**SUPPLEMENTAL MATERIAL**

**CRISPR-Cas9 Screen Reveals a *MYCN*-amplified Neuroblastoma Dependency on EZH2**

Liying Chen, Gabriela Alexe, Neekesh V. Dharia, Linda Ross, Amanda Balboni Iniguez, Amy Saur Conway, Emily Jue Wang, Veronica Veschi, Norris Lam, Jun Qi, W. Clay Gustafson, Nicole Nasholm, Francisca Vazquez, Barbara A. Weir, Glenn S. Cowley, Levi D. Ali, Sasha Pantel, Guozhi Jiang, William F. Harrington, Yenarae Lee, Amy Goodale, Rakela Lubonja, John M. Krill-Burger, Robin M. Meyers, Aviad Tsherniak, David E. Root, James E. Bradner, Todd R. Golub, Charles W. M. Roberts, William C. Hahn, William A. Weiss, Carol J. Thiele, and Kimberly Stegmaier

**SUPPLEMENTAL METHODS**

**Cell Lines**

SIMA and MHH-NB-11 were maintained in RPMI (Cellgro) supplemented with 10% fetal bovine serum (Sigma-Aldrich) and 1% penicillin-streptomycin with glutamine (Cellgro). All other neuroblastoma cell lines were maintained in DMEM (Cellgro) supplemented with 10% fetal bovine serum (Sigma-Aldrich) and 1% penicillin-streptomycin with glutamine (Cellgro). All cell lines were cultured at 37°C in a humidified atmosphere containing 5% $CO_2$.

**Determination of cell viability**

Cell viability was assessed using the CellTiter-Glo Luminescent Cell Viability Assay (Promega). Luminescent readings were obtained using the FLUOstar Omega microplate reader (BMG Labtech). Cells were treated across a range of concentrations and area under curve was calculated from ATP luminescence measurements after 5 days of treatment using log-transformed, normalized data in GraphPad Prism 6.0 (GraphPad Software, Inc.). Cell viability was also determined following pLKO.1 lentiviral shRNA-mediated knockdown or CRISPR-Cas9-mediated knockout of *EZH2*. ATP content was measured at multiple time points after transduction.

**Flow Cytometry**

Apoptosis was measured using the Annexin V: APC Apoptosis Detection Kit as per the manufacturer's protocol (BD Pharmingen). Cell cycle was determined by measuring DNA content using propidium iodide staining.

***In Vivo* Studies**

*Inducible shRNA experiment:* The human neuroblastoma cell line NGP was stably transduced with a TET-inducible *EZH2* shRNA to generate an NGP-sh*EZH2* cell line. Tumor xenografts were established by injecting $2 \times 10^6$ NGP-sh*EZH2* cells in the left flank of 5-week-old female athymic nude mice (Taconic). When tumors reached 75-150 $mm^3$, animals were stratified into cohorts that received doxycycline-chow or regular chow ($n$=10 per group). Tumor growth was monitored with a caliper 3 times a week. In each group, 5 tumors were collected and protein lysate analyzed for EZH2 expression and target inhibition on Day 20 after starting treatment. Statistical significance of survival curves was determined by a log-rank (Mantel-Cox) test and variance of the tumor volume between doxycycline and control was determined by two-way ANOVA. All xenograft studies were approved by the Animal Care and Use Committee of the National Cancer Institute, and all mice treatments, including their housing, were in accordance with the institutional guidelines (PB-023).

*Drug treatment experiment with JQEZ5:* Tumor xenografts were established in NOD/SCID/gamma female mice using $2 \times 10^6$ Kelly cells resuspended in 30% matrigel and injected into the flank. After cell implantation, mice were randomized into cohorts to be treated with 100 mg/kg JQEZ5 ($n$=10) or vehicle (10% HP-β-CD/90% water) ($n$=10) delivered by daily IP injection for 7 days, followed by a 5-day holiday and subsequently treated with 75 mg/kg JQEZ5 or vehicle for 9 days. Tumor volume was measured by caliper twice weekly and animals were sacrificed when tumor volumes exceeded 2,000 $mm^3$. All animal studies were conducted under the auspices of protocols approved by the Dana-Farber Cancer Institute Animal Care and Use Committee**.**

*Drug treatment experiment with GSK126:* Tumor xenografts were established in NOD/SCID/gamma female mice using $2 \times 10^6$ human neuroblastoma cell CHP-212, SK-N-BE(2), or SH-SY-5Y, resuspended in 30% matrigel and injected into the flank. After cell implantation, mice were randomized into cohorts to be treated with 150 mg/kg GSK126 or vehicle (20% Captisol pH4.5) delivered by daily IP injection. Tumor volume was measured by caliper twice weekly and animals were sacrificed when tumor volumes exceeded 2,000 $mm^3$. All animal studies were conducted under the auspices of protocols approved by the Dana-Farber Cancer Institute Animal Care and Use Committee**.**

**CRISPR-Cas9 Screening**

The CRISPR-Cas9 screen was performed using the Avana library containing 73,372 guides and an average of 4 guides per gene. The library contains approximately 1,000 guides that do not target any location in the reference genome as negative controls.

The version of Avana data is available on the Achilles Portal with the recent publication of the CERES algorithm (1). This dataset contains 341 cell lines, including 11 neuroblastoma lines: CHP-212, IMR-32, Kelly, KP-N-YN, MHH-NB-11, NB1, SK-N-BE(2), SK-N-AS, SK-N-DZ, SK-N-FI, and SIMA. Initially, cancer cell lines were transduced with Cas9 using a lentiviral system. Cell lines that met criteria, including acceptable Cas9 activity measuring ability to knockout transduced GFP, appropriate growth properties and other parameters, were then screened with the Avana library. A pool of guides was transduced into a population of cells. The cells were cultured for 21 days in vitro, and at the end of the assay, barcodes for each guide were sequenced for each cell line in replicate.

The sgRNA read count data were deconvoluted from sequence reads by using PoolQ. A series of quality control pre-processing steps was performed to remove samples with poor replicate reproducibility, as well as guides that have low representation in the initial plasmid pool. The replicates that failed fingerprinting and the replicates with less than 15 million reads were removed and then the replicate read counts were scaled to 1 million total reads per replicate. The replicate pairs with Pearson correlation coefficients < 0.7 and the sgRNAs with low representation in the pDNA reference library were filtered out. Next, the log fold-change (logFC) from pDNA reference was calculated and the replicates with logFC SSMD between positive and negative control sgRNAs > -0.5 were removed. The replicate logFC data were Z-MAD normalized and the gene scores were inferred by running the computational tool CERES (1) and then normalized with lists of core cell-essential and non-essential genes. CERES was developed to computationally correct the copy-number effect and to infer true underlying effect of gene-knockout as described in (1). CERES models the observed normalized log-fold change for each sgRNA and cell line as the linear combination of gene-knockout and copy-number effects with coefficients giving the guide activities. Copy-number effects are fit with a linear piece-wise model in each cell line. Once all parameters have been fit, the inferred gene scores and guide activity scores are extracted and reported.

**Independent Component Analysis**

Independent Component Analysis (ICA) (2, 3) was applied to the CERES CRISPR-Cas9 gene-level data to identify the dependencies significantly associated with the neuroblastoma lineage. ICA is a machine learning data decomposition technique for revealing hidden non-Gaussian independent factors that are able to accurately deconvolve the data signal.

ICA models the CERES CRISPR-Cas9 gene dependency scores as a weighted sum of independent component signals, each component capturing a different biological process associated with the tumor lineage dependencies. The genes having the largest projection onto a component (estimated based on the cut-off ICA Z-score $\geq$ 2.5) are representative for the biological process associated with the component and are assigned as the "leading edge" gene set for the component.

Prior to performing ICA, the CERES gene scores were rank normalized per sample, i.e., the gene level dependency scores were replaced with their rank within each sample. A robust set of 100 independent components was identified from the CERES CRISPR-Cas9 screening rank normalized data by averaging 500 runs of the FastICA v1.2.1 procedure (4) implemented in R v3.2 (https://cran.r-project.org/web/packages/fastICA).

The comparative marker selection method implemented in GenePattern v3.9.10 was applied for ranking the independent components based on the Signal to Noise Ratio (SNR) scores that differentiate the neuroblastoma cell lines from all other cell lines. The top 3 independent components that were identified as significantly associated with depletion in neuroblastoma cells vs. other cell lines (SNR $\leq$ -0.5, permutation $P \leq 0.05$, False Discovery Rate (FDR) $\leq 0.05$) were labeled IC1, IC2 and IC3 and used to project the CERES dependency data (Figure 1A).

The *k*-nearest neighbor classification model implemented in the R v3.2 package rminer, (http://cran.r-project.org/package=rminer) was trained for $k = 3$ on the CERES data projected on the independent components IC1, IC2 and IC3, which are associated with neuroblastoma depletion. This model was shown to accurately separate the neuroblastoma cells from the other cell lines (mean error for 10-fold cross validation 0.026).

The top 100 leading edge genes associated with the components IC1, IC2 and IC3 are presented in Supplementary Table S1A. The PRC2 complex genes *EZH2, EED, SUZ12* were included in

the leading edge gene set for the component IC3. Gene set enrichment analysis (GSEA) vs. the MSigDB c2.all v5.1 collection (Broad Institute) was performed for the leading edge genes of the independent components IC1, IC2 and IC3 and revealed that each of the leading gene sets were enriched in “PRC2 targets” gene set signatures.

**Single-sample Gene Set Enrichment Analysis for Neuroblastoma Dependencies**

A single-sample GSEA (ssGSEA) analysis (5-7) on the CERES dependency data across the Mammalian Protein Complexes in the CORUM Database available from the ConsensusPathDB platform (8, 9) was performed to further validate the functional association of the PRC2 complex with neuroblastoma dependencies in the CRISPR-Cas9 screening data.

Single-sample GSEA (ssGSEA) is a variant of the GSEA method that assigns to each individual sample, represented as a ranked list of genes, an Enrichment Score (ES) with respect to each gene set in a given collection of pathways. The ssGSEA ES is calculated as a running sum statistic by walking down across the ranked list of genes, increasing the sum when encountering genes in the gene set and decreasing it when encountering genes not in the gene set. The significance of the ES is estimated based on a permutation *P*-value and adjusted for multiple hypotheses testing through FDR. A positive ES denotes a significant overlap of the signature gene set with groups of genes at the top of the ranked list, while a negative ES denotes a significant overlap of the signature gene set with groups of genes at the bottom of the ranked list. For each sample, the ES was further transformed into a Z-score by subtracting the average of the ES’s assigned to all other samples and by dividing the result to their standard deviation.

While GSEA generates a gene set’s enrichment score with respect to phenotypic differences across a collection of samples within a dataset, ssGSEA calculates a separate enrichment score for each pairing of sample and gene set, independent of phenotype labeling. In this manner, ssGSEA transforms a single sample's gene expression profile to a gene set enrichment profile. A gene set's enrichment score represents the activity level of the biological process in which the gene set's members are coordinately up- or down-regulated. The gene set representation has an unsupervised biological interpretability and can be further analyzed with statistical and machine learning methods.

The ssGSEA Z-scores for a gene set vs. a tumor cell line in the CRISPR-Cas9 screening data describe the level of dependency of the gene set vs. the cell line, based on the significance cut-off Z-score for depletion ≤ -1.

The EED_EZH2 protein complex (gene members *EED, EZH2, SUZ12, RBBP4, AEBP2*) showed a significant dependency associated with the neuroblastoma cell lines vs. all other cell lines ($P$ = 0.006, Mann-Whitney non-parametric t-test) and scored as most depleted in the neuroblastoma lineage (average Z-score = -1.48 across the neuroblastoma lineage, average Z-score = 0.05 across all other lineages). The distribution of the ssGSEA Z-scores for the EED_EZH2 protein complex across the lineages showed a significant variability across the lineages in the CERES data (1-way ANOVA F score = 3.05, $P < 0.0001$).

**ChIP-seq and ChIP-qPCR**

Crosslinking was performed in fresh cell culture medium containing 1% formaldehyde with gentle rotation for 5 mins in room temperature. Fixation was stopped by the addition of glycine (125 mM final concentration). Fixed cells were trypsinized, washed twice in ice-cold PBS, and then resuspended in 3-x$10^6$ cells/130 μl SDS lysis buffer (1% SDS, 10 mM EDTA, 50 mM Tris-HCl, pH 8.1, supplemented with fresh Complete mini-protease inhibitor cocktail (Roche, Indianapolis, IN)). Chromatin was sheared to about 200bp fragments by Covaris ultrasonication. Centrifugation was used to remove debris at 4°C for 10 mins at top speed. The supernatant was diluted 1:10 using ice-cold ChIP dilution buffer (0.01% SDS, 1.1% Triton-X100, 1.2 mM EDTA, 16.7 mM Tris-HCl, 167 mM NaCl pH 8.1, supplemented with fresh Complete mini-protease inhibitor cocktail). Five percent of the diluted sample was saved as input controls and the remainder of the diluted sample was used for immunoprecipitation with antibodies overnight at 4°C. Precipitates were washed sequentially with ice cold low salt wash (0.1% SDS, 1% Triton-X-100, 2 mM EDTA, 20 mM Tris-HCl, pH 8.1, 150 mM NaCl), high salt wash (0.1% SDS, 1% Triton-X-100, 2 mM EDTA, 20 mM Tris-HCl, pH 8.1, 500 mM NaCl), LiCl wash (0.25 M LiCl, 1% IGEPALCA-630, 1% deoxycholic acid, 1 mM EDTA, 10 mM Tris-HCl, pH 8.1) and then twice with TE (1 mM EDTA, 10 mM Tris-HCl, pH 8.1). They were then eluted and reverse cross-linked in elution/reverse cross-linking buffer (1% SDS, 0.1 M NaHCO3, 0.2 M NaCl) for 5 hours. Eluted DNA fragments were purified with Qiagen PCR purification kit and analyzed by qPCR, or barcoded with a NEBNext DNA library preparation kit (NEB, Ipswich, MA) and subjected to sequencing on Illumina HiSeq 2000 platform.

Antibodies used in ChIP experiments are: anti-EZH2 (Cell Signaling 5246S); anti-MYCN (Santa Cruz sc-53993); anti-H3K27me3 (Millipore 07-449); anti-H3K4me3 (Abcam ab8580).

Primer sequences for ChIP-qPCR: *MCM7* forward: GCGGGAGGTGAAGAAGGCC; *MCM7* reverse: CTGTGGCCGGCCAACCG; *ZIC3* forward: CGGTGTGTAATTCGGGAAGTG; *ZIC3* reverse: GCCAAGCGTTGACCCTTTAG; *EZH2* (TSS-300bp) forward: CTGCACACCGCCTTCCT; *EZH2* (TSS-300bp) reverse: CCGCCGTCTCTTTGTTCTT; *EZH2* (TSS-200bp) forward: CCAGTGGCGTCCCTTACAG; *EZH2* (TSS-200bp) reverse: TGCGCTCAGGGCTCGT; *EZH2* (TSS) forward: AAAAGCGATGGCGATTGG; *EZH2* (TSS) reverse: GGCTCCACTGCCTTCTGAGT.

**ChIP-seq Data Analysis**

All of the ChIP-seq data sets were aligned using Bowtie v2.2.3 (10, 11) to the build version NCBI37/hg19 of the human genome. Quality control tests were performed based on the FastQC v.0.11.2 software (Babraham Bioinformatics, http://www.bioinformatics.babraham.ac.uk/projects/fastqc/) and by using the ChIPQC library available from Bioconductor v3.2 (12).

The ChIP-seq peaks for EZH2 and H3K4me3 were identified using MACS v1.4.3, and the ChIP-seq broad peaks for H3K27me3 were identified using MACS v.2.0.10 (13) with the cut-off 1e-05 for the *P*-value. The peaks were annotated by using the Annotate Peaks function available in the Homer v4.7 package (14).

The relative ChIP occupancy signal in the gene promoter regions expressed in units of reads per million mapped reads per bp (rpm/bp) was computed for each mark by using the DeepTools v2.2.3 software (15) as the ratio between the area under curve (AUC) of the mark normalized signal vs. the AUC of the background input signal. Gene promoters were defined as the +/- 5 kb regions around the gene transcription start site (TSS). The gene targets for EZH2 and H3K27me3 were identified separately for each of the Kelly and LAN-1 cells as the genes with high relative occupancy of EZH2 or H3K27me3, respectively, ChIP signal in the promoter. The “high” level for the relative occupancy signal in the promoter regions was estimated based on the cut-off 1.5 for the ratio of the AUC signal of the mark vs. the AUC signal of the input. In addition, “core” lists of gene targets for EZH2 andH3K27me3 were defined by intersecting the target gene sets for Kelly and LAN-1 cell lines. The lists of gene targets for EZH2 and H3K27me3 are provided in

Supplemental Table 3**.** The correlation between the relative promoter signal for H3K27me3 and the relative promoter signal for EZH2 across the hg19 genes was tested for significance by using the rcorr function available in the Hmisc R v3.4 library.

Actively transcribed genes were assessed based on the existence of significantly enriched regions of H3K4me3 within +/- 5 kb of the TSS, combined with the Z-score of genome-wide expression > 1. In order to verify that these genes were not bivalently marked or repressed, we assayed the repressive histone mark H3K27me3 and required that no significantly enriched region for H3K27me3 overlapped within +/- 5kb of the TSS gene promoter region.

The ChIP-seq data for this study is available for download from the Gene Expression Omnibus (GEO) repository (GSE85432) upon manuscript publication.

**Metagene Representation of Gene Promoter Occupancy**

The metagene representations of global genome-wide average ChIP-seq signal promoter occupancy for EZH2, H3K27me3 and H3K4me3 were performed as described in (16) based on the expression data for cells cultured in baseline growth conditions, available for the Kelly cells in the CCLE database (17) and for the LAN-1 cells in the Gene Expression Omnibus GSE56552 data (18). The genes for each data set were grouped into three categories: highly expressed (Z-score for genome-wide log2 RMA expression $\geq 1.5$), medium expressed (absolute Z-score for genome-wide log2 RMA expression $\leq 0.5$) and poorly expressed (Z-score for genome-wide log2 RMA expression $\leq -1.5$). The metagenes for the EZH2, H3K27me3 and H3K4me3 relative ChIP signal occupancy at promoters were created for 500 randomly selected genes from each of the three categories. The ChIP-seq signal was mapped to the +/- 10kb regions flanking TSS. The TSS +/- 10kb regions were aligned and split into 50 bp bins. The normalized ChIP-seq signal occupancy with background input subtracted was then computed as the “Area under the Curve” density signal in rpm/bp units in the flanked regions. Finally, the meta-representations were derived based on the average normalized ChIP signal across the 500 genes selected from the highly expressed, medium expressed and poorly expressed categories.

**GSEA for EZH2 and H3K27me3 Target Genes**

The GSEA v2.2.0 software (6, 7) was utilized to identify gene sets that have a significant overlap with the genes marked by EZH2 and by H3K27me3. First the hg19 genes were ranked based on the H3K27me3, respectively based on the EZH2 relative ChIP-seq occupancy signal in the

promoter. The goal of GSEA was to identify the gene sets that are distributed at the top or at the bottom of the ranked list of genes. For this purpose, the Pre-Rank GSEA module was run across the comprehensive collection c2 of 4,726 curated canonical pathways and gene sets, available in the MSigDB v5.1 database http://www.broadinstitute.org/gsea/msigdb/index.jsp (6). Gene sets with a nominal $P \leq 0.05$ and an FDR $\leq 0.25$ for the Kolmogorov-Smirnov enrichment test were considered significant hits. The gene sets identified as significantly enriched in gene targets for EZH2 and H3K27me3 were further tested for association with the PRC2 complex by applying the two-tailed Fisher exact test. Of the 4,726 gene sets available in the c2 collection of MSigDB, 83 were manually annotated as related to the PRC2 complex.

In addition, the lists of core gene targets for EZH2 (361 genes) and H3K27me3 (428 genes) were further tested for significant overlap with the MSigDB v5.1 c2 collection of 4,726 curated canonical pathways based on the "Investigate GeneSets" module available in MSigDB. The significance of the overlap was assessed based on a hypergeometric test, with the 0.05 cut-offs for the *P*-value and the FDR.

**Genome-wide Expression Analysis**

Kelly and LAN-1 cells were treated in duplicate with 2 μM GSK126 or DMSO for 2 or 5 days. Total RNA was extracted with an RNeasy Kit (Qiagen) and profiled by RNA sequencing (HiSeq, Illumina) at the Center for Cancer Computational Biology (CCCB) at the Dana-Farber Cancer Institute.

**RNA-seq Data Processing**

Quality control tests for the mapped reads were performed using the FASTQC software (www.bioinformatics.babraham.ac.uk/projects/fastqc/). The reads were aligned to the GRCh37/hg19 human genes by using Tophat2 v2 (19). Quality control tests for the aligned reads and for the replicate consistency were performed by using the qualimap v2.2 (20) and the SARTools (21) pipelines. The total number of reads for individual samples ranged from 17 to 24 Mb. The average percentage of uniquely mapped reads in the aligned data was 86.50%, with a standard deviation 2.3%. The RNA-seq data for this study is available for download from the Gene Expression Omnibus (GEO) repository (GSE85432) upon manuscript publication.

Gene level reads and gene level expression estimated as log2(FPKM) scores were computed using the Feature Counts method implemented in the Bioconductor v3.2 RSubread package (22).

The genome-wide expression data were projected onto a heatmap by using the GENE-E software (http://www.broadinstitute.org/cancer/software/GENE-E/). The overall significance of the differential expression between the control and treatment phenotypes was estimated by using the EdgeR method available from the Bioconductor v3.2 EdgeR library (23) with the significance cut-off $P \leq 0.05$ for the posterior probability.

**Comparative Marker Analysis**

The 16 samples available in the data were analyzed for changes in expression induced by GSK126 vs DMSO at days 2 and 5 in individual cell lines and in both cell lines. The Comparative Marker Selection module from GenePattern v3.9.6 (24) was employed to identify individual genes that were differentially expressed between treated and vehicle conditions. The analysis was performed on the gene level expression data estimated as log2(FPKM) by applying a 2-sided signal-to-noise ratio (SNR) test followed by 1,000 permutations of the phenotype labels. The settings for the SNR parameters were log-transformed-data: yes, complete: no, balanced: no, smooth *P*-values: yes. Molecular signatures for genes down-regulated (respectively up-regulated) by GSK126 vs. DMSO were defined based on the cut-offs: absolute fold change for log2(FPKM) expression $\geq 1.5$ (for "stringent" signatures), absolute fold change for log2(FPKM) expression $\geq 0.5$ (for "relaxed" signatures), permutation $P \leq 0.05$, Benjamini-Hochberg false discovery rate (FDR) $\leq 0.05$.

The differential changes in expression induced by GSK126 were first identified separately for the Kelly and LAN-1 cells. "Core" lists of differentially upregulated and downregulated genes were defined by intersecting the lists of genes differentially upregulated or downregulated by GSK126 in each of the Kelly and LAN-1 cell lines. The GSK126 "stringent" de-repression signature at day 5 consists of 348 genes upregulated between treated samples vs. vehicle in Kelly cells 244 genes upregulated in LAN-1 cells, and 30 core genes upregulated in both cell lines. The GSK126 "relaxed" de-repression signature at day 5 consists of 1,346 genes upregulated between treated samples vs. vehicle in Kelly cells, 1,187 genes upregulated in LAN-1 cells, and 248 core genes up-regulated in both cell lines.

**GSEA for the Expression Changes Induced by GSK126**

GSEA v2.1.0 software (6, 7) was used to identify functional associations of the molecular phenotypes induced by GSK126 with a compendia of gene signatures: (a) the MSigDB v5.1 collection c2 of 4,726 curated pathways and experimental gene sets, (b) the MSigDB v5.1

collection c5 of 825 Gene Ontology – Biological Processes gene sets, (c) the lists of gene targets for EZH2 and H3K27me3 identified in our ChIP-seq experiments, and (d) signatures of genes repressed in *MYCN*-amplified and high-risk neuroblastoma tumors.

The signatures of genes repressed in *MYCN*-amplified or high-risk neuroblastoma tumors were derived from two primary neuroblastoma gene expression datasets: the Affymetrix U133 A GSE12460 (25) data describing 64 tumors, and the RNA-seq GSE49711 (26) data describing 498 tumors. Gene sets with less than 15 genes or more than 500 genes were excluded from the analysis. Gene sets with a nominal $P \leq 0.05$ and FDR $\leq 0.25$ were considered significant hits. The results were visualized on GSEA plots, heatmaps and networks for selected gene signatures.

The Enrichment Map v2.1.0 software (27) was employed to organize the significantly enriched gene sets into a network called an "enrichment map." In the enrichment map, the nodes correspond to the gene sets and the edges reflect the overlap between the gene sets corresponding to the nodes according to the two-tailed Fisher exact test. The size of a node correlates with the enrichment *P*-value for the gene set associated to the node. The hubs correspond to collections of gene sets with a unifying functional group label.

**Association of the EZH2 Target Gene and GSK126 De-repression Signatures with *MYCN*-amplified Status in Primary Neuroblastoma Tumors**

The EZH2 gene signatures identified in the ChIP-seq and the RNA-seq experiments in our study were further tested for association with the *MYCN*-amplified status and the high-risk neuroblastoma phenotypes in primary tumors. The two neuroblastoma gene expression datasets: GSE12460 (25), describing 64 tumors, and GSE49711 (26), describing 498 tumors, were analyzed for this purpose.

**Drug Synergy Screening and Analysis for Combinations with GSK126**

The EZH2 inhibitor GSK126 was screened *in vitro* for the synergistic combination with a panel of 10 small molecules. The screening was performed on Kelly cells. The synergistic activity of the *in vitro* GSK126 combinations was assessed based on the Delta Bliss Sum Negative (DBSumNeg) score with the conservative synergy cutoff DBSumNeg < -3 (28). The DBSumNeg score was introduced as a new metric to quantify the synergy of the combination of two drugs across all dose combinations tested and was computed simply as the sum of the synergistic deviations from the Excess over Bliss model (29).

