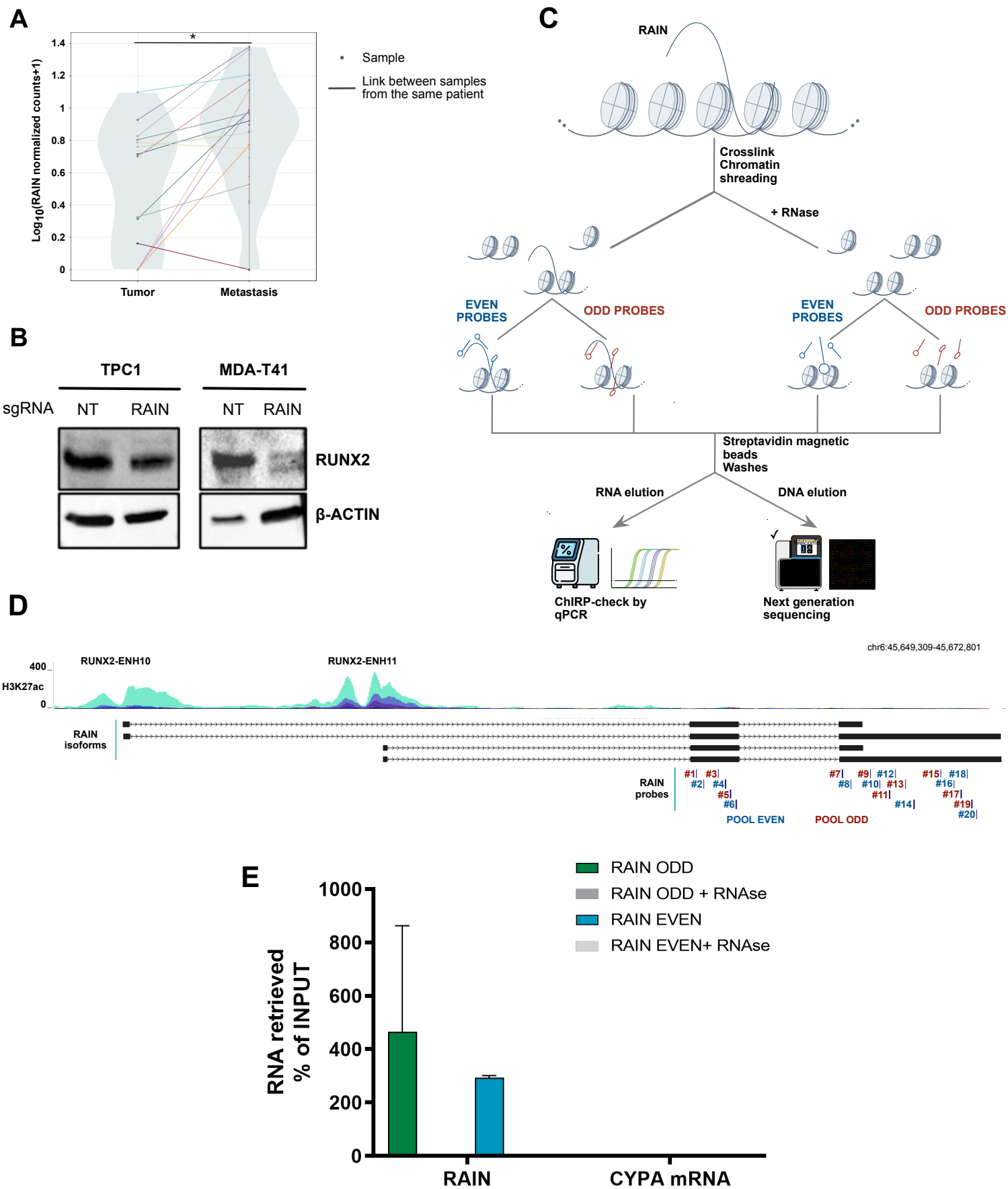
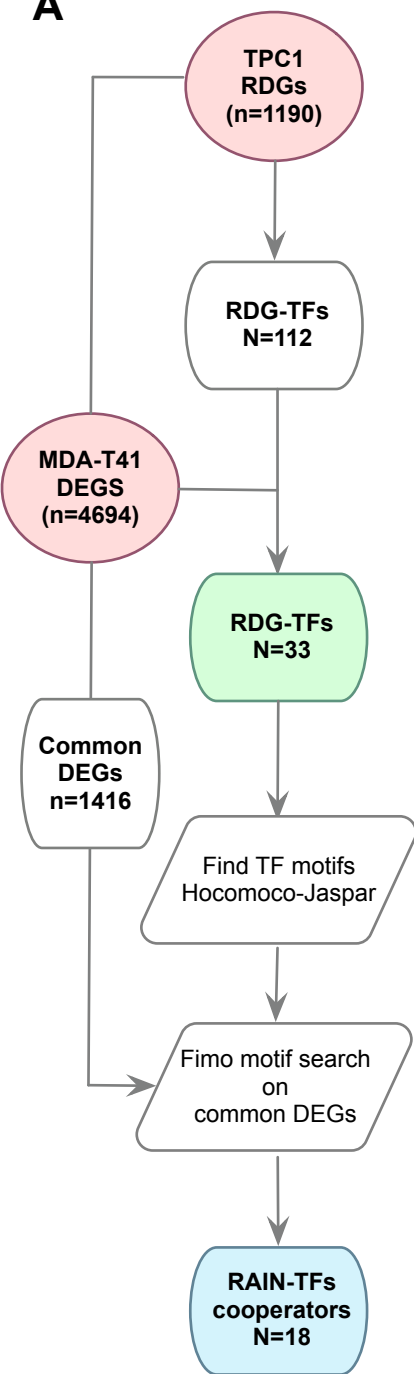


