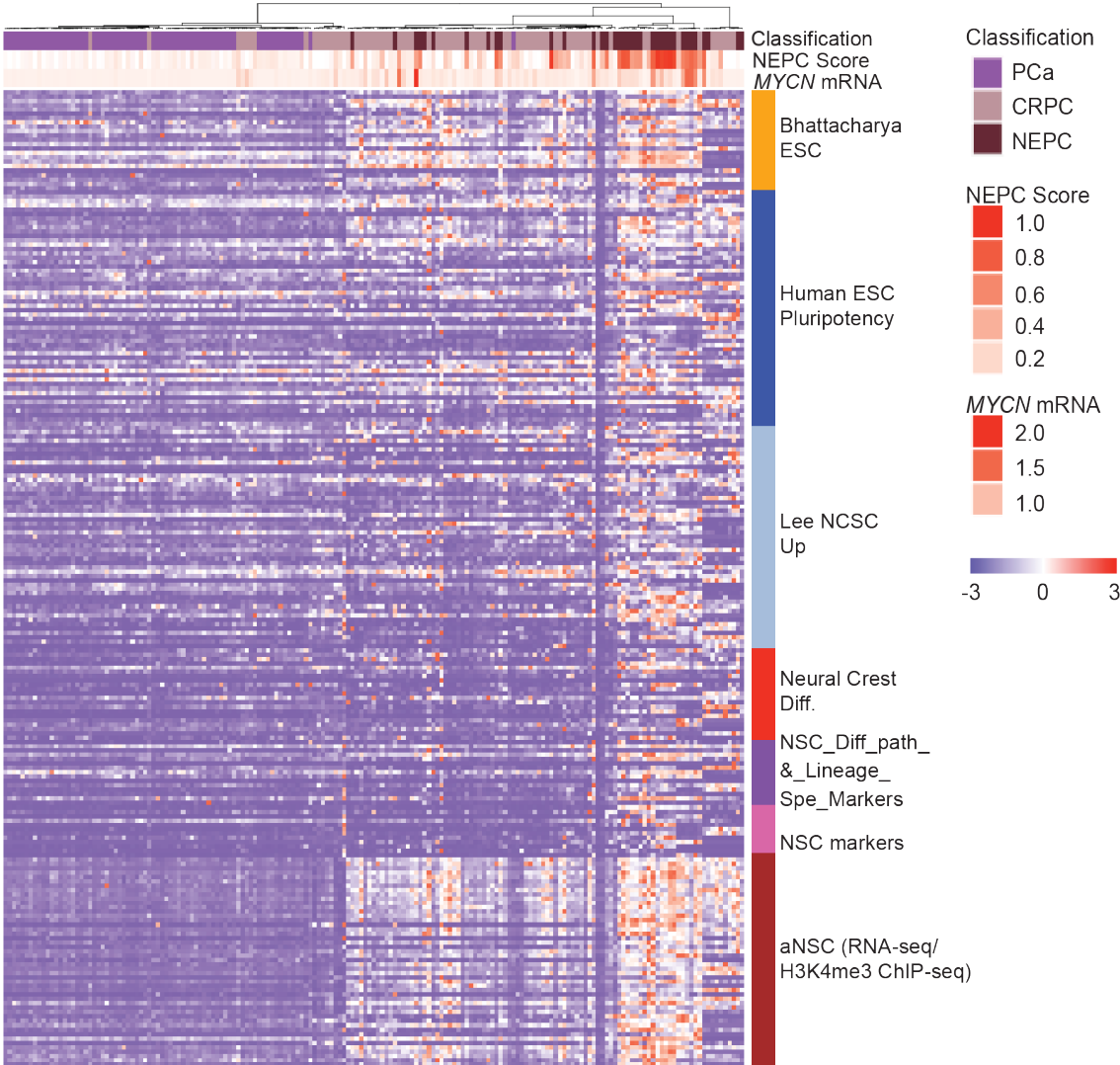


Supplemental Figures

A



B

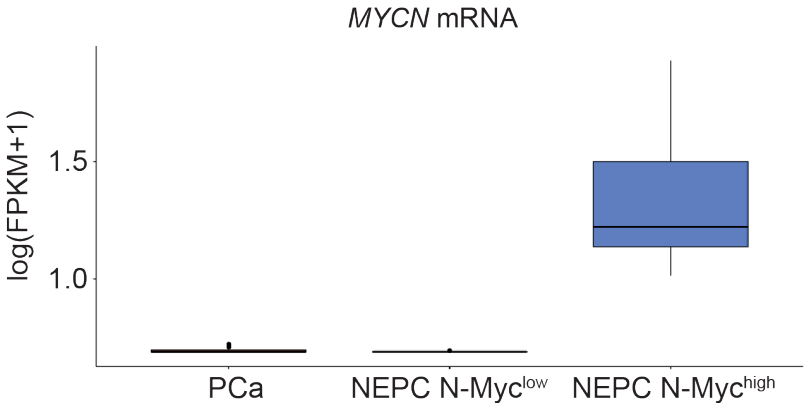


Figure S1. Clinical NEPC is associated with neural lineage.
A) Clustering of PCa (n = 66), CRPC (n = 73) and NEPC (n = 36) patient samples classified based on the expression level of the leading edge genes of each geneset (NEPC versus PCa) indicated on the right. **B)** Expression of MYCN in PCa, NEPC N-Myc^{low} or NEPC N-Myc^{high} patients. Graph depicts the median value between the 25th and 75th percentiles with whiskers indicating the range within 1.5 IQR.

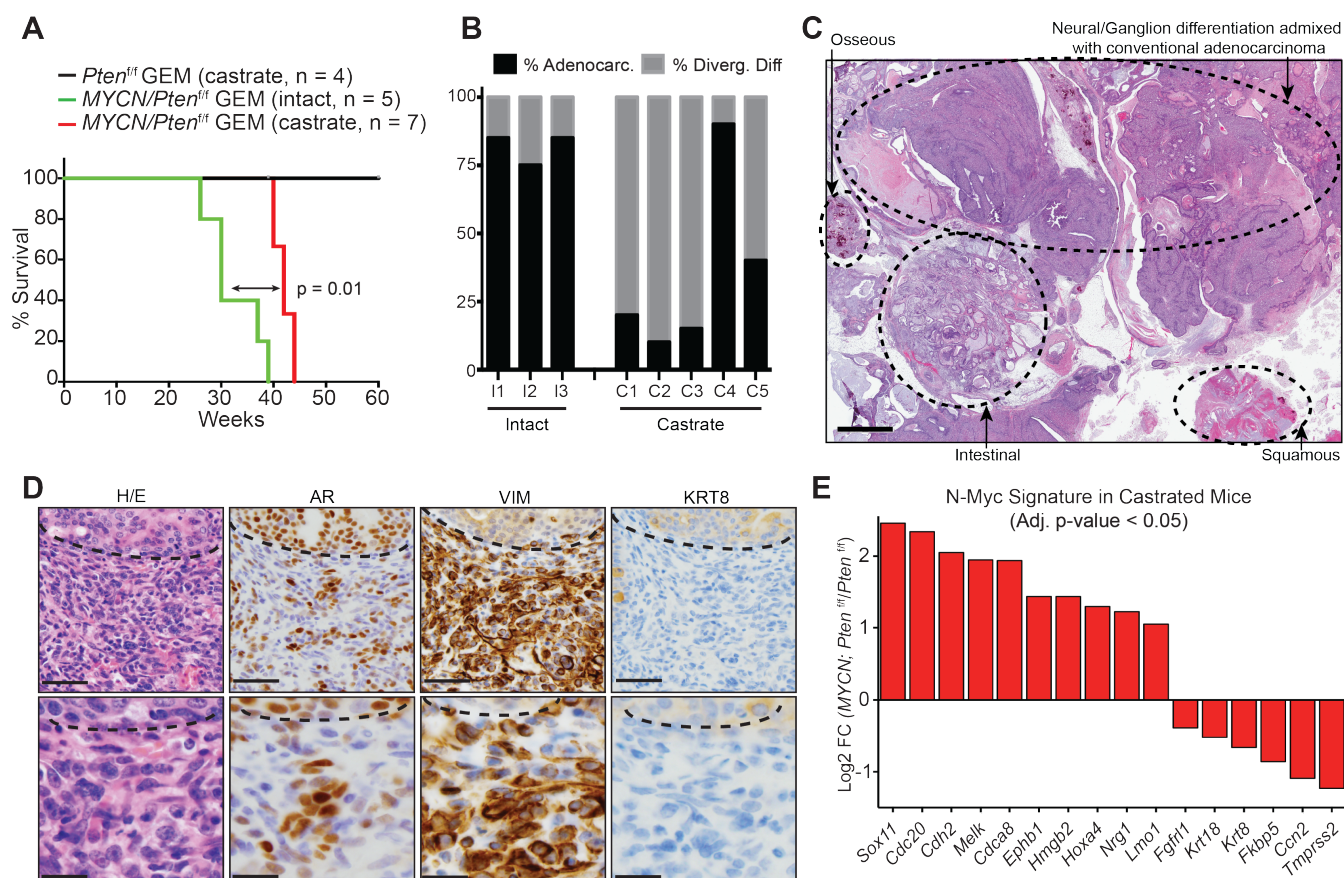


Figure S2. N-Myc promotes the acquisition of alternative lineage states in response to castration.

