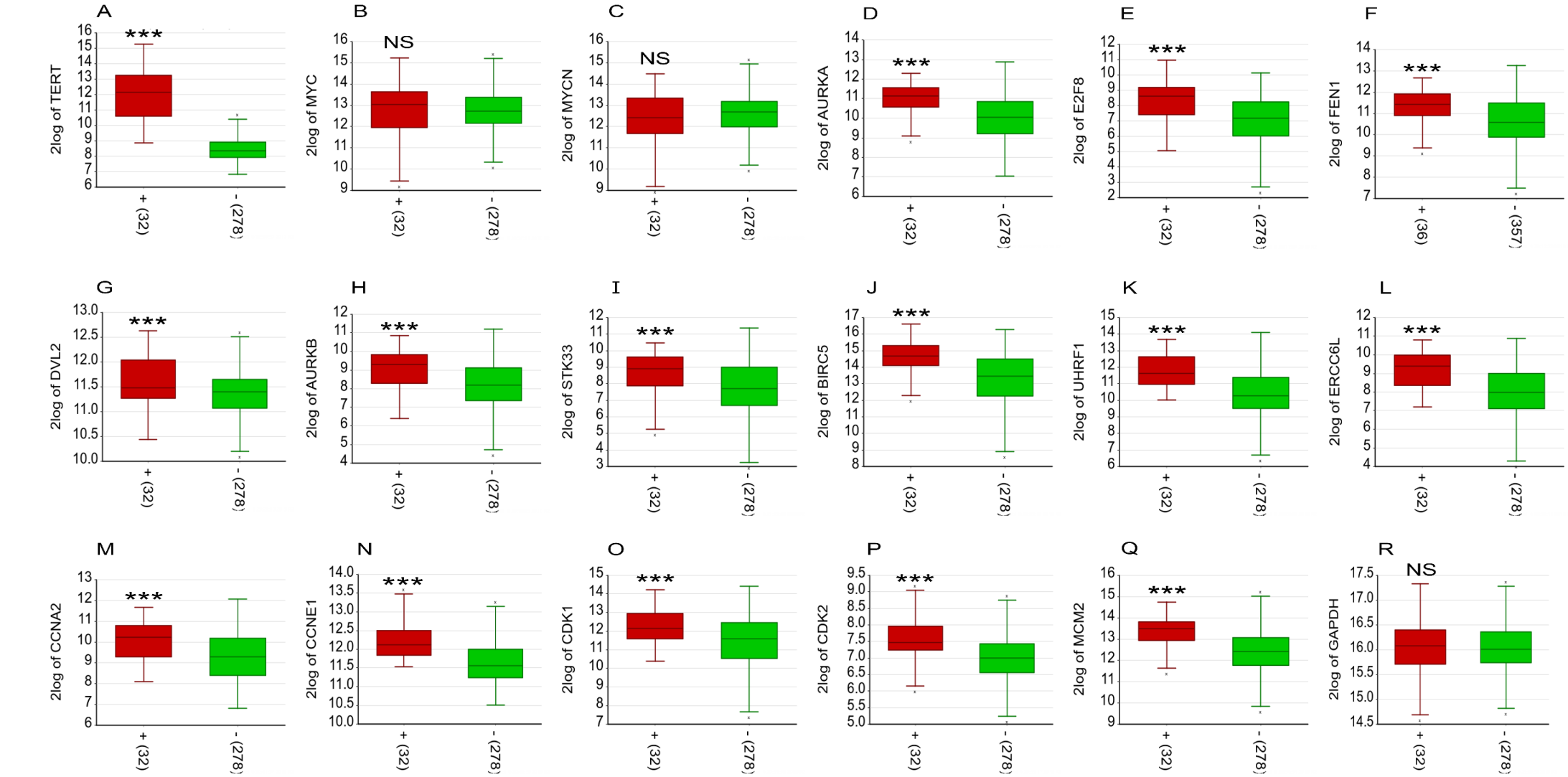
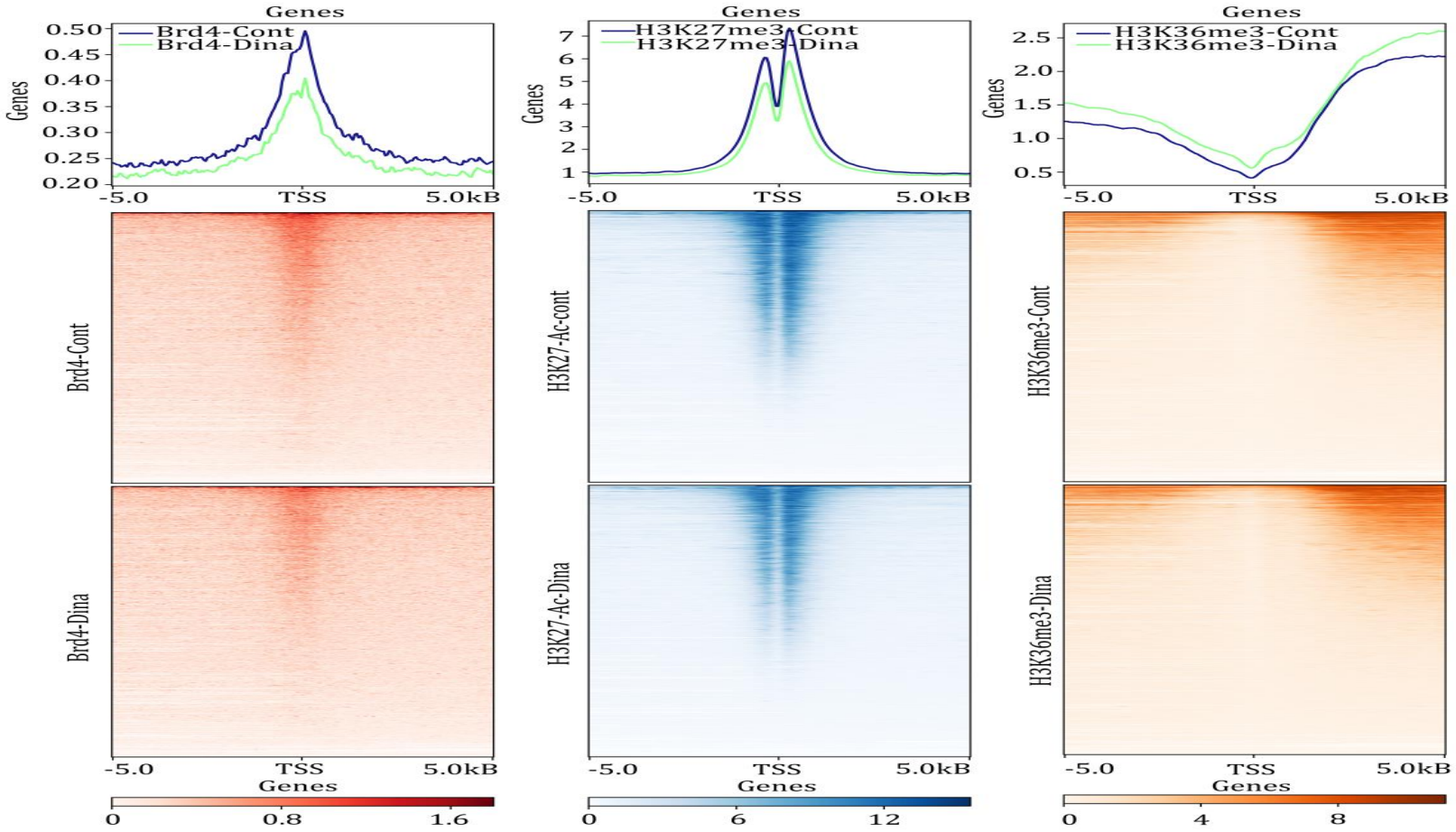
Supplementary figure S1



