	. R ^u	CHI CHI	APart	13 Chil	RS AS	Ames	Ames Ar	2180 CH	21ac AP	2386 (NY	, by
_	0.69	0.69	0.67	0.64	0.68	0.68	0.85	0.85	0.83	1.00	H3K9ac_AP
-	0.71	0.71	0.70	0.67	0.64	0.63	0.80	0.81	1.00	0.83	H3K9ac_CNT
ſ	0.59	0.59	0.60	0.56	0.73	0.72	0.97	1.00	0.81	0.85	H3K27ac_AP
	0.55	0.56	0.56	0.52	0.75	0.73	1.00	0.97	0.80	0.85	H3K27ac_CNT
ſ	0.35	0.35	0.37	0.35	0.94	1.00	0.73	0.72	0.63	0.68	H3K4me3_AP
1	0.35	0.35	0.37	0.35	1.00	0.94	0.75	0.73	0.64	0.68	H3K4me3_CNT
	0.91	0.91	0.94	1.00	0.35	0.35	0.52	0.56	0.67	0.64	panH3_AP
	0.93	0.93	1.00	0.94	0.37	0.37	0.56	0.60	0.70	0.67	panH3_CNT
ſ	0.94	1.00	0.93	0.91	0.35	0.35	0.56	0.59	0.71	0.69	input_AP
ſ	1.00	0.94	0.93	0.91	0.35	0.35	0.55	0.59	0.71	0.69	input_CNT
0.	0 0.	.1 0	.2 0.	.3 0.	.4 0	.5 0.	.6 0	.7 0	.8 0	.9 1	.0

Figure S1: Correlation of the reads obtained for all the histone modifications in the ChIP sequencing data. This correlation plot shows a greater correlation between the acetylation marks, H3K27ac and H3K9ac than between the H3K4me3 methylmark and the two acetylation marks. There is also good correlation for each mark regarding its occupancy in control and ALP treatments. This represents the *in situ* scenarios for these histone modifications at various locations on the chromatin (Fig. 1A).

	Motif Logo	CENTRIMO enrichment pattern	No of centrally enriched sites	Predicted TFBS
	GGCCAGTATAAAAGTCGCAAGATCTATTAT	some the so	107	Hoxd12
Cluster 1	GGTGATACTOCACTAACTGATGAAAACACA	MM	94	Nkx1-2
	GTTTGTATACAAGTAAATTGCAATAACACG	www.	117	MSX
	ATCTGTC	mon	206	NEUROD1
	AGTGATAT	MWWWWW	167	Six3
	AGA9ATAA	MMM May	197	Gata3
	GATA_CTATATCAAC_CATACCAACATGCT	mmy	114	Hic1/Foxl1
	aaAGaCAITGAaTTcAaAGAAIIAICAGGA	MM	190	Bbx
	GGTzqqazTATzGAAzAqqzCaATzzT	. Mur	73	NFATC1
	Cagata	-250 250	1330	GATA1:TAL1
2	TATTICCA	MMM	309	NFATC2/FOXB1
Cluster 2	AGzAGCA	www.	271	Osr1
	TACATGTA	-330 250	1311	Irx3
	SAST LCAST	www.	2142	PRDM1
		230 250	1281	DMRT3
	ALCATAIG.I	MMM MMM	903	BHLHE22
	ATTAALA		1739	Ipf 1
	I AAAGG A	Mar March -250 250	3498	TCF7L2
Cluster 3	TAAC SIII	MM	2619	MYBL2_DBD
	AA IAGA CA	-330 350	878	RORA
	CCACTI A		2043	Nkx2-5
	F-GGGTCA	-150 250	4319	Rara
	SCEPTIAL OF C	-100 - 200	4299	Тbр
			1597	SNAI2
	CTTGGCA		2710	NFIC
	TGA_TGACAG_		2540	PBX3
	<u>_C_CAGCA-G_</u>	man	2460	Zic3

Figure S2: Central enrichment of motifs on the intergenic regions displaying occupancy of the H3K27ac, H3K9ac and H3K4me3 modifications. Upon identifying the intergenic regions displaying occupancy of H3K27ac mark, they were retrieved. These were classified into 3 k-means clusters based on combinatorial occupancy of the three activating histone marks and subjected to motif enrichment analysis using the MEME suite package (Fig. 2A). The first column shows the motif identified on the intergenic regions using the DREME and FIMO tools in the online MEME suite package. The 2nd column shows the pattern of motif enrichment on the DNA sequences and the 3rd column shows the number of centrally enriched peaks for each of the transcription factors listed in the 4th column. The total number of motifs identified for each transcription factor in each cluster is given in Fig. 2E.