**Chou-Talalay Combination Index for Loewe Additivity**

To assess whether individual treatment combinations were synergistic, additive, or antagonistic we computed the combination index (CI) scores for Loewe Additivity based on the Chou-Talalay Median Effect model (30-32) as implemented in CalcuSyn v2.11 (http://www.biosoft.com/w/calcusyn.htm). The median effect model states that the effect *x* of a dose of a drug is described by the equation $x/(1-x) = (d/D_{IC50})^m$, where $D_{IC50}$ is the $IC_{50}$ dose of the drug, and *m* is a parameter that estimated from the dose-effect curve kinetics of the drug: *m* = 1 (hyperbolic), *m* > 1 (sigmoidal), *m* < 1 (flat sigmoidal). Loewe additivity is a dose-effect model which states that additivity occurs in a two-drug combination if the sum of the ratios of the dose vs. the median-effect for each individual drug is $d_1/D_{IC50,1} + d_2/D_{IC50,2} = 1$, where $d_1$, $d_2$ are the doses for the two drugs, and $D_{IC50,1}$ and $D_{IC50,2}$ represent the IC50 doses (median-effect) for the two drugs, respectively. Chou and Talalay (30) showed that Loewe equations are valid for enzyme inhibitors with similar mechanisms of action -- either competitive or non-competitive toward the substrate.

The Chou-Talalay Combination Index for Loewe Additivity model assigns a quantitative measure to any given effect *x* produced by the combination of dose $d_1$ of drug 1 and dose $d_2$ of drug 2: $CI = d_1/Dx_1 + d_2/Dx_2$ , where $Dx_1$ is the dose of drug 1 that alone produces the effect *x* and $Dx_2$ is the dose of drug 2 that alone produces the effect *x*, as estimated from the median effect model. For any given endpoint of the effect measurement CI estimates synergism (CI < 0.8), strong synergism (CI < 0.6), antagonism (CI > 1.2), strong antagonism (CI > 1.4) or additive effect (CI in the range 0.8-1.2). The drug combinations were analyzed based on two types of diagnostic plots:

*Effect-oriented* plots: the effect *x* of the drug combination on the X axis, and $CI = d_1/D_{x1} + d_2/D_{x2}$ on the Y axis

*Dose-oriented* (isobologram) plots: $d_1/D_{x1}$ on the X axis, $d_2/D_{x2}$ on the Y axis, along with the Loewe additivity isobole line: $d_1/D_{IC50,1} + d_2/D_{IC50,2} = 1$

## SUPPLEMENTAL FIGURE LEGENDS

**Supplemental Figure 1. Neuroblastoma Cell Lines Are Dependent on PRC2 Complex and EZH2.** (**A**) EED-EZH2 Complex dependency Z-score in neuroblastoma versus all other cell lines in the CRISPR-Cas9 screen based on single sample GSEA. (**B**) The correlation of relative dependency on *EED* and *EZH2* (*left*), *SUZ12* and *EZH2* (*middle*), or *SUZ12* and *EED* (*right*), in each of the neuroblastoma cell lines. X-axis and Y-axis show the gene CERES dependency score. (**C**) Heat map showing *EZH2*, *EED*, and *SUZ12* dependency scores in all cell lines in the screen. (**D**) Immunoblot showing the effect of *EZH2* CRISPR-Cas9 knockout or *EZH2* shRNA knockdown on the H3K27me3 levels in SK-N-BE(2). (**E**) Immunoblot showing the EZH2 expression before or after EZH2 replacement with control (*GFP*), *EZH2* wildtype (*EZH2*-WT), or *EZH2* triple point-mutant (*EZH2*-TM). (**F**) Cell viability assay before or after EZH2 replacement with control (*GFP*), *EZH2* wildtype (*EZH2*-WT), or *EZH2* triple point-mutant (*EZH2*-TM). Shown is a representative of two independent experiments. Mean ± SD of eight technical replicates is shown.

**Supplemental Figure 2. Pharmacological Inhibition of EZH2 in *MYCN*-amplified Neuroblastoma *in Vitro***. (**A**) Immunoblot showing dose-dependent target inhibition by JQEZ5 (*left*) or GSK126 (*right*) in neuroblastoma cell lines. Total H3 served as control for H3K27me3. (**B**) Mann-Whitney test of area under curve response to EZH2 inhibitors comparing *MYCN*-amplified and *MYCN*-nonamplified neuroblastoma. (**C**) Flow cytometry analysis for Annexin V and PI staining in neuroblastoma cell lines treated with 3 μM JQEZ5, GSK126 or DMSO control for 8-10 days.

**Supplemental Figure 3. Genome-wide EZH2 Binding Pattern in *MYCN*-amplified Neuroblastoma LAN-1 cells**. (**A**) Metagene analysis showing the average ChIP-seq binding signals of EZH2, H3K27me3 or H3K4me3 for 500 randomly selected genes in each of three categories based on the gene expression level (highly expressed, medium expressed and poorly expressed). X-axis shows the distance in kb to transcription start site (TSS). (**B**) Scatter plot showing correlation between EZH2 relative binding signal and H3K27me3 relative binding signal in the promoter region. (**C**) Gene track showing high binding signal for EZH2 and H3K27me3 and low binding signal for H3K4me3 in two published, validated EZH2 targets. (**D**) Box plots of expression values for (*top*) EZH2 target genes versus non-EZH2 target genes and (*bottom*) H3K27me3 target genes versus non-H3K27me3 target genes in LAN-1 cells. (**E**) GSEA volcano

plot showing enrichment of published PRC2 target signatures from MSigDB v5.1 among genes with (*top*) high EZH2 binding signal or (*bottom*) high H3K27me3 binding signal in LAN-1 cells. (**F**) Enrichment of Benporath PRC2 target signature among genes with (*top*) high EZH2 promoter binding signal or (*bottom*) high H3K27me3 promoter binding signal in LAN-1 cells.

**Supplemental Figure 4. Side-by-side Heatmaps of EZH2 and H3K27me3 ChIP-seq AUC Signal.** The 4,536 EZH2 peaks ±4kb in Kelly cells are shown on the left and the 1,936 EZH2 peaks ±4kb in LAN-1 cells on the right. The color scale indicates average signal on a 10-base pair window.

**Supplemental Figure 5. GSEA Showing the Effect of GSK126 Treatment on Neuroblastoma Cell Lines (Kelly and LAN-1) and Single Sample GSEA of Neuroblastoma Tumors.** (**A**) GSEA showing enrichment for the previously published gene signatures after treatment with EPZ-6438 (GSE79859) in the expression profiles following GSK126 treatment. (**B**) GSEA showing enrichment of neurite development and axonogenesis signatures in genes upregulated by GSK126. (**C**) Single sample GSEA in primary neuroblastoma tumor expression datasets GSE12460 and GSE49711.

**Supplemental Figure 6. Isobologram Plots Demonstrate Synergy of Panobinostat and GSK126 in Kelly, SK-N-BE(2), LAN-1 and CHP-212 on Day 6.** Shown is a representative of two to three independent experiments.

## SUPPLEMENTAL TABLE LEGENDS

**Supplemental Table 1. (A)** Top 100 leading edge genes for the top 3 independent components IC1, IC2 and IC3 that are associated with the neuroblastoma lineage in the CRISPR-Cas9 CERES dependency data. The genes are ranked based on their Z-score per component. Leading edge genes were selected based on cut-off Z-score ≥ 2.5. PRC2 complex genes are highlighted bold. **(B)** Sensitivity AUC scores for the EZH2 inhibitors GSK126 (day 5), JQEZ5 (day 5) and dependency scores for EZH2, EED, and SUZ12 across the neuroblastoma cell lines in the study.

**Supplemental Table 2.** Top 50 GSEA significant hits for EZH2 and H3K27me3 ChIP-seq target genes in Kelly and LAN-1 cells using the MSigDB v5.1 collection c2 of 4,726 pathways and

experimental gene sets. For each significant gene set hit the table shows if the gene set is related to the PRC2 complex (1= yes, 0=no), the size of the gene set, the GSEA normalized enrichment score (NES), *P* and false discovery rate (FDR). The MSigDB gene sets are ranked in decreasing order based on the NES. **(A)** Top 50 GSEA hits for EZH2 ChIP-seq target genes in Kelly cells. PRC2 related gene sets are significantly over-represented in the collection of GSEA hits (odds-ratios = 9.5, $P < 0.001$, according to the two-tailed Fisher exact test). **(B)** Top 50 GSEA hits for H3K27me3 ChIP-seq target genes in Kelly cells. PRC2 related gene sets are significantly over-represented in the collection of GSEA hits (odds-ratios = 8.1, $P < 0.001$, according to the two-tailed Fisher exact test). **(C)** Top 50 GSEA hits for EZH2 ChIP-seq target genes in LAN-1 cells. PRC2 related gene sets are significantly over-represented in the collection of GSEA hits (odds-ratios = 7.9, $P < 0.001$ according to the two-tailed Fisher exact test). **(D)** Top 50 GSEA hits for H3K27me3 ChIP-seq target genes in LAN-1 cells. PRC2 related gene sets are significantly over-represented in the collection of GSEA hits (odds-ratios = 9.5, $P < 0.001$ according to the two-tailed Fisher exact test).

**Supplemental Table 3.** Custom neuroblastoma PRC2 signatures consisting of the top 300 EZH2 and H3K27me3 ChIP-seq target genes in Kelly and LAN-1 cell lines. Shown in table are the EZH2 and H3K27me3 promoter relative binding signal in Kelly and LAN-1 cells. Genes were ranked in decreasing order based on the promoter binding signal in the highlighted ranking score column. The high level for the relative occupancy signal in the promoter regions was estimated based on the cut-off 1.5 for the ratio of the AUC ChIP-seq signal of the mark vs. the AUC signal of the input. **(A)** Custom neuroblastoma PRC2 signature consisting of the top 300 EZH2 ChIP-seq target genes in Kelly cells. **(B)** Custom neuroblastoma PRC2 signature consisting of the top 300 H3K27me3 ChIP-seq target genes in Kelly cells. **(C)** Custom neuroblastoma PRC2 signature consisting of the top 300 EZH2 ChIP-seq target genes in LAN-1 cells. **(D)** Custom neuroblastoma PRC2 signature consisting of the top 300 H3K27me3 ChIP-seq target genes in LAN-1 cells.

**Supplemental Table 4.** Top 60 significant GSEA hits for EZH2 and H3K27me3 ChIP-seq target genes in Kelly and LAN-1 cells using the MSigDB v5.1 c5 collection of 25 Gene Ontology (GO) gene sets related to biological processes. For each gene set hit the table shows if the gene set is related to any of the 15 Neural Development signatures available in the MSigDB c5 collection (1= yes, 0=no), the size of the gene set, the GSEA normalized enrichment score (NES), *P* and false discovery rate (FDR). The significance cut-offs were 0.05 for *P* and 0.25 for FDR. The top 60 gene set hits are ranked in decreasing order based on the NES. **(A)** Top 60 GSEA hits for

EZH2 ChIP-seq target genes in Kelly cells. Neural Development related gene sets are significantly over-represented in the collection of GSEA hits (odds-ratios = 51.03, $P < 0.001$, according to the two-tailed Fisher exact test). **(B)** Top 60 GSEA hits for EZH2 ChIP-seq target genes in LAN-1 cells. Neural Development related gene sets are significantly over-represented in the collection of GSEA hits (odds-ratios = 39.73, $P < 0.001$, according to the two-tailed Fisher exact test).

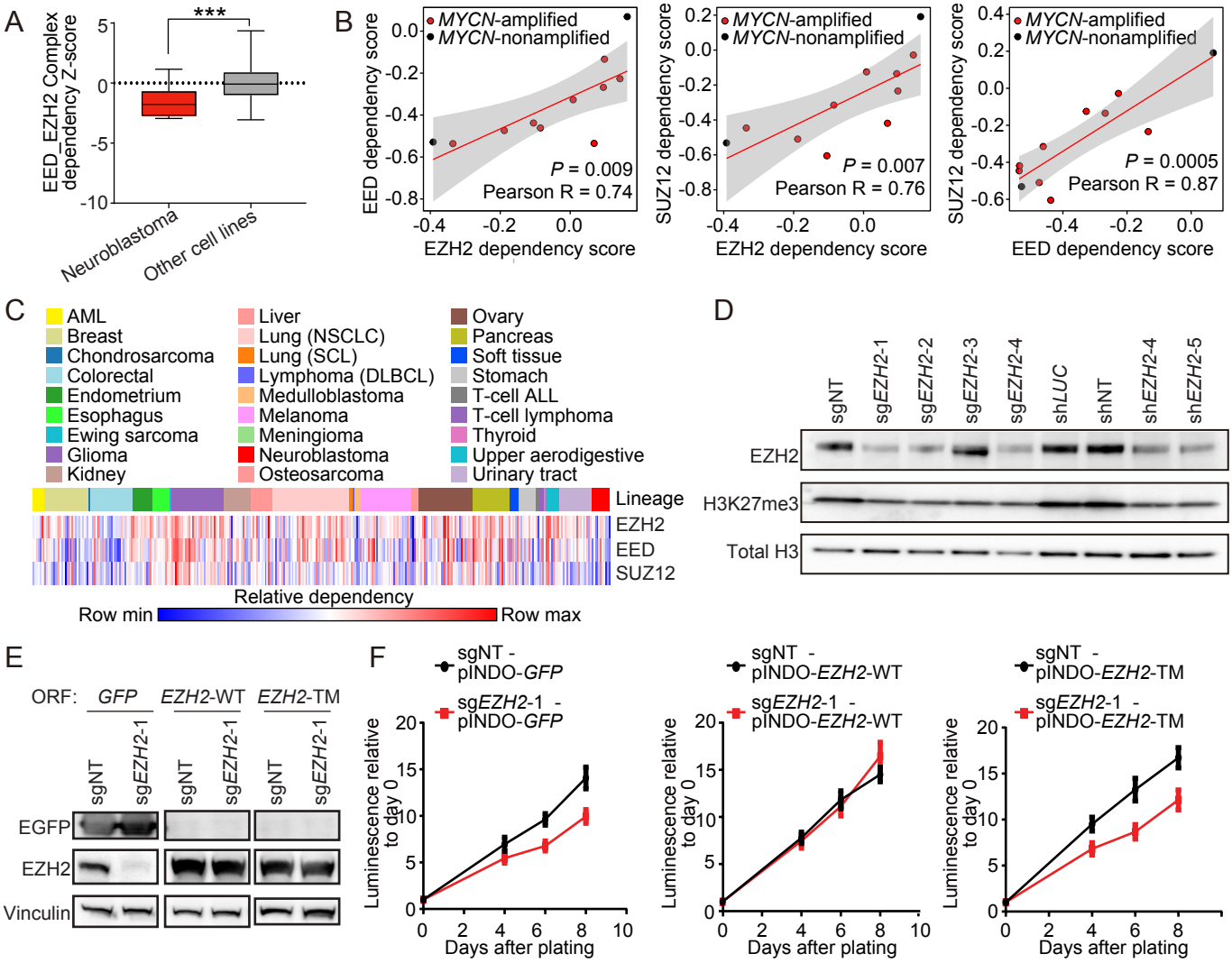
**Supplemental Table 5.** The shRNA sequences and the CRISPR-Cas9 sgRNA sequences targeting *MYCN* and *EZH2* that were used in this study.

**REFERENCES**

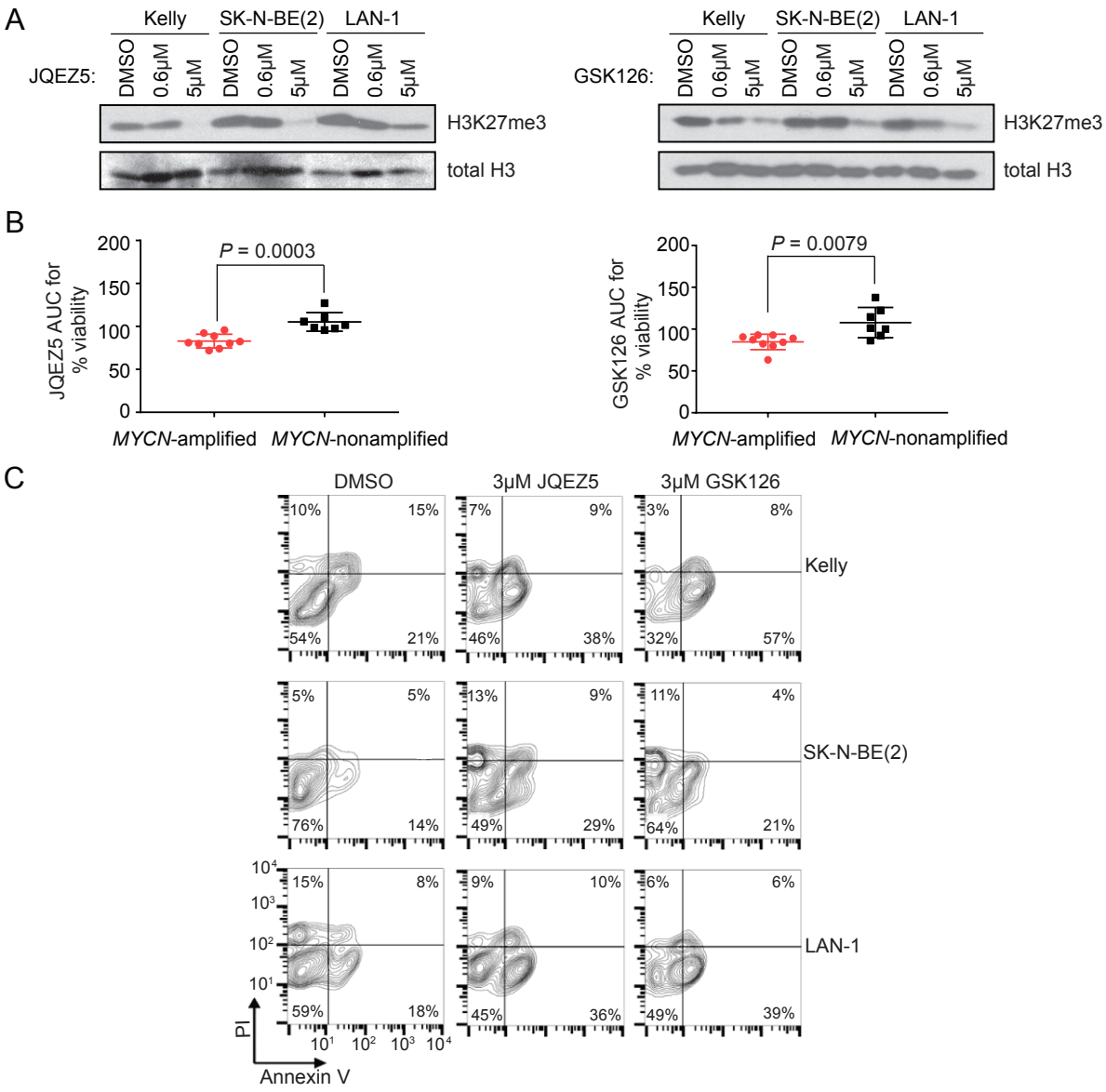

1. Meyers RM, Bryan JG, McFarland JM, Weir BA, Sizemore AE, Xu H, Dharia NV, Montgomery PG, Cowley GS, Pantel S, et al. Computational correction of copy-number effect improves specificity of CRISPR-Cas9 essentiality screens in cancer cells. *Nature Genetics.* 2017: in press.
2. Comon P. Independent component analysis, a new concept? *Signal processing.* 1994;36(3):287-314.
3. Hyvärinen A, Karhunen J, and Oja E. Independent component analysis. *Willey, New York.* 2001.
4. Hyvärinen A. Fast and robust fixed-point algorithms for independent component analysis. *IEEE Trans Neural Netw.* 1999;10(3):626-34.
5. Barbie DA, Tamayo P, Boehm JS, Kim SY, Moody SE, Dunn IF, Schinzel AC, Sandy P, Meylan E, Scholl C, et al. Systematic RNA interference reveals that oncogenic KRAS-driven cancers require TBK1. *Nature.* 2009;462(7269):108-12.
6. Subramanian A, Tamayo P, Mootha VK, Mukherjee S, Ebert BL, Gillette MA, Paulovich A, Pomeroy SL, Golub TR, Lander ES, et al. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc Natl Acad Sci U S A.* 2005;102(43):15545-50.
7. Mootha VK, Lindgren CM, Eriksson KF, Subramanian A, Sihag S, Lehar J, Puigserver P, Carlsson E, Ridderstrale M, Laurila E, et al. PGC-1alpha-responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes. *Nat Genet.* 2003;34(3):267-73.
8. Kamburov A, Pentchev K, Galicka H, Wierling C, Lehrach H, and Herwig R. ConsensusPathDB: toward a more complete picture of cell biology. *Nucleic Acids Res.* 2011;39(Database issue):D712-7.
9. Kamburov A, Wierling C, Lehrach H, and Herwig R. ConsensusPathDB--a database for integrating human functional interaction networks. *Nucleic Acids Res.* 2009;37(Database issue):D623-8.
10. Langmead B. Aligning short sequencing reads with Bowtie. *Curr Protoc Bioinformatics.* 2010;Chapter 11(Unit 11 7.
11. Langmead B, and Salzberg SL. Fast gapped-read alignment with Bowtie 2. *Nat Methods.* 2012;9(4):357-9.
12. Carroll TS, Liang Z, Salama R, Stark R, and de Santiago I. Impact of artifact removal on ChIP quality metrics in ChIP-seq and ChIP-exo data. *Front Genet.* 2014;5(75.
13. Feng J, Liu T, Qin B, Zhang Y, and Liu XS. Identifying ChIP-seq enrichment using MACS. *Nat Protoc.* 2012;7(9):1728-40.
14. Heinz S, Benner C, Spann N, Bertolino E, Lin YC, Laslo P, Cheng JX, Murre C, Singh H, and Glass CK. Simple combinations of lineage-determining transcription factors prime cis-regulatory elements required for macrophage and B cell identities. *Mol Cell.* 2010;38(4):576-89.
15. Ramirez F, Dundar F, Diehl S, Gruning BA, and Manke T. deepTools: a flexible platform for exploring deep-sequencing data. *Nucleic Acids Res.* 2014;42(Web Server issue):W187-91.

16. Loven J, Hoke HA, Lin CY, Lau A, Orlando DA, Vakoc CR, Bradner JE, Lee TI, and Young RA. Selective inhibition of tumor oncogenes by disruption of super-enhancers. *Cell.* 2013;153(2):320-34.
17. Barretina J, Caponigro G, Stransky N, Venkatesan K, Margolin AA, Kim S, Wilson CJ, Lehar J, Kryukov GV, Sonkin D, et al. The Cancer Cell Line Encyclopedia enables predictive modelling of anticancer drug sensitivity. *Nature.* 2012;483(7391):603-7.
18. Dassi E, Greco V, Sidarovich V, Zuccotti P, Arseni N, Scaruffi P, Tonini GP, and Quattrone A. Multi-omic profiling of MYCN-amplified neuroblastoma cell-lines. *Genom Data.* 2015;6(285-7.
19. Kim D, Pertea G, Trapnell C, Pimentel H, Kelley R, and Salzberg SL. TopHat2: accurate alignment of transcriptomes in the presence of insertions, deletions and gene fusions. *Genome Biol.* 2013;14(4):R36.
20. Garcia-Alcalde F, Okonechnikov K, Carbonell J, Cruz LM, Gotz S, Tarazona S, Dopazo J, Meyer TF, and Conesa A. Qualimap: evaluating next-generation sequencing alignment data. *Bioinformatics.* 2012;28(20):2678-9.
21. Hugo Varet J-YC, Marie-Agnès Dillies. SARTools: a DESeq2- and edgeR-based R pipeline for comprehensive differential analysis of RNA-Seq data. *bioRxiv.* 2015.
22. Liao Y, Smyth GK, and Shi W. featureCounts: an efficient general purpose program for assigning sequence reads to genomic features. *Bioinformatics.* 2014;30(7):923-30.
23. Robinson MD, McCarthy DJ, and Smyth GK. edgeR: a Bioconductor package for differential expression analysis of digital gene expression data. *Bioinformatics.* 2010;26(1):139-40.
24. Reich M, Liefeld T, Gould J, Lerner J, Tamayo P, and Mesirov JP. GenePattern 2.0. *Nat Genet.* 2006;38(5):500-1.
25. Janoueix-Lerosey I, Lequin D, Brugieres L, Ribeiro A, de Pontual L, Combaret V, Raynal V, Puisieux A, Schleiermacher G, Pierron G, et al. Somatic and germline activating mutations of the ALK kinase receptor in neuroblastoma. *Nature.* 2008;455(7215):967-70.
26. Wang C, Gong B, Bushel PR, Thierry-Mieg J, Thierry-Mieg D, Xu J, Fang H, Hong H, Shen J, Su Z, et al. The concordance between RNA-seq and microarray data depends on chemical treatment and transcript abundance. *Nat Biotechnol.* 2014;32(9):926-32.
27. Merico D, Isserlin R, Stueker O, Emili A, and Bader GD. Enrichment map: a network-based method for gene-set enrichment visualization and interpretation. *PLoS One.* 2010;5(11):e13984.
28. Mott BT, Eastman RT, Guha R, Sherlach KS, Siriwardana A, Shinn P, McKnight C, Michael S, Lacerda-Queiroz N, Patel PR, et al. High-throughput matrix screening identifies synergistic and antagonistic antimalarial drug combinations. *Sci Rep.* 2015;5(13891.
29. Bliss CI. The calculation of microbial assays. *Bacteriol Rev.* 1956;20(4):243-58.
30. Chou TC, and Talalay P. Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors. *Adv Enzyme Regul.* 1984;22(27-55.