(A) Survival curve of castrated or intact GEM as indicated. Survival analysis was performed using the Kaplan-Meier estimator (log-rank test). (B) Percentage of tumor foci with adenocarcinoma or divergent differentiated tumor tissue in 10-12 month old intact or castrated *Pb-Cre*^{+/-}; *Pten*^{fl/fl}; *LSL-MYCN*^{+/-} mice based on pathologist assessment. (C) Low power photomicrograph of a representative H&E-stained section from mouse C1 (B) showing the diversity of indicated histologies (dotted lines) (scale bar = 3mm). (D) Higher magnification (scale bar = 50μm) photomicrograph images of H/E staining or IHC staining for epithelial (AR and KRT8) or mesenchymal (VIM) marker on 4μm serial sections from mouse C5 (B). Dotted lines indicate conventional adenocarcinoma adjacent to mixed lineage cells. (E) Examples of deregulated genes in *Pb-Cre*^{+/-}; *Pten*^{fl/fl}; *LSL-MYCN*^{+/-} mice versus *Pten*^{fl/fl} mice following castration (n = 3 biological replicates per condition).

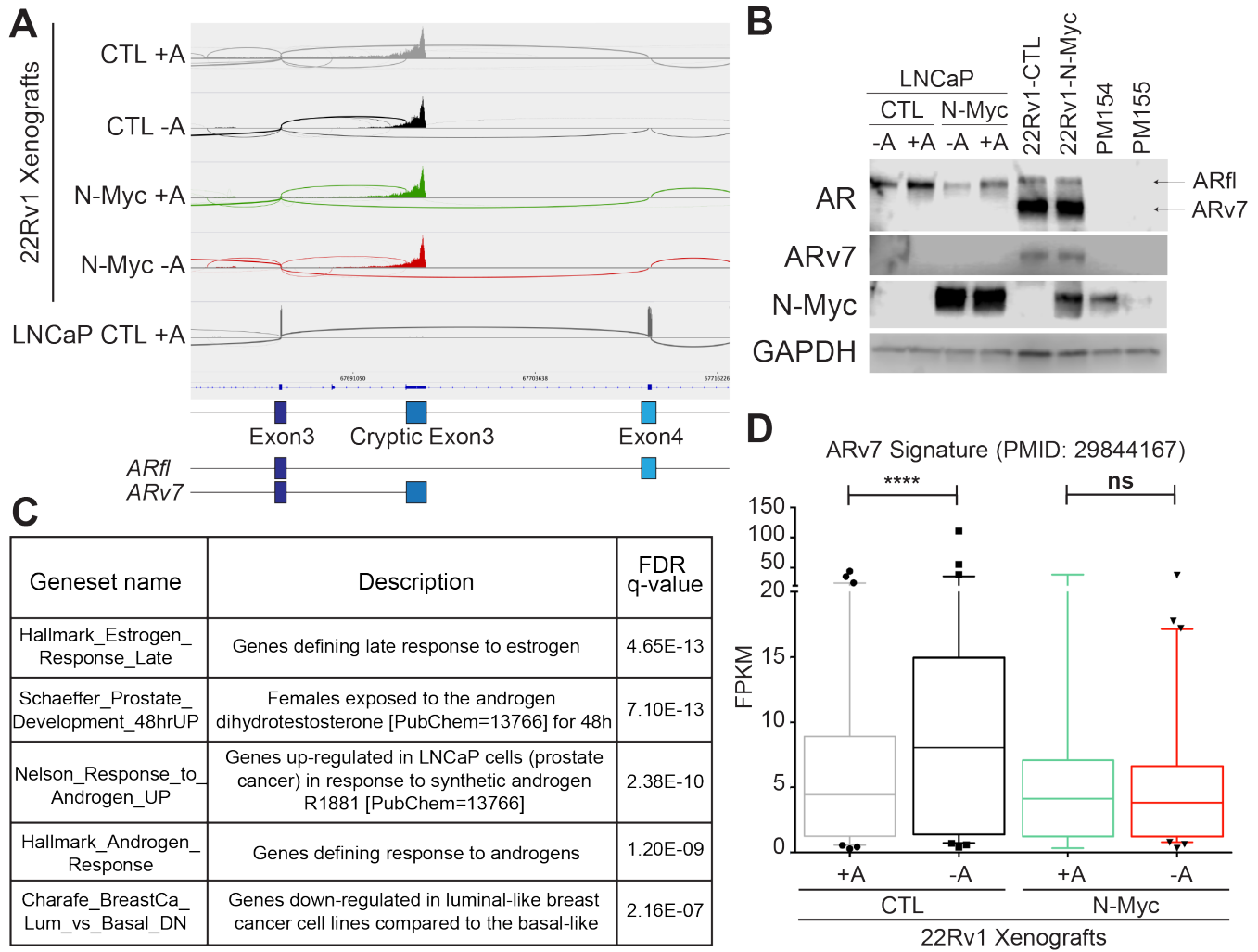


Figure S3. Expression of ARv7 signatures are downregulated by N-Myc.

(A) Splicing map of *AR* RNA-seq transcripts from 22Rv1-CTL and 22Rv1-N-Myc xenografts grown in intact (+A) or castrated (-A) recipients showing splicing and inclusion of cryptic exon 3 (encoding ARv7). LNCaP cells depicted as a negative control. (B) Western blot for AR, ARv7 and N-Myc across LNCaP cell models, 22Rv1 cell models, and NEPC patient-derived organoids. (C) Results of GSEA performed on the significantly downregulated genes in castrated recipients [Figure 2C]. (D) Expression levels of ARv7 signature genes in 22Rv1 xenografts as indicated. Graph depicts the median value between the 25th and 75th percentiles with whiskers indicating the range between the 10th and 90th percentiles. **** p < 0.0001, Friedman test.