Supplementary FIGURE 1

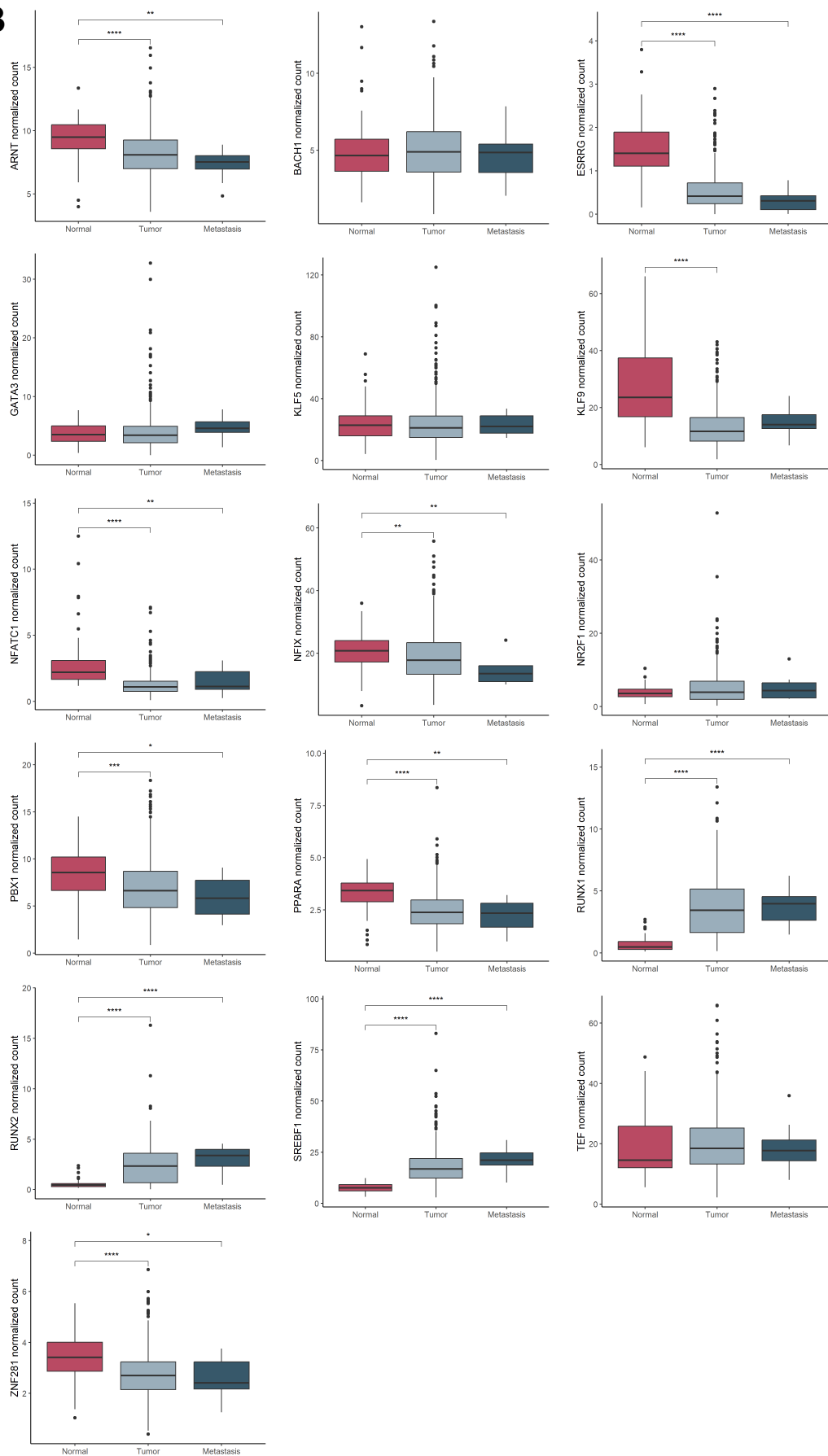


Supplementary FIGURE 2

A



B



Supplementary Figure Legends

Supplementary Figure S1 A. Violin plot showing RAIN expression in matched primary tumors, and metastases from 14 patients included in the publicly available cohort. Colored dots represent the samples. Colored lines link samples from the same patients. *p-value<0.05 **B.** Western Blot showing RUNX2 protein level in RAIN KD (RAINsgRNA) and control (NTsgRNA) cells. **C.** Schematic overview of the ChIRP-seq approach. **D.** Screenshot of RAIN locus from Genome Browser. Track represents H3K27ac signal at RAIN promoters in different cell lines, genomic regions of RUNX2 ENH10 and ENH11 are highlighted on top of H3K27ac track. All RAIN isoforms and genomic mapping of ChIRP probes are shown. **E.** Control of ChIRP experiment in qRT-PCR. CYPA mRNA was used as negative control.

Supplementary Figure S2 A. Schematic workflow of FIMO analysis. **B.** Boxplots showing the expression levels of 16 out of 18 RAIN-TFs putative cooperators in THCA-TCGA dataset. Gene expression was evaluated by comparing Normal tissue with Primary Tumor and Metastatic lesions. *p-value<0.05; ** p-value<0.01, ***p-value<0.001; ****p-value<0.0001.

