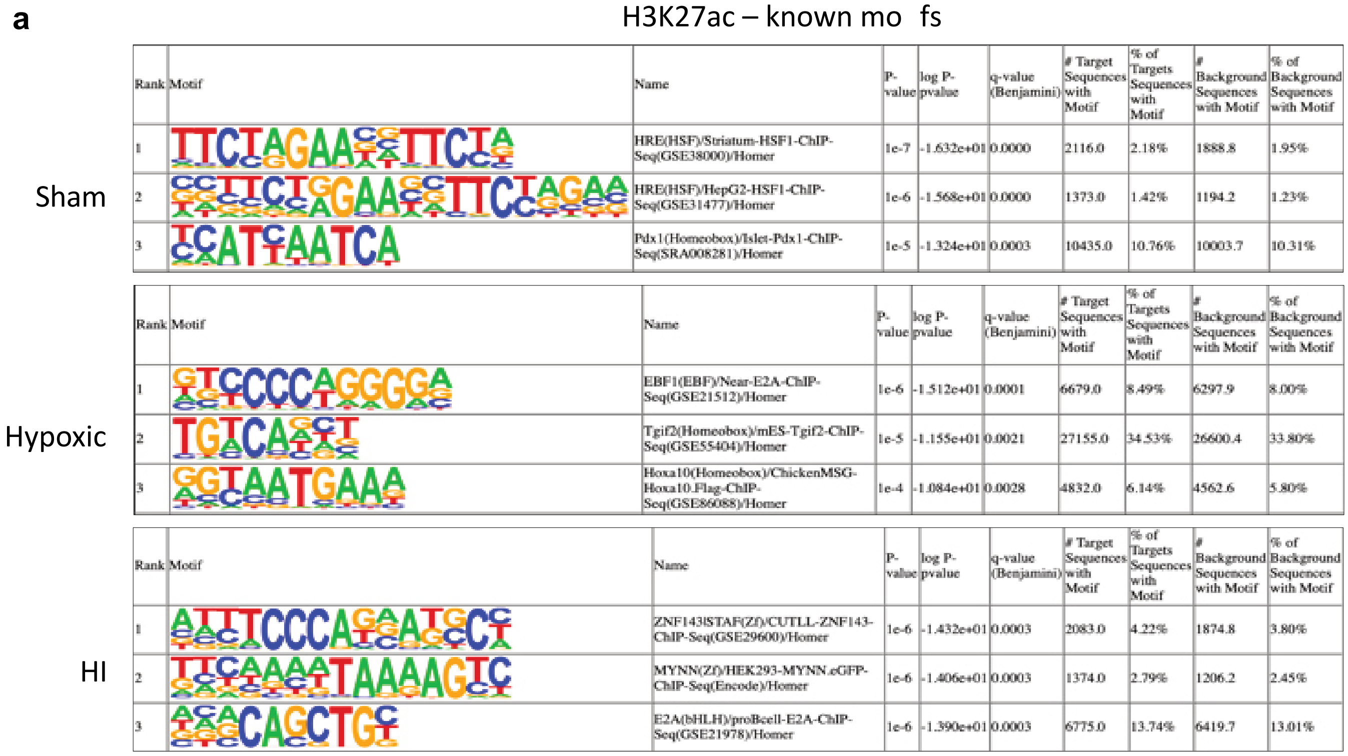
HI



Rank	Motif	P-value	log P-pvalue	% of Targets	% of Background	STD(Bg STD)	Best Match/Details
1		1e-31	-7.350e+01	0.16%	0.01%	57.0bp (50.0bp)	Foxq1/MA0040.1/Jaspar(0.761) More Information | Similar Motifs Found
2		1e-26	-6.099e+01	0.14%	0.01%	53.0bp (34.6bp)	TBX4/MA0806.1/Jaspar(0.649) More Information | Similar Motifs Found
3		1e-22	-5.198e+01	0.12%	0.01%	51.1bp (36.1bp)	Foxq1/MA0040.1/Jaspar(0.602) More Information | Similar Motifs Found

Supplementary Figure 4. Motif analysis results show the top three enriched known and de novo motifs for H3K4me3.