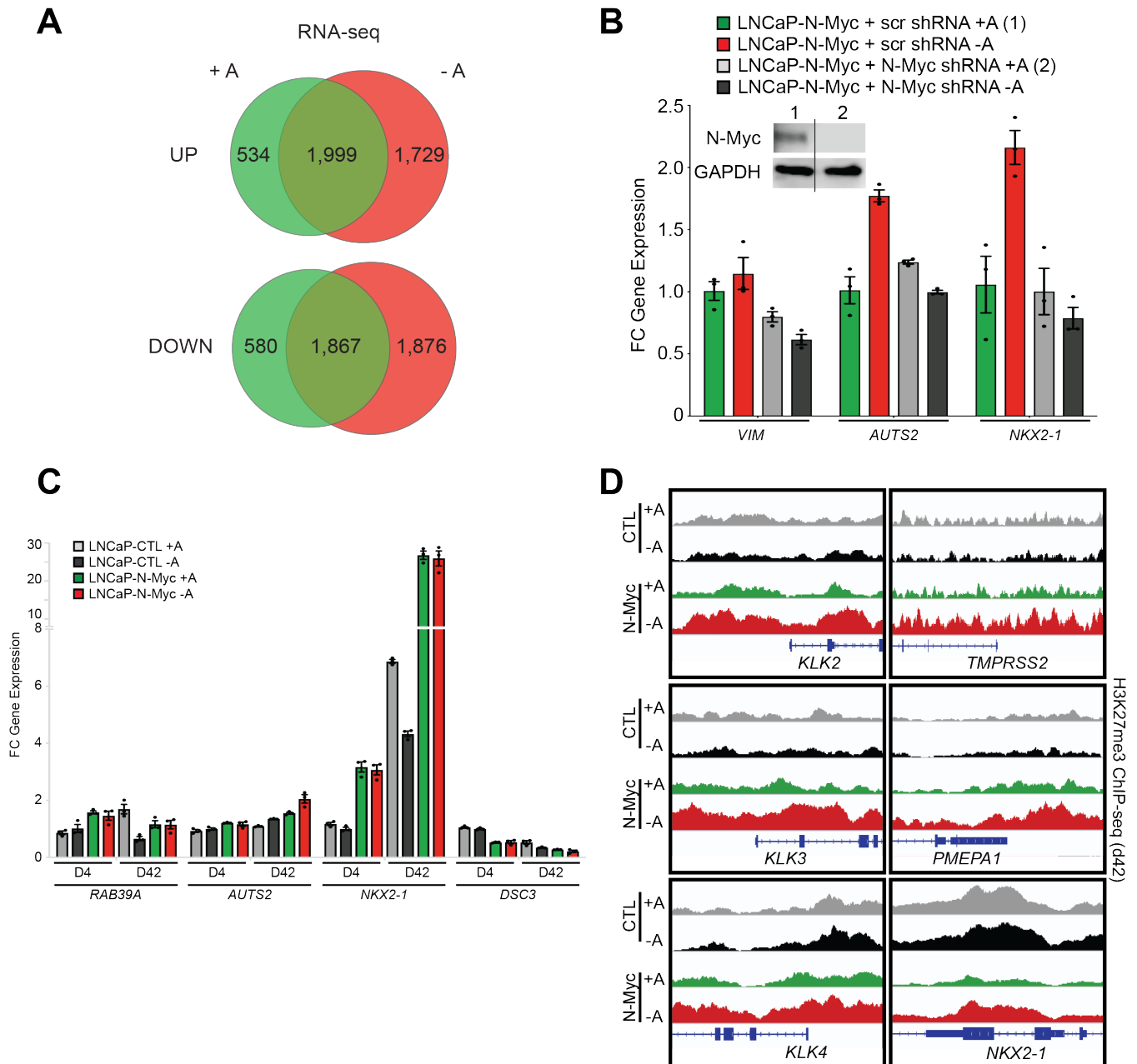


Figure S4. AR signaling alters the N-Myc transcriptome *in vitro*.

(A) Differentially expressed genes (adj. p-value < 0.05) measured by RNA-seq in LNCaP N-Myc cells versus CTL cells as indicated. (B) Fold change gene expression based on qRT-PCR data (n = 3 technical replicates per condition) of a known N-Myc target gene (*VIM*) and neural-lineage associated genes (*AUTS2*, *NKX2-1*), in LNCaP N-Myc cells following knockdown of N-Myc as indicated (see Western Blot inset). Lanes were run on the same gel but were noncontiguous. (C) Fold change gene expression of neural (*RAB39A*, *AUTS2*, *NKX2-1*) or epithelial (*DSC3*) lineage-associated genes measured by qRT-PCR as indicated (n = 3 technical replicates per condition). (D) H3K27me3 levels in the indicated conditions at D42.

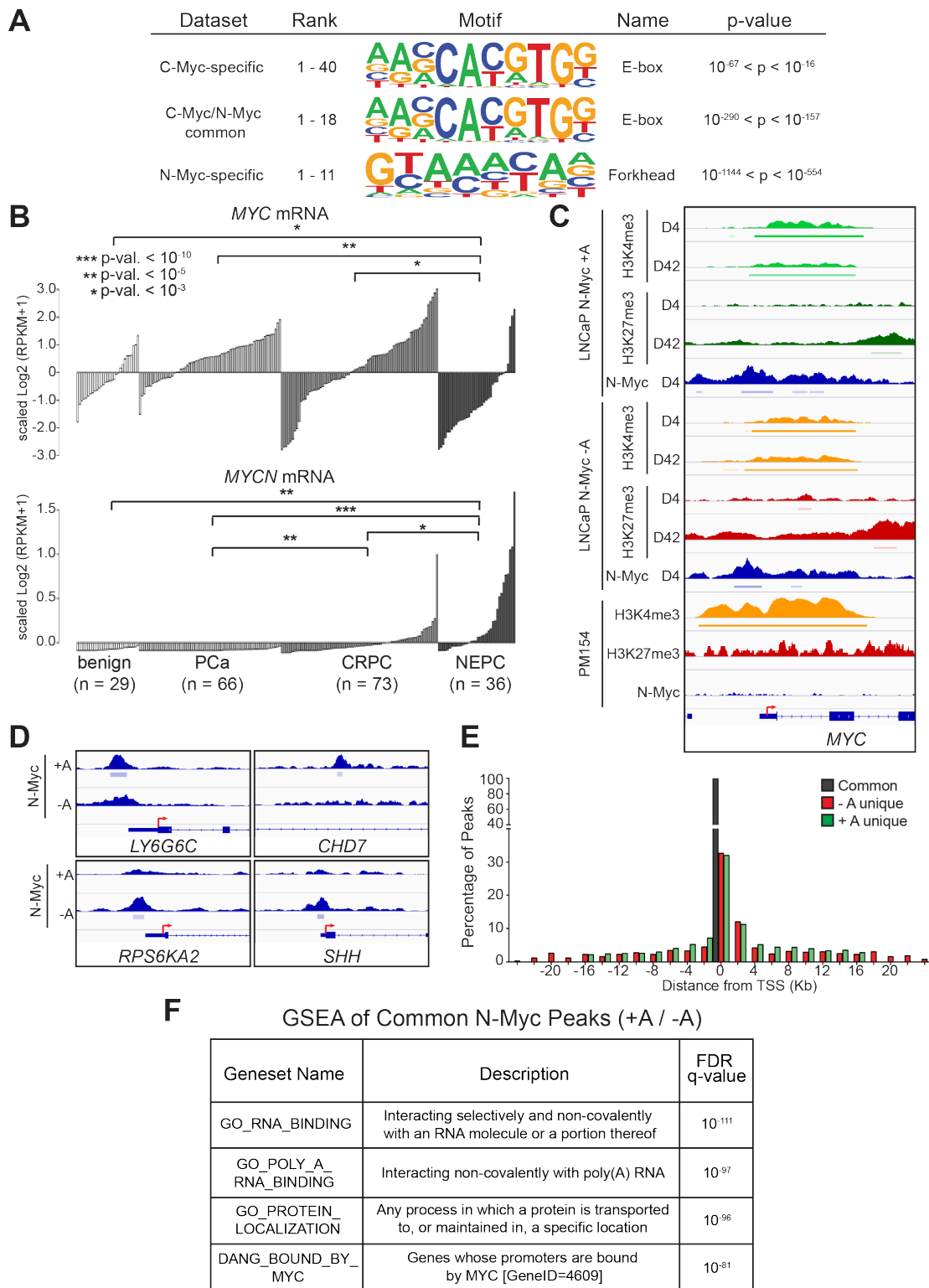


Figure S5. C-Myc downregulation in cell lines and NEPC patient samples.

(A) Motif analysis performed on C-Myc-specific peaks, N-Myc specific peaks, or C-Myc/N-Myc common peaks in LNCaP cells. Significance determined by hypergeometric test. (B) *MYC* and *MYCN* gene expression in benign, PCa, CRPC and NEPC patient samples. Significance determined by Wilcoxon test. (C) N-Myc, C-Myc and histone binding at *MYC* locus in the indicated cells and conditions. (D) Examples of N-Myc binding sites unique to the presence or absence of androgen. (E) Distribution around TSS of N-Myc peaks in indicated conditions. Only the closest 50% of peaks to TSS are shown for clarity. (F) Results of GSEA performed on the N-Myc-bound peaks that are common in the presence or absence of androgen and located within 100bp of a TSS.