Supplementary Table 1 CRISPRi sgRNA sequences

Name	Target	Sequence
RAINsgRNA	RAIN gene body	GCAATACTCCCTCCTGCCAT
NTsgRNA	-	CTGAAAAAGGAAGGAGTTGA

Supplementary Table 2 List of qPCR primers

Target	Forward primer	Reverse primer
<i>Primers for gene expression</i>		
RUNX2	GCTCTTCTTACTGAGAGTGGAAGG	GTGCCTAGGCGCATTTC
RAIN	CTCAAAGCAAGTCGCCAAAG	CCTGTGATCTGCCCTTTAGC
ACTB	ACCTTCTACAATGAGCTGCG	CCTGGATAGCAACGTACATGG
CYP4	GACCCAACACAAATGGTTCC	TTTCACTTTGCCAAACACCA
<i>Primers for ChIP</i>		
RUNX1-P1	CTGTGGGTTGGTGATGCTC	AGCCTGGCAGTGTGAGAAGT
RUNX1-P2	GGCTGGTCCTCTGGTTTGT	TGGCTGCCTTCCGAAGAGT
RUNX2-P2	ACCATGGTGGAGATCATCG	GGCAGGGTCTTGTTGCAG
TGFB2 prom	TAGACATGCCGCCCTTCTTC	TGCTGCGGTTTTGAGAGCTC
TGFA prom	GACCATTTTACGGGCGGGC	CCCTGCCTAGTCTGCGTCTT
TGFA ENH	CCTGTGGCATTGAGGGTG	TGAATCCCTGTCTGGCCACT
SPARC ENH	CACTGAACGGCTCGCTTCC	GGCGGAGATGATTTACACCA
CXXC5 prom	TACCCAAGCCTCCCTAAGCC	GCCGTCCCAGACCCTAAAAC
GLI3 intron	GCAGGGCTTTGAAAACGCAC	TAGTAACCCAGCTTTGCGGT
FLNB intron	CCCCACATACTCCAACAAGCA	CTTGGGTATGCAGTGACGCT
EGR3 prom	GGTCGAGGATGTGCGGTTTT	GGGATTTCAGTGCACGTGTT
TGFB1 prom	TGTTGTACAGGGCGAGCAC	CAGATCCTGTCCAAGCTGCG
CDH6 prom	GGCTCCGTTGGCTATGCATA	GGGCTCTCTCTGATTGGC
RUNX2 UP	TCTCAAGGTGCCTGTCTGC	TGAAGTTTGGCCTCTGGTCT