a



H3K27ac – known motifs

Sham

Rank	Motif	Name	P-value	log P-pvalue	q-value (Benjamini)	# Target Sequences with Motif	% of Targets Sequences with Motif	# Background Sequences with Motif	% of Background Sequences with Motif
1		HRE(HSF)/Striatum-HSF1-ChIP-Seq(GSE38000)/Homer	1e-7	-1.632e+01	0.0000	2116.0	2.18%	1888.8	1.95%
2		HRE(HSF)/HepG2-HSF1-ChIP-Seq(GSE31477)/Homer	1e-6	-1.568e+01	0.0000	1373.0	1.42%	1194.2	1.23%
3		Pdx1(Homeobox)/Islet-Pdx1-ChIP-Seq(SRA008281)/Homer	1e-5	-1.324e+01	0.0003	10435.0	10.76%	10003.7	10.31%

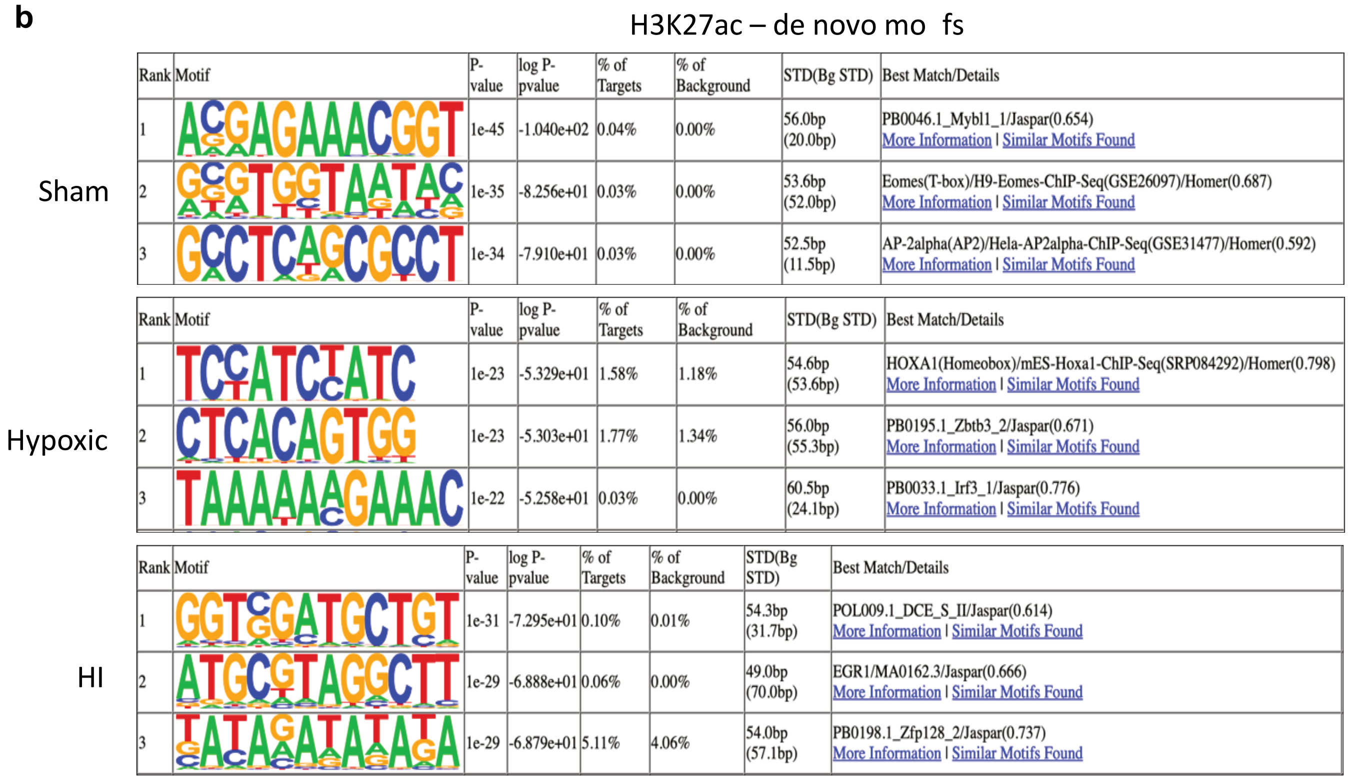
Hypoxic

Rank	Motif	Name	P-value	log P-pvalue	q-value (Benjamini)	# Target Sequences with Motif	% of Targets Sequences with Motif	# Background Sequences with Motif	% of Background Sequences with Motif
1		EBF1(EBF)/Near-E2A-ChIP-Seq(GSE21512)/Homer	1e-6	-1.512e+01	0.0001	6679.0	8.49%	6297.9	8.00%
2		Tgif2(Homeobox)/mES-Tgif2-ChIP-Seq(GSE55404)/Homer	1e-5	-1.155e+01	0.0021	27155.0	34.53%	26600.4	33.80%
3		Hoxa10(Homeobox)/ChickenMSG-Hoxa10.Flag-ChIP-Seq(GSE86088)/Homer	1e-4	-1.084e+01	0.0028	4832.0	6.14%	4562.6	5.80%