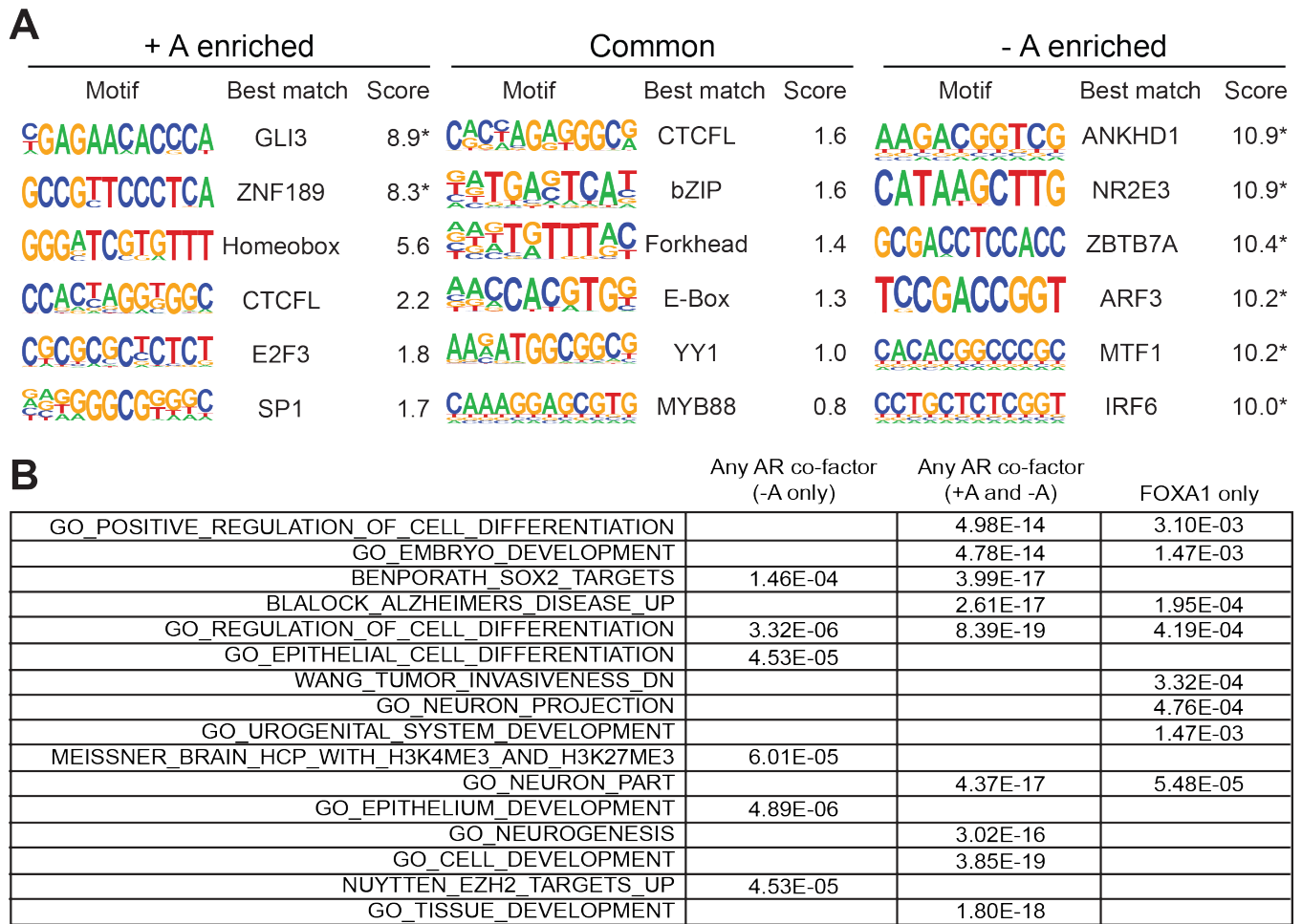


Figure S6. Characterization of dynamic N-Myc binding sites.

(A) Motif analysis of N-Myc peaks in the indicated conditions. Motifs are listed with their best predicted match to a known protein family. (B) Table of FDR q-values of the significantly enriched genesets that were among the top 50 in the GSEA analysis performed for the indicated N-Myc and AR co-factor co-bound genes. Blank cells indicate that the specific geneset did not appear in the top 50 for the indicated GSEA analysis.

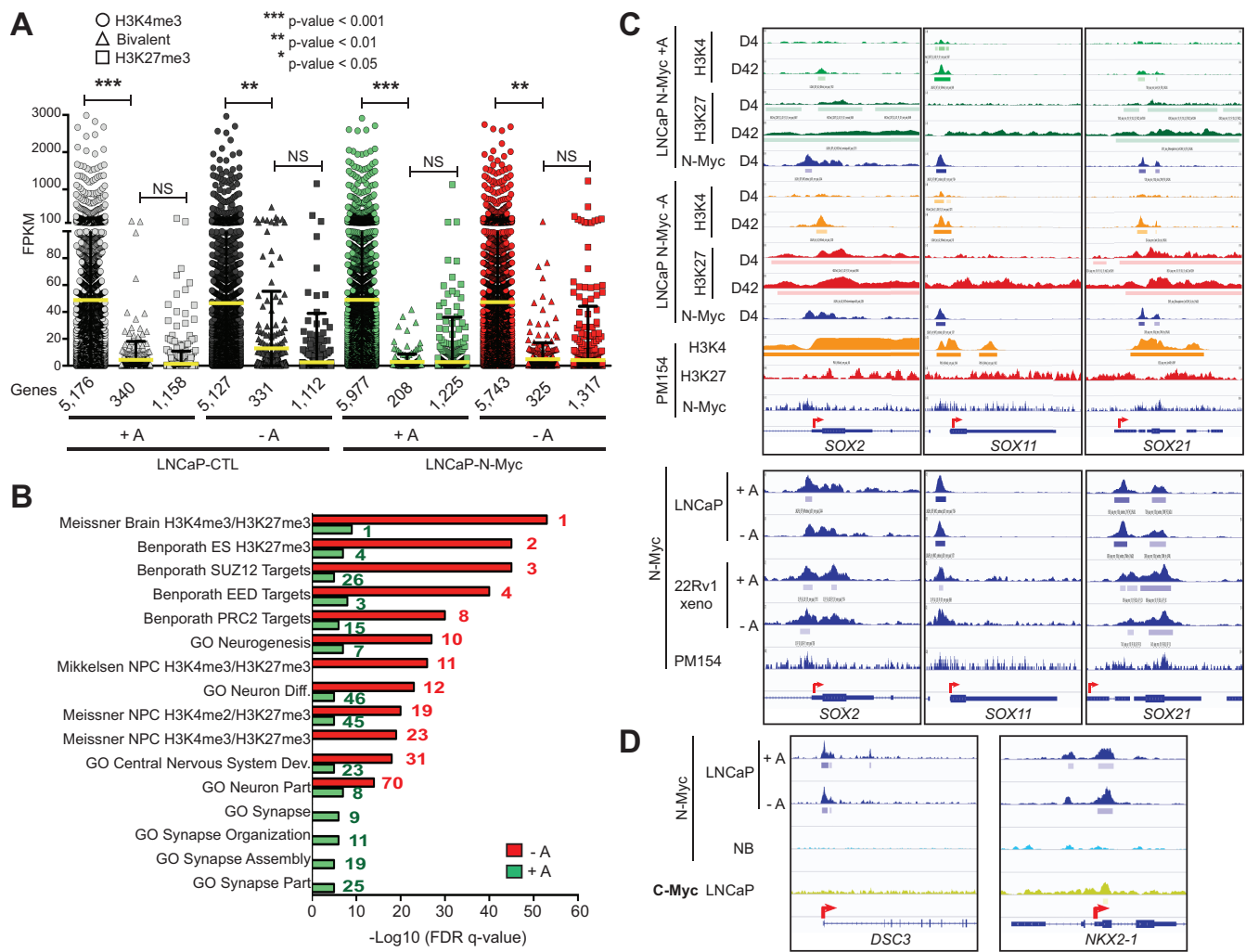


Figure S7. N-Myc regulates bivalency and gene expression.

(A) RNA-seq gene expression of the H3K4me3 only, H3K27me3 only and bivalent marked genes in the indicated cells and conditions. Statistical significance was assessed with Tukey's multiple comparison test. (B) GSEA results and ranking of genesets enriched in bivalent and N-Myc bound genes in the indicated conditions. (C) ChIP-seq tracks for N-Myc, H3K4me3 and H3K27me3 at the *SOX2*, *SOX11* and *SOX21* loci in the different models and indicated conditions. (D) ChIP-seq tracks for N-Myc in LNcaP-N-Myc cells with and without androgen, C-Myc in LNcaP cells with androgen, or N-Myc in BE2C neuroblastoma cells at the indicated genes.