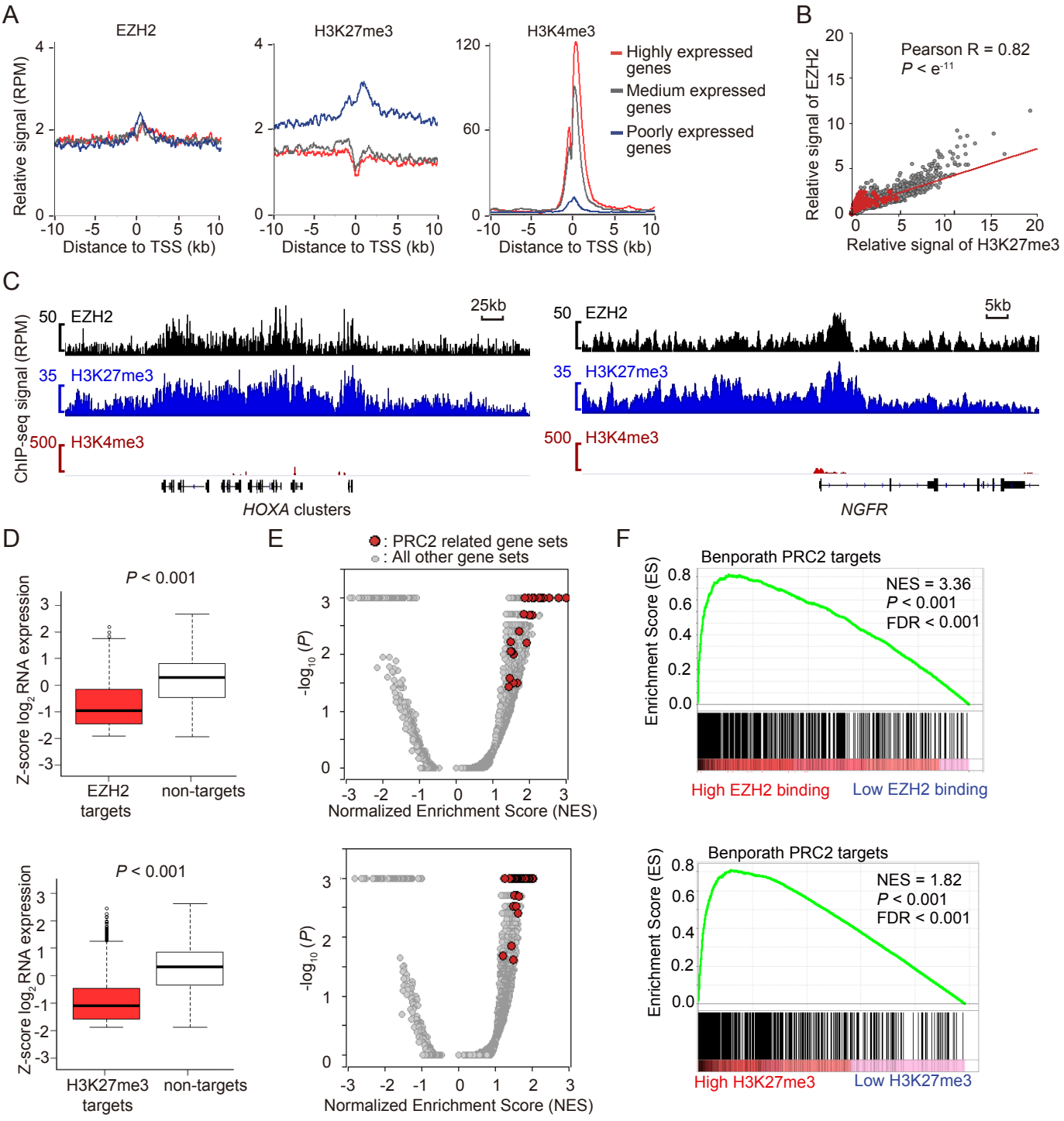
31. Chou T-C. Theoretical basis, experimental design, and computerized simulation of synergism and antagonism in drug combination studies. *Pharmacological reviews.* 2006;58(3):621-81.
32. Chou TC. Drug combination studies and their synergy quantification using the Chou-Talalay method. *Cancer Res.* 2010;70(2):440-6.



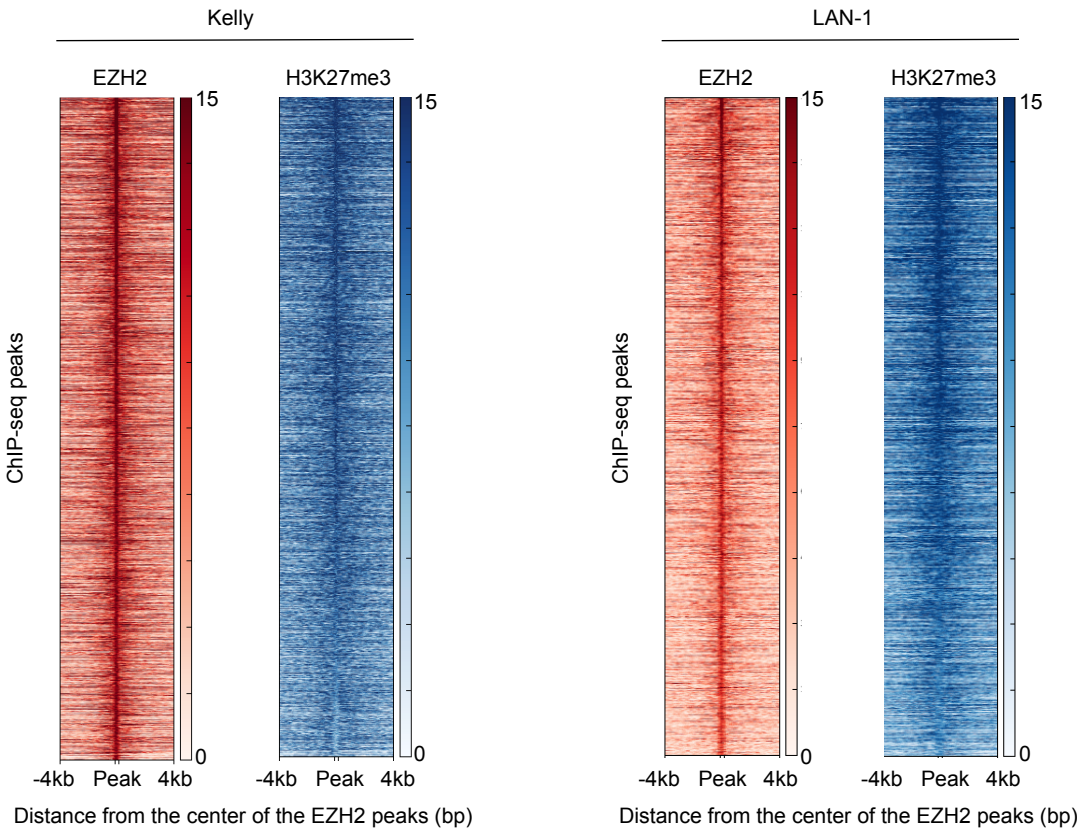

**Supplemental Figure 1. Neuroblastoma Cell Lines Are Dependent on PRC2 Complex and EZH2.** (**A**) EED-EZH2 Complex dependency Z-score in neuroblastoma versus all other cell lines in the CRISPR-Cas9 screen based on single sample GSEA. (**B**) The correlation of relative dependency on *EED* and *EZH2* (*left*), *SUZ12* and *EZH2* (*middle*), or *SUZ12* and *EED* (*right*), in each of the neuroblastoma cell lines. X-axis and Y-axis show the gene CERES dependency score. (**C**) Heat map showing EZH2, EED and SUZ12 dependency scores in all cell lines in the screen. (**D**) Immunoblot showing the effect of *EZH2* CRISPR-Cas9 knockout or *EZH2* shRNA knockdown on the H3K27me3 levels in SK-N-BE(2). (**E**) Immunoblot showing the EZH2 expression before or after EZH2 replacement with control (*GFP*), *EZH2* wild-type (*EZH2*-WT), or *EZH2* triple point-mutant (*EZH2*-TM). (**F**) Cell viability assay before or after EZH2 replacement with control (*GFP*), *EZH2* wild-type (*EZH2*-WT), or *EZH2* triple point-mutant (*EZH2*-TM). Shown is a representative of two independent experiments. Mean ± SD of eight technical replicates is shown.



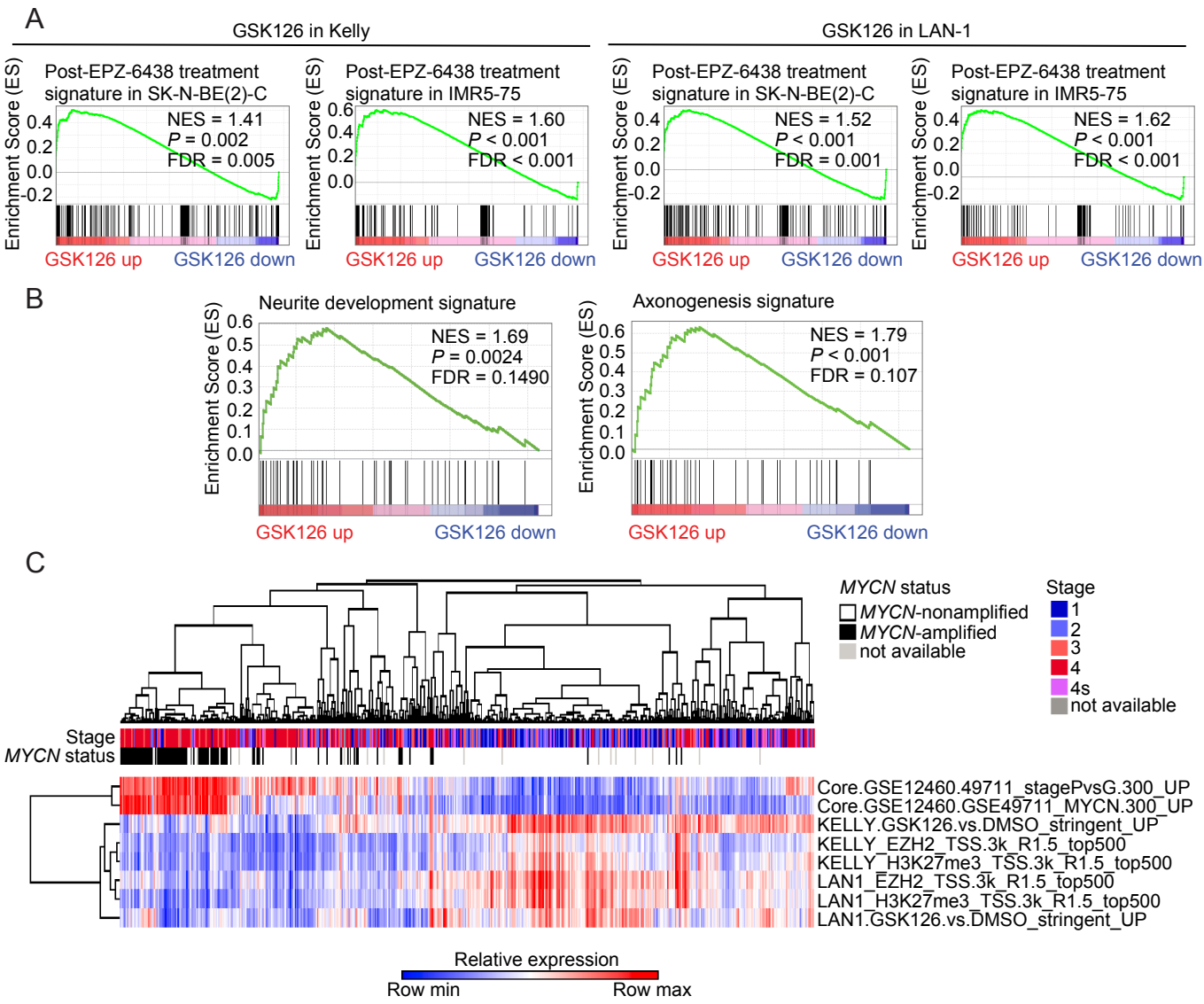

**Supplemental Figure 2. Pharmacological Inhibition of EZH2 in *MYCN*-amplified Neuroblastoma *in Vitro*.** (**A**) Immunoblot showing dose-dependent target inhibition by JQEZ5 (*left*) or GSK126 (*right*) in neuroblastoma cell lines. Total H3 served as control for H3K27me3. (**B**) Mann-Whitney test of area under curve response to EZH2 inhibitors comparing *MYCN*-amplified and *MYCN*-nonamplified neuroblastoma. (**C**) Flow cytometry analysis for Annexin V and PI staining in neuroblastoma cell lines treated with 3 μM JQEZ5, GSK126 or DMSO control for 8-10 days.



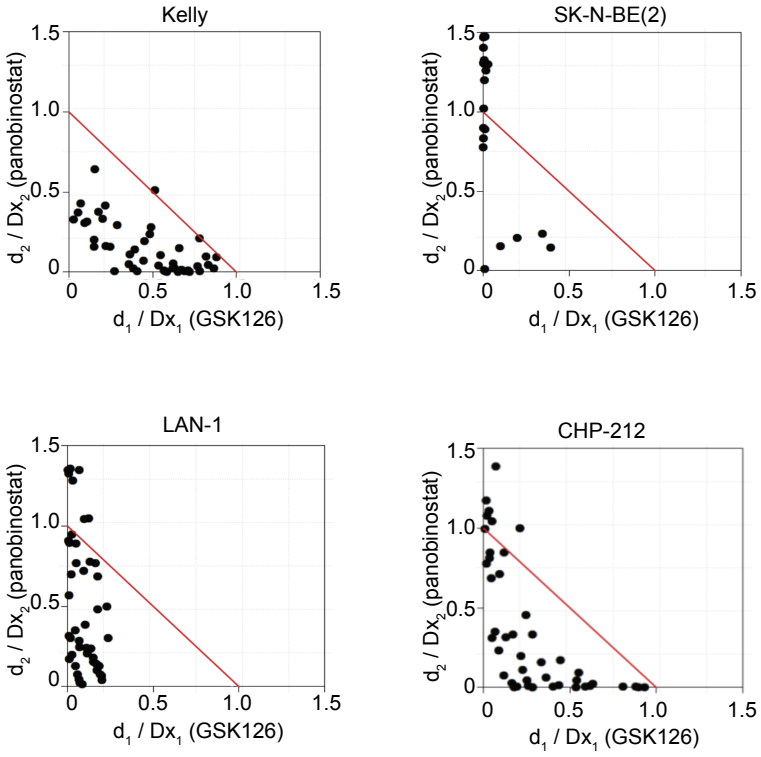

**Supplemental Figure 3. Genome-wide EZH2 Binding Pattern in *MYCN*-amplified Neuroblastoma LAN-1 cells**. (**A**) Metagene analysis showing the average ChIP-seq binding signals of EZH2, H3K27me3 or H3K4me3 for 500 randomly selected genes in each of three categories based on the gene expression level (highly expressed, medium expressed and poorly expressed). X-axis shows the distance in kb to transcription start site (TSS). (**B**) Scatter plot showing correlation between EZH2 relative binding signal and H3K27me3 relative binding signal in the promoter region. (**C**) Gene track showing high binding signal for EZH2 and H3K27me3 and low binding signal for H3K4me3 in two published, validated EZH2 targets. (**D**) Box plots of expression values for (*top*) EZH2 target genes versus non-EZH2 target genes and (*bottom*) H3K27me3 target genes versus non-H3K27me3 target genes in LAN-1 cells. (**E**) GSEA volcano plot showing enrichment of published PRC2 target signatures from MSigDB v5.1 among genes with (*top*) high EZH2 binding signal or (*bottom*) high H3K27me3 binding signal in LAN-1 cells. (**F**) Enrichment of Benporath PRC2 target signature among genes with (*top*) high EZH2 promoter binding signal or (*bottom*) high H3K27me3 promoter binding signal in LAN-1 cells.




**Supplemental Figure 4. Side-by-side Heatmaps of EZH2 and H3K27me3 ChIP-seq AUC Signal.** The 4,536 EZH2 peaks ±4kb in Kelly cells are shown on the left and the 1,936 EZH2 peaks ±4kb in LAN-1 cells on the right. The color scale indicates average signal on a 10-base pair window.




**Supplemental Figure 5. GSEA Showing the Effect of GSK126 Treatment on Neuroblastoma Cell Lines (Kelly and LAN-1) and Single Sample GSEA of Neuroblastoma Tumors.** (**A**) GSEA showing enrichment for the previously published gene signatures after treatment with EPZ-6438 (GSE79859) in the expression profiles following GSK126 treatment. (**B**) GSEA showing enrichment of neurite development and axonogenesis signatures in genes upregulated by GSK126. (**C**) Single sample GSEA in primary neuroblastoma tumor expression datasets GSE12460 and GSE49711.




**Supplemental Figure 6. Isobologram Plots Demonstrate Synergy of Panobinostat and GSK126 in Kelly, SK-N-BE(2), LAN-1 and CHP-212 on Day 6.** Shown is a representative of two to three independent experiments.

**Supplemental Table 1. (A)** Top 100 leading edge dependencies for the top 3 independent components IC1, IC2 and IC3 that are associated with the neuroblastoma lineage in the CRISPR-Cas9 CERES dependency data. The dependencies are ranked based on their Z-score per component. Leading edge dependencies were selected based on cut-off Z-score ≥ 2.5. PRC2 complex dependencies are highlighted bold.

| # | IC1 leading dependencies | IC1 component Z-score | IC2 leading dependencies | IC2 component Z-score | IC3 leading dependencies | IC3 component Z-score |
|---|---|---|---|---|---|---|
| 1 | TXK | 7.20 | AFMID | 7.99 | TAF5L | 24.03 |
| 2 | CWH43 | 6.94 | TMEM105 | 7.93 | SUPT20H | 23.13 |
| 3 | TLR6 | 6.74 | ITGB4 | 7.64 | TADA2B | 22.74 |
| 4 | FBXL5 | 6.74 | SPHK1 | 7.32 | TADA1 | 22.32 |
| 5 | WDR19 | 6.52 | TNRC6C | 7.20 | SUPT7L | 16.68 |
| 6 | MRFAP1L1 | 6.46 | SSTR2 | 7.13 | TAF6L | 13.21 |
| 7 | FAM114A1 | 6.17 | P4HB | 6.93 | MED13 | 12.20 |
| 8 | GRXCR1 | 6.01 | TRIM65 | 6.80 | KAT2A | 11.20 |
| 9 | CLRN2 | 5.95 | TK1 | 6.76 | USP22 | 11.15 |
| 10 | CNGA1 | 5.91 | CCDC40 | 6.72 | MED19 | 10.12 |
| 11 | RELL1 | 5.88 | CD300LF | 6.51 | SMARCD1 | 8.87 |
| 12 | LDB2 | 5.82 | ST6GALNAC2 | 6.48 | MED24 | 8.63 |
| 13 | UBE2K | 5.76 | CACNG4 | 6.42 | CCNC | 8.54 |
| 14 | S100P | 5.72 | C17orf77 | 6.40 | MED13L | 8.28 |
| 15 | UCHL1 | 5.67 | FADS6 | 6.37 | BRD9 | 8.12 |
| 16 | ZAR1 | 5.65 | ABCA8 | 6.32 | PAXIP1 | 7.71 |
| 17 | ZCCHC4 | 5.65 | VEZF1 | 6.23 | MED15 | 7.61 |
| 18 | PCDH7 | 5.63 | PRCD | 6.19 | EP300 | 7.53 |
| 19 | TMEM33 | 5.60 | TEX19 | 6.09 | NIPBL | 7.39 |
| 20 | LRPAP1 | 5.57 | FOXK2 | 5.94 | ATXN7 | 7.36 |
| 21 | BLOC1S4 | 5.55 | CBX2 | 5.91 | MED23 | 7.01 |
| 22 | TMEM156 | 5.51 | CYTH1 | 5.85 | GLTSCR1 | 6.77 |
| 23 | DOK7 | 5.39 | ST6GALNAC1 | 5.85 | MED16 | 6.74 |
| 24 | USP17L13 | 5.37 | LOC100653515 | 5.76 | MLLT1 | 6.34 |
| 25 | LGI2 | 5.10 | WBP2 | 5.75 | PRR12 | 6.11 |
| 26 | SEL1L3 | 5.09 | MRC2 | 5.71 | CCDC101 | 5.90 |
| 27 | TBC1D1 | 4.97 | CPSF4L | 5.63 | MBNL1 | 5.70 |
| 28 | CD38 | 4.94 | GPRC5C | 5.58 | CREBBP | 5.22 |
| 29 | KCTD8 | 4.93 | TMEM235 | 5.56 | ANKRD52 | 5.17 |
| 30 | MFSD10 | 4.89 | RNF213 | 5.55 | DOT1L | 5.00 |
| **31** | ACOX3 | 4.65 | SCAF8 | 5.55 | **EED** | 5.00 |
| 32 | PHOX2B | 4.60 | SYNGR2 | 5.55 | TCEB3 | 4.95 |
| 33 | CHRNA9 | 4.60 | WDR45B | 5.49 | KLHDC3 | 4.88 |
| 34 | GRK4 | 4.59 | FOXJ1 | 5.38 | CHD2 | 4.85 |
| 35 | ATP10D | 4.59 | CD79B | 5.37 | PTP4A1 | 4.80 |
| 36 | DCAF4L1 | 4.59 | TIMP2 | 5.33 | PAGR1 | 4.77 |
| 37 | CORIN | 4.55 | MIF4GD | 5.32 | YWHAE | 4.64 |
| **38** | HMX1 | 4.55 | LLGL2 | 5.24 | **SUZ12** | 4.63 |
| 39 | APBB2 | 4.48 | GDPD1 | 5.17 | TNFAIP3 | 4.61 |
| 40 | ABLIM2 | 4.48 | PPP1R27 | 5.09 | RING1 | 4.58 |
| 41 | CCKAR | 4.42 | FAM195B | 5.08 | TADA3 | 4.50 |
| **42** | WHSC1 | 4.42 | GGA3 | 5.06 | **EZH2** | 4.49 |
| 43 | STIM2 | 4.40 | SDK2 | 5.04 | HDAC2 | 4.44 |
| 44 | LCORL | 4.40 | CACNG5 | 4.97 | C11orf30 | 4.42 |
| 45 | SLC30A9 | 4.38 | ACOX1 | 4.95 | MAPKAPK2 | 4.41 |
| 46 | ATE1 | 4.36 | PRR29 | 4.95 | TAF11 | 4.35 |
| 47 | MXD4 | 4.32 | DNAI2 | 4.94 | KEAP1 | 4.30 |
| 48 | RNF212 | 4.24 | OXLD1 | 4.90 | MAU2 | 4.23 |
| 49 | RBKS | 4.23 | PRPSAP1 | 4.89 | ATF7IP | 4.19 |
| 50 | SH3TC1 | 4.20 | SEC14L1 | 4.80 | STAG1 | 4.13 |

| # | IC1 leading dependencies | IC1 component Z-score | IC2 leading dependencies | IC2 component Z-score | IC3 leading dependencies | IC3 component Z-score |
|---|---|---|---|---|---|---|
| 51 | HHAT | 4.18 | PRKCA | 4.80 | MED1 | 4.11 |
| 52 | KCNIP4 | 4.16 | ENDOV | 4.75 | PITPNB | 4.01 |
| 53 | HMGXB3 | 4.16 | SLC38A10 | 4.72 | ATXN2L | 3.94 |
| 54 | POLN | 4.13 | SECTM1 | 4.69 | EHMT2 | 3.89 |
| 55 | SH3BP2 | 4.11 | PTRH2 | 4.65 | MED25 | 3.88 |
| 56 | TBC1D23 | 4.10 | GPR142 | 4.62 | SPIN1 | 3.86 |
| 57 | CRIPAK | 4.10 | CD300C | 4.59 | ASB7 | 3.86 |
| 58 | KLB | 4.03 | CEP95 | 4.58 | TRAF3 | 3.78 |
| 59 | HS3ST1 | 4.02 | CARD14 | 4.52 | FOXA2 | 3.70 |
| 60 | KLHL5 | 4.01 | UNK | 4.50 | CSRNP1 | 3.70 |
| 61 | CPZ | 4.01 | BAIAP2 | 4.48 | MORF4L1 | 3.67 |
| 62 | GNG10 | 3.97 | FBF1 | 4.48 | C10orf12 | 3.67 |
| 63 | PHLDB1 | 3.94 | LRRC45 | 4.48 | PCGF1 | 3.61 |
| 64 | MYL12B | 3.91 | SMIM5 | 4.46 | SIN3B | 3.59 |
| 65 | FGFBP2 | 3.90 | SGSH | 4.43 | BTAF1 | 3.57 |
| 66 | GNPDA2 | 3.90 | MAFG | 4.41 | FOXA1 | 3.48 |
| 67 | FAM174B | 3.89 | DHX40 | 4.41 | ACPT | 3.37 |
| 68 | CC2D2A | 3.85 | KIAA0195 | 4.40 | KAT6A | 3.32 |
| 69 | CCAR2 | 3.84 | GH1 | 4.40 | SIRT1 | 3.30 |
| 70 | SMIM20 | 3.82 | CDR2L | 4.37 | CCNF | 3.26 |
| 71 | ISL1 | 3.81 | CASKIN2 | 4.37 | LACTB2 | 3.25 |
| 72 | NSUN7 | 3.78 | GALK1 | 4.35 | APOA5 | 3.22 |
| 73 | DCAF16 | 3.77 | KCNJ16 | 4.34 | MTA2 | 3.21 |
| 74 | TLR1 | 3.74 | NAT9 | 4.33 | ATXN7L3 | 3.21 |
| 75 | PPARGC1A | 3.73 | ENGASE | 4.31 | SP1 | 3.20 |
| 76 | DEFB131 | 3.73 | EDF1 | 4.30 | NABP2 | 3.16 |
| 77 | YIPF7 | 3.72 | HID1 | 4.28 | CLC | 3.16 |
| 78 | SLIT2 | 3.71 | SMIM6 | 4.26 | POLR2M | 3.15 |
| 79 | TLR10 | 3.69 | ZNF750 | 4.25 | PAIP1 | 3.14 |
| 80 | LARP4B | 3.63 | CYGB | 4.22 | FBXL14 | 3.14 |
| 81 | UBE3D | 3.61 | AANAT | 4.15 | CCNE1 | 3.14 |
| 82 | BEND4 | 3.60 | OTOP2 | 4.13 | UBE2K | 3.14 |
| 83 | CASP7 | 3.59 | PRR11 | 4.13 | MTHFD1 | 3.10 |
| 84 | FGFR3 | 3.59 | RNF157 | 4.12 | HEATR3 | 3.10 |
| 85 | FZD8 | 3.58 | MAP2K6 | 4.12 | FAM159B | 3.10 |
| 86 | TNNI1 | 3.58 | TMC6 | 4.09 | HTT | 3.09 |
| 87 | ZNF292 | 3.57 | RFNG | 4.04 | ZNF143 | 3.09 |
| 88 | ADD1 | 3.56 | CANT1 | 4.03 | ARF6 | 3.09 |
| 89 | NWD2 | 3.55 | KIRREL3 | 4.02 | THAP4 | 3.08 |
| 90 | QDPR | 3.55 | EVPL | 4.01 | ROCK1 | 3.07 |
| 91 | RBPJ | 3.54 | EFCAB3 | 4.01 | MYCN | 3.07 |
| 92 | SLC34A2 | 3.53 | KPNA2 | 4.00 | AFF4 | 3.06 |
| 93 | SPICE1 | 3.52 | NOTUM | 3.99 | CAB39 | 3.06 |
| 94 | LRRTM3 | 3.49 | YPEL2 | 3.97 | KDM1A | 3.06 |
| 95 | SHISA3 | 3.49 | DUS1L | 3.97 | CKS1B | 3.04 |
| 96 | LARP7 | 3.49 | TRAPPC13 | 3.97 | ZNF217 | 3.04 |
| 97 | TEC | 3.47 | MFSD11 | 3.93 | ATG101 | 3.04 |
| 98 | OCIAD1 | 3.46 | UNC13D | 3.93 | SERTAD2 | 3.03 |
| 99 | BOD1L1 | 3.45 | PCTP | 3.93 | KLF5 | 3.03 |
| 100 | SLC26A1 | 3.44 | RNFT1 | 3.92 | RANBP9 | 3.03 |

**Supplemental Table 1. (B)** Sensitivity AUC scores for the EZH2 inhibitors GSK126 (day 5), JQEZ5 (day 5) and dependency scores for EZH2, EED and SUZ12 across the neuroblastoma cell lines in the study.

| # | Cell line | *MYCN* status | AUC score GSK126 day 5 | AUC score JQEZ5 day 5 | EZH2 dependency score | EED dependency score | SUZ12 dependency score |
|---|---|---|---|---|---|---|---|
| 1 | CHP-212 | Amplified | 89.150 | 95.720 | -0.335 | -0.536 | -0.446 |
| 2 | IMR-32 | Amplified | 92.850 | 79.670 | 0.098 | -0.134 | -0.234 |
| 3 | Kelly | Amplified | 87.230 | 80.270 | -0.188 | -0.474 | -0.510 |
| 4 | LAN-1 | Amplified | 92.880 | 92.250 | na | na | na |
| 5 | MHH-NB-11 | Amplified | 90.510 | 82.370 | 0.095 | -0.268 | -0.135 |
| 6 | NB-1 | Amplified | 82.350 | 71.890 | 0.068 | -0.535 | -0.419 |
| 7 | NGP | Amplified | 79.980 | 88.700 | na | na | na |
| 8 | SIMA | Amplified | 84.230 | 81.000 | -0.085 | -0.461 | -0.315 |
| 9 | SK-N-BE(2) | Amplified | 63.240 | 74.070 | -0.105 | -0.438 | -0.605 |
| 10 | ACN | Non-amplified | 122.400 | 110.200 | na | na | na |
| 11 | CHLA-15 | Non-amplified | 100.100 | 97.660 | na | na | na |
| 12 | GI-M-EN | Non-amplified | 101.200 | 95.670 | na | na | na |
| 13 | SH-SY-5Y | Non-amplified | 86.250 | 98.660 | na | na | na |
| 14 | SK-N-AS | Non-amplified | 92.440 | 101.500 | -0.392 | -0.529 | -0.531 |
| 15 | SK-N-FI | Non-amplified | 137.700 | 127.000 | 0.163 | 0.069 | 0.191 |
| 16 | SK-N-SH | Non-amplified | 114.500 | 105.700 | na | na | na |

**Supplemental Table 2.** Top 50 GSEA significant hits for EZH2 and H3K27me3 ChIP-seq target genes in Kelly and LAN-1 cells using the MSigDB v5.1 collection c2 of 4,726 pathways and experimental gene sets. For each significant gene set hit the table shows if the gene set is related to the PRC2 complex (1= yes, 0=no), the size of the gene set, the GSEA normalized enrichment score (NES), *P* and false discovery rate (FDR). The MSigDB gene sets are ranked in decreasing order based on the NES.