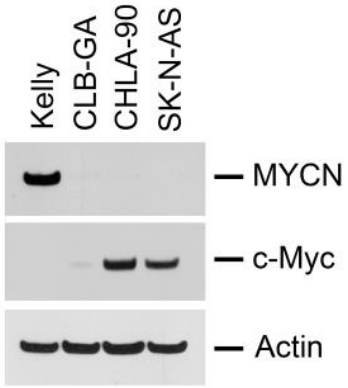
Supplementary Fig. S1. Elevated mRNA expression of *TERT* and *TERT*-associated genes in NB with *TERT* gene rearrangement. A total of 310 NB patients without *MYCN* amplification within the Tumor Neuroblastoma (*TERT*)-Fischer-394-custom dataset were assigned into two subgroups: 32 patients with (+) and 278 patients without (-) *TERT* gene rearrangement. The mRNA expression obtained from Microarray analysis between the two subgroups were analyzed within the R2 platform server. (A-R) Dot plots showing mRNA expression levels of *TERT* and multiple *TERT*-associated genes. Each dot represents a value from an individual patient.

Supplementary figure S2



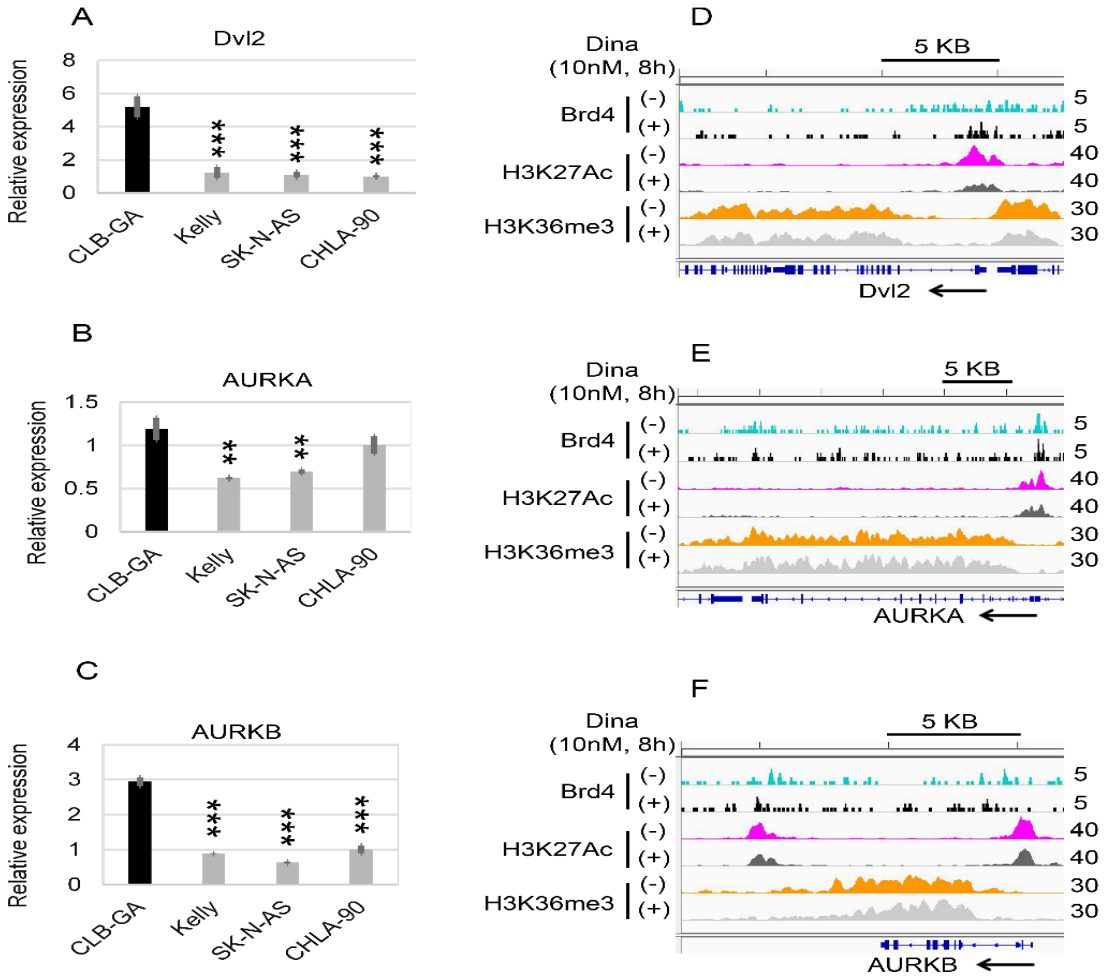
Supplementary Fig. S2. Effects of dinaciclib on genome-wide chromatin occupancy of epigenetic modulators in CLB-GA cells. The binding profiles for Brd4, H3K27Ac, and H3K36me3 were examined in the presence or absence of dinaciclib at 10 nM for 8 h using computeMatrix in reference-point mode. The density and composite mapping relative to the reference genomic positions before (5 kb upstream) and after (5 kb downstream) the TSS with 50 bp bins were shown. The top panel histograms show the average genome-wide occupancies surrounding the TSS in the presence or absence of dinaciclib. The lower panels of density heat maps show genome-wide chromatin occupancy and effects of dinaciclib.