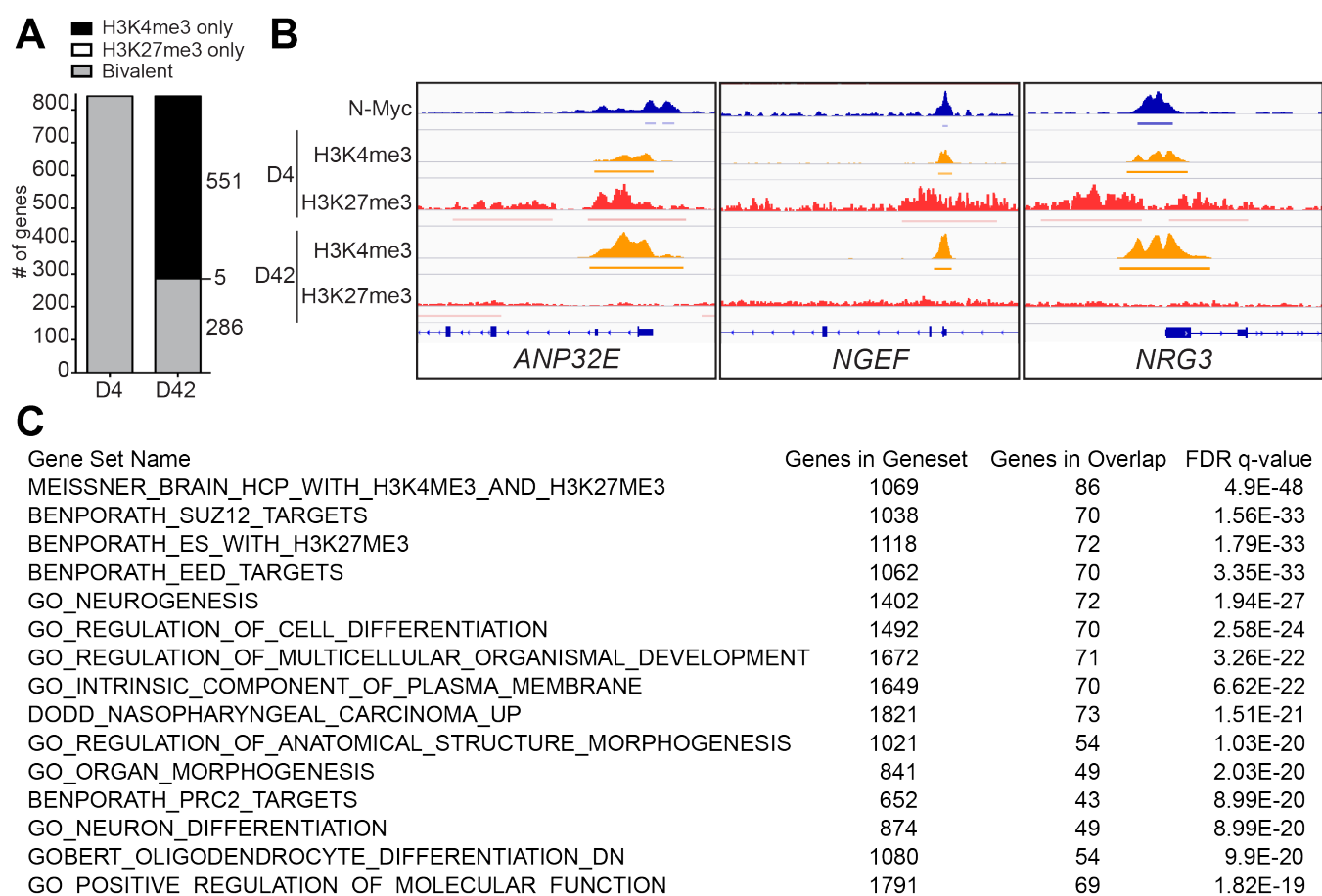


Figure S8. Bivalently marked genes at D4 lose H3K27me3 at D42.

(A) Quantification of the number of genes that were bivalently marked and N-Myc bound at D4 [left] and their status at D42 [right] (B) ChIP-seq tracks of N-Myc binding, H3K4me3, and H3K27me3 in LNCaP-N-Myc cells at the indicated genes, in the indicated conditions. (C) Results of GSEA performed on the 551 genes that were bivalent at D4 but became H3K4me3 only at D42.

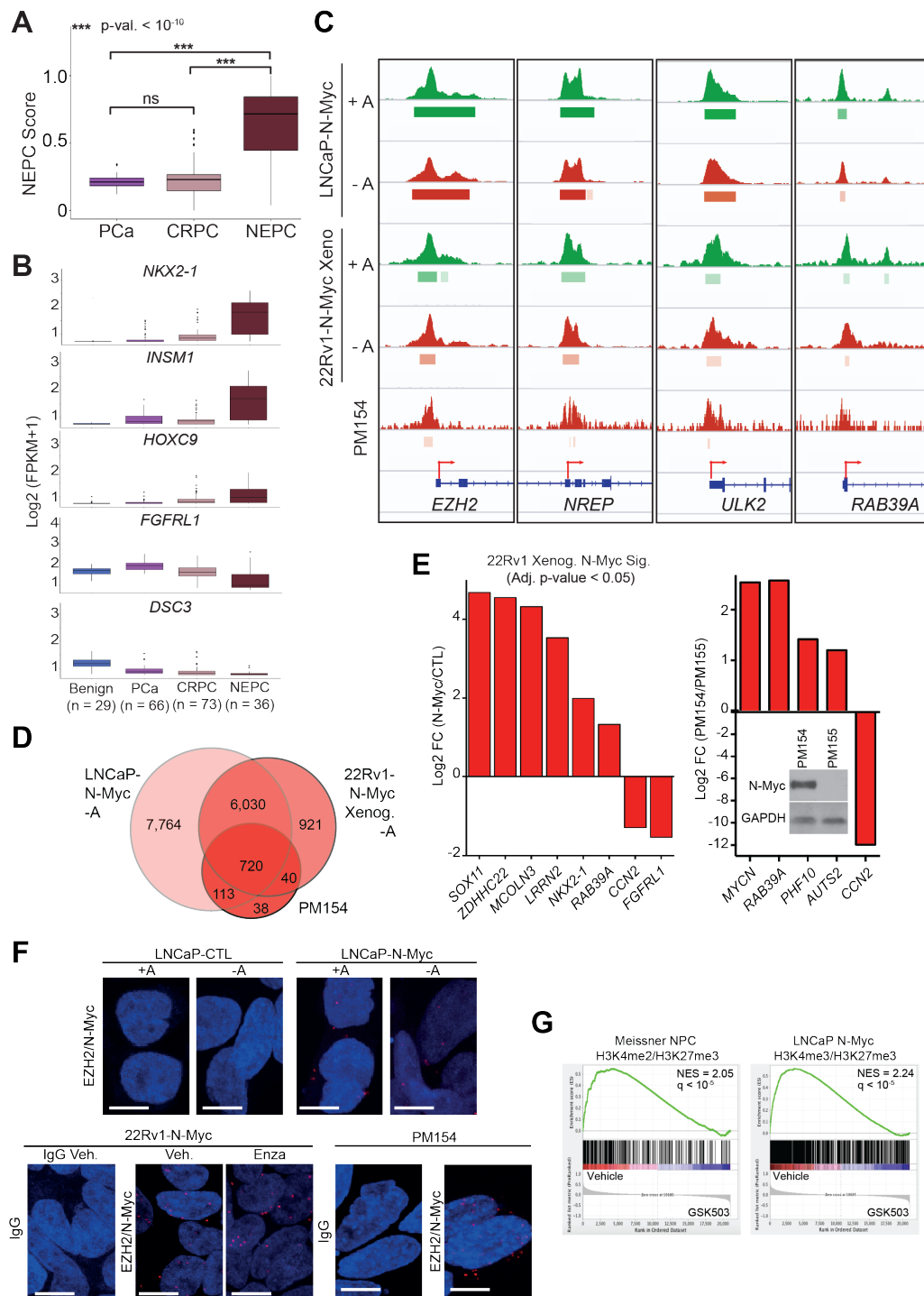


Figure S9. Validation of N-Myc induced bivalent genes in models and patient samples.