**(A)** Top 50 GSEA hits for EZH2 ChIP-seq target genes in Kelly cells. PRC2 related gene sets are significantly over-represented in the collection of GSEA hits (odds-ratios = 9.5, $P < 0.001$, according to the two-tailed Fisher exact test).

| Rank | Gene Set | PRC2 Complex | Size | NES | *P* | FDR |
|---|---|---|---|---|---|---|
| 1 | MEISSNER_BRAIN_HCP_WITH_H3K27ME3 | 1 | 263 | 3.57 | 0.0000 | 0.0000 |
| 2 | BENPORATH_PRC2_TARGETS | 1 | 615 | 3.44 | 0.0000 | 0.0000 |
| 3 | MIKKELSEN_NPC_HCP_WITH_H3K27ME3 | 1 | 332 | 3.30 | 0.0000 | 0.0000 |
| 4 | MEISSNER_NPC_HCP_WITH_H3K4ME2_AND_H3K27ME3 | 1 | 339 | 3.27 | 0.0000 | 0.0000 |
| 5 | MEISSNER_NPC_HCP_WITH_H3K27ME3 | 1 | 78 | 3.27 | 0.0000 | 0.0000 |
| 6 | BENPORATH_EED_TARGETS | 1 | 999 | 3.25 | 0.0000 | 0.0000 |
| 7 | BENPORATH_SUZ12_TARGETS | 1 | 984 | 3.24 | 0.0000 | 0.0000 |
| 8 | MIKKELSEN_IPS_WITH_HCP_H3K27ME3 | 1 | 99 | 3.18 | 0.0000 | 0.0000 |
| 9 | MIKKELSEN_MEF_HCP_WITH_H3K27ME3 | 1 | 569 | 3.15 | 0.0000 | 0.0000 |
| 10 | MIKKELSEN_MCV6_HCP_WITH_H3K27ME3 | 1 | 418 | 3.13 | 0.0000 | 0.0000 |
| 11 | SCHLESINGER_METHYLATED_DE_NOVO_IN_CANCER | 1 | 85 | 3.03 | 0.0000 | 0.0000 |
| 12 | MEISSNER_BRAIN_HCP_WITH_H3K4ME2_AND_H3K27ME3 | 1 | 56 | 2.86 | 0.0000 | 0.0000 |
| 13 | REACTOME_REGULATION_OF_BETA_CELL_DEVELOPMENT | 0 | 30 | 2.73 | 0.0000 | 0.0000 |
| 14 | RORIE_TARGETS_OF_EWSR1_FLI1_FUSION_UP | 0 | 27 | 2.66 | 0.0000 | 0.0000 |
| 15 | MIKKELSEN_NPC_HCP_WITH_H3K4ME3_AND_H3K27ME3 | 1 | 205 | 2.61 | 0.0000 | 0.0000 |
| 16 | KEGG_MATURITY_ONSET_DIABETES_OF_THE_YOUNG | 0 | 25 | 2.61 | 0.0000 | 0.0000 |
| 17 | MCGARVEY_SILENCED_BY_METHYLATION_IN_COLON_CANCER | 0 | 40 | 2.55 | 0.0000 | 0.0002 |
| 18 | KEGG_HEDGEHOG_SIGNALING_PATHWAY | 0 | 56 | 2.55 | 0.0000 | 0.0002 |
| 19 | RIZ_ERYTHROID_DIFFERENTIATION_6HR | 0 | 40 | 2.52 | 0.0000 | 0.0000 |
| 20 | THEODOROU_MAMMARY_TUMORIGENESIS | 0 | 28 | 2.49 | 0.0000 | 0.0000 |
| 21 | LI_WILMS_TUMOR | 0 | 25 | 2.48 | 0.0000 | 0.0007 |
| 22 | WANG_LSD1_TARGETS_UP | 0 | 23 | 2.46 | 0.0000 | 0.0008 |
| 23 | LIEN_BREAST_CARCINOMA_METAPLASTIC | 0 | 35 | 2.45 | 0.0000 | 0.0000 |
| 24 | MATZUK_IMPLANTATION_AND_UTERINE | 0 | 22 | 2.43 | 0.0000 | 0.0013 |
| 25 | RIZ_ERYTHROID_DIFFERENTIATION_APOBEC2 | 0 | 24 | 2.43 | 0.0000 | 0.0000 |
| 26 | NIKOLSKY_BREAST_CANCER_5P15_AMPLICON | 0 | 25 | 2.43 | 0.0000 | 0.0000 |
| 27 | MARTENS_TRETINOIN_RESPONSE_UP | 0 | 803 | 2.41 | 0.0000 | 0.0015 |
| 28 | WONG_ENDMETRIUM_CANCER_UP | 0 | 25 | 2.41 | 0.0000 | 0.0000 |
| 29 | RIZ_ERYTHROID_DIFFERENTIATION_HEMGN | 0 | 31 | 2.40 | 0.0000 | 0.0000 |
| 30 | SCHLESINGER_H3K27ME3_IN_NORMAL_AND_METHYLATED_IN_CANCER | 1 | 28 | 2.39 | 0.0000 | 0.0000 |
| 31 | LEIN_CEREBELLUM_MARKERS | 0 | 80 | 2.36 | 0.0000 | 0.0035 |
| 32 | WANG_THOC1_TARGETS_DN | 0 | 18 | 2.36 | 0.0000 | 0.0035 |
| 33 | RIZ_ERYTHROID_DIFFERENTIATION_HBZ | 0 | 41 | 2.35 | 0.0000 | 0.0000 |
| 34 | SHIN_B_CELL_LYMPHOMA_CLUSTER_9 | 0 | 19 | 2.35 | 0.0000 | 0.0000 |
| 35 | LIU_CDX2_TARGETS_UP | 0 | 35 | 2.34 | 0.0000 | 0.0000 |
| 36 | MEISSNER_NPC_HCP_WITH_H3K4ME2 | 1 | 477 | 2.31 | 0.0000 | 0.0070 |
| 37 | KEGG_BASAL_CELL_CARCINOMA | 0 | 55 | 2.31 | 0.0000 | 0.0069 |
| 38 | AIGNER_ZEB1_TARGETS | 0 | 34 | 2.31 | 0.0000 | 0.0001 |
| 39 | REACTOME_CLASS_B_2_SECRETIN_FAMILY_RECEPTORS | 0 | 87 | 2.29 | 0.0000 | 0.0001 |
| 40 | KONDO_PROSTATE_CANCER_HCP_WITH_H3K27ME3 | 1 | 95 | 2.28 | 0.0000 | 0.0115 |
| 41 | DAWSON_METHYLATED_IN_LYMPHOMA_TCL1 | 0 | 57 | 2.27 | 0.0000 | 0.0001 |
| 42 | PEREZ_TP53_AND_TP63_TARGETS | 0 | 194 | 2.26 | 0.0000 | 0.0001 |
| 43 | NIKOLSKY_BREAST_CANCER_16P13_AMPLICON | 0 | 113 | 2.26 | 0.0000 | 0.0001 |
| 44 | WANG_MLL_TARGETS | 0 | 280 | 2.25 | 0.0000 | 0.0155 |
| 45 | SCHRAETS_MLL_TARGETS_DN | 0 | 32 | 2.23 | 0.0000 | 0.0200 |
| 46 | BEGUM_TARGETS_OF_PAX3_FOXO1_FUSION_DN | 0 | 45 | 2.23 | 0.0000 | 0.0002 |
| 47 | ROZANOV_MMP14_TARGETS_DN | 0 | 33 | 2.23 | 0.0000 | 0.0002 |
| 48 | MEISSNER_NPC_HCP_WITH_H3K4ME3_AND_H3K27ME3 | 1 | 139 | 2.21 | 0.0000 | 0.0242 |
| 49 | YAO_TEMPORAL_RESPONSE_TO_PROGESTERONE_CLUSTER_4 | 0 | 15 | 2.20 | 0.0000 | 0.0286 |
| 50 | MEISSNER_NPC_HCP_WITH_H3_UNMETHYLATED | 1 | 505 | 2.19 | 0.0000 | 0.0301 |

**Supplemental Table 2. (B)** Top 50 GSEA hits for H3K27me3 ChIP-seq target genes in Kelly cells. PRC2 related gene sets are significantly over-represented in the collection of GSEA hits (odds-ratios = 8.1, $P < 0.001$, according to the two-tailed Fisher exact test).

| Rank | Gene Set | PRC2 Complex | Size | NES | *P* | FDR |
|---|---|---|---|---|---|---|
| 1 | MEISSNER_NPC_HCP_WITH_H3K27ME3 | 1 | 78 | 1.82 | 0.0000 | 0.0000 |
| 2 | MEISSNER_BRAIN_HCP_WITH_H3K27ME3 | 1 | 263 | 1.80 | 0.0000 | 0.0000 |
| 3 | RORIE_TARGETS_OF_EWSR1_FLI1_FUSION_UP | 0 | 27 | 1.69 | 0.0000 | 0.0056 |
| 4 | MIKKELSEN_NPC_HCP_WITH_H3K27ME3 | 1 | 332 | 1.69 | 0.0000 | 0.0042 |
| 5 | BENPORATH_PRC2_TARGETS | 1 | 615 | 1.68 | 0.0000 | 0.0000 |
| 6 | SHIN_B_CELL_LYMPHOMA_CLUSTER_9 | 0 | 19 | 1.67 | 0.0000 | 0.0000 |
| 7 | MIKKELSEN_IPS_WITH_HCP_H3K27ME3 | 1 | 99 | 1.66 | 0.0000 | 0.0130 |
| 8 | AIGNER_ZEB1_TARGETS | 0 | 34 | 1.65 | 0.0000 | 0.0000 |
| 9 | YAO_TEMPORAL_RESPONSE_TO_PROGESTERONE_CLUSTER_4 | 0 | 15 | 1.65 | 0.0000 | 0.0115 |
| 10 | WONG_ENDMETRIUM_CANCER_UP | 0 | 25 | 1.65 | 0.0000 | 0.0000 |
| 11 | WANG_THOC1_TARGETS_DN | 0 | 18 | 1.64 | 0.0010 | 0.0171 |
| 12 | KEGG_MATURITY_ONSET_DIABETES_OF_THE_YOUNG | 0 | 25 | 1.64 | 0.0000 | 0.0153 |
| 13 | MEISSNER_NPC_HCP_WITH_H3K4ME2_AND_H3K27ME3 | 1 | 339 | 1.64 | 0.0000 | 0.0156 |
| 14 | DAZARD_UV_RESPONSE_CLUSTER_G28 | 0 | 18 | 1.64 | 0.0010 | 0.0141 |
| 15 | MATZUK_IMPLANTATION_AND_UTERINE | 0 | 22 | 1.62 | 0.0000 | 0.0189 |
| 16 | MIKKELSEN_MEF_HCP_WITH_H3K27ME3 | 1 | 569 | 1.62 | 0.0000 | 0.0189 |
| 17 | MATZUK_EMBRYONIC_GERM_CELL | 0 | 19 | 1.61 | 0.0000 | 0.0209 |
| 18 | REACTOME_REGULATION_OF_BETA_CELL_DEVELOPMENT | 0 | 30 | 1.61 | 0.0000 | 0.0206 |
| 19 | BENPORATH_EED_TARGETS | 1 | 999 | 1.61 | 0.0000 | 0.0001 |
| 20 | YAO_HOXA10_TARGETS_VIA_PROGESTERONE_DN | 0 | 17 | 1.61 | 0.0020 | 0.0212 |
| 21 | BENPORATH_SUZ12_TARGETS | 1 | 984 | 1.60 | 0.0000 | 0.0001 |
| 22 | HE_PTEN_TARGETS_UP | 0 | 16 | 1.59 | 0.0010 | 0.0002 |
| 23 | SHIN_B_CELL_LYMPHOMA_CLUSTER_5 | 0 | 16 | 1.59 | 0.0000 | 0.0002 |
| 24 | RIZ_ERYTHROID_DIFFERENTIATION_APOBEC2 | 0 | 24 | 1.59 | 0.0000 | 0.0002 |
| 25 | MIKKELSEN_MCV6_HCP_WITH_H3K27ME3 | 1 | 418 | 1.59 | 0.0000 | 0.0344 |
| 26 | REACTOME_OLFACTORY_SIGNALING_PATHWAY | 0 | 298 | 1.56 | 0.0000 | 0.0005 |
| 27 | GAURNIER_PSMD4_TARGETS | 0 | 52 | 1.56 | 0.0000 | 0.0664 |
| 28 | LIEN_BREAST_CARCINOMA_METAPLASTIC | 0 | 35 | 1.56 | 0.0010 | 0.0004 |
| 29 | LI_WILMS_TUMOR | 0 | 25 | 1.55 | 0.0010 | 0.0779 |
| 30 | STREICHER_LSM1_TARGETS_DN | 0 | 19 | 1.55 | 0.0010 | 0.0006 |
| 31 | CUI_TCF21_TARGETS_DN | 0 | 28 | 1.55 | 0.0010 | 0.0815 |
| 32 | SCHLESINGER_H3K27ME3_IN_NORMAL_AND_METHYLATED_IN_CANCER | 1 | 28 | 1.54 | 0.0020 | 0.0006 |
| 33 | REACTOME_GABA_SYNTHESIS_RELEASE_REUPTAKE_AND_DEGRADATION | 0 | 17 | 1.54 | 0.0020 | 0.0899 |
| 34 | SCHLESINGER_METHYLATED_DE_NOVO_IN_CANCER | 0 | 85 | 1.54 | 0.0000 | 0.0006 |
| 35 | MEISSNER_BRAIN_HCP_WITH_H3K4ME2_AND_H3K27ME3 | 1 | 56 | 1.54 | 0.0000 | 0.0933 |
| 36 | WANG_BARRETTS_ESOPHAGUS_AND_ESOPHAGUS_CANCER_DN | 0 | 35 | 1.53 | 0.0000 | 0.0009 |
| 37 | KEGG_OLFACTORY_TRANSDUCTION | 0 | 362 | 1.53 | 0.0000 | 0.0932 |
| 38 | SMID_BREAST_CANCER_RELAPSE_IN_PLEURA_DN | 0 | 23 | 1.53 | 0.0030 | 0.0906 |
| 39 | PYEON_CANCER_HEAD_AND_NECK_VS_CERVICAL_DN | 0 | 20 | 1.53 | 0.0010 | 0.0879 |
| 40 | HINATA_NFKB_TARGETS_KERATINOCYTE_DN | 0 | 22 | 1.53 | 0.0010 | 0.0864 |
| 41 | BIOCARTA_ALK_PATHWAY | 0 | 37 | 1.53 | 0.0000 | 0.0885 |
| 42 | CHARAFE_BREAST_CANCER_BASAL_VS_MESENCHYMAL_UP | 0 | 114 | 1.53 | 0.0000 | 0.0010 |
| 43 | FARMER_BREAST_CANCER_CLUSTER_1 | 0 | 41 | 1.52 | 0.0000 | 0.0009 |
| 44 | MIKKELSEN_MCV6_LCP_WITH_H3K27ME3 | 1 | 27 | 1.52 | 0.0020 | 0.1006 |
| 45 | LEE_NAIVE_T_LYMPHOCYTE | 0 | 16 | 1.52 | 0.0010 | 0.1017 |
| 46 | REACTOME_IMMUNOREGULATORY_INTERACTIONS_BETWEEN_A_LYMPHOID_ | 0 | 54 | 1.52 | 0.0000 | 0.0015 |
| 47 | GU_PDEF_TARGETS_DN | 0 | 37 | 1.51 | 0.0000 | 0.1110 |
| 48 | RIZ_ERYTHROID_DIFFERENTIATION_6HR | 0 | 40 | 1.51 | 0.0000 | 0.0014 |
| 49 | SHIN_B_CELL_LYMPHOMA_CLUSTER_2 | 0 | 29 | 1.51 | 0.0010 | 0.0012 |
| 50 | RIZ_ERYTHROID_DIFFERENTIATION_HBZ | 0 | 41 | 1.51 | 0.0010 | 0.0014 |

**Supplemental Table 2. (C)** Top 50 GSEA hits for EZH2 ChIP-seq target genes in LAN-1 cells. PRC2 related gene sets are significantly over-represented in the collection of GSEA hits (odds-ratios = 7.9, $P < 0.001$ according to the two-tailed Fisher exact test).

| Rank | Gene Set | PRC2 Complex | Size | NES | *P* | FDR |
|---|---|---|---|---|---|---|
| 1 | MEISSNER_BRAIN_HCP_WITH_H3K27ME3 | 1 | 262 | 3.74 | 0.0000 | 0.0000 |
| 2 | MIKKELSEN_NPC_HCP_WITH_H3K27ME3 | 1 | 333 | 3.65 | 0.0000 | 0.0000 |
| 3 | MEISSNER_NPC_HCP_WITH_H3K27ME3 | 1 | 79 | 3.57 | 0.0000 | 0.0000 |
| 4 | MEISSNER_NPC_HCP_WITH_H3K4ME2_AND_H3K27ME3 | 1 | 338 | 3.51 | 0.0000 | 0.0000 |
| 5 | MIKKELSEN_MCV6_HCP_WITH_H3K27ME3 | 1 | 419 | 3.44 | 0.0000 | 0.0000 |
| 6 | MIKKELSEN_IPS_WITH_HCP_H3K27ME3 | 1 | 100 | 3.43 | 0.0000 | 0.0000 |
| 7 | BENPORATH_PRC2_TARGETS | 1 | 617 | 3.36 | 0.0000 | 0.0000 |
| 8 | MIKKELSEN_MEF_HCP_WITH_H3K27ME3 | 1 | 568 | 3.25 | 0.0000 | 0.0000 |
| 9 | MARTENS_TRETINOIN_RESPONSE_UP | 0 | 804 | 3.01 | 0.0000 | 0.0000 |
| 10 | BENPORATH_SUZ12_TARGETS | 1 | 987 | 2.99 | 0.0000 | 0.0000 |
| 11 | SCHLESINGER_METHYLATED_DE_NOVO_IN_CANCER | 0 | 86 | 2.83 | 0.0000 | 0.0000 |
| 12 | MIKKELSEN_NPC_HCP_WITH_H3K4ME3_AND_H3K27ME3 | 1 | 204 | 2.78 | 0.0000 | 0.0000 |
| 13 | LI_WILMS_TUMOR | 0 | 26 | 2.77 | 0.0000 | 0.0000 |
| 14 | REACTOME_REGULATION_OF_BETA_CELL_DEVELOPMENT | 0 | 30 | 2.57 | 0.0000 | 0.0000 |
| 15 | KEGG_HEDGEHOG_SIGNALING_PATHWAY | 0 | 56 | 2.55 | 0.0000 | 0.0001 |
| 16 | MEISSNER_NPC_HCP_WITH_H3K4ME3_AND_H3K27ME3 | 1 | 139 | 2.52 | 0.0000 | 0.0001 |
| 17 | NIKOLSKY_BREAST_CANCER_5P15_AMPLICON | 0 | 26 | 2.51 | 0.0000 | 0.0000 |
| 18 | NIKOLSKY_BREAST_CANCER_16P13_AMPLICON | 0 | 114 | 2.46 | 0.0000 | 0.0000 |
| 19 | REACTOME_CLASS_B_2_SECRETIN_FAMILY_RECEPTORS | 0 | 87 | 2.44 | 0.0000 | 0.0013 |
| 20 | RIZ_ERYTHROID_DIFFERENTIATION_6HR | 0 | 40 | 2.42 | 0.0000 | 0.0000 |
| 21 | RIZ_ERYTHROID_DIFFERENTIATION_APOBEC2 | 0 | 24 | 2.41 | 0.0000 | 0.0000 |
| 22 | WINNEPENNINCKX_MELANOMA_METASTASIS_DN | 0 | 41 | 2.40 | 0.0000 | 0.0016 |
| 23 | MEISSNER_NPC_HCP_WITH_H3K4ME2 | 1 | 476 | 2.39 | 0.0000 | 0.0018 |
| 24 | RIZ_ERYTHROID_DIFFERENTIATION_12HR | 0 | 42 | 2.38 | 0.0000 | 0.0000 |
| 25 | MEISSNER_BRAIN_HCP_WITH_H3K4ME2_AND_H3K27ME3 | 1 | 56 | 2.37 | 0.0000 | 0.0020 |
| 26 | FUKUSHIMA_TNFSF11_TARGETS | 0 | 15 | 2.36 | 0.0000 | 0.0021 |
| 27 | KEGG_BASAL_CELL_CARCINOMA | 0 | 55 | 2.31 | 0.0000 | 0.0038 |
| 28 | WANG_THOC1_TARGETS_DN | 0 | 19 | 2.31 | 0.0000 | 0.0000 |
| 29 | REACTOME_POTASSIUM_CHANNELS | 0 | 97 | 2.30 | 0.0000 | 0.0046 |
| 30 | KONDO_PROSTATE_CANCER_HCP_WITH_H3K27ME3 | 1 | 95 | 2.29 | 0.0000 | 0.0047 |
| 31 | THEODOROU_MAMMARY_TUMORIGENESIS | 0 | 28 | 2.28 | 0.0000 | 0.0000 |
| 32 | RORIE_TARGETS_OF_EWSR1_FLI1_FUSION_UP | 0 | 27 | 2.28 | 0.0011 | 0.0050 |
| 33 | CAMPS_COLON_CANCER_COPY_NUMBER_UP | 0 | 86 | 2.28 | 0.0000 | 0.0049 |
| 34 | PARK_TRETINOIN_RESPONSE_AND_PML_RARA_FUSION | 0 | 29 | 2.28 | 0.0000 | 0.0048 |
| 35 | LEIN_CEREBELLUM_MARKERS | 0 | 80 | 2.28 | 0.0000 | 0.0046 |
| 36 | MCGARVEY_SILENCED_BY_METHYLATION_IN_COLON_CANCER | 0 | 41 | 2.27 | 0.0000 | 0.0048 |
| 37 | HANN_RESISTANCE_TO_BCL2_INHIBITOR_UP | 0 | 35 | 2.26 | 0.0000 | 0.0051 |
| 38 | HOQUE_METHYLATED_IN_CANCER | 1 | 56 | 2.25 | 0.0000 | 0.0000 |
| 39 | MIKKELSEN_ES_ICP_WITH_H3K27ME3 | 1 | 39 | 2.24 | 0.0000 | 0.0000 |
| 40 | MATZUK_IMPLANTATION_AND_UTERINE | 0 | 22 | 2.24 | 0.0011 | 0.0058 |
| 41 | MEISSNER_NPC_HCP_WITH_H3_UNMETHYLATED | 1 | 506 | 2.24 | 0.0000 | 0.0058 |
| 42 | KEGG_MATURITY_ONSET_DIABETES_OF_THE_YOUNG | 0 | 25 | 2.23 | 0.0000 | 0.0063 |
| 43 | RIZ_ERYTHROID_DIFFERENTIATION_HBZ | 0 | 41 | 2.23 | 0.0000 | 0.0001 |
| 44 | LOPES_METHYLATED_IN_COLON_CANCER_UP | 0 | 27 | 2.22 | 0.0000 | 0.0067 |
| 45 | CERIBELLI_PROMOTERS_INACTIVE_AND_BOUND_BY_NFY | 0 | 33 | 2.18 | 0.0000 | 0.0001 |
| 46 | REACTOME_VOLTAGE_GATED_POTASSIUM_CHANNELS | 0 | 43 | 2.15 | 0.0000 | 0.0148 |
| 47 | BEGUM_TARGETS_OF_PAX3_FOXO1_FUSION_DN | 0 | 44 | 2.15 | 0.0000 | 0.0002 |
| 48 | HALMOS_CEBPA_TARGETS_DN | 0 | 44 | 2.14 | 0.0000 | 0.0161 |
| 49 | VALK_AML_WITH_FLT3_ITD | 0 | 39 | 2.14 | 0.0000 | 0.0002 |
| 50 | NIKOLSKY_BREAST_CANCER_20Q12_Q13_AMPLICON | 0 | 136 | 2.14 | 0.0000 | 0.0003 |