Supplementary figure S3



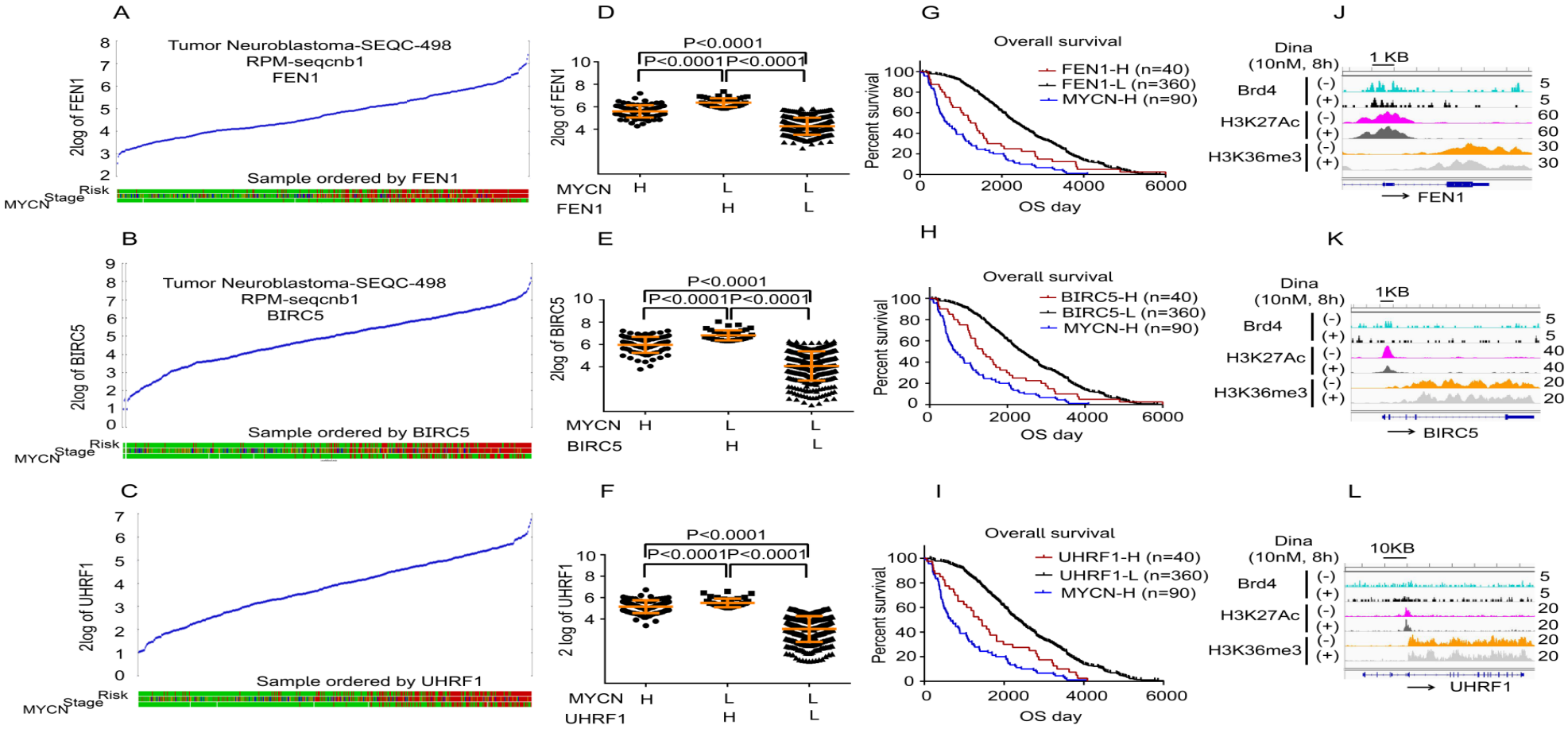
Supplementary Fig. S3: C-Myc and MYCN protein expression in four NB cell lines. Western blotting of c-Myc, MYCN, and actin in Kelly, CLB-GA, CHLA-90, and SK-N-AS cell lines.

