

Supplementary Table 1: (a) Top driver genes regulating modules enriched in major pathways of cancer.

(b) Alterations of the top drivers across all cancer sites

(c) Comparison of average number of enriched gene sets per module in 100 random permutations vs. the actual modules per cancer.

(a) Top driver genes regulating modules enriched in major pathways of cancer

Angiogenesis (43 enriched modules)

	BLCA	BRCA	COADREAD	GBM	HNSC	KIRC	LAML	LUAD	LUSC	OV	UCEC	Total number of regulated modules
Number of enriched modules	6	3	3	7	4	4	2	3	2	6	3	43
FSTL1	2	1	0	0	0	0	0	1	1	1	2	8
EMILIN1	0	0	0	1	0	0	0	2	1	1	2	7
BIRC3	2	0	0	3	0	0	0	0	0	0	0	5
SOCS3	2	0	2	0	0	0	0	0	0	0	0	4
CD248	3	0	0	0	0	0	1	0	0	0	0	4
PPP1R3B	0	0	0	4	0	0	0	0	0	0	0	4
NUAK1	0	0	1	0	0	0	0	1	0	1	0	3
SPARCL1	1	0	0	0	0	0	0	2	0	0	0	3
CIS	2	0	0	1	0	0	0	0	0	0	0	3
IL1B	1	0	0	0	1	0	0	0	0	1	0	3
OLFML1	0	1	0	0	0	0	0	0	0	0	2	3
ANGPTL2	0	1	0	0	0	0	0	0	1	0	1	3
CDO1	0	0	1	0	0	0	0	1	0	0	0	2
MSC	2	0	0	0	0	0	0	0	0	0	0	2
MME	0	0	1	0	1	0	0	0	0	0	0	2
SRPX2	0	0	0	2	0	0	0	0	0	0	0	2
CLIP3	2	0	0	0	0	0	0	0	0	0	0	2
WIPF1	2	0	0	0	0	0	0	0	0	0	0	2
VIM	1	0	0	0	1	0	0	0	0	0	0	2
RCN3	2	0	0	0	0	0	0	0	0	0	0	2
PDLIM2	2	0	0	0	0	0	0	0	0	0	0	2
SERPINB1	1	0	0	0	0	0	0	0	0	1	0	2
MCL1	2	0	0	0	0	0	0	0	0	0	0	2
TRIP13	0	1	0	0	0	0	0	0	0	1	0	2
CHEK1	0	0	0	0	0	0	0	1	0	1	0	2
MIDN	1	0	0	0	1	0	0	0	0	0	0	2
ANXA2	0	0	0	2	0	0	0	0	0	0	0	2
DTL	0	0	0	2	0	0	0	0	0	0	0	2
TUBA1C	0	0	0	2	0	0	0	0	0	0	0	2
GPR171	0	1	0	0	0	0	0	0	1	0	0	2
MMP14	0	0	0	1	0	0	0	0	1	0	0	2
INHBA	0	0	0	0	2	0	0	0	0	0	0	2
DDR2	0	0	0	0	0	0	0	1	0	0	1	2
CCL5	0	1	0	0	0	0	0	0	0	0	1	2
PTPN7	0	1	0	0	0	0	0	0	0	0	1	2
PTPRCAP	0	1	0	0	0	0	0	0	0	0	1	2
RRM2	0	1	0	0	0	0	0	1	0	0	0	2
SNRK	0	0	0	0	0	0	0	2	0	0	0	2
KNTC1	0	1	0	0	0	0	0	1	0	0	0	2
ACTA2	0	0	0	0	0	0	0	0	0	1	1	2
PCOLCE	0	1	0	0	0	0	0	0	0	1	0	2
CTSK	0	1	0	0	0	0	0	0	0	0	1	2
CD247	0	1	0	0	0	0	0	0	0	0	1	2
CD27	0	1	0	0	0	0	1	0	0	0	0	2
GLT25D2	0	0	0	0	0	0	2	0	0	0	0	2

Hypoxia (44 enriched modules)

	BLCA	BRCA	COADREAD	GBM	HNSC	KIRC	LAML	LUAD	LUSC	OV	UCEC	Total number of regulated modules
Number of enriched modules	4	2	3	8	3	2	2	7	1	10	2	44
BIRC3	2	0	0	3	0	0	0	0	0	0	0	5
SRPX2	0	0	0	4	0	0	0	1	0	0	0	5
PPP1R3B	0	0	0	5	0	0	0	0	0	0	0	5
CD248	2	0	1	0	0	0	1	0	0	0	0	4
CHEK1	0	0	0	0	0	0	0	2	0	2	0	4
IL1B	1	0	0	0	1	0	0	0	0	2	0	4