**Supplemental Table 2. (D)** Top 50 GSEA hits for H3K27me3 ChIP-seq target genes in LAN-1 cells. PRC2 related gene sets are significantly over-represented in the collection of GSEA hits (odds-ratios = 9.5, $P < 0.001$ according to the two-tailed Fisher exact test).

| Rank | Gene Set | PRC2 Complex | Size | NES | *P* | FDR |
|---|---|---|---|---|---|---|
| 1 | MEISSNER_NPC_HCP_WITH_H3K27ME3 | 1 | 79 | 2.03 | 0.0000 | 0.0000 |
| 2 | MEISSNER_BRAIN_HCP_WITH_H3K27ME3 | 1 | 262 | 1.99 | 0.0000 | 0.0000 |
| 3 | MIKKELSEN_NPC_HCP_WITH_H3K27ME3 | 1 | 333 | 1.92 | 0.0000 | 0.0003 |
| 4 | MIKKELSEN_IPS_WITH_HCP_H3K27ME3 | 1 | 100 | 1.88 | 0.0000 | 0.0004 |
| 5 | NIKOLSKY_BREAST_CANCER_5P15_AMPLICON | 0 | 26 | 1.87 | 0.0000 | 0.0000 |
| 6 | LI_WILMS_TUMOR | 0 | 26 | 1.85 | 0.0000 | 0.0011 |
| 7 | MEISSNER_NPC_HCP_WITH_H3K4ME2_AND_H3K27ME3 | 1 | 338 | 1.85 | 0.0000 | 0.0009 |
| 8 | BENPORATH_PRC2_TARGETS | 1 | 617 | 1.82 | 0.0000 | 0.0000 |
| 9 | KEGG_MATURITY_ONSET_DIABETES_OF_THE_YOUNG | 0 | 25 | 1.80 | 0.0000 | 0.0035 |
| 10 | MIKKELSEN_MCV6_HCP_WITH_H3K27ME3 | 1 | 419 | 1.80 | 0.0000 | 0.0039 |
| 11 | SCHLESINGER_METHYLATED_DE_NOVO_IN_CANCER | 0 | 86 | 1.78 | 0.0000 | 0.0000 |
| 12 | MIKKELSEN_MEF_HCP_WITH_H3K27ME3 | 1 | 568 | 1.78 | 0.0000 | 0.0061 |
| 13 | KEGG_HEDGEHOG_SIGNALING_PATHWAY | 0 | 56 | 1.78 | 0.0000 | 0.0060 |
| 14 | REACTOME_REGULATION_OF_BETA_CELL_DEVELOPMENT | 0 | 30 | 1.77 | 0.0000 | 0.0000 |
| 15 | RORIE_TARGETS_OF_EWSR1_FLI1_FUSION_UP | 0 | 27 | 1.77 | 0.0000 | 0.0000 |
| 16 | CERIBELLI_PROMOTERS_INACTIVE_AND_BOUND_BY_NFY | 0 | 33 | 1.74 | 0.0000 | 0.0163 |
| 17 | LOPES_METHYLATED_IN_COLON_CANCER_UP | 0 | 27 | 1.74 | 0.0000 | 0.0001 |
| 18 | MARTENS_TRETINOIN_RESPONSE_UP | 0 | 804 | 1.72 | 0.0000 | 0.0261 |
| 19 | BEGUM_TARGETS_OF_PAX3_FOXO1_FUSION_DN | 0 | 44 | 1.72 | 0.0000 | 0.0002 |
| 20 | BENPORATH_SUZ12_TARGETS | 1 | 987 | 1.71 | 0.0000 | 0.0002 |
| 21 | FUKUSHIMA_TNFSF11_TARGETS | 0 | 15 | 1.70 | 0.0011 | 0.0420 |
| 22 | WATANABE_COLON_CANCER_MSI_VS_MSS_UP | 0 | 26 | 1.70 | 0.0000 | 0.0003 |
| 23 | ZHENG_RESPONSE_TO_ARSENITE_UP | 0 | 18 | 1.69 | 0.0000 | 0.0002 |
| 24 | THEODOROU_MAMMARY_TUMORIGENESIS | 0 | 28 | 1.69 | 0.0000 | 0.0003 |
| 25 | RIZ_ERYTHROID_DIFFERENTIATION_APOBEC2 | 0 | 24 | 1.69 | 0.0000 | 0.0004 |
| 26 | SHIN_B_CELL_LYMPHOMA_CLUSTER_5 | 0 | 16 | 1.69 | 0.0000 | 0.0003 |
| 27 | VALK_AML_WITH_FLT3_ITD | 0 | 39 | 1.69 | 0.0000 | 0.0452 |
| 28 | REACTOME_NA_CL_DEPENDENT_NEUROTRANSMITTER_TRANSPORTERS | 0 | 17 | 1.69 | 0.0010 | 0.0005 |
| 29 | KEGG_BASAL_CELL_CARCINOMA | 0 | 55 | 1.68 | 0.0000 | 0.0513 |
| 30 | MAHADEVAN_IMATINIB_RESISTANCE_DN | 0 | 20 | 1.68 | 0.0020 | 0.0005 |
| 31 | MATZUK_IMPLANTATION_AND_UTERINE | 0 | 22 | 1.68 | 0.0000 | 0.0536 |
| 32 | VANDESLUIS_COMMD1_TARGETS_GROUP_4_DN | 0 | 15 | 1.68 | 0.0011 | 0.0526 |
| 33 | WANG_THOC1_TARGETS_DN | 0 | 19 | 1.67 | 0.0000 | 0.0540 |
| 34 | RIZ_ERYTHROID_DIFFERENTIATION_12HR | 0 | 42 | 1.67 | 0.0000 | 0.0007 |
| 35 | REACTOME_ACTIVATED_POINT_MUTANTS_OF_FGFR2 | 0 | 16 | 1.66 | 0.0021 | 0.0669 |
| 36 | LOPES_METHYLATED_IN_COLON_CANCER_DN | 0 | 28 | 1.66 | 0.0000 | 0.0005 |
| 37 | HALMOS_CEBPA_TARGETS_DN | 0 | 44 | 1.66 | 0.0000 | 0.0005 |
| 38 | RIZ_ERYTHROID_DIFFERENTIATION_HBZ | 0 | 41 | 1.66 | 0.0000 | 0.0008 |
| 39 | REACTOME_CLASS_B_2_SECRETIN_FAMILY_RECEPTORS | 0 | 87 | 1.65 | 0.0000 | 0.0010 |
| 40 | MEISSNER_BRAIN_HCP_WITH_H3K4ME2_AND_H3K27ME3 | 1 | 56 | 1.65 | 0.0000 | 0.0813 |
| 41 | MIKKELSEN_NPC_HCP_WITH_H3K4ME3_AND_H3K27ME3 | 1 | 204 | 1.65 | 0.0000 | 0.0792 |
| 42 | LU_TUMOR_ANGIOGENESIS_UP | 0 | 25 | 1.65 | 0.0020 | 0.0776 |
| 43 | REACTOME_REGULATION_OF_GENE_EXPRESSION_IN_BETA_CELLS | 0 | 20 | 1.64 | 0.0021 | 0.0012 |
| 44 | KORKOLA_CORRELATED_WITH_POU5F1 | 0 | 34 | 1.64 | 0.0010 | 0.0894 |
| 45 | ALONSO_METASTASIS_DN | 0 | 23 | 1.63 | 0.0020 | 0.0928 |
| 46 | PARK_TRETINOIN_RESPONSE_AND_PML_RARA_FUSION | 0 | 29 | 1.63 | 0.0000 | 0.0924 |
| 47 | HANN_RESISTANCE_TO_BCL2_INHIBITOR_UP | 0 | 35 | 1.63 | 0.0000 | 0.0008 |
| 48 | MIKKELSEN_MCV6_LCP_WITH_H3K27ME3 | 1 | 27 | 1.62 | 0.0010 | 0.1012 |
| 49 | FIGUEROA_AML_METHYLATION_CLUSTER_5_DN | 0 | 47 | 1.62 | 0.0000 | 0.1020 |
| 50 | RIZ_ERYTHROID_DIFFERENTIATION_6HR | 0 | 40 | 1.62 | 0.0000 | 0.0016 |

**Supplemental Table 3.** Custom neuroblastoma PRC2 signatures consisting of the top 300 EZH2 and H3K27me3 ChIP-seq target genes in Kelly and LAN-1 cell lines. Shown in table are the EZH2 and H3K27me3 promoter relative binding signal in Kelly and LAN-1 cells. Genes were ranked in decreasing order based on the promoter binding signal in the highlighted ranking score column. The high level for the relative occupancy signal in the promoter regions was estimated based on the cut-off 1.5 for the ratio of the AUC ChIP-seq signal of the mark vs the AUC signal of the input.

**(A)** Custom neuroblastoma PRC2 signature consisting of the top 300 EZH2 ChIP-seq target genes in Kelly cells.

| # | Gene | **Kelly rel AUC EZH2 (ranking score)** | Kelly rel AUC H3K27me3 | LAN-1 rel AUC EZH2 | LAN-1 rel AUC H3K27me3 |
|---|---|---|---|---|---|
| 1 | *NFATC1* | 32.51 | 23.21 | 8.52 | 11.65 |
| 2 | *PAX2* | 18.04 | 13.13 | 9.27 | 11.36 |
| 3 | *PDGFA* | 17.82 | 12.54 | 6.60 | 9.41 |
| 4 | *LBX1* | 17.76 | 10.41 | 5.29 | 8.45 |
| 5 | *NKX1-1* | 17.14 | 8.88 | 2.30 | 3.80 |
| 6 | *SOX8* | 16.45 | 12.54 | 5.57 | 11.05 |
| 7 | *PRDM12* | 15.81 | 8.51 | 5.55 | 6.50 |
| 8 | *SIGIRR* | 13.33 | 18.72 | 1.50 | 2.04 |
| 9 | *LHX5* | 12.77 | 10.54 | 5.23 | 7.65 |
| 10 | *ZIC1* | 12.60 | 10.24 | 0.88 | 0.39 |
| 11 | *FOXL2* | 12.53 | 10.62 | 4.23 | 6.50 |
| 12 | *EN2* | 12.41 | 10.34 | 6.53 | 9.53 |
| 13 | *SORCS3* | 12.35 | 11.54 | 3.49 | 6.60 |
| 14 | *HOXC12* | 12.26 | 10.61 | 4.52 | 7.43 |
| 15 | *LMX1B* | 12.23 | 10.09 | 6.93 | 9.23 |
| 16 | *FOXF1* | 12.13 | 7.53 | 5.56 | 8.73 |
| 17 | *GATA4* | 12.04 | 10.44 | 3.35 | 5.17 |
| 18 | *FOXF2* | 12.04 | 7.84 | 4.29 | 6.86 |
| 19 | *HES4* | 11.41 | 10.22 | 1.18 | 0.49 |
| 20 | *IRX1* | 11.30 | 7.80 | 3.52 | 7.59 |
| 21 | *ZIC2* | 11.22 | 7.69 | 6.31 | 9.76 |
| 22 | *TBX15* | 10.94 | 8.77 | 3.14 | 6.40 |
| 23 | *EVX1* | 10.74 | 9.50 | 3.28 | 7.78 |
| 24 | *OLIG2* | 10.30 | 9.01 | 4.33 | 8.13 |
| 25 | *GBX2* | 10.23 | 9.71 | 1.19 | 1.74 |
| 26 | *IRX2* | 10.20 | 7.85 | 3.54 | 6.33 |
| 27 | *HOXB8* | 10.05 | 7.42 | 8.66 | 12.41 |
| 28 | *BARX1* | 10.02 | 6.81 | 2.71 | 5.38 |
| 29 | *EMX1* | 9.97 | 8.39 | 5.55 | 8.53 |
| 30 | *NKX2-2* | 9.70 | 7.01 | 5.16 | 9.46 |
| 31 | *GATA6* | 9.63 | 7.77 | 4.69 | 8.26 |
| 32 | *MN1* | 9.51 | 7.56 | 6.66 | 12.22 |
| 33 | *TFAP2C* | 9.41 | 7.83 | 2.67 | 5.29 |
| 34 | *OTX2* | 9.36 | 8.40 | 2.81 | 5.81 |
| 35 | *LHX2* | 9.36 | 8.05 | 3.08 | 5.21 |
| 36 | *EGR3* | 9.29 | 8.00 | 2.30 | 3.47 |
| 37 | *FLT4* | 9.28 | 12.36 | 2.97 | 7.02 |
| 38 | *ATHL1* | 9.17 | 12.57 | 1.56 | 1.63 |
| 39 | *SOX21* | 9.15 | 9.13 | 2.51 | 5.47 |
| 40 | *HOXB7* | 8.92 | 7.41 | 7.55 | 12.16 |
| 41 | *NKX2-5* | 8.84 | 7.82 | 3.05 | 5.01 |
| 42 | *SOX3* | 8.83 | 6.40 | 3.18 | 5.20 |
| 43 | *SIM2* | 8.78 | 6.87 | 3.54 | 5.86 |
| 44 | *PRDM16* | 8.72 | 7.89 | 8.90 | 15.23 |
| 45 | *ALX4* | 8.59 | 8.11 | 3.48 | 7.03 |
| 46 | *VENTX* | 8.56 | 8.51 | 5.50 | 11.58 |
| 47 | *OVOL1* | 8.56 | 7.78 | 2.62 | 6.07 |
| 48 | *ZIC5* | 8.54 | 7.21 | 3.91 | 7.16 |
| 49 | *PAX7* | 8.40 | 7.11 | 5.88 | 8.93 |
| 50 | *BNC1* | 8.38 | 7.42 | 2.35 | 3.49 |
| 51 | *TNFRSF18* | 8.31 | 10.59 | 2.88 | 7.59 |
| 52 | *GATA5* | 8.28 | 7.51 | 4.87 | 9.10 |
| 53 | *SALL3* | 8.15 | 8.20 | 1.79 | 4.52 |
| 54 | *NKX2-3* | 8.14 | 7.07 | 5.10 | 9.02 |
| 55 | *SOX14* | 8.04 | 8.74 | 2.79 | 5.51 |
| 56 | *FOXB1* | 8.04 | 8.62 | 2.70 | 6.34 |
| 57 | *HOXA6* | 8.04 | 7.37 | 3.08 | 6.71 |
| 58 | *HOXA5* | 8.04 | 7.37 | 3.08 | 6.71 |
| 59 | *HOXA7* | 8.04 | 7.37 | 3.08 | 6.71 |
| 60 | *PRDM13* | 7.89 | 8.12 | 2.00 | 3.95 |
| 61 | *ZIC4* | 7.82 | 7.84 | 0.89 | 0.58 |
| 62 | *HOXA11* | 7.81 | 8.34 | 4.68 | 9.05 |
| 63 | *PPL* | 7.71 | 9.56 | 2.13 | 5.44 |
| 64 | *DMRTA2* | 7.70 | 7.32 | 1.51 | 3.30 |
| 65 | *GCGR* | 7.69 | 7.45 | 1.23 | 3.03 |
| 66 | *KLF2* | 7.66 | 8.67 | 2.82 | 5.26 |

| # | Gene | **Kelly rel AUC EZH2 (ranking score)** | Kelly rel AUC H3K27me3 | LAN-1 rel AUC EZH2 | LAN-1 rel AUC H3K27me3 |
|---|---|---|---|---|---|
| 67 | *IRX4* | 7.61 | 8.30 | 6.13 | 10.81 |
| 68 | *NKX2-8* | 7.59 | 7.92 | 3.05 | 7.71 |
| 69 | *SLC32A1* | 7.47 | 9.07 | 2.24 | 5.10 |
| 70 | *LHX1* | 7.46 | 8.95 | 5.24 | 7.60 |
| 71 | *TBX1* | 7.40 | 7.56 | 5.43 | 9.21 |
| 72 | *UTF1* | 7.39 | 8.17 | 2.56 | 6.89 |
| 73 | *EBF2* | 7.34 | 8.07 | 4.17 | 8.26 |
| 74 | *NOTCH1* | 7.30 | 5.72 | 5.71 | 11.09 |
| 75 | *GPR123* | 7.18 | 8.41 | 3.10 | 5.83 |
| 76 | *HOXB9* | 7.13 | 7.04 | 4.66 | 8.97 |
| 77 | *SHH* | 7.02 | 7.95 | 4.44 | 7.17 |
| 78 | *INHBB* | 6.99 | 7.35 | 5.49 | 8.34 |
| 79 | *CBFA2T3* | 6.95 | 8.67 | 4.14 | 10.05 |
| 80 | *HOXB6* | 6.94 | 7.83 | 4.51 | 9.53 |
| 81 | *HOXB5* | 6.94 | 7.83 | 4.51 | 9.53 |
| 82 | *BARX2* | 6.94 | 6.93 | 3.52 | 5.40 |
| 83 | *LHX6* | 6.90 | 7.47 | 2.69 | 4.31 |
| 84 | *CACNA1H* | 6.89 | 7.06 | 1.75 | 2.00 |
| 85 | *FOXC2* | 6.81 | 6.05 | 2.35 | 5.54 |
| 86 | *FIBCD1* | 6.78 | 9.20 | 5.36 | 11.43 |
| 87 | *ONECUT1* | 6.77 | 7.06 | 1.84 | 4.11 |
| 88 | *DMRT3* | 6.77 | 7.01 | 3.36 | 8.10 |
| 89 | *TPSG1* | 6.75 | 6.30 | 1.86 | 1.40 |
| 90 | *PRDM14* | 6.72 | 7.58 | 1.70 | 1.96 |
| 91 | *SLC24A4* | 6.64 | 9.46 | 2.18 | 5.48 |
| 92 | *RREB1* | 6.63 | 5.92 | 2.33 | 4.45 |
| 93 | *HOXB4* | 6.61 | 7.13 | 2.95 | 5.82 |
| 94 | *THPO* | 6.57 | 8.06 | 2.02 | 2.76 |
| 95 | *TTLL10* | 6.57 | 6.47 | 2.62 | 5.85 |
| 96 | *FOXA1* | 6.56 | 6.96 | 1.37 | 2.21 |
| 97 | *EFNA2* | 6.51 | 8.34 | 1.27 | 1.50 |
| 98 | *FOXP2* | 6.49 | 6.79 | 2.95 | 4.56 |
| 99 | *NEUROD2* | 6.45 | 6.48 | 6.29 | 9.43 |
| 100 | *CXCL16* | 6.44 | 10.12 | 3.15 | 7.32 |
| 101 | *TLX1* | 6.43 | 6.76 | 3.29 | 6.68 |
| 102 | *MSX1* | 6.42 | 6.87 | 2.69 | 4.67 |
| 103 | *COMP* | 6.40 | 7.23 | 3.43 | 5.72 |
| 104 | *CHRD* | 6.37 | 7.82 | 2.22 | 2.94 |
| 105 | *ESPN* | 6.37 | 7.44 | 2.99 | 6.65 |
| 106 | *GAD2* | 6.23 | 7.11 | 2.79 | 6.86 |
| 107 | *PAX3* | 6.23 | 6.80 | 3.34 | 6.17 |
| 108 | *AJAP1* | 6.22 | 8.11 | 3.91 | 8.24 |
| 109 | *LHX4* | 6.22 | 5.80 | 2.08 | 3.66 |
| 110 | *ZMYND15* | 6.18 | 9.62 | 3.15 | 7.36 |
| 111 | *GAD1* | 6.18 | 7.14 | 2.02 | 5.26 |
| 112 | *LMX1A* | 6.17 | 5.86 | 2.23 | 4.89 |
| 113 | *FGFRL1* | 6.15 | 8.12 | 1.69 | 2.00 |
| 114 | *NR2E1* | 6.13 | 6.13 | 2.45 | 5.08 |
| 115 | *CDX2* | 6.12 | 5.20 | 11.43 | 19.24 |
| 116 | *C1ORF94* | 6.11 | 9.61 | 2.77 | 5.73 |
| 117 | *MUC5B* | 6.04 | 8.93 | 3.85 | 9.44 |
| 118 | *OVOL2* | 6.03 | 6.56 | 2.42 | 5.27 |
| 119 | *DRD4* | 6.02 | 6.10 | 1.38 | 0.59 |
| 120 | *OTP* | 6.02 | 6.02 | 2.48 | 5.32 |
| 121 | *EN1* | 5.94 | 5.66 | 3.19 | 6.39 |
| 122 | *HES2* | 5.92 | 6.57 | 3.95 | 8.22 |
| 123 | *RELN* | 5.90 | 9.95 | 1.72 | 3.82 |
| 124 | *PRKCZ* | 5.89 | 7.47 | 3.29 | 7.65 |
| 125 | *NPTX1* | 5.89 | 6.01 | 6.66 | 10.93 |
| 126 | *KLHDC7B* | 5.88 | 6.71 | 1.71 | 2.95 |
| 127 | *SLC30A3* | 5.84 | 7.27 | 1.25 | 0.63 |
| 128 | *POU4F3* | 5.84 | 7.03 | 2.42 | 4.85 |
| 129 | *COL12A1* | 5.81 | 7.17 | 0.81 | 1.07 |
| 130 | *GSC* | 5.81 | 6.41 | 2.56 | 4.98 |
| 131 | *ICAM5* | 5.80 | 8.51 | 1.33 | 0.54 |
| 132 | *HBB* | 5.79 | 2.15 | 2.06 | 1.55 |
| 133 | *NTN1* | 5.78 | 5.89 | 2.09 | 5.38 |
| 134 | *DGKQ* | 5.77 | 7.79 | 1.26 | 0.74 |
| 135 | *GPC4* | 5.77 | 7.36 | 2.91 | 6.04 |
| 136 | *TFAP2A* | 5.75 | 5.83 | 3.45 | 6.21 |
| 137 | *FZD10* | 5.72 | 6.68 | 2.64 | 6.25 |
| 138 | *HOXC13* | 5.67 | 7.55 | 1.93 | 5.08 |
| 139 | *HTRA1* | 5.67 | 7.30 | 2.40 | 4.04 |
| 140 | *HOXC11* | 5.67 | 5.50 | 3.26 | 5.74 |
| 141 | *PAX9* | 5.67 | 5.27 | 4.15 | 6.77 |
| 142 | *ATP2A3* | 5.66 | 7.38 | 2.13 | 5.91 |