HI

Rank	Motif	Name	P-value	log P-pvalue	q-value (Benjamini)	# Target Sequences with Motif	% of Targets Sequences with Motif	# Background Sequences with Motif	% of Background Sequences with Motif
1		ZNF143|STAF(Zf)/CUTLL-ZNF143-ChIP-Seq(GSE29600)/Homer	1e-6	-1.432e+01	0.0003	2083.0	4.22%	1874.8	3.80%
2		MYNN(Zf)/HEK293-MYNN.eGFP-ChIP-Seq(Encode)/Homer	1e-6	-1.406e+01	0.0003	1374.0	2.79%	1206.2	2.45%
3		E2A(bHLH)/proBcell-E2A-ChIP-Seq(GSE21978)/Homer	1e-6	-1.390e+01	0.0003	6775.0	13.74%	6419.7	13.01%

b



H3K27ac – de novo motifs

Sham

Rank	Motif	P-value	log P-pvalue	% of Targets	% of Background	STD(Bg STD)	Best Match/Details
1		1e-45	-1.040e+02	0.04%	0.00%	56.0bp (20.0bp)	PB0046.1_Mybl1_1/Jaspar(0.654) More Information | Similar Motifs Found
2		1e-35	-8.256e+01	0.03%	0.00%	53.6bp (52.0bp)	Eomes(T-box)/H9-Eomes-ChIP-Seq(GSE26097)/Homer(0.687) More Information | Similar Motifs Found
3		1e-34	-7.910e+01	0.03%	0.00%	52.5bp (11.5bp)	AP-2alpha(AP2)/Hela-AP2alpha-ChIP-Seq(GSE31477)/Homer(0.592) More Information | Similar Motifs Found