Supplementary figure S4



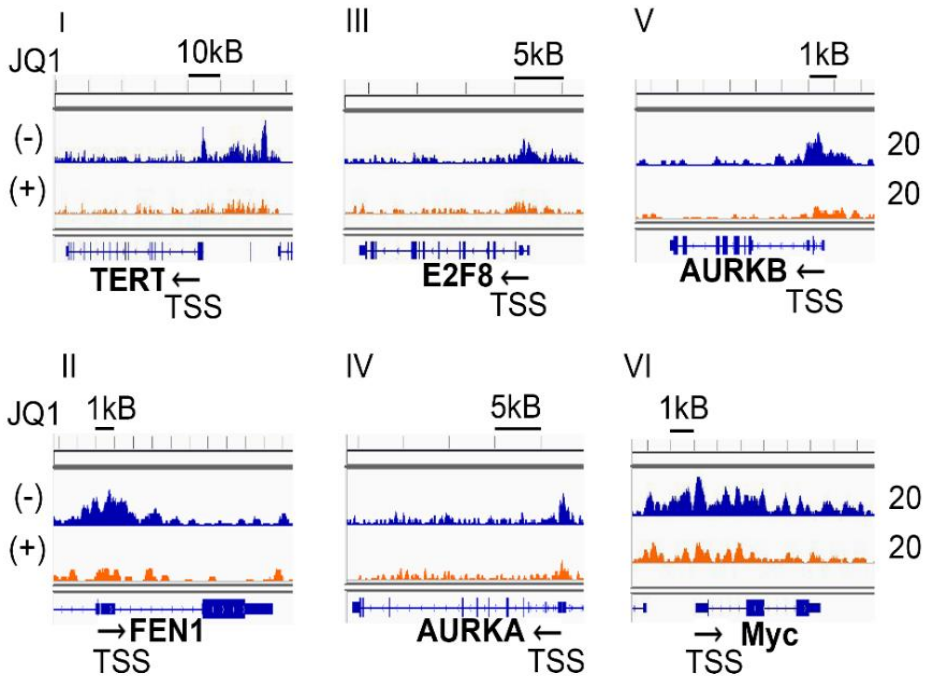
Supplementary Fig. S4: Effects of dinaciclib on the chromatin occupancy of epigenetic modulators at *Dvl2*, *AURKA*, and *AURKB* and in CLB-GA cells. (A-C) Comparison of mRNA expression of *Dvl2* (**A**), *AURKA* (**B**), and *AURKB* (**C**) in human NB cell lines CLB-GA, Kelly, SK-N-AS, and CHLA-90. (**D-F**) Effects of dinaciclib on binding of Brd4, H3K27Ac, and H3K36me3 to the promoters or enhancers of *Dvl2*, *AURKA*, and *AURKB* in CLB-GA cells. Cells were treated with dinaciclib at 10 nM and 100 nM for 8 h, followed by CHIP-seq analysis.

Supplementary figure S5



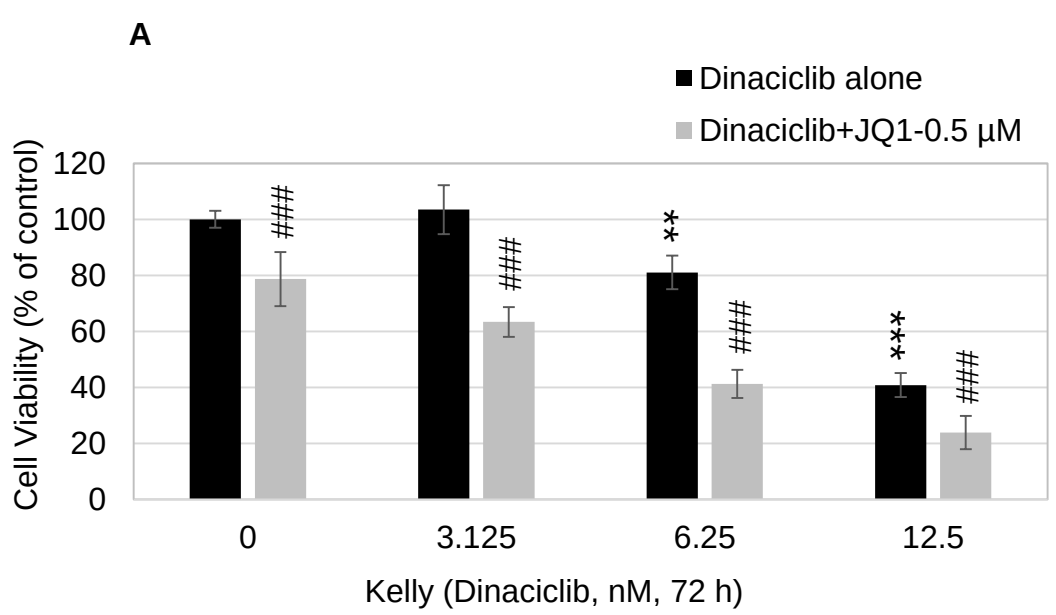
Supplementary Fig. S5. Association of overexpression of *FEN1*, *BIRC5*, and *UHRF1* with poor prognosis and effects of dinaciclib on chromatin occupancy of epigenetic modulators in CLB-GA cells. (A-C) Association of high mRNA expression of *FEN1*, *BIRC5*, and *UHRF1* with high risk and advanced stage of NB in a subpopulation of NB expressing high levels of *FEN1* (**A**), *BIRC5* (**B**), and *UHRF1* (**C**) in the GSE62564 dataset as analyzed with R2 genomics analysis and visualization application platform. (**D-F**) Dot plots showing the mRNA expression levels of *FEN1*, *BIRC5*, and *UHRF1* in *MYCN*-H subgroup (n=90), /*FEN1BIRC5*/*UHRF1* high (top 10%, n=40), and *MYCN*-L plus *FEN1*/*BIRC5*/*UHRF1* low (n=360). Each dot represents a value from an individual patient. (**G-I**) Comparison of the overall survival among the above subpopulations of NB patients. (**J-L**) Effects of dinaciclib on binding of Brd4, H3K27Ac, and H3K36me3 to the promoters or enhancers of *FEN1*/*BIRC5*/*UHRF1*. CLB-GA cells were treated in the absence or presence of 10 nM dinaciclib for 8 h, followed by ChIP-seq. Genome browser (hg38) views of ChIP-seq peaks at various gene loci.