WIPF1	2	0	0	0	0	0	0	0	0	0	0	1	3
CIS	2	0	0	1	0	0	0	0	0	0	0	0	3
MCL1	2	0	0	0	0	0	0	0	0	1	0	3	
SOCS3	2	0	1	0	0	0	0	0	0	0	0	3	
KNTC1	0	1	0	0	0	0	0	2	0	0	0	3	
ACTA2	0	0	0	0	0	0	0	0	0	3	0	3	
NUAK1	0	0	1	0	0	0	0	0	0	2	0	3	
MME	0	0	1	0	2	0	0	0	0	0	0	3	
DTL	0	0	0	2	0	0	0	0	0	1	0	3	
FAM83D	0	0	0	0	0	0	0	3	0	0	0	3	
NNMT	0	0	0	0	0	0	0	0	0	3	0	3	
EV12A	0	0	0	0	0	0	0	0	0	3	0	3	
ALPK2	0	0	0	0	0	0	0	0	0	3	0	3	
CD274	2	0	0	0	0	0	0	0	0	0	0	2	
BATF	0	0	0	2	0	0	0	0	0	0	0	2	
FSYL1	1	0	0	0	0	0	0	0	0	1	0	2	
SERPINB1	1	0	0	0	0	0	0	0	0	1	0	2	
TRIP13	0	1	0	0	0	0	0	0	0	1	0	2	
C16orf54	0	1	1	0	0	0	0	0	0	0	0	2	
RRM2	0	1	0	0	0	0	0	1	0	0	0	2	
GPR171	0	1	0	0	1	0	0	0	0	0	0	2	
TRIM22	0	0	1	1	0	0	0	0	0	0	0	2	
ATP10A	0	0	1	0	0	0	0	1	0	0	0	2	
PTPRC	0	1	0	0	0	0	0	0	0	0	1	2	
TGFB3	0	0	1	0	0	0	0	0	0	1	0	2	
SLA	0	0	0	1	0	0	0	0	0	0	1	2	
ANXA2	0	0	0	2	0	0	0	0	0	0	0	2	
RNF149	0	0	0	2	0	0	0	0	0	0	0	2	
KIAA0247	0	0	0	1	0	0	0	0	0	1	0	2	
TUBA1C	0	0	0	2	0	0	0	0	0	0	0	2	
ACTN1	0	0	0	1	0	0	0	1	0	0	0	2	
EGLN3	0	0	0	0	0	0	0	2	0	0	0	2	
ANGPT2	0	0	0	0	1	0	0	1	0	0	0	2	
GLT2SD2	0	0	0	0	0	0	2	0	0	0	0	2	
FAP	0	0	0	0	0	0	0	2	0	0	0	2	
MYBL2	0	0	0	0	0	0	0	2	0	0	0	2	
RHOH	0	0	0	0	0	0	0	0	0	1	1	2	
KCNN4	0	0	0	0	0	0	0	2	0	0	0	2	
LCP2	0	0	0	0	0	0	0	0	0	1	1	2	
RUNX2	0	0	0	0	0	0	0	0	0	2	0	2	
PTTG2	0	0	0	0	0	0	0	0	0	2	0	2	
GPNMB	0	0	0	0	0	0	0	0	0	2	0	2	
RARRES3	0	0	1	0	0	0	1	0	0	0	0	2	
ACAP1	0	0	0	1	0	0	0	0	0	0	0	2	
CD247	0	0	0	1	0	0	0	0	0	0	0	2	
GPR171	0	0	0	1	0	0	0	0	0	0	0	2	
AOAH	0	0	0	0	0	0	0	0	0	0	0	2	
IL2RG	0	0	0	0	0	0	0	0	0	0	0	2	