(A) Distribution of NEPC Score across PCa, CRPC and NEPC patients. Graph depicts the median value between the 25th and 75th percentiles with whiskers indicating the range within 1.5 IQR, Student's unpaired two-tailed t test. (B) Box plots of the mRNA expression for the indicated genes in benign, PCa, CRPC and NEPC clinical samples. (C) ChIP-seq tracks of N-Myc binding in LNCaP-N-Myc (n = 2 biological replicates per condition), 22Rv1-N-Myc xenografts (n = 2 biological replicates per condition) and PM154 cells at the indicated genes, in the indicated conditions. (D) Overlap of the numbers of genes bound by N-Myc in LNCaP-N-Myc, 22Rv1-N-Myc and PM154 cells. (E) Log₂ fold change (N-Myc vs CTL xenografts from castrated mice, left) and log₂ fold change (PM154 versus PM155, right) of indicated genes after validation of N-Myc expression by Western Blot (see inset). (F) Proximity ligation assay showing EZH2 and N-Myc interactions in the indicated cells and conditions (scale bar = 5 μ m). (G) Enrichment plots of the Meissner NPC H3K4me2/H3K27me3 and LNCaP N-Myc bivalent genesets from PM154 cells in the indicated conditions.

Supplemental Tables

Table S1. Neuronal lineage and AR signaling-associated genesets.

Gene list	Human Embryonic Stem Cell Pluripotency	Bhattacharya_Embryonic_Stem_Cell	Ramalho_Stemness_Up	Boquest_Stem_Cell_Up	Lee_Neural_Crest_Stem_Cell_Up	Neural Crest Differentiation	Neural Stem Cell Differentiation Pathways and Lineage-specific Markers
From	Pathcards	GSEA Broad Institute	GSEA Broad Institute	GSEA Broad Institute	GSEA Broad Institute	Pathcards	Pathcards
Size	186	89	206	260	146	102	79

Gene List	Neural Stem Cell Markers	UP In Activated NSC Vs Quiescent NSC	UP In Quiescent NSC Vs Activated NSC	UP In NPC Vs Activated NSC	UP In Activated NSC Vs NPC	UP In Activated NSC Vs Quiescent NSC H3K4me3 And Expressed In Our Data aNSC	Hallmark_Androgen_Response
From	Rndsystems	PMID 28099854	PMID 28099854	PMID 28099854	PMID 28099854	PMID 28099854 Overlap With Our Data From aNSC	GSEA Broad Institute
Size	58	2287	606	357	385	1670	101

Gene list	Go_Neuron_Differentiation	Go_Neuron_Fate_Commitment	Go_Neurogenesis	Go_Neural_Crest_Cell_Differentiation	Go_Stem_Cell_Differentiation	Go_Neuronal_Stem_Cell_Population_Maintenance	Smith signature ASC (only used for comparison with LNCaP cell data.)
From	GSEA Broad Institute	GSEA Broad Institute	GSEA Broad Institute	GSEA Broad Institute	GSEA Broad Institute	GSEA Broad Institute	PMID 30232014
Size	874	67	1402	75	190	19	50

Table S2. Top 50 N-Myc interacting proteins identified by RIME.

		Peptide Counts				Log ₂ Signal/Noise FC (N-Myc / IgG)	
Uniprot	Name	IgG DHT	N-Myc DHT	IgG EtOH	N-Myc EtOH	DHT	EtOH
Q92804	TAF15	1	99	0	89	10.0	9.8
P04198	MYCN	0	86	0	95	9.8	10.2
Q96AE4	FUBP1	5	162	4	146	9.3	9.1
Q01844	EWSR1	1	71	0	59	9.2	9.1
P35637	FUS	4	81	6	76	8.8	8.1
P08621	SNRNP70	0	84	0	70	8.8	8.1
Q96PK6	RBM14	5	128	7	113	8.8	7.9
Q92945	KHSRP	7	152	11	150	8.7	8.1
P17844	DDX5	9	121	12	124	8.4	6.8
P23246	SFPQ	14	235	18	190	8.1	6.1
Q9Y4A5	TRRAP	0	181	0	184	8.1	8.1
Q16630	CPSF6	1	57	4	47	7.6	6.7
P49750	YLPM1	0	153	1	141	7.6	7.4
P14866	HNRNPL	13	124	14	100	7.6	5.7
P38159	RBMX	25	176	25	177	7.5	6.8
P51991	HNRNPA3	24	139	33	134	7.5	5.6
Q92841	DDX17	22	155	31	143	7.4	5.6
P09651	HNRNPA1	19	162	22	147	7.1	6.3
O14979	HNRNPDL	3	48	5	50	7.1	5.5
Q14103	HNRNPD	4	73	4	70	7.1	6.9
Q07666	KHDRBS1	7	67	5	63	7.0	6.8
Q8IXT5	RBM12B	2	86	4	62	6.9	6.4
P61978	HNRNPK	19	160	21	135	6.9	5.8
P22626	HNRNPA2B1	29	165	40	162	6.9	5.3
Q8WXF1	PSPC1	3	68	2	59	6.9	6.7
Q9BUJ2	HNRNPUL1	2	90	1	79	6.9	7.0
Q9HCD5	NCOA5	2	80	2	61	6.8	6.8
P09012	SNRPA	0	26	0	26	6.8	6.2
Q07955	SRSF1	12	73	12	67	6.7	6.2
Q12906	ILF3	8	125	8	121	6.7	6.0
O43809	NUDT21	4	53	2	45	6.7	6.6
Q8N684	CPSF7	5	46	5	39	6.7	5.5
Q13242	SRSF9	5	59	8	56	6.6	5.8
Q14011	CIRBP	0	18	0	20	6.6	6.3
O43390	HNRNPR	6	97	8	79	6.5	4.9
Q13151	HNRNPA0	7	65	12	61	6.5	4.5
Q9NWH9	SLTM	1	72	3	66	6.5	6.1
Q13228	SELENBP1	4	59	4	62	6.5	6.6
Q9BWF3	RBM4	2	46	3	36	6.4	5.9
Q15637	SF1	0	47	0	37	6.4	5.7
Q15717	ELAVL1	11	66	19	68	6.4	3.8
Q15067	ACOX1	2	56	0	54	6.4	6.3
P31942	HNRNPH3	5	53	7	51	6.3	5.0
P98179	RBM3	2	25	0	24	6.2	6.8
P51659	HSD17B4	16	107	22	120	6.2	4.6
Q9H0D6	XRN2	0	45	0	50	6.1	6.3
P22307	SCP2	2	68	3	80	6.1	6.1
Q15424	SAFB	7	74	3	57	6.0	5.1
P61244	MAX	0	28	0	28	6.0	6.0
Q96124	FUBP3	3	60	2	53	6.0	5.6

Table S3. 966 bivalent and N-Myc bound genes. (1/3)