| # | Gene | **Kelly rel AUC EZH2 (ranking score)** | Kelly rel AUC H3K27me3 | LAN-1 rel AUC EZH2 | LAN-1 rel AUC H3K27me3 |
|---|---|---|---|---|---|
| 143 | *OLIG3* | 5.62 | 5.29 | 2.88 | 7.35 |
| 144 | *RASSF7* | 5.55 | 6.14 | 2.50 | 4.68 |
| 145 | *DSP* | 5.53 | 5.78 | 3.27 | 5.91 |
| 146 | *ITGB2* | 5.47 | 8.13 | 3.50 | 8.17 |
| 147 | *GABRD* | 5.45 | 6.21 | 4.40 | 10.95 |
| 148 | *DLX4* | 5.43 | 6.36 | 2.61 | 6.21 |
| 149 | *EMX2OS* | 5.41 | 5.62 | 3.05 | 5.72 |
| 150 | *GRWD1* | 5.41 | 3.46 | 0.76 | 0.75 |
| 151 | *SIX1* | 5.40 | 7.25 | 2.66 | 4.73 |
| 152 | *HOXA10* | 5.39 | 6.64 | 2.80 | 6.33 |
| 153 | *BARHL1* | 5.38 | 5.73 | 5.29 | 8.60 |
| 154 | *ATAD3C* | 5.37 | 7.68 | 1.28 | 0.98 |
| 155 | *WNT7B* | 5.34 | 6.44 | 4.23 | 7.47 |
| 156 | *HS3ST6* | 5.33 | 6.64 | 2.23 | 4.82 |
| 157 | *TPSD1* | 5.31 | 6.81 | 1.66 | 1.57 |
| 158 | *ADAM3A* | 5.27 | 3.14 | 0.53 | 0.48 |
| 159 | *HMX2* | 5.22 | 6.65 | 3.79 | 6.95 |
| 160 | *LHX3* | 5.22 | 3.61 | 3.77 | 4.98 |
| 161 | *OLIG1* | 5.21 | 8.98 | 1.96 | 4.63 |
| 162 | *FOXQ1* | 5.21 | 6.59 | 4.25 | 9.51 |
| 163 | *NFIX* | 5.20 | 5.28 | 2.65 | 4.57 |
| 164 | *FOXD2* | 5.20 | 4.79 | 2.40 | 4.90 |
| 165 | *MMP25* | 5.18 | 5.95 | 2.74 | 4.96 |
| 166 | *NOG* | 5.15 | 6.75 | 2.74 | 6.11 |
| 167 | *OSR1* | 5.14 | 6.57 | 1.85 | 4.65 |
| 168 | *FGF3* | 5.14 | 4.72 | 3.92 | 7.28 |
| 169 | *CSMD2* | 5.11 | 8.14 | 2.74 | 5.74 |
| 170 | *TCF21* | 5.10 | 9.71 | 1.84 | 4.65 |
| 171 | *FOXL1* | 5.10 | 7.18 | 1.88 | 5.11 |
| 172 | *NEUROG3* | 5.08 | 6.19 | 3.22 | 6.91 |
| 173 | *SIX6* | 5.08 | 4.86 | 2.53 | 4.39 |
| 174 | *NRK* | 5.04 | 7.20 | 1.04 | 1.75 |
| 175 | *FOXE1* | 5.03 | 6.18 | 1.13 | 2.84 |
| 176 | *ACSS1* | 5.01 | 6.90 | 1.88 | 3.88 |
| 177 | *SIM1* | 5.01 | 5.82 | 1.34 | 3.10 |
| 178 | *SLC4A11* | 5.01 | 5.62 | 1.97 | 3.05 |
| 179 | *PTRF* | 5.00 | 6.52 | 3.08 | 5.68 |
| 180 | *PPAP2C* | 4.98 | 7.77 | 1.91 | 4.34 |
| 181 | *WTIP* | 4.98 | 5.11 | 1.29 | 0.55 |
| 182 | *MAF* | 4.97 | 6.50 | 2.05 | 5.02 |
| 183 | *HOXA13* | 4.96 | 5.46 | 2.15 | 5.17 |
| 184 | *ITGB4* | 4.94 | 8.19 | 2.05 | 5.52 |
| 185 | *CRLF1* | 4.93 | 5.45 | 2.29 | 4.78 |
| 186 | *SP8* | 4.90 | 5.50 | 6.33 | 11.39 |
| 187 | *GUCY2D* | 4.88 | 5.64 | 1.45 | 3.94 |
| 188 | *PRDM6* | 4.87 | 6.81 | 2.25 | 4.10 |
| 189 | *T* | 4.85 | 5.25 | 1.93 | 4.51 |
| 190 | *FEZF2* | 4.82 | 5.55 | 3.51 | 6.40 |
| 191 | *FAM110C* | 4.81 | 7.04 | 1.90 | 3.44 |
| 192 | *IGF2BP2* | 4.81 | 6.92 | 1.67 | 3.60 |
| 193 | *SCN4B* | 4.78 | 8.17 | 1.95 | 5.22 |
| 194 | *GRIN3B* | 4.78 | 6.07 | 1.61 | 3.06 |
| 195 | *SMARCA2* | 4.78 | 5.41 | 1.76 | 2.20 |
| 196 | *ALDH1A2* | 4.77 | 8.75 | 1.29 | 1.97 |
| 197 | *IHH* | 4.76 | 5.31 | 1.49 | 2.76 |
| 198 | *KCNA1* | 4.76 | 4.64 | 2.44 | 4.45 |
| 199 | *FOXD3* | 4.75 | 5.43 | 4.14 | 7.56 |
| 200 | *SOX17* | 4.74 | 5.11 | 1.66 | 4.03 |
| 201 | *ICOSLG* | 4.74 | 4.56 | 3.57 | 8.03 |
| 202 | *TWIST2* | 4.73 | 4.78 | 1.66 | 3.88 |
| 203 | *FAM83H* | 4.72 | 6.27 | 2.36 | 3.78 |
| 204 | *SCO2* | 4.71 | 4.93 | 1.32 | 1.30 |
| 205 | *CYP26A1* | 4.68 | 5.70 | 2.77 | 6.30 |
| 206 | *HOXA2* | 4.68 | 4.71 | 3.84 | 7.46 |
| 207 | *LONRF3* | 4.63 | 5.97 | 1.59 | 3.04 |
| 208 | *NRN1* | 4.63 | 5.48 | 1.50 | 3.30 |
| 209 | *KRTAP10-12* | 4.58 | 7.05 | 2.06 | 4.25 |
| 210 | *C21ORF90* | 4.58 | 7.05 | 2.06 | 4.25 |
| 211 | *KRTAP10-11* | 4.58 | 7.05 | 2.06 | 4.25 |
| 212 | *MUC2* | 4.58 | 6.12 | 2.27 | 6.64 |
| 213 | *WNT1* | 4.54 | 5.06 | 4.12 | 8.96 |
| 214 | *BMP4* | 4.53 | 5.65 | 1.35 | 2.33 |
| 215 | *KISS1R* | 4.52 | 4.93 | 2.14 | 3.89 |
| 216 | *RIPK4* | 4.51 | 7.77 | 2.22 | 5.85 |
| 217 | *SLITRK2* | 4.48 | 7.13 | 2.35 | 7.34 |
| 218 | *HEY2* | 4.48 | 5.81 | 1.68 | 3.64 |

| # | Gene | **Kelly rel AUC EZH2 (ranking score)** | Kelly rel AUC H3K27me3 | LAN-1 rel AUC EZH2 | LAN-1 rel AUC H3K27me3 |
|---|---|---|---|---|---|
| 219 | *SLC1A1* | 4.47 | 7.16 | 2.12 | 4.99 |
| 220 | *BMP6* | 4.46 | 5.44 | 2.88 | 5.72 |
| 221 | *ATP8A2* | 4.45 | 5.99 | 3.18 | 8.23 |
| 222 | *LOC401463* | 4.45 | 5.58 | 1.01 | 2.50 |
| 223 | *HOXB3* | 4.42 | 5.69 | 2.82 | 6.31 |
| 224 | *HOXB2* | 4.42 | 5.69 | 2.82 | 6.31 |
| 225 | *TFAP2E* | 4.42 | 5.22 | 1.19 | 0.58 |
| 226 | *SSTR5* | 4.39 | 3.92 | 1.69 | 2.07 |
| 227 | *RAX* | 4.38 | 7.16 | 0.70 | 0.67 |
| 228 | *IRF4* | 4.36 | 5.31 | 1.89 | 4.79 |
| 229 | *ACHE* | 4.35 | 4.17 | 2.55 | 3.26 |
| 230 | *FOXE3* | 4.34 | 5.63 | 1.31 | 3.57 |
| 231 | *TP73* | 4.32 | 3.33 | 0.82 | 0.41 |
| 232 | *MATK* | 4.31 | 5.59 | 1.43 | 3.75 |
| 233 | *FAM43B* | 4.30 | 5.90 | 1.22 | 0.40 |
| 234 | *PFKL* | 4.30 | 5.54 | 1.61 | 2.45 |
| 235 | *PAX1* | 4.29 | 5.65 | 3.62 | 7.48 |
| 236 | *SCT* | 4.29 | 5.42 | 1.33 | 0.68 |
| 237 | *HOXC10* | 4.28 | 5.17 | 5.37 | 10.33 |
| 238 | *PAPLN* | 4.26 | 6.54 | 2.05 | 2.32 |
| 239 | *GRTP1* | 4.26 | 6.41 | 1.05 | 1.07 |
| 240 | *NPR3* | 4.26 | 5.92 | 0.93 | 1.06 |
| 241 | *TBX5* | 4.26 | 4.34 | 3.10 | 6.09 |
| 242 | *BACE2* | 4.22 | 7.57 | 2.44 | 6.38 |
| 243 | *PRRX1* | 4.22 | 6.31 | 2.41 | 4.27 |
| 244 | *DLX2* | 4.22 | 5.65 | 1.71 | 2.64 |
| 245 | *MT1G* | 4.21 | 6.39 | 1.97 | 5.74 |
| 246 | *GADD45B* | 4.21 | 5.96 | 1.07 | 1.37 |
| 247 | *ICAM4* | 4.20 | 5.62 | 1.13 | 0.57 |
| 248 | *GJB2* | 4.20 | 5.41 | 1.83 | 4.53 |
| 249 | *PHLDA2* | 4.19 | 3.95 | 2.52 | 5.94 |
| 250 | *PCSK6* | 4.18 | 5.30 | 1.19 | 1.87 |
| 251 | *FBLN5* | 4.17 | 7.83 | 1.55 | 2.75 |
| 252 | *THBD* | 4.16 | 6.61 | 1.35 | 2.91 |
| 253 | *PFKFB3* | 4.16 | 5.83 | 1.59 | 0.87 |
| 254 | *NKD2* | 4.16 | 4.38 | 2.73 | 6.11 |
| 255 | *MYO5B* | 4.14 | 7.40 | 3.30 | 7.61 |
| 256 | *MAD2L2* | 4.14 | 6.19 | 1.69 | 2.27 |
| 257 | *GPR50* | 4.12 | 6.02 | 1.03 | 1.29 |
| 258 | *RGL3* | 4.12 | 5.83 | 1.67 | 2.51 |
| 259 | *GRIN2C* | 4.12 | 4.10 | 2.09 | 3.50 |
| 260 | *CACNG2* | 4.11 | 5.84 | 1.57 | 4.34 |
| 261 | *PIK3CD* | 4.10 | 5.87 | 1.51 | 3.01 |
| 262 | *ZNF92* | 4.10 | 3.63 | 2.15 | 2.66 |
| 263 | *BCL2L11* | 4.10 | 3.20 | 1.33 | 1.29 |
| 264 | *MRGPRX3* | 4.08 | 8.67 | 1.09 | 1.53 |
| 265 | *NR5A1* | 4.08 | 3.31 | 2.11 | 3.69 |
| 266 | *GLI3* | 4.06 | 5.52 | 3.02 | 7.17 |
| 267 | *WNT7A* | 4.05 | 4.43 | 2.51 | 5.13 |
| 268 | *FAM20A* | 4.04 | 6.52 | 1.17 | 2.38 |
| 269 | *SLC16A6* | 4.04 | 6.52 | 1.17 | 2.38 |
| 270 | *WIPI1* | 4.04 | 6.52 | 1.17 | 2.38 |
| 271 | *NTSR1* | 4.03 | 5.10 | 1.89 | 4.55 |
| 272 | *ROBO3* | 4.01 | 7.66 | 1.46 | 5.18 |
| 273 | *CDC42EP5* | 4.01 | 6.61 | 2.36 | 4.96 |
| 274 | *MT1M* | 4.01 | 5.43 | 2.69 | 6.93 |
| 275 | *HMHA1* | 4.01 | 5.16 | 2.80 | 5.96 |
| 276 | *SNAPC2* | 4.01 | 3.32 | 1.59 | 0.87 |
| 277 | *PDGFRA* | 4.00 | 4.27 | 1.07 | 1.31 |
| 278 | *SLC22A18AS* | 3.98 | 3.26 | 2.89 | 6.41 |
| 279 | *HOXA1* | 3.97 | 5.21 | 2.57 | 5.60 |
| 280 | *HOXB13* | 3.97 | 5.13 | 4.07 | 8.80 |
| 281 | *MUC6* | 3.96 | 6.09 | 2.84 | 5.90 |
| 282 | *HS3ST3B1* | 3.96 | 4.61 | 1.93 | 3.25 |
| 283 | *MGC12916* | 3.96 | 4.61 | 1.93 | 3.25 |
| 284 | *HTR2C* | 3.95 | 7.93 | 1.58 | 2.74 |
| 285 | *DUSP8* | 3.94 | 6.54 | 3.76 | 4.88 |
| 286 | *ADRA1A* | 3.94 | 6.19 | 1.02 | 1.36 |
| 287 | *PTPRT* | 3.93 | 4.97 | 2.17 | 3.99 |
| 288 | *PPP2R2C* | 3.92 | 5.93 | 2.43 | 5.46 |
| 289 | *NEUROG1* | 3.92 | 5.35 | 0.85 | 1.30 |
| 290 | *FOSL1* | 3.91 | 5.41 | 2.50 | 5.35 |
| 291 | *KCNK4* | 3.91 | 3.91 | 2.40 | 3.58 |
| 292 | *BAD* | 3.90 | 3.34 | 2.40 | 3.03 |
| 293 | *GFI1* | 3.89 | 5.38 | 2.28 | 4.26 |
| 294 | *SVEP1* | 3.88 | 8.02 | 0.60 | 0.40 |

| # | Gene | **Kelly rel AUC EZH2 (ranking score)** | Kelly rel AUC H3K27me3 | LAN-1 rel AUC EZH2 | LAN-1 rel AUC H3K27me3 |
|---|---|---|---|---|---|
| 295 | *BAIAP3* | 3.88 | 7.16 | 1.56 | 2.90 |
| 296 | *DLX3* | 3.88 | 5.68 | 3.13 | 6.67 |
| 297 | *HBM* | 3.86 | 6.74 | 3.26 | 8.62 |
| 298 | *CACNA1E* | 3.86 | 5.71 | 1.82 | 4.82 |
| 299 | *MMEL1* | 3.84 | 6.59 | 2.77 | 6.20 |
| 300 | *CRIM1* | 3.83 | 4.87 | 1.29 | 2.58 |

**Supplemental Table 3. (B)** Custom neuroblastoma PRC2 signature consisting of the top 300 H3K27me3 ChIP-seq target genes in Kelly cells.

| # | Gene | **Kelly rel AUC H3K27me3 (ranking score)** | Kelly rel AUC EZH2 | LAN-1 rel AUC H3K27me3 | LAN-1 rel AUC EZH2 |
|---|---|---|---|---|---|
| 1 | *NFATC1* | 23.21 | 32.51 | 11.65 | 8.52 |
| 2 | *SIGIRR* | 18.72 | 13.33 | 2.04 | 1.50 |
| 3 | *PAX2* | 13.13 | 18.04 | 11.36 | 9.27 |
| 4 | *ATHL1* | 12.57 | 9.17 | 1.63 | 1.56 |
| 5 | *PDGFA* | 12.54 | 17.82 | 9.41 | 6.60 |
| 6 | *SOX8* | 12.54 | 16.45 | 11.05 | 5.57 |
| 7 | *FLT4* | 12.36 | 9.28 | 7.02 | 2.97 |
| 8 | *SORCS3* | 11.54 | 12.35 | 6.60 | 3.49 |
| 9 | *FOXL2* | 10.62 | 12.53 | 6.50 | 4.23 |
| 10 | *HOXC12* | 10.61 | 12.26 | 7.43 | 4.52 |
| 11 | *TNFRSF18* | 10.59 | 8.31 | 7.59 | 2.88 |
| 12 | *LHX5* | 10.54 | 12.77 | 7.65 | 5.23 |
| 13 | *GATA4* | 10.44 | 12.04 | 5.17 | 3.35 |
| 14 | *LBX1* | 10.41 | 17.76 | 8.45 | 5.29 |
| 15 | *EN2* | 10.34 | 12.41 | 9.53 | 6.53 |
| 16 | *ZIC1* | 10.24 | 12.60 | 0.39 | 0.88 |
| 17 | *HES4* | 10.22 | 11.41 | 0.49 | 1.18 |
| 18 | *CXCL16* | 10.12 | 6.44 | 7.32 | 3.15 |
| 19 | *LMX1B* | 10.09 | 12.23 | 9.23 | 6.93 |
| 20 | *RELN* | 9.95 | 5.90 | 3.82 | 1.72 |
| 21 | *GBX2* | 9.71 | 10.23 | 1.74 | 1.19 |
| 22 | *TCF21* | 9.71 | 5.10 | 4.65 | 1.84 |
| 23 | *ZMYND15* | 9.62 | 6.18 | 7.36 | 3.15 |
| 24 | *C1ORF94* | 9.61 | 6.11 | 5.73 | 2.77 |
| 25 | *PPL* | 9.56 | 7.71 | 5.44 | 2.13 |
| 26 | *EVX1* | 9.50 | 10.74 | 7.78 | 3.28 |
| 27 | *SLC24A4* | 9.46 | 6.64 | 5.48 | 2.18 |
| 28 | *FIBCD1* | 9.20 | 6.78 | 11.43 | 5.36 |
| 29 | *SOX21* | 9.13 | 9.15 | 5.47 | 2.51 |
| 30 | *SLC32A1* | 9.07 | 7.47 | 5.10 | 2.24 |
| 31 | *OLIG2* | 9.01 | 10.30 | 8.13 | 4.33 |
| 32 | *ZFYVE28* | 9.01 | 3.56 | 5.62 | 2.95 |
| 33 | *OLIG1* | 8.98 | 5.21 | 4.63 | 1.96 |
| 34 | *LHX1* | 8.95 | 7.46 | 7.60 | 5.24 |
| 35 | *MUC5B* | 8.93 | 6.04 | 9.44 | 3.85 |
| 36 | *KLK6* | 8.93 | 3.80 | 4.82 | 2.37 |
| 37 | *NKX1-1* | 8.88 | 17.14 | 3.80 | 2.30 |
| 38 | *TBX15* | 8.77 | 10.94 | 6.40 | 3.14 |
| 39 | *ALDH1A2* | 8.75 | 4.77 | 1.97 | 1.29 |
| 40 | *SOX14* | 8.74 | 8.04 | 5.51 | 2.79 |
| 41 | *KLF2* | 8.67 | 7.66 | 5.26 | 2.82 |
| 42 | *CBFA2T3* | 8.67 | 6.95 | 10.05 | 4.14 |
| 43 | *MRGPRX3* | 8.67 | 4.08 | 1.53 | 1.09 |
| 44 | *FOXB1* | 8.62 | 8.04 | 6.34 | 2.70 |
| 45 | *PRDM12* | 8.51 | 15.81 | 6.50 | 5.55 |
| 46 | *VENTX* | 8.51 | 8.56 | 11.58 | 5.50 |
| 47 | *ICAM5* | 8.51 | 5.80 | 0.54 | 1.33 |
| 48 | *GPR123* | 8.41 | 7.18 | 5.83 | 3.10 |
| 49 | *OTX2* | 8.40 | 9.36 | 5.81 | 2.81 |
| 50 | *EMX1* | 8.39 | 9.97 | 8.53 | 5.55 |
| 51 | *HOXA11* | 8.34 | 7.81 | 9.05 | 4.68 |
| 52 | *EFNA2* | 8.34 | 6.51 | 1.50 | 1.27 |
| 53 | *IRX4* | 8.30 | 7.61 | 10.81 | 6.13 |
| 54 | *SALL3* | 8.20 | 8.15 | 4.52 | 1.79 |
| 55 | *ITGB4* | 8.19 | 4.94 | 5.52 | 2.05 |
| 56 | *UTF1* | 8.17 | 7.39 | 6.89 | 2.56 |
| 57 | *SCN4B* | 8.17 | 4.78 | 5.22 | 1.95 |
| 58 | *CSMD2* | 8.14 | 5.11 | 5.74 | 2.74 |
| 59 | *ITGB2* | 8.13 | 5.47 | 8.17 | 3.50 |
| 60 | *PRDM13* | 8.12 | 7.89 | 3.95 | 2.00 |
| 61 | *FGFRL1* | 8.12 | 6.15 | 2.00 | 1.69 |
| 62 | *ALX4* | 8.11 | 8.59 | 7.03 | 3.48 |
| 63 | *AJAP1* | 8.11 | 6.22 | 8.24 | 3.91 |
| 64 | *EBF2* | 8.07 | 7.34 | 8.26 | 4.17 |
| 65 | *LOC284379* | 8.07 | 2.84 | 5.71 | 1.53 |
| 66 | *THPO* | 8.06 | 6.57 | 2.76 | 2.02 |
| 67 | *LHX2* | 8.05 | 9.36 | 5.21 | 3.08 |
| 68 | *SVEP1* | 8.02 | 3.88 | 0.40 | 0.60 |
| 69 | *EGR3* | 8.00 | 9.29 | 3.47 | 2.30 |
| 70 | *SHH* | 7.95 | 7.02 | 7.17 | 4.44 |
| 71 | *HTR2C* | 7.93 | 3.95 | 2.74 | 1.58 |
| 72 | *NKX2-8* | 7.92 | 7.59 | 7.71 | 3.05 |
| 73 | *PRDM16* | 7.89 | 8.72 | 15.23 | 8.90 |

| # | Gene | **Kelly rel AUC H3K27me3 (ranking score)** | Kelly rel AUC EZH2 | LAN-1 rel AUC H3K27me3 | LAN-1 rel AUC EZH2 |
|---|---|---|---|---|---|
| 74 | *IRX2* | 7.85 | 10.20 | 6.33 | 3.54 |
| 75 | *FOXF2* | 7.84 | 12.04 | 6.86 | 4.29 |
| 76 | *ZIC4* | 7.84 | 7.82 | 0.58 | 0.89 |
| 77 | *TFAP2C* | 7.83 | 9.41 | 5.29 | 2.67 |
| 78 | *HOXB6* | 7.83 | 6.94 | 9.53 | 4.51 |
| 79 | *HOXB5* | 7.83 | 6.94 | 9.53 | 4.51 |
| 80 | *FBLN5* | 7.83 | 4.17 | 2.75 | 1.55 |
| 81 | *NKX2-5* | 7.82 | 8.84 | 5.01 | 3.05 |
| 82 | *CHRD* | 7.82 | 6.37 | 2.94 | 2.22 |
| 83 | *IRX1* | 7.80 | 11.30 | 7.59 | 3.52 |
| 84 | *DGKQ* | 7.79 | 5.77 | 0.74 | 1.26 |
| 85 | *OVOL1* | 7.78 | 8.56 | 6.07 | 2.62 |
| 86 | *GATA6* | 7.77 | 9.63 | 8.26 | 4.69 |
| 87 | *PPAP2C* | 7.77 | 4.98 | 4.34 | 1.91 |
| 88 | *RIPK4* | 7.77 | 4.51 | 5.85 | 2.22 |
| 89 | *ZIC2* | 7.69 | 11.22 | 9.76 | 6.31 |
| 90 | *ATAD3C* | 7.68 | 5.37 | 0.98 | 1.28 |
| 91 | *ROBO3* | 7.66 | 4.01 | 5.18 | 1.46 |
| 92 | *PRDM14* | 7.58 | 6.72 | 1.96 | 1.70 |
| 93 | *BACE2* | 7.57 | 4.22 | 6.38 | 2.44 |
| 94 | *MN1* | 7.56 | 9.51 | 12.22 | 6.66 |
| 95 | *TBX1* | 7.56 | 7.40 | 9.21 | 5.43 |
| 96 | *HOXC13* | 7.55 | 5.67 | 5.08 | 1.93 |
| 97 | *FOXF1* | 7.53 | 12.13 | 8.73 | 5.56 |
| 98 | *GATA5* | 7.51 | 8.28 | 9.10 | 4.87 |
| 99 | *LHX6* | 7.47 | 6.90 | 4.31 | 2.69 |
| 100 | *PRKCZ* | 7.47 | 5.89 | 7.65 | 3.29 |
| 101 | *KRT85* | 7.46 | 3.50 | 3.01 | 1.36 |
| 102 | *GCGR* | 7.45 | 7.69 | 3.03 | 1.23 |
| 103 | *ESPN* | 7.44 | 6.37 | 6.65 | 2.99 |
| 104 | *HOXB8* | 7.42 | 10.05 | 12.41 | 8.66 |
| 105 | *BNC1* | 7.42 | 8.38 | 3.49 | 2.35 |
| 106 | *HOXB7* | 7.41 | 8.92 | 12.16 | 7.55 |
| 107 | *MYO5B* | 7.40 | 4.14 | 7.61 | 3.30 |
| 108 | *ATP2A3* | 7.38 | 5.66 | 5.91 | 2.13 |
| 109 | *HOXA6* | 7.37 | 8.04 | 6.71 | 3.08 |
| 110 | *HOXA5* | 7.37 | 8.04 | 6.71 | 3.08 |
| 111 | *HOXA7* | 7.37 | 8.04 | 6.71 | 3.08 |
| 112 | *GPC4* | 7.36 | 5.77 | 6.04 | 2.91 |
| 113 | *INHBB* | 7.35 | 6.99 | 8.34 | 5.49 |
| 114 | *DMRTA2* | 7.32 | 7.70 | 3.30 | 1.51 |
| 115 | *HTRA1* | 7.30 | 5.67 | 4.04 | 2.40 |
| 116 | *KIRREL* | 7.30 | 3.03 | 2.98 | 1.41 |
| 117 | *SLC30A3* | 7.27 | 5.84 | 0.63 | 1.25 |
| 118 | *SIX1* | 7.25 | 5.40 | 4.73 | 2.66 |
| 119 | *COMP* | 7.23 | 6.40 | 5.72 | 3.43 |
| 120 | *ZIC5* | 7.21 | 8.54 | 7.16 | 3.91 |
| 121 | *NRK* | 7.20 | 5.04 | 1.75 | 1.04 |
| 122 | *FOXL1* | 7.18 | 5.10 | 5.11 | 1.88 |
| 123 | *COL12A1* | 7.17 | 5.81 | 1.07 | 0.81 |
| 124 | *SLC1A1* | 7.16 | 4.47 | 4.99 | 2.12 |
| 125 | *RAX* | 7.16 | 4.38 | 0.67 | 0.70 |
| 126 | *BAIAP3* | 7.16 | 3.88 | 2.90 | 1.56 |
| 127 | *GAD1* | 7.14 | 6.18 | 5.26 | 2.02 |
| 128 | *HOXB4* | 7.13 | 6.61 | 5.82 | 2.95 |
| 129 | *SLITRK2* | 7.13 | 4.48 | 7.34 | 2.35 |
| 130 | *PAX7* | 7.11 | 8.40 | 8.93 | 5.88 |
| 131 | *GAD2* | 7.11 | 6.23 | 6.86 | 2.79 |
| 132 | *PVALB* | 7.10 | 3.03 | 5.90 | 2.48 |
| 133 | *NKX2-3* | 7.07 | 8.14 | 9.02 | 5.10 |
| 134 | *CACNA1H* | 7.06 | 6.89 | 2.00 | 1.75 |
| 135 | *ONECUT1* | 7.06 | 6.77 | 4.11 | 1.84 |
| 136 | *KRTAP10-12* | 7.05 | 4.58 | 4.25 | 2.06 |
| 137 | *C21ORF90* | 7.05 | 4.58 | 4.25 | 2.06 |
| 138 | *KRTAP10-11* | 7.05 | 4.58 | 4.25 | 2.06 |
| 139 | *PDPN* | 7.05 | 3.12 | 4.31 | 1.60 |
| 140 | *SLC6A20* | 7.05 | 2.87 | 2.27 | 1.47 |
| 141 | *HOXB9* | 7.04 | 7.13 | 8.97 | 4.66 |
| 142 | *FAM110C* | 7.04 | 4.81 | 3.44 | 1.90 |
| 143 | *POU4F3* | 7.03 | 5.84 | 4.85 | 2.42 |
| 144 | *NKX2-2* | 7.01 | 9.70 | 9.46 | 5.16 |
| 145 | *DMRT3* | 7.01 | 6.77 | 8.10 | 3.36 |
| 146 | *NFE2L3* | 7.01 | 3.56 | 1.06 | 1.24 |
| 147 | *CD1D* | 6.99 | 2.90 | 5.29 | 2.24 |
| 148 | *IL27* | 6.99 | 2.18 | 1.86 | 1.41 |
| 149 | *FOXA1* | 6.96 | 6.56 | 2.21 | 1.37 |