**Epithelial Mesenchymal Transition (12 enriched modules)**

	BLCA	BRCA	COADREAD	GBM	HNSC	KIRC	LAML	LUAD	LUSC	OV	UCEC	Total number of regulated modules
Number of enriched modules	1	0	2	1	2	2	0	1	0	3	0	12
TGFB3	0	0	1	0	0	1	0	0	0	1	0	3
NUAK1	0	0	1	0	0	0	0	0	0	2	0	3
CD248	1	0	1	0	0	0	0	0	0	0	0	2
FSYL1	0	0	0	0	0	1	0	0	0	1	0	2
MCL1	1	0	0	0	0	0	0	0	0	1	0	2
SOCS3	1	0	1	0	0	0	0	0	0	0	0	2
MIDN	1	0	0	0	1	0	0	0	0	0	0	2
PPP1R15A	0	0	0	0	0	0	0	1	0	1	0	2
NNMT	0	0	0	0	0	0	0	0	0	2	0	2
EV12A	0	0	0	0	0	0	0	0	0	2	0	2
ACTA2	0	0	0	0	0	0	0	0	0	2	0	2
RUNX2	0	0	0	0	0	0	0	0	0	2	0	2
ALPK2	0	0	0	0	0	0	0	0	0	2	0	2

**Cell cycle (22 enriched modules)**

	BLCA	BRCA	COADREAD	GBM	HNSC	KIRC	LAML	LUAD	LUSC	OV	UCEC	Total number of regulated modules
Number of enriched modules	1	2	1	3	1	2	2	3	1	5	1	22
HIST1H2AE	1	1	1	0	0	0	0	1	1	0	1	6
CHEK1	0	0	0	0	0	0	0	2	0	2	0	4
HIST1H3G	1	0	1	0	1	0	0	0	0	0	0	3
KNTC1	0	1	0	0	0	0	0	2	0	0	0	3
HIST1H2BJ	0	1	0	0	0	0	0	1	1	0	0	3
HIST1H3H	0	1	0	0	0	1	0	0	1	0	0	3
DTL	0	0	0	2	0	0	0	0	0	1	0	3
NCAPG2	0	0	0	0	0	1	1	0	0	1	0	3
TPX2	0	0	0	0	0	0	0	0	0	2	0	2
TRIP13	0	1	0	0	0	0	0	0	0	1	0	2
RRM2	0	1	0	0	0	0	0	1	0	0	0	2
ENSA	0	1	0	0	0	0	0	0	1	0	0	2
HIST1H1D	0	1	0	0	0	0	0	0	1	0	0	2
HIST1H3D	0	1	0	0	0	0	0	1	0	0	0	2
HIVEP2	0	0	0	2	0	0	0	0	0	0	0	2
TUBA1C	0	0	0	2	0	0	0	0	0	0	0	2
HINT3	0	0	0	1	0	1	0	0	0	0	0	2
FIG4	0	0	0	0	0	1	0	1	0	0	0	2
MYBL2	0	0	0	0	0	0	0	2	0	0	0	2
EZH2	0	0	0	0	0	0	0	0	0	2	0	2
PTTG2	0	0	0	0	0	0	0	0	0	2	0	2

**Immune response (100 enriched modules)**

	BLCA	BRCA	COADREAD	GBM	HNSC	KIRC	LAML	LUAD	LUSC	OV	UCEC	Total number of regulated modules
Number of enriched modules	11	8	8	9	12	7	7	9	9	11	9	100
CCL5	0	2	0	0	2	1	0	2	2	3	2	14
TNFAIP8L2	7	1	0	1	0	0	0	0	0	0	1	10
IL2RB	6	0	0	0	0	0	1	3	0	0	0	10
GPR171	0	2	0	1	4	0	0	0	2	1	0	10
BIRC3	6	0	0	3	0	0	0	0	0	0	0	9
OAS2	1	1	0	1	1	0	1	1	1	1	1	9
TRIM22	0	0	3	1	1	0	0	1	1	2	0	9
TBC1D10C	0	0	0	1	7	1	0	0	0	0	0	9
PPP1R16B	3	1	0	0	0	0	0	2	2	0	0	8
RARRES3	2	0	0	2	1	0	0	1	0	1	1	8
LAPTM5	0	1	0	0	0	2	0	0	0	3	2	8
DOK2	0	1	4	0	0	0	0	0	0	2	1	8
SLA	0	0	3	3	0	0	0	0	0	0	2	8
LCP1	0	0	0	0	4	1	0	3	0	0	0	8
GBP4	0	0	0	0	4	0	0	2	1	1	0	8
LCP2	0	0	0	0	0	0	0	0	1	4	3	8
PREX1	0	0	0	0	7	0	0	0	0	0	0	7
WIPF1	5	0	0	0	0	0	0	0	0	0	1	6
CTSS	1	0	0	0	5	0	0	0	0	0	0	6
PTPN7	0	3	0	0	0	1	0	0	0	0	2	6
GPR65	0	1	0	0	0	1	0	4	0	0	0	6
DAPP1	0	0	1	2	0	2	0	0	0	0	1	6
PLEK	0	0	0	1	0	0	0	0	0	3	2	6
PTPN22	0	0	0	1	0	0	0	1	3	1	0	6
NCF2	0	0	0	0	0	1	0	0	1	3	1	6
RCSL1	0	0	0	0	0	0	0	3	3	0	0	6
C1S	3	0	0	1	1	0	0	0	0	0	0	5
CD274	4	0	0	0	0	0	0	1	0	0	0	5
SOCS3	2	0	2	0	0	0	0	0	0	0	1	5
IL1B	1	0	0	0	1	0	0	0	0	3	0	5
ACAP1	0	4	0	0	0	1	0	0	0	0	0	5
PTPRCAP	0	2	0	0	0	1	0	0	0	1	1	5
SLAMF8	0	2	0	0	0	1	0	0	0	0	2	5
NCKAP1L	0	0	2	0	0	3	0	0	0	0	0	5
CD6	0	0	0	1	4	0	0	0	0	0	0	5
PTPRC	0	1	0	0	0	0	0	3	0	0	1	5
FPR2	0	0	4	0	0	0	1	0	0	0	0	5
PPP1R3B	0	0	0	4	0	0	1	0	0	0	0	5
SLCO2B1	0	0	0	0	0	1	0	0	0	3	1	5
ITK	0	0	0	0	0	0	1	0	4	0	0	5