AACS	AMIGO1	BCL11A	CASC10	CHSY3	DISP3	EPHB1	FHL1
AACSP1	AMOTL2	BDNF	CASC4	CITED4	DIXDC1	EPHB3	FIGN
ABCC8	AMZ2	BEAN1	CASKIN1	CMPK2	DLC1	EPHB6	FJX1
ABLIM1	ANKRD19P	BEGAIN	CASZ1	CMTM8	DLG5	ERC2	FLJ43315
ABLIM2	ANKRD20A1	BEND3	CBARP	CNIH3	DOCK11	ERG	FLT3
ABR	ANKRD20A12P	BEND7	CBFA2T3	CNTFR	DOCK3	ERO1A	FMNL2
ACD	ANKRD20A2	BHLHE41	CCDC122	CNTN4	DOCK5	ESPNP	FMNL3
ACOXL	ANKRD26P1	BICD2	CCDC3	CNTNAP2	DPYSL3	ESRRB	FOXC1
ACTB	ANOS1	BIK	CCDC85A	CNTNAP3	DPYSL4	EXTL3-AS1	FOXD1
ADAM11	ANP32E	BMI1	CCM2L	CNTNAP3P2	DST	EYA2	FOXD3-AS1
ADAM12	ANTXR2	BMP6	CCND2	COL13A1	DTNA	FAM105A	FOXF1
ADAM23	APBB1	BMP8B	CCNO	COL19A1	DUSP22	FAM120B	FOXN3
ADAMTS14	APC2	BMPR1B	CCSER1	COL4A3	DUSP26	FAM135A	FOXO6
ADAMTS15	APCDD1	BRSK2	CD24	COLGALT2	DUSP6	FAM167A	FOXP2
ADAMTS17	AQP4	BSN	CD302	CORO2B	DUSP9	FAM184A	FSCN1
ADAMTS7	ARAP2	BTBD11	CD55	CPLX1	DUXAP10	FAM189A1	FST
ADAMTS9-AS1	ARC	BTBD17	CD8A	CPNE2	DYRK2	FAM189A2	FSTL3
ADAMTSL3	ARHGAP20	BTC	CDC14B	CR2	DYRK3	FAM196A	FSTL4
ADAP1	ARHGAP22	BVES	CDC20B	CREB5	DZIP1	FAM19A5	FYN
ADARB2	ARHGAP23	C11orf96	CDC27	CREG2	EBF3	FAM208A	FZD3
ADCY5	ARHGAP45	C14orf132	CDC42EP3	CRIM1	EBF4	FAM20C	FZD8
ADGRA2	ARHGDIG	C14orf37	CDK13	CSPG5	EDN2	FAM212A	GABRA5
ADGRB1	ARHGEF25	C16orf74	CDK18	CT62	EEF2KMT	FAM222A	GABRB3
ADGRB2	ARHGEF3	C17orf102	CDK6	CTGF	EFNA3	FAM27B	GABRD
ADGRB3	ARHGEF4	C19orf25	CDKN1C	CTHRC1	EFNB3	FAM27C	GAD1
ADGRE5	ARID3C	C19orf81	CDKN2A	CTIF	EGFL7	FAM46A	GALNT12
ADGRL2	ARNTL2	C1QL1	CDYL	CTNND2	EGFLAM	FAM49B	GALNT14
ADRA2A	ASIC1	C22orf34	CECR2	CTSC	EGR3	FAM65B	GALNT16
ADRA2B	ASMTL	C2CD4A	CECR6	CTSF	EGR4	FAM69C	GALNT9
ADRA2C	ASPHD2	C2orf72	CELF4	CTTNBP2	EHBP1L1	FAM74A1	GAS1
AFAP1	ATL1	C3orf70	CELSR1	CUX1	EIF4E3	FAM78A	GAS6-AS1
AFF3	ATP12A	C3orf80	CEP85L	CWH43	ELAVL2	FAM90A7P	GDF6
AGAP1-IT1	ATP6V1C2	C5orf38	CERK	CXADRP3	ELFN1	FANK1	GJC1
AGAP2-AS1	ATRNL1	C7orf33	CFAP99	CYP26A1	ELFN2	FBLIM1	GLI3
AGPS	AUTS2	C8orf34-AS1	CFD	CYP2E1	ELMOD1	FBXL16	GLIPR2
AHNAK	B3GAT1	CACHD1	CHAC1	DACT1	EMBP1	FCGR2A	GLIS1
AHNAK2	B3GNT4	CACNA1C	CHD7	DBH	EMID1	FENDRR	GLIS2
AHR	B4GALNT3	CACNA1H	CHN1	DCAKD	EN2	FEZ1	GNAI1
AHRR	BACH2	CACNB4	CHN2	DDAH1	EOMES	FGF22	GNAO1
AIF1L	BAGE2	CACNG4	CHRM3	DEFA5	EPB41L1	FGF8	GNAQ
AK5	BAHD1	CADM1	CHRM4	DENND3	EPB41L2	FGF9	GNB4
ALDH1A3	BARX2	CAMK1D	CHRNA7	DENND5B	EPB41L4A-AS2	FGFR2	GNG4
ALS2CL	BATF3	CAMK2N2	CHST11	DIRAS1	EPHA7	FGFR3	GOLGA7B
AMER3	BCAR3	CARD10	CHST13	DISC1	EPHA8	FGFRL1	GOLGA8A

Table S3. 966 bivalent and N-Myc bound genes. (2/3)

GPAT3	IGF2BP2	KIAA1456	LOC101927827	MAST1	MTSS1	NR6A1	PCDHB11
GPM6B	IGF2BP3	KIAA1644	LOC101927989	MB21D2	MYC	NRG1	PCDHB2
GPR153	IGSF11	KIF13B	LOC101928416	MCAM	MYLK	NRG2	PCOLCE2
GPR35	IGSF9B	KIF26B	LOC101928674	MCF2L2	MYO5B	NRG3	PCSK5
GPR37	IL15RA	KIT	LOC101929237	MCIDAS	MYRF	NRP2	PDE4A
GPRIN2	IL17RD	KLF14	LOC101929468	MCTP1	N4BP3	NRXN2	PDLIM2
GRIK4	IL24	KREMEN2	LOC102723354	MDGA1	NATD1	NSG1	PDLIM3
GRIN2C	INSM1	KRTAP5-11	LOC102723780	MDGA2	NAV2	NTN1	PDZD2
GRM8	INSM2	KSR1	LOC102724344	MDK	NECAB2	NTNG2	PEAK1
GUCY1A2	INTS10	L3MBTL4	LOC102724421	MECOM	NECTIN3	NTRK2	PEPD
GXYLT2	IQCJ-SCHIP1-AS1	LAMA1	LOC105379477	MED12L	NEFL	NUAK1	PEX5L
HACD1	IQSEC2	LAMC3	LOC389895	MEGF6	NEGR1	NUP210	PFKFB3
HAR1B	IRS4	LARGE2	LOC400927-CSNK1E	MEIS2	NEURL1-AS1	NXNL2	PGBD5
HAS3	ISM1	LGI2	LOC440040	METRNL	NEUROG2	NXPH2	PHF19
HCN2	ITGA2	LGI3	LOC440461	MGAT5B	NFATC1	NXPH4	PHF21B
HECW2	ITGB3	LHX4	LOC642929	MGC12916	NFATC2	OAT	PHF24
HEG1	ITGB4	LINC00265	LOC643201	MIR132	NFE2L3	OGDHL	PHLDA1
HES1	ITPKA	LINC00266-1	LOC645166	MIR212	NGEF	OLFM1	PHTF2
HEY1	ITPRIPL1	LINC00273	LOC650293	MIR302B	NHS	OLFM2	PIGZ
HEY2	JADE2	LINC00350	LOC653653	MIR3132	NIM1K	ONECUT1	PIK3CD-AS2
HFM1	JAK3	LINC00417	LOC654342	MIR3648-2	NKAIN1	OR8G2	PIP4K2A
HIC1	JAKMIP3	LINC00621	LOC728739	MIR3665	NKAIN2	OSBP2	PIP5K1B
HMX1	KANK1	LINC00693	LOC729652	MIR3667	NKD1	OSMR	PITPNC1
HNF1B	KANK3	LINC00937	LOC729732	MIR3687-2	NKD2	OTOP1	PITPNM3
HOXB-AS3	KAZN	LINC00942	LRCOL1	MIR3688-2	NKX1-2	OTP	PKDCC
HOXB8	KBTBD11	LINC00960	LRFN5	MIR4477B	NKX2-1	OVOL1	PKIA
HOXB9	KCNC1	LINC00963	LRP12	MIR4694	NKX2-2	OXR1	PLAGL1
HOXC9	KCNC3	LINC01336	LRP4	MIR5481I	NKX2-8	P2RX2	PLCB1
HOXD12	KCNC4	LINC01389	LRRC7	MIR54812	NKX6-1	P2RX5	PLCG2
HOXD13	KCND3	LINC01607	LRRC75A	MIR54813	NLGN1	P2RY1	PLCL2
HPSE	KCNIP3	LINC01876	LRRC8C	MIR5692A1	NLRP6	P3H2-AS1	PLEKHG1
HRH3	KCNJ12	LINC02043	LRRN2	MIR6081	NMU	P4HA3	PLEKHG5
HRK	KCNJ4	LINC02076	LTBP4	MIR663A	NOC2L	PALD1	PLEKHO1
HS3ST3A1	KCNK13	LINC02139	MAD2L2	MIR6724-1	NOG	PALM2	PLOD2
HS3ST3B1	KCNMA1	LKAAEAR1	MAEL	MIR6724-4	NOL4L	PAM	PLPP4
HS6ST3	KCNMB4	LMO1	MAF	MIR7160	NOTUM	PAPPA	PLPPR1
HTR6	KCNQ1	LMO2	MAMLD1	MIR7641-2	NPPC	PAQR5	PLXNA2
HTR7	KCNQ2	LOC100271832	MAP3K21	MLLT10P1	NPTX2	PAQR9-AS1	PLXNA4
HTRA1	KCNS2	LOC100288152	MAP6D1	MMP17	NR2F1	PARP11	PLXNC1
HUNK	KCNS3	LOC100288866	MAP7D3	MMP24	NR2F1-AS1	PAX1	PLXND1
ICAM5	KDEL3	LOC100505588	MAPK4	MMP25	NR3C1	PCDH11X	POPDC3
IGDCC3	KIAA1024	LOC100506368	MAPK8IP2	MN1	NR3C2	PCDH8	POTEB
IGDCC4	KIAA1211L	LOC101926913	MAPKAPK3	MSI1	NR4A3	PCDH9	POTEB2
IGF1R	KIAA1324L	LOC101927708	MAPRE2	MSRB3	NR5A2	PCDHAC2	POTEB3