| # | Gene | **Kelly rel AUC H3K27me3 (ranking score)** | Kelly rel AUC EZH2 | LAN-1 rel AUC H3K27me3 | LAN-1 rel AUC EZH2 |
|---|---|---|---|---|---|
| 150 | *BARX2* | 6.93 | 6.94 | 5.40 | 3.52 |
| 151 | *IGF2BP2* | 6.92 | 4.81 | 3.60 | 1.67 |
| 152 | *DFNB31* | 6.92 | 3.37 | 2.14 | 0.94 |
| 153 | *ACSS1* | 6.90 | 5.01 | 3.88 | 1.88 |
| 154 | *SIM2* | 6.87 | 8.78 | 5.86 | 3.54 |
| 155 | *MSX1* | 6.87 | 6.42 | 4.67 | 2.69 |
| 156 | *BARX1* | 6.81 | 10.02 | 5.38 | 2.71 |
| 157 | *TPSD1* | 6.81 | 5.31 | 1.57 | 1.66 |
| 158 | *PRDM6* | 6.81 | 4.87 | 4.10 | 2.25 |
| 159 | *PAX3* | 6.80 | 6.23 | 6.17 | 3.34 |
| 160 | *FOXP2* | 6.79 | 6.49 | 4.56 | 2.95 |
| 161 | *TCF15* | 6.79 | 3.26 | 2.39 | 1.42 |
| 162 | *TLX1* | 6.76 | 6.43 | 6.68 | 3.29 |
| 163 | *NOG* | 6.75 | 5.15 | 6.11 | 2.74 |
| 164 | *HBM* | 6.74 | 3.86 | 8.62 | 3.26 |
| 165 | *XKR4* | 6.72 | 3.49 | 3.23 | 1.39 |
| 166 | *KLHDC7B* | 6.71 | 5.88 | 2.95 | 1.71 |
| 167 | *FZD10* | 6.68 | 5.72 | 6.25 | 2.64 |
| 168 | *HMX2* | 6.65 | 5.22 | 6.95 | 3.79 |
| 169 | *HOXA10* | 6.64 | 5.39 | 6.33 | 2.80 |
| 170 | *HS3ST6* | 6.64 | 5.33 | 4.82 | 2.23 |
| 171 | *GPR78* | 6.64 | 3.04 | 3.66 | 1.44 |
| 172 | *VSIG2* | 6.63 | 2.69 | 2.59 | 1.35 |
| 173 | *SERPINA9* | 6.63 | 2.54 | 2.12 | 1.10 |
| 174 | *SCNN1G* | 6.63 | 2.49 | 3.72 | 1.68 |
| 175 | *THBD* | 6.61 | 4.16 | 2.91 | 1.35 |
| 176 | *CDC42EP5* | 6.61 | 4.01 | 4.96 | 2.36 |
| 177 | *FOXQ1* | 6.59 | 5.21 | 9.51 | 4.25 |
| 178 | *MMEL1* | 6.59 | 3.84 | 6.20 | 2.77 |
| 179 | *HES2* | 6.57 | 5.92 | 8.22 | 3.95 |
| 180 | *OSR1* | 6.57 | 5.14 | 4.65 | 1.85 |
| 181 | *OVOL2* | 6.56 | 6.03 | 5.27 | 2.42 |
| 182 | *PAPLN* | 6.54 | 4.26 | 2.32 | 2.05 |
| 183 | *DUSP8* | 6.54 | 3.94 | 4.88 | 3.76 |
| 184 | *PTRF* | 6.52 | 5.00 | 5.68 | 3.08 |
| 185 | *FAM20A* | 6.52 | 4.04 | 2.38 | 1.17 |
| 186 | *SLC16A6* | 6.52 | 4.04 | 2.38 | 1.17 |
| 187 | *WIPI1* | 6.52 | 4.04 | 2.38 | 1.17 |
| 188 | *MAF* | 6.50 | 4.97 | 5.02 | 2.05 |
| 189 | *PPP1R1A* | 6.49 | 2.81 | 4.18 | 1.79 |
| 190 | *NEUROD2* | 6.48 | 6.45 | 9.43 | 6.29 |
| 191 | *TMPRSS2* | 6.48 | 3.55 | 3.37 | 1.59 |
| 192 | *TTLL10* | 6.47 | 6.57 | 5.85 | 2.62 |
| 193 | *WNT7B* | 6.44 | 5.34 | 7.47 | 4.23 |
| 194 | *AIRE* | 6.43 | 3.55 | 3.17 | 1.71 |
| 195 | *GSC* | 6.41 | 5.81 | 4.98 | 2.56 |
| 196 | *GRTP1* | 6.41 | 4.26 | 1.07 | 1.05 |
| 197 | *GALP* | 6.41 | 3.38 | 1.58 | 0.80 |
| 198 | *RIPK3* | 6.41 | 3.10 | 4.32 | 1.61 |
| 199 | *SOX3* | 6.40 | 8.83 | 5.20 | 3.18 |
| 200 | *ATP10A* | 6.40 | 3.81 | 4.31 | 1.60 |
| 201 | *MT1G* | 6.39 | 4.21 | 5.74 | 1.97 |
| 202 | *DLX4* | 6.36 | 5.43 | 6.21 | 2.61 |
| 203 | *CYP46A1* | 6.34 | 3.15 | 1.88 | 1.36 |
| 204 | *VGLL2* | 6.33 | 3.82 | 2.52 | 0.79 |
| 205 | *PRRX1* | 6.31 | 4.22 | 4.27 | 2.41 |
| 206 | *TPSG1* | 6.30 | 6.75 | 1.40 | 1.86 |
| 207 | *MSLN* | 6.29 | 3.72 | 4.73 | 1.72 |
| 208 | *FAM83H* | 6.27 | 4.72 | 3.78 | 2.36 |
| 209 | *PTHLH* | 6.26 | 3.05 | 3.36 | 1.70 |
| 210 | *IQGAP2* | 6.26 | 2.35 | 1.57 | 1.14 |
| 211 | *KRT5* | 6.23 | 2.70 | 3.45 | 1.32 |
| 212 | *RDH8* | 6.22 | 3.64 | 4.38 | 1.51 |
| 213 | *GABRD* | 6.21 | 5.45 | 10.95 | 4.40 |
| 214 | *ADAMTS8* | 6.21 | 2.99 | 2.36 | 1.41 |
| 215 | *GNGT2* | 6.21 | 2.88 | 5.79 | 2.46 |
| 216 | *NEUROG3* | 6.19 | 5.08 | 6.91 | 3.22 |
| 217 | *MAD2L2* | 6.19 | 4.14 | 2.27 | 1.69 |
| 218 | *ADRA1A* | 6.19 | 3.94 | 1.36 | 1.02 |
| 219 | *MRGPRX4* | 6.19 | 2.14 | 2.39 | 1.19 |
| 220 | *FOXE1* | 6.18 | 5.03 | 2.84 | 1.13 |
| 221 | *USP51* | 6.18 | 2.16 | 0.65 | 1.07 |
| 222 | *TREML4* | 6.18 | 2.07 | 3.65 | 1.34 |
| 223 | *CALCR* | 6.17 | 3.34 | 1.40 | 1.26 |
| 224 | *SYCN* | 6.17 | 3.24 | 3.65 | 1.42 |
| 225 | *SLC26A1* | 6.17 | 3.20 | 3.33 | 1.69 |

| # | Gene | **Kelly rel AUC H3K27me3 (ranking score)** | Kelly rel AUC EZH2 | LAN-1 rel AUC H3K27me3 | LAN-1 rel AUC EZH2 |
|---|---|---|---|---|---|
| 226 | *NKX3-1* | 6.16 | 3.10 | 1.01 | 1.02 |
| 227 | *TKTL1* | 6.15 | 2.87 | 0.73 | 0.89 |
| 228 | *RASSF7* | 6.14 | 5.55 | 4.68 | 2.50 |
| 229 | *NR2E1* | 6.13 | 6.13 | 5.08 | 2.45 |
| 230 | *MUC2* | 6.12 | 4.58 | 6.64 | 2.27 |
| 231 | *KLK10* | 6.11 | 3.60 | 4.32 | 2.03 |
| 232 | *VDR* | 6.11 | 2.20 | 2.91 | 0.93 |
| 233 | *DRD4* | 6.10 | 6.02 | 0.59 | 1.38 |
| 234 | *PAX8* | 6.10 | 3.72 | 3.18 | 1.67 |
| 235 | *MUC6* | 6.09 | 3.96 | 5.90 | 2.84 |
| 236 | *DNMT3L* | 6.09 | 2.83 | 3.11 | 1.37 |
| 237 | *HCK* | 6.08 | 3.02 | 2.75 | 1.07 |
| 238 | *GRIN3B* | 6.07 | 4.78 | 3.06 | 1.61 |
| 239 | *IL22RA1* | 6.07 | 2.28 | 5.40 | 2.15 |
| 240 | *NRGN* | 6.06 | 2.96 | 1.91 | 1.41 |
| 241 | *FOXC2* | 6.05 | 6.81 | 5.54 | 2.35 |
| 242 | *KCNT1* | 6.05 | 3.46 | 10.73 | 4.40 |
| 243 | *LOC442028* | 6.04 | 2.60 | 2.38 | 0.71 |
| 244 | *PIGR* | 6.04 | 1.89 | 4.93 | 2.24 |
| 245 | *OTP* | 6.02 | 6.02 | 5.32 | 2.48 |
| 246 | *GPR50* | 6.02 | 4.12 | 1.29 | 1.03 |
| 247 | *NPTX1* | 6.01 | 5.89 | 10.93 | 6.66 |
| 248 | *SLC5A5* | 6.01 | 3.41 | 2.28 | 1.18 |
| 249 | *ATP12A* | 6.00 | 3.00 | 4.69 | 1.84 |
| 250 | *NHSL1* | 6.00 | 2.73 | 0.37 | 0.62 |
| 251 | *ATP8A2* | 5.99 | 4.45 | 8.23 | 3.18 |
| 252 | *CACNG6* | 5.99 | 3.51 | 4.15 | 2.53 |
| 253 | *CYP2A6* | 5.99 | 2.37 | 3.32 | 1.17 |
| 254 | *TMCO4* | 5.98 | 3.40 | 3.77 | 1.55 |
| 255 | *LONRF3* | 5.97 | 4.63 | 3.04 | 1.59 |
| 256 | *PRSS22* | 5.97 | 3.21 | 4.53 | 2.05 |
| 257 | *GADD45B* | 5.96 | 4.21 | 1.37 | 1.07 |
| 258 | *COL5A3* | 5.96 | 3.34 | 4.81 | 1.64 |
| 259 | *ACRC* | 5.96 | 2.52 | 0.65 | 0.78 |
| 260 | *GJB1* | 5.96 | 2.52 | 0.65 | 0.78 |
| 261 | *ITGB1BP2* | 5.96 | 2.52 | 0.65 | 0.78 |
| 262 | *TAF1* | 5.96 | 2.52 | 0.65 | 0.78 |
| 263 | *OGT* | 5.96 | 2.52 | 0.65 | 0.78 |
| 264 | *NONO* | 5.96 | 2.52 | 0.65 | 0.78 |
| 265 | *MMP25* | 5.95 | 5.18 | 4.96 | 2.74 |
| 266 | *FFAR2* | 5.95 | 2.78 | 3.73 | 1.54 |
| 267 | *PPP2R2C* | 5.93 | 3.92 | 5.46 | 2.43 |
| 268 | *RREB1* | 5.92 | 6.63 | 4.45 | 2.33 |
| 269 | *NPR3* | 5.92 | 4.26 | 1.06 | 0.93 |
| 270 | *UST* | 5.92 | 3.76 | 1.41 | 0.81 |
| 271 | *ACOXL* | 5.92 | 3.76 | 2.77 | 0.93 |
| 272 | *FAM43B* | 5.90 | 4.30 | 0.40 | 1.22 |
| 273 | *SFRP2* | 5.90 | 3.67 | 2.08 | 1.48 |
| 274 | *NTN1* | 5.89 | 5.78 | 5.38 | 2.09 |
| 275 | *PIK3CD* | 5.87 | 4.10 | 3.01 | 1.51 |
| 276 | *CNR2* | 5.87 | 2.51 | 2.82 | 1.72 |
| 277 | *LMX1A* | 5.86 | 6.17 | 4.89 | 2.23 |
| 278 | *GRP* | 5.86 | 2.30 | 1.71 | 1.67 |
| 279 | *CACNG2* | 5.84 | 4.11 | 4.34 | 1.57 |
| 280 | *TFAP2A* | 5.83 | 5.75 | 6.21 | 3.45 |
| 281 | *PFKFB3* | 5.83 | 4.16 | 0.87 | 1.59 |
| 282 | *RGL3* | 5.83 | 4.12 | 2.51 | 1.67 |
| 283 | *MLXIPL* | 5.83 | 3.15 | 4.13 | 1.48 |
| 284 | *SIM1* | 5.82 | 5.01 | 3.10 | 1.34 |
| 285 | *HEY2* | 5.81 | 4.48 | 3.64 | 1.68 |
| 286 | *LHX4* | 5.80 | 6.22 | 3.66 | 2.08 |
| 287 | *FAM3B* | 5.79 | 2.98 | 6.64 | 2.49 |
| 288 | *DSP* | 5.78 | 5.53 | 5.91 | 3.27 |
| 289 | *TMEM30B* | 5.78 | 2.95 | 1.56 | 1.22 |
| 290 | *FXYD7* | 5.78 | 2.91 | 2.45 | 1.18 |
| 291 | *TCP10L* | 5.77 | 3.71 | 2.67 | 1.50 |
| 292 | *IL1RL2* | 5.76 | 3.12 | 2.57 | 1.04 |
| 293 | *NOTCH2* | 5.74 | 3.51 | 2.46 | 1.69 |
| 294 | *KLK11* | 5.74 | 2.36 | 5.36 | 2.24 |
| 295 | *CST9* | 5.74 | 2.16 | 2.68 | 1.15 |
| 296 | *BARHL1* | 5.73 | 5.38 | 8.60 | 5.29 |
| 297 | *ATP8B1* | 5.73 | 3.09 | 1.58 | 0.91 |
| 298 | *NOTCH1* | 5.72 | 7.30 | 11.09 | 5.71 |
| 299 | *CACNA1E* | 5.71 | 3.86 | 4.82 | 1.82 |
| 300 | *NR5A2* | 5.71 | 3.14 | 3.98 | 1.94 |

**Supplemental Table 3. (C)** Custom neuroblastoma PRC2 signature consisting of the top 300 EZH2 ChIP-seq target genes in LAN-1 cells.

| # | Gene | **LAN-1 rel AUC EZH2 (ranking score)** | LAN-1 rel AUC H3K27me3 | Kelly rel AUC EZH2 | Kelly rel AUC H3K27me3 |
|---|---|---|---|---|---|
| 1 | *CDX2* | 11.43 | 19.24 | 6.12 | 5.20 |
| 2 | *PAX2* | 9.27 | 11.36 | 18.04 | 13.13 |
| 3 | *PRDM16* | 8.90 | 15.23 | 8.72 | 7.89 |
| 4 | *HOXB8* | 8.66 | 12.41 | 10.05 | 7.42 |
| 5 | *NFATC1* | 8.52 | 11.65 | 32.51 | 23.21 |
| 6 | *TMEM132E* | 7.84 | 13.22 | 0.94 | 0.27 |
| 7 | *HOXB7* | 7.55 | 12.16 | 8.92 | 7.41 |
| 8 | *EBF3* | 7.49 | 11.34 | 3.11 | 4.15 |
| 9 | *LMX1B* | 6.93 | 9.23 | 12.23 | 10.09 |
| 10 | *HOXC9* | 6.85 | 10.57 | 0.95 | 0.63 |
| 11 | *SERPINA2* | 6.66 | 16.44 | 1.36 | 4.41 |
| 12 | *MN1* | 6.66 | 12.22 | 9.51 | 7.56 |
| 13 | *NPTX1* | 6.66 | 10.93 | 5.89 | 6.01 |
| 14 | *PDGFA* | 6.60 | 9.41 | 17.82 | 12.54 |
| 15 | *EN2* | 6.53 | 9.53 | 12.41 | 10.34 |
| 16 | *SP8* | 6.33 | 11.39 | 4.90 | 5.50 |
| 17 | *ZIC2* | 6.31 | 9.76 | 11.22 | 7.69 |
| 18 | *NEUROD2* | 6.29 | 9.43 | 6.45 | 6.48 |
| 19 | *IRX4* | 6.13 | 10.81 | 7.61 | 8.30 |
| 20 | *PAX7* | 5.88 | 8.93 | 8.40 | 7.11 |
| 21 | *NOTCH1* | 5.71 | 11.09 | 7.30 | 5.72 |
| 22 | *SOX8* | 5.57 | 11.05 | 16.45 | 12.54 |
| 23 | *FOXF1* | 5.56 | 8.73 | 12.13 | 7.53 |
| 24 | *EMX1* | 5.55 | 8.53 | 9.97 | 8.39 |
| 25 | *PRDM12* | 5.55 | 6.50 | 15.81 | 8.51 |
| 26 | *KLK12* | 5.50 | 12.51 | 2.39 | 5.49 |
| 27 | *VENTX* | 5.50 | 11.58 | 8.56 | 8.51 |
| 28 | *INHBB* | 5.49 | 8.34 | 6.99 | 7.35 |
| 29 | *TBX1* | 5.43 | 9.21 | 7.40 | 7.56 |
| 30 | *ZNF469* | 5.42 | 12.27 | 1.07 | 0.75 |
| 31 | *HOXC10* | 5.37 | 10.33 | 4.28 | 5.17 |
| 32 | *FIBCD1* | 5.36 | 11.43 | 6.78 | 9.20 |
| 33 | *BARHL1* | 5.29 | 8.60 | 5.38 | 5.73 |
| 34 | *LBX1* | 5.29 | 8.45 | 17.76 | 10.41 |
| 35 | *LHX1* | 5.24 | 7.60 | 7.46 | 8.95 |
| 36 | *LHX5* | 5.23 | 7.65 | 12.77 | 10.54 |
| 37 | *NKX2-2* | 5.16 | 9.46 | 9.70 | 7.01 |
| 38 | *NKX2-3* | 5.10 | 9.02 | 8.14 | 7.07 |
| 39 | *CDH4* | 4.99 | 8.46 | 1.37 | 1.04 |
| 40 | *GATA5* | 4.87 | 9.10 | 8.28 | 7.51 |
| 41 | *PDGFB* | 4.84 | 7.90 | 3.69 | 3.76 |
| 42 | *GATA6* | 4.69 | 8.26 | 9.63 | 7.77 |
| 43 | *HOXA11* | 4.68 | 9.05 | 7.81 | 8.34 |
| 44 | *HOXB9* | 4.66 | 8.97 | 7.13 | 7.04 |
| 45 | *HOXC12* | 4.52 | 7.43 | 12.26 | 10.61 |
| 46 | *HOXB6* | 4.51 | 9.53 | 6.94 | 7.83 |
| 47 | *HOXB5* | 4.51 | 9.53 | 6.94 | 7.83 |
| 48 | *CBX4* | 4.50 | 5.24 | 3.71 | 2.98 |
| 49 | *SHH* | 4.44 | 7.17 | 7.02 | 7.95 |
| 50 | *CLCNKB* | 4.41 | 9.42 | 0.70 | 0.23 |
| 51 | *GABRD* | 4.40 | 10.95 | 5.45 | 6.21 |
| 52 | *KCNT1* | 4.40 | 10.73 | 3.46 | 6.05 |
| 53 | *OLIG2* | 4.33 | 8.13 | 10.30 | 9.01 |
| 54 | *GRIK3* | 4.31 | 6.58 | 0.86 | 0.34 |
| 55 | *FOXF2* | 4.29 | 6.86 | 12.04 | 7.84 |
| 56 | *TTYH1* | 4.27 | 8.53 | 2.97 | 5.03 |
| 57 | *KIAA0125* | 4.26 | 10.03 | 1.67 | 0.97 |
| 58 | *HIC1* | 4.26 | 5.13 | 3.00 | 3.96 |
| 59 | *FOXQ1* | 4.25 | 9.51 | 5.21 | 6.59 |
| 60 | *NUDT14* | 4.23 | 10.15 | 1.52 | 1.97 |
| 61 | *WNT7B* | 4.23 | 7.47 | 5.34 | 6.44 |
| 62 | *FOXL2* | 4.23 | 6.50 | 12.53 | 10.62 |
| 63 | *CDH15* | 4.22 | 10.54 | 2.88 | 4.81 |
| 64 | *EBF2* | 4.17 | 8.26 | 7.34 | 8.07 |
| 65 | *PKNOX2* | 4.16 | 9.10 | 1.40 | 0.92 |
| 66 | *PAX9* | 4.15 | 6.77 | 5.67 | 5.27 |
| 67 | *CBFA2T3* | 4.14 | 10.05 | 6.95 | 8.67 |
| 68 | *FOXD3* | 4.14 | 7.56 | 4.75 | 5.43 |
| 69 | *MADCAM1* | 4.13 | 6.45 | 3.64 | 4.11 |
| 70 | *WNT1* | 4.12 | 8.96 | 4.54 | 5.06 |
| 71 | *SOHLH1* | 4.08 | 9.91 | 3.47 | 5.48 |
| 72 | *HOXB13* | 4.07 | 8.80 | 3.97 | 5.13 |
| 73 | *SLC9A3* | 4.05 | 8.47 | 3.60 | 4.52 |

| # | Gene | **LAN-1 rel AUC EZH2 (ranking score)** | LAN-1 rel AUC H3K27me3 | Kelly rel AUC EZH2 | Kelly rel AUC H3K27me3 |
|---|---|---|---|---|---|
| 74 | *BAHCC1* | 4.02 | 6.37 | 1.20 | 0.39 |
| 75 | *SOX18* | 3.98 | 7.65 | 3.42 | 2.69 |
| 76 | *HES2* | 3.95 | 8.22 | 5.92 | 6.57 |
| 77 | *CYP26B1* | 3.95 | 6.69 | 3.22 | 3.81 |
| 78 | *COL18A1* | 3.94 | 7.79 | 2.07 | 1.54 |
| 79 | *FGF3* | 3.92 | 7.28 | 5.14 | 4.72 |
| 80 | *AJAP1* | 3.91 | 8.24 | 6.22 | 8.11 |
| 81 | *ZIC5* | 3.91 | 7.16 | 8.54 | 7.21 |
| 82 | *KLHDC7A* | 3.86 | 8.71 | 0.70 | 0.22 |
| 83 | *MUC5B* | 3.85 | 9.44 | 6.04 | 8.93 |
| 84 | *HOXA2* | 3.84 | 7.46 | 4.68 | 4.71 |
| 85 | *HMX2* | 3.79 | 6.95 | 5.22 | 6.65 |
| 86 | *LHX3* | 3.77 | 4.98 | 5.22 | 3.61 |
| 87 | *DUSP8* | 3.76 | 4.88 | 3.94 | 6.54 |
| 88 | *KCNK9* | 3.72 | 5.60 | 2.69 | 2.66 |
| 89 | *SDK2* | 3.70 | 8.36 | 1.35 | 1.34 |
| 90 | *CDKN1C* | 3.70 | 6.60 | 2.03 | 2.21 |
| 91 | *WIZ* | 3.69 | 2.08 | 1.31 | 1.50 |
| 92 | *RUNX1* | 3.67 | 7.49 | 1.90 | 4.04 |
| 93 | *POU3F3* | 3.63 | 7.20 | 3.82 | 3.87 |
| 94 | *PAX1* | 3.62 | 7.48 | 4.29 | 5.65 |
| 95 | *IRS4* | 3.62 | 6.51 | 3.31 | 4.81 |
| 96 | *MAGEA11* | 3.60 | 6.89 | 0.81 | 2.18 |
| 97 | *ICOSLG* | 3.57 | 8.03 | 4.74 | 4.56 |
| 98 | *DAAM2* | 3.54 | 7.98 | 0.83 | 0.71 |
| 99 | *IRX2* | 3.54 | 6.33 | 10.20 | 7.85 |
| 100 | *SIM2* | 3.54 | 5.86 | 8.78 | 6.87 |
| 101 | *IRX1* | 3.52 | 7.59 | 11.30 | 7.80 |
| 102 | *BARX2* | 3.52 | 5.40 | 6.94 | 6.93 |
| 103 | *ARC* | 3.51 | 8.25 | 1.24 | 0.13 |
| 104 | *FEZF2* | 3.51 | 6.40 | 4.82 | 5.55 |
| 105 | *ITGB2* | 3.50 | 8.17 | 5.47 | 8.13 |
| 106 | *ITPR3* | 3.49 | 7.83 | 2.61 | 3.90 |
| 107 | *SORCS3* | 3.49 | 6.60 | 12.35 | 11.54 |
| 108 | *COL13A1* | 3.48 | 8.46 | 0.94 | 1.39 |
| 109 | *ALX4* | 3.48 | 7.03 | 8.59 | 8.11 |
| 110 | *NCKIPSD* | 3.48 | 1.68 | 0.84 | 0.17 |
| 111 | *JAG2* | 3.47 | 9.45 | 0.98 | 0.22 |
| 112 | *TAL1* | 3.46 | 6.49 | 3.62 | 3.44 |
| 113 | *TFAP2A* | 3.45 | 6.21 | 5.75 | 5.83 |
| 114 | *COMP* | 3.43 | 5.72 | 6.40 | 7.23 |
| 115 | *TPPP* | 3.41 | 1.49 | 1.85 | 0.43 |
| 116 | *DMRT3* | 3.36 | 8.10 | 6.77 | 7.01 |
| 117 | *GATA4* | 3.35 | 5.17 | 12.04 | 10.44 |
| 118 | *HSPB7* | 3.34 | 7.55 | 0.90 | 0.42 |
| 119 | *PAX3* | 3.34 | 6.17 | 6.23 | 6.80 |
| 120 | *FLT1* | 3.33 | 7.03 | 3.55 | 4.22 |
| 121 | *NKX6-1* | 3.32 | 7.17 | 1.21 | 0.79 |
| 122 | *MYO5B* | 3.30 | 7.61 | 4.14 | 7.40 |
| 123 | *PRKCZ* | 3.29 | 7.65 | 5.89 | 7.47 |
| 124 | *NTF3* | 3.29 | 7.23 | 2.45 | 3.69 |
| 125 | *TLX1* | 3.29 | 6.68 | 6.43 | 6.76 |
| 126 | *EVX1* | 3.28 | 7.78 | 10.74 | 9.50 |
| 127 | *DSP* | 3.27 | 5.91 | 5.53 | 5.78 |
| 128 | *HBM* | 3.26 | 8.62 | 3.86 | 6.74 |
| 129 | *HOXC11* | 3.26 | 5.74 | 5.67 | 5.50 |
| 130 | *NEUROG3* | 3.22 | 6.91 | 5.08 | 6.19 |
| 131 | *VMO1* | 3.22 | 4.75 | 2.37 | 4.02 |
| 132 | *ACTRT2* | 3.21 | 9.03 | 2.88 | 5.14 |
| 133 | *CHST1* | 3.21 | 7.33 | 0.91 | 0.97 |
| 134 | *ADSSL1* | 3.21 | 2.44 | 3.61 | 1.87 |
| 135 | *EN1* | 3.19 | 6.39 | 5.94 | 5.66 |
| 136 | *ATP8A2* | 3.18 | 8.23 | 4.45 | 5.99 |
| 137 | *PLCH2* | 3.18 | 7.48 | 1.10 | 0.36 |
| 138 | *CABP7* | 3.18 | 6.08 | 2.10 | 1.80 |
| 139 | *NETO1* | 3.18 | 5.92 | 0.89 | 0.41 |
| 140 | *SOX3* | 3.18 | 5.20 | 8.83 | 6.40 |
| 141 | *SLC22A18* | 3.16 | 4.51 | 2.09 | 2.20 |
| 142 | *ZMYND15* | 3.15 | 7.36 | 6.18 | 9.62 |
| 143 | *CXCL16* | 3.15 | 7.32 | 6.44 | 10.12 |
| 144 | *NTNG2* | 3.14 | 7.77 | 1.11 | 1.01 |
| 145 | *TBX15* | 3.14 | 6.40 | 10.94 | 8.77 |
| 146 | *DLX3* | 3.13 | 6.67 | 3.88 | 5.68 |
| 147 | *SFMBT2* | 3.11 | 6.59 | 3.10 | 4.49 |
| 148 | *GPR101* | 3.11 | 6.05 | 3.80 | 5.63 |
| 149 | *LSP1* | 3.10 | 7.06 | 0.65 | 0.21 |