CD5	0	0	0	0	0	0	0	0	2	2	1	0	5
RHOH	0	0	0	0	0	0	0	0	1	0	3	1	5

**Apoptosis (50 enriched modules)**

	BLCA	BRCA	COADREAD	GBM	HNSC	KIRC	LAML	LUAD	LUSC	OV	UCEC	Total number of regulated modules
Number of enriched modules	3	3	3	11	4	5	1	3	3	9	5	50
OAS2	1	1	0	1	2	0	0	1	1	1	1	9
TRIM22	0	0	1	1	2	0	0	0	1	1	0	6
BIRC3	2	0	0	3	0	0	0	0	0	0	0	5
RARRES3	0	0	0	2	0	0	0	1	0	1	0	4
PARP9	2	0	0	0	0	0	0	0	1	0	1	4
IL1B	1	0	0	0	1	0	0	0	0	2	0	4
CCL5	0	1	0	0	0	0	0	0	1	1	1	4
PSMB8	0	1	0	2	0	0	0	0	0	1	0	4
BST2	0	0	1	2	0	0	0	1	0	0	0	4
SRPX2	0	0	0	3	0	1	0	0	0	0	0	4
CD274	3	0	0	0	0	0	0	0	0	0	0	3
IRF7	1	0	0	1	1	0	0	0	0	0	0	3
SP100	0	0	0	0	1	0	0	1	1	0	0	3
BATF2	0	1	0	0	0	0	0	0	1	1	0	3
ETV7	0	1	0	0	1	0	0	0	0	0	1	3
MX2	0	1	0	0	1	0	0	0	0	1	0	3
OAS1	0	1	0	0	0	0	0	0	0	1	1	3
PPP1R3B	0	0	0	3	0	0	0	0	0	0	0	3
IFI35	0	0	0	1	0	0	0	0	0	1	1	3
EPSTI1	0	0	0	0	2	0	0	0	0	0	1	3
XAF1	0	0	0	0	0	0	0	0	1	1	1	3