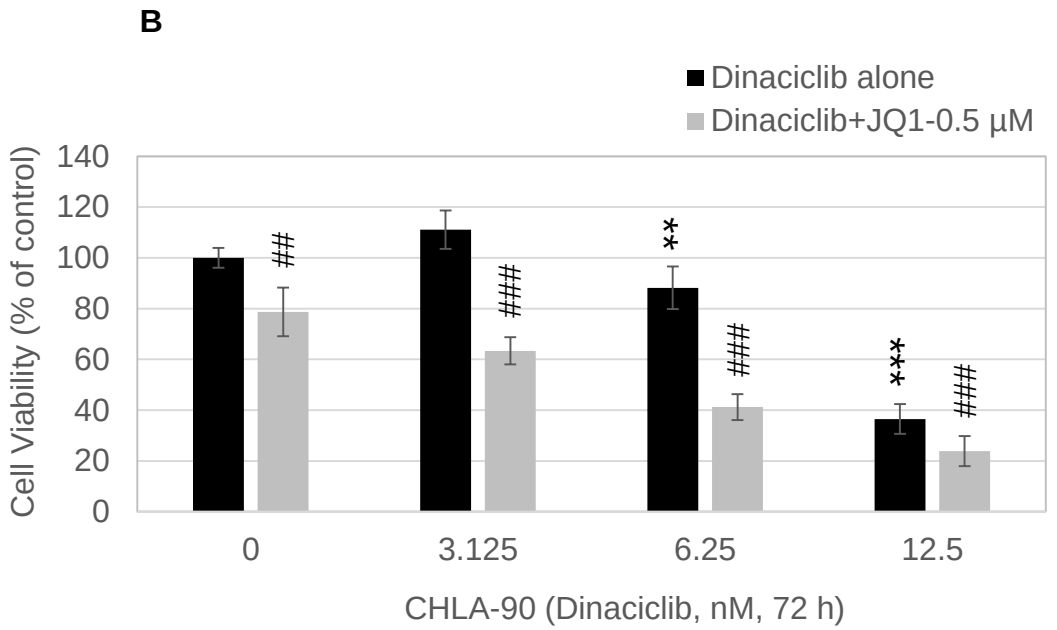
Supplementary figure S6

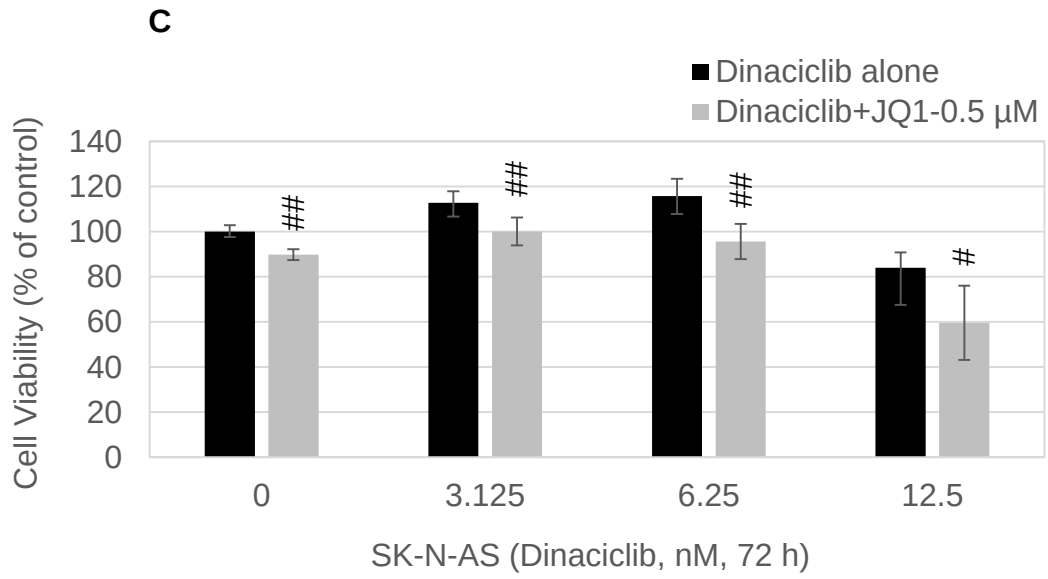


Supplementary Fig. S6. JQ1 sensitive Brd4 binding profiles in OCI-AML3 cells. Effects of JQ1 on Brd4 binding to the promoters or enhancers of *TERT*, *E2F8*, *FEN1*, *AURKA*, and *AURKB* in NPMc+ OCI-AML cells with active Brd4 pathways. Analysis was performed using ChIP -seq data, previously published and deposited at GEO with accession number GSE104745(25). Cells were treated in the absence or presence of 0.5 µM JQ1 for 24 h, followed by Brd4-ChIP-seq. Genome browser (hg38) views of ChIP-seq peaks at the following loci. The location of each gene is shown at the bottom of the panels and the calculated ChIP-seq enrichment values are indicated on the right.