Supplementary Table 3 List of RAIN probes used for ChIRP

Name	Sequence	Pool
RAIN ChIRP_probe1	ACCTGGGGAAAAGGCCTGAG	ODD
RAIN ChIRP_probe2	AGAGATGGTCGAAGGGCAAC	EVEN
RAIN ChIRP_probe3	CCATTAGTTGGCATCCGAAA	ODD
RAIN ChIRP_probe4	GTCTGTTTCACGCTGAAACG	EVEN
RAIN ChIRP_probe5	TTTTTCTGCTAGACGCTCAA	ODD
RAIN ChIRP_probe6	CTTTGGCGACTTGCTTTGAG	EVEN
RAIN ChIRP_probe7	TTTAGTTGATGCCGGTTTTG	ODD
RAIN ChIRP_probe8	TAAGCTACCTAGATGGGTTC	EVEN
RAIN ChIRP_probe9	AAGCCATAACAGCCCTAAAG	ODD
RAIN ChIRP_probe10	TACACCATGTGAGTGACCAT	EVEN
RAIN ChIRP_probe11	AATCACACCGATTCTGGTTT	ODD
RAIN ChIRP_probe12	GTTGTGACAGTGCTATTGAC	EVEN
RAIN ChIRP_probe13	CTTTGACCCACAGTACTACT	ODD
RAIN ChIRP_probe14	CATAGACTGAGAGCCAAGGG	EVEN
RAIN ChIRP_probe15	TTGGTAAAGGAAGACGGCCA	ODD
RAIN ChIRP_probe16	TGCTACCAAGAGGAAGTCTA	EVEN
RAIN ChIRP_probe17	TTGGTAAGGTTCCCTTGTTTT	ODD
RAIN ChIRP_probe18	AGAGCCATCACGTTGGACAG	EVEN
RAIN ChIRP_probe19	GACGAGAGAGGAGGGTGATA	ODD
RAIN ChIRP_probe20	CTTGGACCTTGGGATACTAA	EVEN

Supplementary Table 4 Clinical features of PTC patients selected for Nanostring analysis

Metastatic Samples (DM)						Control Samples (CTRL)					
Sample	Age	Sex	pN	pT	pSTAGE	Sample	Age	Sex	pN	pT	pSTAGE
DM33	51	F	1a	3	3	NO09	66	F	0	1b	1
DM30	47	M	1b	3	4c	NO13	51	F	0	3	3
DM55	82	F	1B	2	2	NO19	68	F	0	2	2
DM01	90	M	1b	4a	4a	NO26	22	M	0	1b	1
DM56	-	M	-	-	-	NO33	67	F	0	2	2
DM51	53	M	1B	3	4a	NO41	57	F	0	2	2
DM34	47	M	0	3	3	NO43	64	F	0	2	2
DM45	19	F	1b	3	2	NO44	59	F	0	1b	1
DM43	22	F	1a	4a	2	NO47	47	F	0	1b	1
DM06	73	M	1b	3	4a	NO53	-	M	0	2	-
DM28	59	F	1b	4a	4a	NO54	-	F	0	1b	-
DM29	58	F	0	3	3	NO57	-	F	0	1b	-
DM12	71	F	1a	4a	4a	CT29	30	M	0	1B	-
DM20	63	M	1b	3	4c	CT52	22	M	0	1A	-
DM04	80	M	1b	3	4a	NO15	57	F	0	1b	1
DM48	63	F	1a	4a	4a	NO20	53	F	0	1b	1
DM15	68	F	1b	3	4a	NO21	63	F	0	3	3
NI74	68	M	1a	3b	-	NO29	64	F	0	3	3
DM37	34	F	1a	3	1	NO32	64	F	0	1b	1
DM41	28	F	1b	3	2	NO35	54	F	0	1b	1
DM52	58	M	0	1b	1	NO36	61	F	0	1b	1
DM14	68	F	1a	3	3	NO46	47	F	0	1b	1
DM21	63	F	0	2	4a	NO58	-	F	0	1a	-
DM07	72	F	1a	3	4c	NO74	-	M	0	1n	-