Figure S3: Differentially expressed transcripts in head vs foot. To identify genes having head-specific expression in *Hydra*, a publicly available dataset was analysed (IDs: SRR6815024-29). The smear plot represents the differentially regulated transcripts in head specific regions with the red dots representing the genes upregulated in a head specific manner and the green dots depict the downregulated genes in head. The head specific genes were used for identifying genes neighbouring to intergenic regions that are differentially modified in response to Wnt/ β -catenin signalling as seen in Fig. 3C, 3D and 3E.



Figure S4: Networks obtained after enrichment analysis and clustering using STRINGdb. Upon identification of a set of head-related genes neighbouring to the intergenic regions that respond to activated Wnt/ β -catenin signalling, they were subjected to a network and interactome analysis. Interaction network obtained using STRING database for the genes commonly found in head and cluster3_4 of Fig. 3C. The KEGG component enrichment is shown in Supplementary Table 7a and the colour codes for the clusters are given in Supplementary Table 7b.

Motif Logo	CENTRIMO enrichment pattern	No of centrally enriched sites	Predicted TFBS
ARGAGEAGEAGEASTICA	www.ww	142	Sp4
CITGESC S. SUIGEGUET TGAACC. CGS	Mar a see	67	ADR1
_C_CAGCAGG	month	711	Zic3
ATCA	many	881	Arid3a
	within	453	Zfp410
SCGCCG S	MMM	207	Erf9
CAcGeez	man	728	Max
	man	454	TCP24
<u>AGGTCATTGACCT</u>	www	518	NR1A4:RXRA
TGTCGGIG_	Mulham	254	AT3G16280
SECCO SE	mm	497	brk
JCCTGA TCAGCA	www.	184	MAFG
	mmm	414	SP3
	white	449	TCFAP2b
AGGTGTGG	wath and	620	Eomes
<u>_cCGGAAgt</u>	mm	601	ELK3
C <u><u><u></u><u></u><u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u></u></u></u>	www.	620	abi4
CCCCGGGGG	mmm	281	Zic1
TGCCA.C	manna	580	Hic1
CGGA	manne	654	STB5
_AGGICA _AGG_CA	1250 250	483	RARA::RXRG
GCGGGAA	month	556	TFDP1

Figure S5: Central enrichment of motifs on the intergenic regions displaying higher occupancy of the H3K27ac neighbouring to genes having expression in head. Intergenic regions showing enhanced H3K27ac occupancy and neighbouring to the genes which display expression in the *Hydra* head were subjected to motif enrichment analysis in the MEME suite (Fig. 3C, 3D). The first column shows the motif identified on the intergenic regions using the DREME and FIMO tools in the online MEME suite package. The 2nd column shows the pattern of motif enrichment on the DNA sequences and the 3rd column shows the number of centrally enriched peaks for each of the transcription factors listed in the 4th column. The total number of motifs identified for each transcription factor is given in Fig. 3E.



Figure S6: Morphology of *Hydra* polyps upon treatment with pharmacological inhibitors. Family images of polyps treated with Vehicle (DMSO), 5 μ M Alsterpaullone (ALP), 3 μ M GSK-J4 which inhibits the JMJD3/UTX histone lysine demethylases and a combinatorial treatment of 3 μ M GSK-J4 and 5 μ M ALP. As seen in Fig. 5A, B, treatment with ALP activates the Wnt/ β -catenin signalling pathway leading to formation of ectopic tentacles all over the *Hydra* polyp. GSK-J4 is an inhibitor of KDM6A/6B histone demethylases and application of this inhibitor in combination with ALP leads to a rescue in the ectopic tentacle phenotype. (Scale bar = 500 μ m).



Figure S7: Whole mount *in situ* hybridisation of polyps treated with pharmacological inhibitors. Family images of whole mount *in situ* hybridisation for Hv_Wnt3a and HyBra1 on Hydra polyps treated with Vehicle (DMSO), 5 µM ALP, 3 µM GSK-J4 which inhibits the JMJD3/UTX histone lysine demethylases and a combinatorial treatment of 3 µM GSK-J4 and 5 µM ALP. As seen in Fig. 5C, treatment with ALP activates the Wnt/ β -catenin signalling pathway leading to formation of multiple head organizer centres expressing Hv_Wnt3a and HyBra1 all over the body column of Hydra. This changes the patterning of the Hydra body axis. GSK-J4 is an inhibitor of KDM6A/6B histone demethylases and application of this inhibitor in combination with ALP leads to a reduction of regions expressing genes that are a signature of the Hydra hypostome. (Scale bar = 500 µm).