Supplementary figure S7





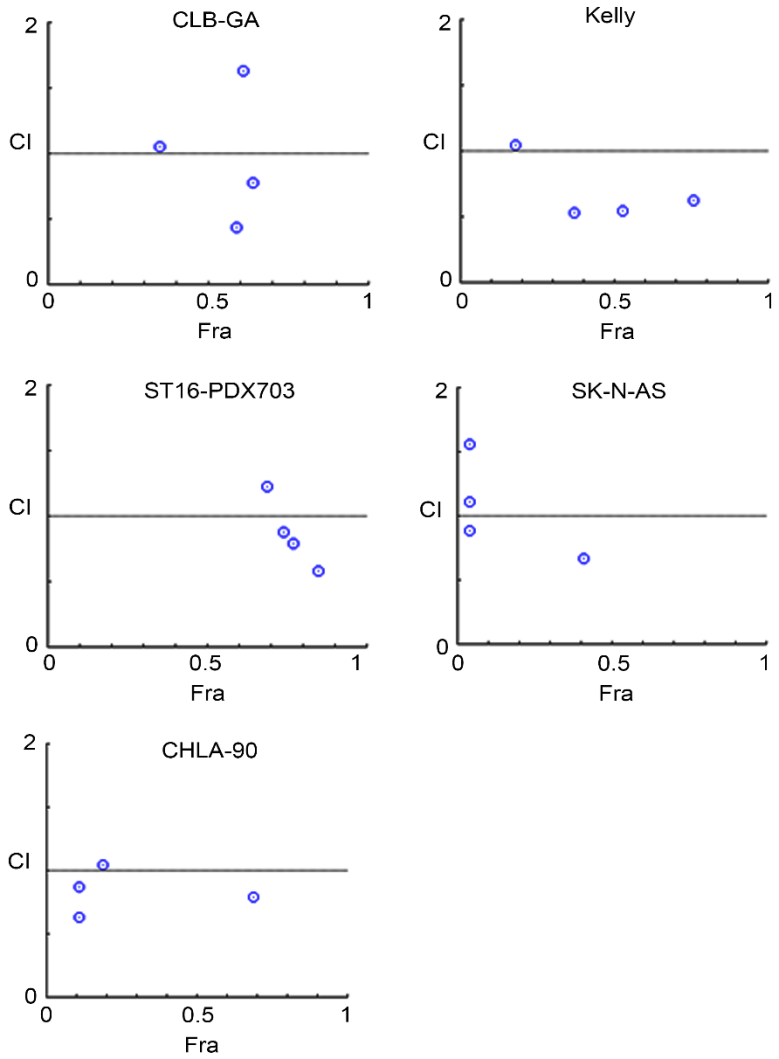


Supplementary Fig. S7. JQ1 and dinaciclib are synergistic or additive in inducing cytotoxicity in NB cell lines. (**A, B, C**) Synergistic or additive effects of JQ1/AZD5153 in combination with dinaciclib. Kelly, SK-N-AS, and CHLA-90 cells were treated with JQ1, AZD5153, or dinaciclib alone or combination at the indicated concentrations for 72 h, followed by MTS assay. Asterisk or Hash is in relation to control or dinaciclib treatment alone, respectively.

Supplementary figure S8

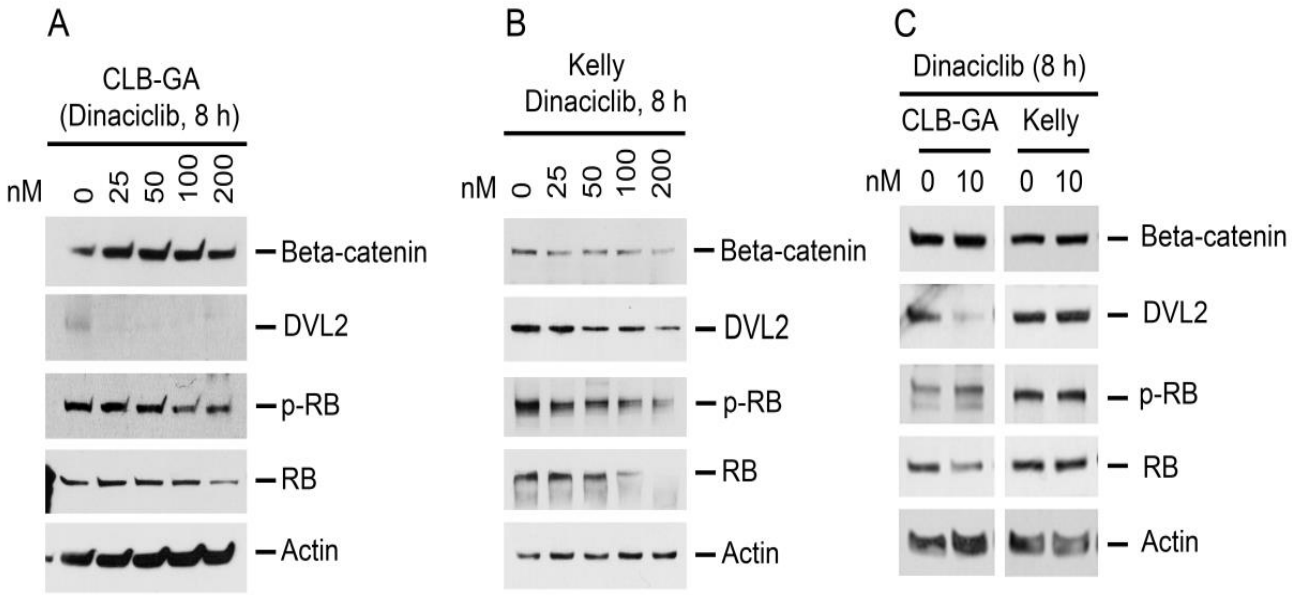
Combination index (CI) values for synergy experiment combining Dinaciclib with Brd4 inhibitor JQ1

NB cells	Dinaciclib (nM)	JQ1 (uM)	Fa	CI
CLB-GA	1.562	0.5	0.28	2.5621
	3.125	0.5	0.35	1.05784
	6.25	0.5	0.59	0.43967
	12.5	0.5	0.64	0.77836
Kelly	1.562	0.5	0.18	1.04492
	3.125	0.5	0.37	0.53231
	6.25	0.5	0.53	0.54914
	12.5	0.5	0.76	0.62749
CHLA-90	1.562	0.5	0.11	0.63388
	3.125	0.5	0.11	0.87632
	6.25	0.5	0.19	1.04526
	12.5	0.5	0.69	0.79491
SK-N-AS	1.562	0.5	0.04	0.88855
	3.125	0.5	0.04	1.11201
	6.25	0.5	0.04	1.55878
	12.5	0.5	0.41	0.66995
ST16-PDX703	1.562	0.5	0.69	1.22675
	3.125	0.5	0.74	0.88005
	6.25	0.5	0.77	0.79571
	12.5	0.5	0.85	0.58324