**Metastases (85 enriched modules)**

	BLCA	BRCA	COADREAD	GBM	HNSC	KIRC	LAML	LUAD	LUSC	OV	UCEC	Total number of regulated modules
Number of enriched modules	11	7	6	7	9	6	2	7	10	14	6	85
FSTL1	2	1	0	0	0	1	0	1	2	3	2	12
EMILIN1	0	0	0	1	0	0	0	1	1	1	3	7
GJB5	1	0	1	0	0	0	0	1	2	0	1	6
CD248	3	0	1	0	0	0	1	0	0	0	0	5
KRT16	2	2	0	0	0	0	0	0	0	1	0	5
OAS2	1	1	0	1	0	0	0	0	0	1	1	5
IL1RN	1	0	0	0	0	0	0	0	4	0	0	5
NUAK1	0	0	1	0	0	0	0	1	0	3	0	5
SDR9C7	0	0	0	0	5	0	0	0	0	0	0	5
BIRC3	2	0	0	2	0	0	0	0	0	0	0	4
IL1B	1	0	0	0	1	0	0	0	0	2	0	4
S100A14	1	0	0	0	0	0	0	0	2	0	1	4
OLFML1	0	1	0	0	0	0	0	0	0	1	2	4
TRIM29	0	1	0	0	0	0	0	0	1	2	0	4
NCCRP1	0	1	0	0	3	0	0	0	0	0	0	4
A2ML1	0	1	0	0	0	0	0	0	2	0	1	4
ACTA2	0	0	0	0	0	0	0	0	0	3	1	4
TGFB3	0	0	1	0	0	1	0	0	0	2	0	4
NNMT	0	0	0	0	0	0	0	0	0	4	0	4
RUNX2	0	0	0	0	0	0	0	0	0	4	0	4
CLIP3	2	0	0	0	0	0	0	0	0	0	1	3
KRT5	1	0	0	0	0	0	0	0	2	0	0	3
TMEM40	1	0	0	0	0	0	0	0	1	1	0	3
MCL1	2	0	0	0	0	0	0	0	0	1	0	3
SOCS3	2	0	1	0	0	0	0	0	0	0	0	3
GNA15	0	0	0	0	0	0	0	1	2	0	0	3
CHEK1	0	0	0	0	0	0	0	1	0	2	0	3
S100A16	1	0	0	0	0	0	0	2	0	0	0	3
PCOLCE	0	1	0	0	0	0	0	0	0	2	0	3
ANGPTL2	0	1	0	0	0	0	0	0	1	0	1	3
KCNJ11	0	1	0	0	0	1	0	1	0	0	0	3
DDR2	0	0	0	0	0	0	0	0	1	1	1	3
OAS1	0	1	0	0	0	0	0	0	0	1	1	3
PSMB8	0	1	0	1	0	0	0	0	0	1	0	3
SFN	0	0	1	0	0	1	0	0	0	0	1	3



HIVEP2	0	0	0	2	0	0	0	0	0	0	0	0	2
KIAA0247	0	0	0	0	0	0	0	0	0	0	2	0	2
TUBA1C	0	0	0	2	0	0	0	0	0	0	0	0	2
HINT3	0	0	0	1	0	1	0	0	0	0	0	0	2
IFI35	0	0	0	1	0	0	0	0	0	0	1	0	2
TMEM71	0	0	0	0	0	0	0	0	0	0	2	0	2
CHI3L1	0	0	0	1	0	0	0	0	0	1	1	0	2
XAF1	0	0	0	0	0	0	0	0	1	1	1	0	2
FIG4	0	0	0	0	0	1	0	1	0	0	0	0	2
MYBL2	0	0	0	0	0	0	0	2	0	0	0	0	2
STMN1	0	0	0	0	0	0	0	0	0	2	0	0	2
TMEM140	0	0	0	0	0	0	0	0	0	2	0	0	2
EZH2	0	0	0	0	0	0	0	0	0	2	0	0	2
PTTG2	0	0	0	0	0	0	0	0	0	2	0	0	2

(b) Alterations of the top drivers across all cancer sites

	BLCA	BRCA	COADREAD	GBM	HNSC	KIRC	LAML	LUAD	LUSC	OV	UCEC
CHEK1	Amplified		Amplified					Amplified		Amplified	
FSTL1	Hypo-methylated	Hyper-methylated				Hyper-methylated		Hyper-methylated	Hyper-methylated	Hypo and hyper-methylated	Hypo and hyper-methylated
TGFB3			Hyper-methylated			Hyper-methylated				Hypo-methylated	
NUAK1			Hyper-methylated		Hypo-methylated			Hypo and hyper-methylated	Hypo and hyper-methylated	Hypo-methylated	Hypo and hyper-methylated
CCL5		Hyper-methylated			Hyper-methylated	Hyper-methylated		Hyper-methylated	Hyper-methylated	Hyper-methylated	Hyper-methylated

(c) Comparison of average number of enriched gene sets per module in 100 random permutations vs. the actual modules per cancer.

Cancer Site	Permuted data:	Actual data
	Average # of gene sets enriched per module, averaged over 100 permutations	Average # of gene sets enriched per module
BLCA	0.2708	27.19
BRCA	0.196	23.02
COADREAD	0.1688	21.12
GBM	0.3855	35.21
HNSC	0.3855	25.03
KIRC	0.1442	20.23
LAML	0.3289	19.24
LUAD	0.1403	24.49
LUSC	0.1931	21.52
OV	0.4029	39.6
UCEC	0.2316	23.49