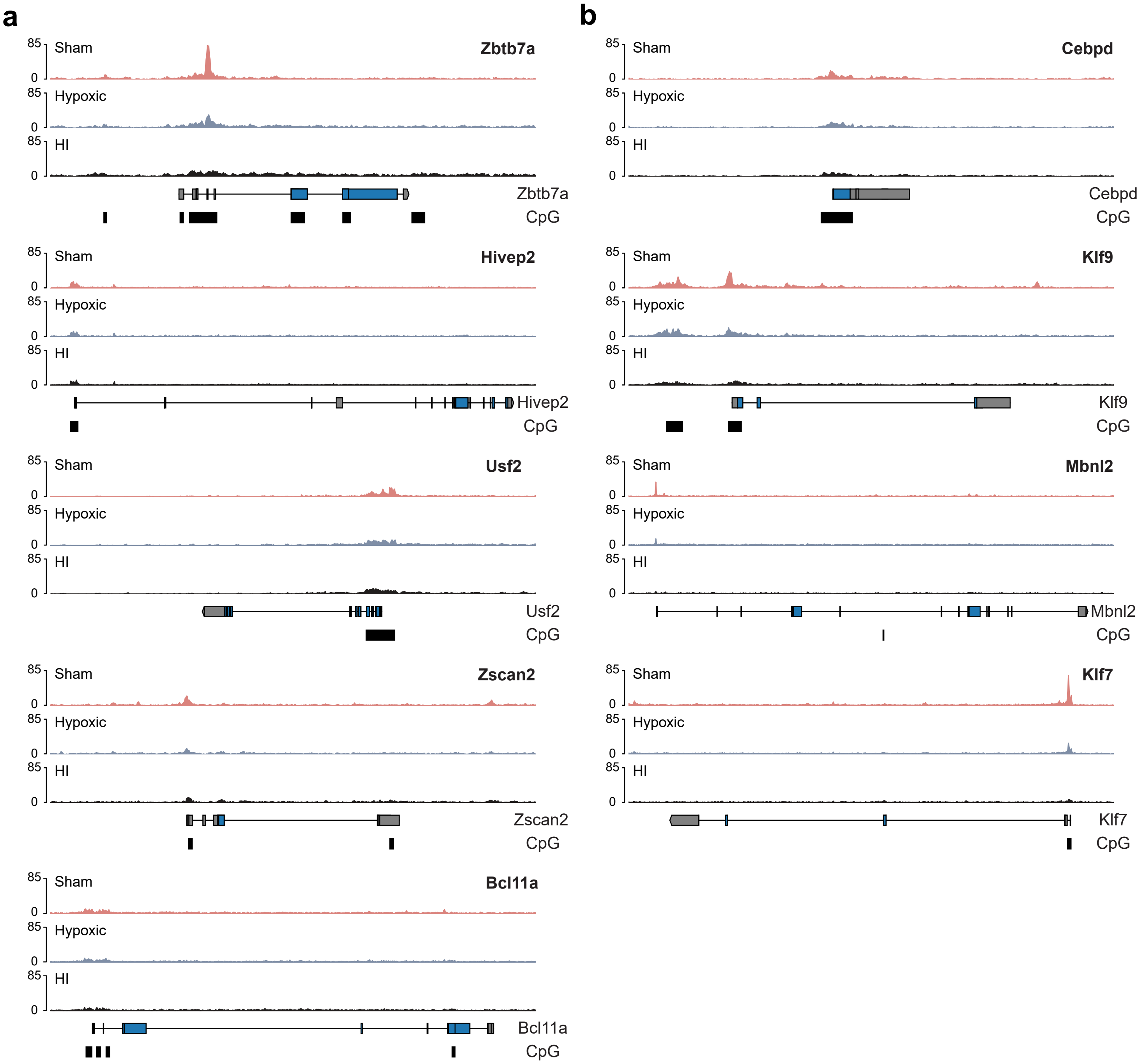
Hypoxic

Rank	Motif	P-value	log P-pvalue	% of Targets	% of Background	STD(Bg STD)	Best Match/Details
1		1e-23	-5.329e+01	1.58%	1.18%	54.6bp (53.6bp)	HOXA1(Homeobox)/mES-Hoxa1-ChIP-Seq(SRP084292)/Homer(0.798) More Information | Similar Motifs Found
2		1e-23	-5.303e+01	1.77%	1.34%	56.0bp (55.3bp)	PB0195.1_Zbtb3_2/Jaspar(0.671) More Information | Similar Motifs Found
3		1e-22	-5.258e+01	0.03%	0.00%	60.5bp (24.1bp)	PB0033.1_Irf3_1/Jaspar(0.776) More Information | Similar Motifs Found

HI

Rank	Motif	P-value	log P-pvalue	% of Targets	% of Background	STD(Bg STD)	Best Match/Details
1		1e-31	-7.295e+01	0.10%	0.01%	54.3bp (31.7bp)	POL009.1_DCE_S_II/Jaspar(0.614) More Information | Similar Motifs Found
2		1e-29	-6.888e+01	0.06%	0.00%	49.0bp (70.0bp)	EGR1/MA0162.3/Jaspar(0.666) More Information | Similar Motifs Found
3		1e-29	-6.879e+01	5.11%	4.06%	54.0bp (57.1bp)	PB0198.1_Zfp128_2/Jaspar(0.737) More Information | Similar Motifs Found

Supplementary Figure 5. Motif analysis results show the top three enriched known and de novo motifs for H3K27ac.



Supplementary Figure 6. Genome track analysis revealed G4 enrichment in genomic regions encoding transcription factors specific to vulnerable (**a**) and resilient (**b**) hippocampal neurons following hypoxia and ischemia. The upper section of each panel presents the G4 signal tracks generated from bigWig files for each experimental condition. Below, the gene annotation track illustrates the exon–intron architecture of the gene of interest, while the CpG track highlights regions enriched in CpG dinucleotides. This integrated view enables the correlation of G4 signal distribution with gene structure and CpG island locations.