Table S3. 966 bivalent and N-Myc bound genes. (3/3)

POU3F1	RASGEF1A	SDC2	SNCAIP	TERT	UPF3A
POU3F2	RBFOX3	SDK1	SNTG2	TEX13C	USP17L10
PPARA	RBM20	SEMA5B	SNX16	TEX15	USP32P1
PPARG	RBPM52	SEMA6B	SOBP	TFEB	UST
PPARGC1A	RCAN2	SERPINE2	SOCS1	TFR2	UTF1
PPFIA2	REEP1	SFMBT2	SOCS2-AS1	TGFBR2	VAMP3
PPMIJ	RFTN1	SGPP2	SORT1	TGFBR3L	VASH1
PPP1R14C	RGMA	SH3GL2	SOWAHA	TLE2	VAV3
PPP1R9A	RGS19	SH3GL3	SOX18	TLK2	VAX1
PPP2R3B	RGS20	SH3PXD2A	SOX7	TMCC3	VGf
PRAG1	RHOBTB1	SH3RF3	SOX8	TMEM158	VGLL3
PRDM16	RHOBTB3	SHANK3	SP8	TMEM163	VIM-AS1
PRDM6	RIC3	SHF	SPATA31A7	TMEM178B	VPS37D
PRDM8	RIMS4	SHISA2	SPHK1	TMEM179	VSTM2L
PREX2	RNA18S5	SHISA3	SPNS2	TMEM191C	VWCE
PRKCQ	RNA28S5	SHISA8	SPRY2	TMEM200C	VWDE
PRKG1	RNA45S5	SIMC1	SPSB1	TMEM229B	WDR38
PRKG2	RNA5-8S5	SIRPA	SPSB4	TMEM266	WIPF3
PRMT8	RNF157	SIX6	SRPX	TMEM56	WNT2B
PROKR1	RNF217	SLC16A10	ST3GAL6	TMEM59L	WNT9B
PROX1	ROPN1	SLC1A2	ST8SIA2	TMEM74B	WSCD1
PRR25	ROR2	SLC22A15	ST8SIA6	TMOD1	WTIP
PRRT4	RORA	SLC22A3	STK32A	TNFRSF11A	XIRP2
PRSS12	RPL23AP82	SLC22A31	STMN3	TNIF	XKR6
PSD2-AS1	RPRML	SLC22A4	STOX1	TP53TG3	ZBED5-AS1
PSMD8	RPS10P7	SLC24A3	STUM	TPBGL	ZBTB18
PTCH1	RPS6KA2	SLC26A2	SV2B	TRABD2B	ZBTB7A
PTGER4P2-CDK2AP2P2	RRN3P2	SLC26A4-AS1	SV2C	TRAF5	ZBTB7C
PTPN21	RTBDN	SLC35D3	SYDE1	TRIB2	ZC3H12C
PTPRD-AS2	RTN4RL1	SLC35F3	SYDE2	TRIM2	ZCCHC18
PTPRM	RTN4RL2	SLC5A2	SYT12	TRIM47	ZDBF2
PXDC1	RUNDC3B	SLC6A17	SYT17	TRIM51	ZEB1
PXYLP1	RUNX1	SLC9A5	SYT9	TRIM7	ZNF215
PYGL	RUNX1T1	SLIT1	TBC1D3P1-DHX40P1	TRIM9	ZNF217
QSER1	RUNX2	SLITRK3	TBX2	TSHZ3	ZNF23
RAB31	SAMD11	SMAD6	TCERG1L	TSLP	ZNF385B
RAB32	SAMD14	SMAGP	TCF4	TSPAN9	ZNF423
RAB39A	SAMD4A	SMIM12	TCF7	TTPA	ZNF454
RADIL	SAMD5	SMO	TCF7L1	TUBB3	ZNF521
RAP1GAP2	SATB1	SMOC2	TCHH	TUBGCP2	ZNF536
RAPGEF4	SCN1B	SMTNL2	TCTE1	UHRF1	ZNF860
RASA3	SCN5A	SMYD2	TDH	ULK2	ZSWIM5
RASA4	SCN8A	SNAP91	TEAD2	UNC5A	
RASA4B	SCRT1	SNAR-D	TENM3	UNCX	

Table S4. Bivalent-associated genesets.

Gene list	MEISSNER_NPC_HCP_ WITH_H3K4ME2_AND_ H3K27ME3	MEISSNER_NPC_HCP_ WITH_H3K4ME3_AND_ H3K27ME3	MEISSNER_BRAIN_HCP_ _WITH_H3K4ME2_AND_ _H3K27ME3	MEISSNER_BRAIN_HCP_ _WITH_H3K4ME3_AND_ _H3K27ME3	MIKKELSEN_NPC_HCP_ _WITH_H3K4ME3_AND_ _H3K27ME3
From	GSEA Broad Institute	GSEA Broad Institute	GSEA Broad Institute	GSEA Broad Institute	GSEA Broad Institute
Size	349	142	59	1069	210

Table S5. Oligonucleotide list.

Human qRT-PCR Primers (<i>ACTB</i>) 5'-CCT CCC TGG AGA AGA GCT A-3' 5'-CCA GAC AGC ACT GTA TTG G-3'	IDT
Human qRT-PCR Primers (<i>AUTS2</i>) 5'-CCT CCT CAT CAC AGC AAC TTC C-3' 5'-GAA GGC ATT GCC ACC AAC TGC-3'	IDT
Human qRT-PCR Primers (<i>CTGF</i>) 5'- GTT CCA AGA CCT GTG GGA TG-3' 5'-TGG AGA TTT TGG GAG TAC GG-3'	IDT
Human qRT-PCR Primers (<i>DSC3</i>) 5'-GCT GTT GCG CTG TCT GAT AA-3' 5'-GGA ATA GGT GCC CAT CTC CT-3'	IDT
Human qRT-PCR Primers (<i>MYCN</i>) 5'-CGA CCA CAA GGC CCT CAG TA-3' 5'-CAG CCT TGG TGT TGG AGG AG-3'	IDT
Human qRT-PCR Primers (<i>NKX2-1</i>) 5'-AGC ACA CGA CTC CGT TCT C-3' 5'-GCC CAC TTT CTT GTA GCT TTC C-3'	IDT
Human qRT-PCR Primers (<i>PHF10</i>) 5'-ATC CAA AAG GAG GCG AAT GG-3' 5'-TCA CTG ACT TGT TCT TGA AGC A-3'	IDT
Human qRT-PCR Primers (<i>RAB39A</i>) 5'-TCG GCG TGG ACT TCT TCT C-3' 5'-ACA TGT TCA AAA GAT CGT CGG T-3'	IDT
Human qRT-PCR Primers (<i>STEAP4</i>) 5'-GAC TGG CTT GAC CAC TGG AT-3' 5'-GCT GAG GAG GTG CTA AAT GG-3'	IDT
Human qRT-PCR Primers (<i>TMPRSS2</i>) 5'-GGA CAG TGT GCA CCT CAA AGA C-3' 5'-TCC CAC GAG GAA GGT CCC-3'	IDT
Human qRT-PCR Primers (<i>VIM</i>) 5'-TCC AGC AGC TTC CTG TAG GT-3' 5'-CCC TCA CCT GTG AAG TGG AT-3'	IDT
Human ChIP-qPCR Primers (<i>NKX2-1</i>) 5'-ATG AGT CCA AAG CAC ACG AC-3' 5'-GCC CAC TTT CTT GTA GCT TTC C-3'	IDT
Human ChIP-qPCR Primers (<i>CHGA</i>) 5'-ACC CCT CCA CAC TTC CCT TC-3' 5'-AGT CAG GCC CAA GTG TCT TG-3'	IDT
siRNA (Control) 5'-AGU GUC CUU GCU GAA CGA CUU-3'	Dharmacon
siRNA (<i>FOXA1</i>) 5'-GAG AGA AAA AAU CAA CAG CUU-3'	Dharmacon