Supplementary Fig. S8. Combination index (CI) values for synergy experiment combining Dinaciclib with Brd4 inhibitor JQ1. The CI was analyzed using CalcuSyn software (Version 2; Biosoft). The CI values of <1, =1, and >1 indicate synergism, additive effect, and antagonism of drugs, respectively. CI table (left) and synergy plots (right) for combining Dinaciclib with Brd4 inhibitor JQ1 in four NB cell lines and primary NB cells. Fa: Fraction of cell growth inhibited.

Supplementary figure S9



Supplementary Fig. S9. Effects of dinaciclib on phosphorylation of Rb in CLB-GA and Kelly cells. CLB-GA cells were treated with dinaciclib at indicated concentrations for 8 h, followed by Western blotting of p-Rb, Rb, and actin.

Supplementary table S1. Primer sequences used in ChIP-qPCR and real-time RT-PCR analysis

CHIP-qPCR primers			
	Forward Sequence	Reverse sequence	Size of PCR product
TERT-P1	5'-GCGGCGCGAGTTTCAG-3'	5'-AGCACCTCGCGGTAGTGG-3'	158 bP
TERT-P2	5'-GTCCTGCCTGAAGGAGCTG-3'	5'-ACCGTGTTGGGCAGGTAG-3'	159 bp
TERT-P3	5'-CTGATTGGCACCTCATGTTG-3'	5'-GACCCTCCTTGGGAATAGGA-3'	181 bp
E2F8-P1	5'-GCTGAACTTTTCCCCCAACT-3'	5'-CCCCCGATTTGAAATTAACC-3'	200 bp
E2F8-P2	5'-GTTGTCCTGGAAACCACGAT-3'	5'-CCCAATAAGGCAAGCAGGTA-3'	150 bp
RT-qPCR primers			
FEN1	5'-ACATGGACTGCCTCACCTTC-3'	5'-CCCAATACCCCGGATACTCT-3'	191 bp
MycN-E2E3	5'-CACAAGGCCCTCAGTACCTC-3'	5'-ACCACGTCGATTTCTTCCTC-3'	95 bp
MycN-E3	5'-CTTCGGTCCAGCTTTCTCAC-3'	5'-GTCCGAGCGTGTTCAATTTT-3'	200 bp
AURKA	TCCTGAGGAGGAACTGGCATCAAA	TACCCAGAGGGCGACCAATTTCAA	96 bp
AURKB	ATCAGCTGCGCAGAGAGATCGAAA	CTGCTCGTCAAATGTGCAGCTCTT	167 bp
TERT	CCAAGTTCCTGCACTGGCTGA	TTCCCGATGCTGCCTGAC	207 bp
Dvl2	5’-GCCTATCCAGGTTCCTCCTC-3’	5’-AGAGCCAGTCAACCACATCC-3’	214 bp
Myc	5’-CTTCTCTCCGTCCTCGGATTCT-3’	5’-GAAGGTGATCCAGACTCTGACCTT-3’	203 bp
CCNA2	5'-TGGAAAGCAAACAGTAAACAGCC-3'	5'-GGGCATCTTCACGCTCTATTT-3'	103 bp
CCND1	5'-GCTCCTGTGCTGCGAAGT-3'	5'-TGTTCCTCGCSGACCTCCAG-3'	201 bp
CCNE1	5'-ACTCAACGTGCAAGCCTCG-3'	5'-GCTCAAGAAAGTGCTGATCCC-3'	141 bp
MCM2	5'-ATGGCGGAATCATCGGAATCC-3'	5'-GGTGAGGGCATCAGTACGC-3'	120 bp
Cdk1	5'-CAGACTAGAAAGTGAAGAGGAAGG-3'	5'-ACTGACCAGGAGGGATAGAATC-3'	191 bp
Cdk2	5'-CCAGGAGTTACTTCTATGCCTGA-3'	5'-TTCATCCAGGGGAGGTACAAC-3'	110 bp
GAPDH	5’-CCCCTTCATTGACCTCAACTACAT-3’	5’-CGCTCCTGGAAGATGGTGA-3’	135 bp

Supplementary table 2. Gene sets enriched in NB patients with *TERT* gene rearrangement (n=32) versus without *TERT* gene rearrangement (n=278) within *MYCN* non-amplified NB of Tumor Neuroblastoma (*TERT*)-Fischer-394-custom

A. Enriched gene set (db:geneset_broad_2015_oncogenic)	Genes	Genes increased	P value
H Broad Institute:RPS14_DN_V1_DN	181	40	2.4E-20
H Broad Institute:CSR_LATE_UP_V1_UP	168	38	4.4E-20
H Broad Institute:PRC2_EZH2_UP_V1_UP	188	37	1.2E-15
H Broad Institute:PRC2_EDD_UP_V1_UP	190	31	1.4E-09
H Broad Institute:VEGF_A_UP_V1_DN	191	31	1.8E-09
H Broad Institute:HOXA9_DN_V1_DN	184	28	1.1E-07
H Broad Institute:MYC_UP_V1_UP	167	26	1.7E-07
H Broad Institute:EGFR_UP_V1_DN	189	24	0.000099
H Broad Institute:E2F3_UP_V1_UP	183	18	0.03

B. Enriched gene sets (db:geneset_broad_2015_curated)	Genes	Genes increased	P value
H Broad Institute:REN_BOUND_BY_E2F	61	35	7.40E-60
Broad Institute:EGUCHI_CELL_CYCLE_RB1_TARGETS	23	19	2.80E-49
Broad Institute:CHICAS_RB1_TARGETS_GROWING	235	45	4.10E-16
Broad Institute:FEVR_CTNNB1_TARGETS_DN	543	112	8.20E-45
Broad Institute:DAIRKEE_TERT_TARGETS_UP	360	41	6.30E-05
H Dana-Farber Cancer Institute:ZHOU_CELL_CYCLE_GENES_IN_IR_RESPONSE_24HR	127	64	1.50E-93
Reactome:REACTOME_CELL_CYCLE_MITOTIC	305	83	3.10E-52
Reactome:REACTOME_DNA_REPLICATION	186	61	1.60E-50
Broad Institute:ODONNELL_TARGETS_OF_MYC_AND_TFRC_DN	45	22	6.20E-31
Broad Institute:ODONNELL_TFRC_TARGETS_DN	131	45	7.60E-40

Supplementary Table S2. The significantly enriched gene sets in NB with *TERT* gene rearrangement. A total of 310 NB patients without *MYCN* amplification within the Tumor Neuroblastoma (*TERT*)-Fischer-394-custom dataset were assigned into two subgroups: 32 patients with *TERT* gene rearrangement and 278 patients without *TERT* gene rearrangement. By analyzing the subgroups of *MYCN* non-amplified NB patients with or without *TERT* rearrangement within R2 platform, the significantly enriched gene sets in the NB patients with *TERT* rearrangement were listed in A (database:geneset_broad_2015_oncogenic) and B (detabase:geneset_broad_2015_curated).

Supplementary table 3. Gene sets enriched in NB patients with high versus low *TERT* within Tumor Neuroblastoma Gene-TARGET-161

A. Enriched gene set (db:geneset_broad_2015_oncogenic)	Genes	Genes increased	P value
H Broad Institute:RPS14_DN_V1_DN	181	53	1.4e-16
H Broad Institute:CSR_LATE_UP_V1_UP	168	47	1.6e-13
H Broad Institute:PRC2_EZH2_UP_V1_UP	188	39	9.2e-12
H Broad Institute:PRC2_EDD_UP_V1_UP	190	48	1.4E-09
H Broad Institute:VEGF_A_UP_V1_DN	191	41	5.5e-07
H Broad Institute:HOXA9_DN_V1_DN	184	32	3.3e-03
H Broad Institute:MYC_UP_V1_UP	167	40	7.1e-08
Broad Institute:CAMP_UP_V1_UP	194	34	1.6e-03
Broad Institute:TBK1_DF_DN	277	44	2.7e-03

B. Enriched gene sets (db:geneset_broad_2015_curated)	Genes	Genes increased	P value
H Broad Institute:REN_BOUND_BY_E2F	61	36	1.2e-35
Broad Institute:EGUCHI_CELL_CYCLE_RB1_TARGETS	23	16	2.2e-19
National Cancer Institute and Nature Publishing Group:PID_E2F_PATHWAY	74	27	1.8e-03
Reactome:REACTOME_E2F_MEDIATED_REGULATION_OF_DNA_REPLICATION	31	16	3.6e-13
Broad Institute:OLSSON_E2F3_TARGETS_DN	47	14	3.3e-05
Broad Institute:CHICAS_RB1_TARGETS_LOW_SERUM	95	31	2.6e-12
Broad Institute:FEVR_CTNNB1_TARGETS_DN	543	147	1.1e-38
Reactome:REACTOME_SIGNALING_BY_WNT	63	13	0.01
Broad Institute:DAIRKEE_TERT_TARGETS_UP	360	91	9.6e-20
NCI, NIH and Nature Publishing Group:PID_TELOMERASE_PATHWAY	68	12	5.7e-03
H Dana-Farber Cancer Institute:ZHOU_CELL_CYCLE_GENES_IN_IR_RESPONSE_24HR	127	72	8.4e-65
Reactome: REACTOME_CELL_CYCLE_MITOTIC	305	105	5.9e-44
Reactome:REACTOME_DNA_REPLICATION	186	79	3.2e-47
Broad Institute:ODONNELL_TARGETS_OF_MYC_AND_TFRC_DN	45	26	1.4e-24
Broad Institute:ODONNELL_TFRC_TARGETS_DN	131	54	2.3e-30
National Cancer Institute and Nature Publishing Group:PID_AURORA_B_PATHWAY	37	17	1.9e-11

Supplementary Table S3. The significantly enriched gene sets in NB with high *TERT* expression. A total of 161 NB patients within the Tumor Neuroblastoma Gene-TARGET-161 dataset were assigned into subgroups with *TERT* high versus low automatically within the R 2 Genomics analysis platform, the significantly enriched gene sets in the NB patients with high *TERT* expression were listed in A (database:geneset_broad_2015_oncogenic) and B (detabase:geneset_broad_2015_curated).

Supplementary table 4: Information on patient samples used in this study

Sample ID		Age	Disease status	Risk	BM Metastasis	MNCs/per ml BM	Stage	MYCN Amp	Chemotherapy
ST15	TC	18Y M	Dx	VLR	NA		1	(-)	None
	PB4044					NA			
ST16	TC	3Y	Dx Refractory	HR	BM metastasis		IV	(+)	None
	BM4045					NA			
ST36	BM4091	2Y	Dx Refractory	HR	BM metastasis	$17X10^6$	IV	(-)	None
	BM4117				BM metastasis	$6.8X10^6$			d20 Cycle 4-ANBL0532-IND
	BM4143				No	$0.6X10^6$			Post Cycle 6-ANBL0532-IND
ST5	BM4130	5Y	Relapsed Refractory	HR	BM metastasis	$6.6X10^6$	IV	(-)	Post cycle 4 ANBL0532
ST53	BM4129	18Y	Relapsed, Refractory	HR	BM metastasis	$15X10^6$	IV	(-)	New relapse