| # | Gene | **LAN-1 rel AUC EZH2 (ranking score)** | LAN-1 rel AUC H3K27me3 | Kelly rel AUC EZH2 | Kelly rel AUC H3K27me3 |
|---|---|---|---|---|---|
| 150 | *TBX5* | 3.10 | 6.09 | 4.26 | 4.34 |
| 151 | *GPR123* | 3.10 | 5.83 | 7.18 | 8.41 |
| 152 | *NEU2* | 3.09 | 6.82 | 1.62 | 3.26 |
| 153 | *HOXA6* | 3.08 | 6.71 | 8.04 | 7.37 |
| 154 | *HOXA5* | 3.08 | 6.71 | 8.04 | 7.37 |
| 155 | *HOXA7* | 3.08 | 6.71 | 8.04 | 7.37 |
| 156 | *GALNT9* | 3.08 | 6.61 | 3.46 | 4.51 |
| 157 | *PTRF* | 3.08 | 5.68 | 5.00 | 6.52 |
| 158 | *LHX2* | 3.08 | 5.21 | 9.36 | 8.05 |
| 159 | *KRT35* | 3.07 | 7.05 | 0.73 | 0.34 |
| 160 | *METRNL* | 3.07 | 3.89 | 2.09 | 2.00 |
| 161 | *NKX2-8* | 3.05 | 7.71 | 7.59 | 7.92 |
| 162 | *EMX2OS* | 3.05 | 5.72 | 5.41 | 5.62 |
| 163 | *COL20A1* | 3.05 | 5.48 | 1.85 | 2.35 |
| 164 | *NKX2-5* | 3.05 | 5.01 | 8.84 | 7.82 |
| 165 | *BCL11B* | 3.03 | 5.57 | 1.42 | 1.16 |
| 166 | *GLI3* | 3.02 | 7.17 | 4.06 | 5.52 |
| 167 | *HOXC8* | 3.01 | 6.43 | 0.95 | 0.26 |
| 168 | *FSCN2* | 3.00 | 6.90 | 2.77 | 3.40 |
| 169 | *TNNI2* | 2.99 | 7.27 | 2.36 | 1.00 |
| 170 | *ESPN* | 2.99 | 6.65 | 6.37 | 7.44 |
| 171 | *CYP24A1* | 2.99 | 6.11 | 1.88 | 3.55 |
| 172 | *FLT4* | 2.97 | 7.02 | 9.28 | 12.36 |
| 173 | *KCNK16* | 2.96 | 7.11 | 0.73 | 0.78 |
| 174 | *APOC3* | 2.96 | 1.32 | 0.96 | 0.28 |
| 175 | *HOXB4* | 2.95 | 5.82 | 6.61 | 7.13 |
| 176 | *ZFYVE28* | 2.95 | 5.62 | 3.56 | 9.01 |
| 177 | *LOC284930* | 2.95 | 4.89 | 0.72 | 1.15 |
| 178 | *FOXP2* | 2.95 | 4.56 | 6.49 | 6.79 |
| 179 | *CPNE9* | 2.95 | 2.12 | 1.30 | 1.15 |
| 180 | *CEACAM21* | 2.94 | 9.33 | 1.97 | 4.36 |
| 181 | *EGFL7* | 2.92 | 8.03 | 1.54 | 1.27 |
| 182 | *CD300C* | 2.91 | 6.96 | 0.75 | 0.43 |
| 183 | *GPC4* | 2.91 | 6.04 | 5.77 | 7.36 |
| 184 | *KIR2DS4* | 2.91 | 4.54 | 2.15 | 5.14 |
| 185 | *PACS2* | 2.91 | 2.02 | 1.30 | 0.54 |
| 186 | *BTBD6* | 2.91 | 2.02 | 1.30 | 0.54 |
| 187 | *KNDC1* | 2.90 | 8.44 | 3.05 | 5.69 |
| 188 | *VGF* | 2.90 | 2.66 | 1.05 | 1.14 |
| 189 | *SMAD7* | 2.90 | 0.95 | 1.07 | 0.35 |
| 190 | *SLC22A18AS* | 2.89 | 6.41 | 3.98 | 3.26 |
| 191 | *WNT10A* | 2.89 | 6.38 | 1.07 | 0.70 |
| 192 | *OTOS* | 2.89 | 5.40 | 2.41 | 4.28 |
| 193 | *TNFRSF18* | 2.88 | 7.59 | 8.31 | 10.59 |
| 194 | *OLIG3* | 2.88 | 7.35 | 5.62 | 5.29 |
| 195 | *BMP6* | 2.88 | 5.72 | 4.46 | 5.44 |
| 196 | *GDF10* | 2.86 | 6.87 | 0.79 | 0.79 |
| 197 | *LIF* | 2.85 | 7.74 | 0.72 | 0.41 |
| 198 | *AGPAT2* | 2.85 | 6.53 | 1.13 | 0.50 |
| 199 | *COL15A1* | 2.85 | 5.76 | 2.44 | 4.27 |
| 200 | *ABTB1* | 2.85 | 1.98 | 0.75 | 0.29 |
| 201 | *MUC6* | 2.84 | 5.90 | 3.96 | 6.09 |
| 202 | *ST14* | 2.83 | 1.00 | 2.46 | 2.72 |
| 203 | *HOXB3* | 2.82 | 6.31 | 4.42 | 5.69 |
| 204 | *HOXB2* | 2.82 | 6.31 | 4.42 | 5.69 |
| 205 | *KLF2* | 2.82 | 5.26 | 7.66 | 8.67 |
| 206 | *FLNA* | 2.82 | 1.97 | 1.35 | 1.06 |
| 207 | *FMNL1* | 2.81 | 6.76 | 1.41 | 1.73 |
| 208 | *SLC8A3* | 2.81 | 6.54 | 1.01 | 0.60 |
| 209 | *CDH22* | 2.81 | 6.11 | 1.12 | 1.10 |
| 210 | *OTX2* | 2.81 | 5.81 | 9.36 | 8.40 |
| 211 | *SIGLEC9* | 2.80 | 8.14 | 2.31 | 5.12 |
| 212 | *EPHA2* | 2.80 | 6.86 | 0.79 | 0.52 |
| 213 | *HOXA10* | 2.80 | 6.33 | 5.39 | 6.64 |
| 214 | *GPRC5C* | 2.80 | 6.11 | 1.17 | 0.57 |
| 215 | *HMHA1* | 2.80 | 5.96 | 4.01 | 5.16 |
| 216 | *PMF1* | 2.80 | 2.26 | 2.07 | 0.69 |
| 217 | *GAD2* | 2.79 | 6.86 | 6.23 | 7.11 |
| 218 | *RASSF5* | 2.79 | 6.59 | 1.98 | 3.13 |
| 219 | *SOX14* | 2.79 | 5.51 | 8.04 | 8.74 |
| 220 | *KCNAB2* | 2.79 | 1.19 | 0.72 | 0.21 |
| 221 | *EPHA8* | 2.78 | 6.90 | 1.21 | 0.70 |
| 222 | *ETV4* | 2.78 | 6.68 | 1.63 | 2.51 |
| 223 | *WNT3* | 2.78 | 5.56 | 1.25 | 1.27 |
| 224 | *C1ORF159* | 2.78 | 4.50 | 3.32 | 3.10 |
| 225 | *CYP26A1* | 2.77 | 6.30 | 4.68 | 5.70 |

| # | Gene | **LAN-1 rel AUC EZH2 (ranking score)** | LAN-1 rel AUC H3K27me3 | Kelly rel AUC EZH2 | Kelly rel AUC H3K27me3 |
|---|---|---|---|---|---|
| 226 | *MMEL1* | 2.77 | 6.20 | 3.84 | 6.59 |
| 227 | *BAI1* | 2.77 | 6.02 | 0.95 | 0.19 |
| 228 | *C1ORF94* | 2.77 | 5.73 | 6.11 | 9.61 |
| 229 | *FGF9* | 2.77 | 5.51 | 0.84 | 0.90 |
| 230 | *KCND3* | 2.76 | 5.82 | 1.56 | 2.43 |
| 231 | *SLC24A3* | 2.76 | 5.65 | 2.61 | 4.32 |
| 232 | *CARD10* | 2.75 | 6.60 | 2.39 | 2.76 |
| 233 | *NOG* | 2.74 | 6.11 | 5.15 | 6.75 |
| 234 | *CSMD2* | 2.74 | 5.74 | 5.11 | 8.14 |
| 235 | *MMP25* | 2.74 | 4.96 | 5.18 | 5.95 |
| 236 | *NKD2* | 2.73 | 6.11 | 4.16 | 4.38 |
| 237 | *DSCAML1* | 2.71 | 6.18 | 1.50 | 1.98 |
| 238 | *BARX1* | 2.71 | 5.38 | 10.02 | 6.81 |
| 239 | *GPR26* | 2.71 | 5.19 | 0.80 | 0.66 |
| 240 | *FOXB1* | 2.70 | 6.34 | 8.04 | 8.62 |
| 241 | *ZBTB7A* | 2.70 | 2.30 | 1.43 | 1.72 |
| 242 | *MT1M* | 2.69 | 6.93 | 4.01 | 5.43 |
| 243 | *MSX1* | 2.69 | 4.67 | 6.42 | 6.87 |
| 244 | *LHX6* | 2.69 | 4.31 | 6.90 | 7.47 |
| 245 | *CLEC11A* | 2.69 | 3.76 | 1.25 | 0.13 |
| 246 | *LMO1* | 2.68 | 5.82 | 0.89 | 0.21 |
| 247 | *PITPNM3* | 2.68 | 5.61 | 0.99 | 1.85 |
| 248 | *FLI1* | 2.67 | 6.99 | 2.62 | 5.01 |
| 249 | *DMRT1* | 2.67 | 6.43 | 3.60 | 4.89 |
| 250 | *GALR2* | 2.67 | 5.49 | 3.28 | 3.12 |
| 251 | *TFAP2C* | 2.67 | 5.29 | 9.41 | 7.83 |
| 252 | *SLC30A2* | 2.67 | 5.27 | 2.89 | 4.33 |
| 253 | *HTR5A* | 2.66 | 6.35 | 2.50 | 5.16 |
| 254 | *SLC17A7* | 2.66 | 5.71 | 1.85 | 3.17 |
| 255 | *SIX1* | 2.66 | 4.73 | 5.40 | 7.25 |
| 256 | *NOTUM* | 2.66 | 3.60 | 3.52 | 2.86 |
| 257 | *CHST7* | 2.66 | 2.67 | 0.87 | 1.61 |
| 258 | *KCNG2* | 2.66 | 2.30 | 2.35 | 4.27 |
| 259 | *DGKG* | 2.65 | 5.88 | 1.93 | 3.38 |
| 260 | *GLIS3* | 2.65 | 5.03 | 3.37 | 3.31 |
| 261 | *NFIX* | 2.65 | 4.57 | 5.20 | 5.28 |
| 262 | *SP6* | 2.64 | 7.86 | 1.99 | 3.90 |
| 263 | *FZD10* | 2.64 | 6.25 | 5.72 | 6.68 |
| 264 | *WFDC1* | 2.63 | 7.14 | 3.00 | 5.52 |
| 265 | *ELN* | 2.63 | 5.82 | 1.24 | 0.37 |
| 266 | *HAMP* | 2.63 | 5.32 | 1.17 | 2.36 |
| 267 | *PTPRE* | 2.63 | 5.25 | 1.29 | 0.88 |
| 268 | *NR2F1* | 2.63 | 4.95 | 0.59 | 0.53 |
| 269 | *CORO2B* | 2.62 | 6.28 | 1.14 | 1.15 |
| 270 | *OVOL1* | 2.62 | 6.07 | 8.56 | 7.78 |
| 271 | *TTLL10* | 2.62 | 5.85 | 6.57 | 6.47 |
| 272 | *CACNA1A* | 2.62 | 5.81 | 2.94 | 4.23 |
| 273 | *PLXDC2* | 2.62 | 4.54 | 0.87 | 0.71 |
| 274 | *SOX13* | 2.61 | 6.43 | 3.72 | 4.80 |
| 275 | *DLX4* | 2.61 | 6.21 | 5.43 | 6.36 |
| 276 | *C3ORF22* | 2.61 | 2.67 | 0.84 | 0.64 |
| 277 | *MYH7* | 2.60 | 6.84 | 1.27 | 1.93 |
| 278 | *UMODL1* | 2.60 | 6.78 | 1.67 | 2.44 |
| 279 | *C21ORF128* | 2.60 | 6.78 | 1.67 | 2.44 |
| 280 | *CTSD* | 2.60 | 4.26 | 1.10 | 0.37 |
| 281 | *MAPK15* | 2.59 | 4.58 | 2.12 | 5.02 |
| 282 | *COL5A1* | 2.58 | 7.59 | 0.91 | 0.82 |
| 283 | *UNC93B1* | 2.58 | 5.95 | 1.59 | 1.65 |
| 284 | *CACNA1S* | 2.58 | 5.62 | 0.94 | 0.69 |
| 285 | *ARHGEF16* | 2.58 | 5.12 | 1.66 | 2.58 |
| 286 | *SLFN5* | 2.58 | 5.11 | 2.35 | 4.77 |
| 287 | *MAG* | 2.57 | 7.04 | 2.12 | 4.04 |
| 288 | *HOXA1* | 2.57 | 5.60 | 3.97 | 5.21 |
| 289 | *ETNK2* | 2.57 | 3.71 | 1.55 | 2.58 |
| 290 | *UTF1* | 2.56 | 6.89 | 7.39 | 8.17 |
| 291 | *GSC* | 2.56 | 4.98 | 5.81 | 6.41 |
| 292 | *HSPA12A* | 2.56 | 4.21 | 1.67 | 1.36 |
| 293 | *CALML6* | 2.56 | 3.44 | 1.51 | 2.85 |
| 294 | *SLC6A18* | 2.55 | 7.39 | 1.72 | 2.18 |
| 295 | *HOXD11* | 2.55 | 6.12 | 1.35 | 1.78 |
| 296 | *KRTAP5-9* | 2.55 | 3.65 | 0.94 | 2.50 |
| 297 | *ACHE* | 2.55 | 3.26 | 4.35 | 4.17 |
| 298 | *RILP* | 2.55 | 1.23 | 1.18 | 0.33 |
| 299 | *PFKP* | 2.54 | 4.24 | 1.24 | 1.55 |
| 300 | *HIPK4* | 2.54 | 2.56 | 1.11 | 2.34 |

**Supplemental Table 3. (D)** Custom neuroblastoma PRC2 signature consisting of the top 300 H3K27me3 ChIP-seq target genes in LAN-1 cells.

| # | Gene | **LAN-1 rel AUC H3K27me3 (ranking score)** | LAN-1 rel AUC EZH2 | Kelly rel AUC H3K27me3 | Kelly rel AUC EZH2 |
|---|---|---|---|---|---|
| 1 | *CDX2* | 19.24 | 11.43 | 5.20 | 6.12 |
| 2 | *SERPINA2* | 16.44 | 6.66 | 4.41 | 1.36 |
| 3 | *PRDM16* | 15.23 | 8.90 | 7.89 | 8.72 |
| 4 | *TMEM132E* | 13.22 | 7.84 | 0.27 | 0.94 |
| 5 | *KLK12* | 12.51 | 5.50 | 5.49 | 2.39 |
| 6 | *HOXB8* | 12.41 | 8.66 | 7.42 | 10.05 |
| 7 | *ZNF469* | 12.27 | 5.42 | 0.75 | 1.07 |
| 8 | *MN1* | 12.22 | 6.66 | 7.56 | 9.51 |
| 9 | *HOXB7* | 12.16 | 7.55 | 7.41 | 8.92 |
| 10 | *NFATC1* | 11.65 | 8.52 | 23.21 | 32.51 |
| 11 | *VENTX* | 11.58 | 5.50 | 8.51 | 8.56 |
| 12 | *FIBCD1* | 11.43 | 5.36 | 9.20 | 6.78 |
| 13 | *SP8* | 11.39 | 6.33 | 5.50 | 4.90 |
| 14 | *PAX2* | 11.36 | 9.27 | 13.13 | 18.04 |
| 15 | *EBF3* | 11.34 | 7.49 | 4.15 | 3.11 |
| 16 | *NOTCH1* | 11.09 | 5.71 | 5.72 | 7.30 |
| 17 | *SOX8* | 11.05 | 5.57 | 12.54 | 16.45 |
| 18 | *GABRD* | 10.95 | 4.40 | 6.21 | 5.45 |
| 19 | *NPTX1* | 10.93 | 6.66 | 6.01 | 5.89 |
| 20 | *IRX4* | 10.81 | 6.13 | 8.30 | 7.61 |
| 21 | *KCNT1* | 10.73 | 4.40 | 6.05 | 3.46 |
| 22 | *HOXC9* | 10.57 | 6.85 | 0.63 | 0.95 |
| 23 | *CDH15* | 10.54 | 4.22 | 4.81 | 2.88 |
| 24 | *HOXC10* | 10.33 | 5.37 | 5.17 | 4.28 |
| 25 | *NUDT14* | 10.15 | 4.23 | 1.97 | 1.52 |
| 26 | *CBFA2T3* | 10.05 | 4.14 | 8.67 | 6.95 |
| 27 | *KIAA0125* | 10.03 | 4.26 | 0.97 | 1.67 |
| 28 | *SOHLH1* | 9.91 | 4.08 | 5.48 | 3.47 |
| 29 | *ZIC2* | 9.76 | 6.31 | 7.69 | 11.22 |
| 30 | *EN2* | 9.53 | 6.53 | 10.34 | 12.41 |
| 31 | *HOXB6* | 9.53 | 4.51 | 7.83 | 6.94 |
| 32 | *HOXB5* | 9.53 | 4.51 | 7.83 | 6.94 |
| 33 | *FOXQ1* | 9.51 | 4.25 | 6.59 | 5.21 |
| 34 | *NKX2-2* | 9.46 | 5.16 | 7.01 | 9.70 |
| 35 | *JAG2* | 9.45 | 3.47 | 0.22 | 0.98 |
| 36 | *MUC5B* | 9.44 | 3.85 | 8.93 | 6.04 |
| 37 | *NEUROD2* | 9.43 | 6.29 | 6.48 | 6.45 |
| 38 | *CLCNKB* | 9.42 | 4.41 | 0.23 | 0.70 |
| 39 | *PDGFA* | 9.41 | 6.60 | 12.54 | 17.82 |
| 40 | *CEACAM21* | 9.33 | 2.94 | 4.36 | 1.97 |
| 41 | *LMX1B* | 9.23 | 6.93 | 10.09 | 12.23 |
| 42 | *TBX1* | 9.21 | 5.43 | 7.56 | 7.40 |
| 43 | *GATA5* | 9.10 | 4.87 | 7.51 | 8.28 |
| 44 | *PKNOX2* | 9.10 | 4.16 | 0.92 | 1.40 |
| 45 | *HOXA11* | 9.05 | 4.68 | 8.34 | 7.81 |
| 46 | *ACTRT2* | 9.03 | 3.21 | 5.14 | 2.88 |
| 47 | *NKX2-3* | 9.02 | 5.10 | 7.07 | 8.14 |
| 48 | *HOXB9* | 8.97 | 4.66 | 7.04 | 7.13 |
| 49 | *WNT1* | 8.96 | 4.12 | 5.06 | 4.54 |
| 50 | *PAX7* | 8.93 | 5.88 | 7.11 | 8.40 |
| 51 | *HOXB13* | 8.80 | 4.07 | 5.13 | 3.97 |
| 52 | *FOXF1* | 8.73 | 5.56 | 7.53 | 12.13 |
| 53 | *KLHDC7A* | 8.71 | 3.86 | 0.22 | 0.70 |
| 54 | *HBM* | 8.62 | 3.26 | 6.74 | 3.86 |
| 55 | *BARHL1* | 8.60 | 5.29 | 5.73 | 5.38 |
| 56 | *EMX1* | 8.53 | 5.55 | 8.39 | 9.97 |
| 57 | *TTYH1* | 8.53 | 4.27 | 5.03 | 2.97 |
| 58 | *SLC9A3* | 8.47 | 4.05 | 4.52 | 3.60 |
| 59 | *CDH4* | 8.46 | 4.99 | 1.04 | 1.37 |
| 60 | *COL13A1* | 8.46 | 3.48 | 1.39 | 0.94 |
| 61 | *LBX1* | 8.45 | 5.29 | 10.41 | 17.76 |
| 62 | *KNDC1* | 8.44 | 2.90 | 5.69 | 3.05 |
| 63 | *SDK2* | 8.36 | 3.70 | 1.34 | 1.35 |
| 64 | *INHBB* | 8.34 | 5.49 | 7.35 | 6.99 |
| 65 | *GATA6* | 8.26 | 4.69 | 7.77 | 9.63 |
| 66 | *EBF2* | 8.26 | 4.17 | 8.07 | 7.34 |
| 67 | *ARC* | 8.25 | 3.51 | 0.13 | 1.24 |
| 68 | *AJAP1* | 8.24 | 3.91 | 8.11 | 6.22 |
| 69 | *ATP8A2* | 8.23 | 3.18 | 5.99 | 4.45 |
| 70 | *HES2* | 8.22 | 3.95 | 6.57 | 5.92 |
| 71 | *ITGB2* | 8.17 | 3.50 | 8.13 | 5.47 |
| 72 | *SIGLEC9* | 8.14 | 2.80 | 5.12 | 2.31 |
| 73 | *OLIG2* | 8.13 | 4.33 | 9.01 | 10.30 |

| # | Gene | **LAN-1 rel AUC H3K27me3 (ranking score)** | LAN-1 rel AUC EZH2 | Kelly rel AUC H3K27me3 | Kelly rel AUC EZH2 |
|---|---|---|---|---|---|
| 74 | *DMRT3* | 8.10 | 3.36 | 7.01 | 6.77 |
| 75 | *ICOSLG* | 8.03 | 3.57 | 4.56 | 4.74 |
| 76 | *EGFL7* | 8.03 | 2.92 | 1.27 | 1.54 |
| 77 | *DAAM2* | 7.98 | 3.54 | 0.71 | 0.83 |
| 78 | *PDGFB* | 7.90 | 4.84 | 3.76 | 3.69 |
| 79 | *SP6* | 7.86 | 2.64 | 3.90 | 1.99 |
| 80 | *ITPR3* | 7.83 | 3.49 | 3.90 | 2.61 |
| 81 | *COL18A1* | 7.79 | 3.94 | 1.54 | 2.07 |
| 82 | *EVX1* | 7.78 | 3.28 | 9.50 | 10.74 |
| 83 | *NTNG2* | 7.77 | 3.14 | 1.01 | 1.11 |
| 84 | *LCN6* | 7.76 | 2.42 | 0.85 | 0.91 |
| 85 | *LIF* | 7.74 | 2.85 | 0.41 | 0.72 |
| 86 | *NKX2-8* | 7.71 | 3.05 | 7.92 | 7.59 |
| 87 | *LHX5* | 7.65 | 5.23 | 10.54 | 12.77 |
| 88 | *PRKCZ* | 7.65 | 3.29 | 7.47 | 5.89 |
| 89 | *SOX18* | 7.65 | 3.98 | 2.69 | 3.42 |
| 90 | *SLC38A3* | 7.64 | 2.47 | 0.65 | 0.87 |
| 91 | *MYO5B* | 7.61 | 3.30 | 7.40 | 4.14 |
| 92 | *LHX1* | 7.60 | 5.24 | 8.95 | 7.46 |
| 93 | *IRX1* | 7.59 | 3.52 | 7.80 | 11.30 |
| 94 | *TNFRSF18* | 7.59 | 2.88 | 10.59 | 8.31 |
| 95 | *COL5A1* | 7.59 | 2.58 | 0.82 | 0.91 |
| 96 | *FOXD3* | 7.56 | 4.14 | 5.43 | 4.75 |
| 97 | *HSPB7* | 7.55 | 3.34 | 0.42 | 0.90 |
| 98 | *RUNX1* | 7.49 | 3.67 | 4.04 | 1.90 |
| 99 | *PAX1* | 7.48 | 3.62 | 5.65 | 4.29 |
| 100 | *PLCH2* | 7.48 | 3.18 | 0.36 | 1.10 |
| 101 | *WNT7B* | 7.47 | 4.23 | 6.44 | 5.34 |
| 102 | *HOXA2* | 7.46 | 3.84 | 4.71 | 4.68 |
| 103 | *HOXC12* | 7.43 | 4.52 | 10.61 | 12.26 |
| 104 | *SLC6A18* | 7.39 | 2.55 | 2.18 | 1.72 |
| 105 | *ZMYND15* | 7.36 | 3.15 | 9.62 | 6.18 |
| 106 | *OLIG3* | 7.35 | 2.88 | 5.29 | 5.62 |
| 107 | *SLITRK2* | 7.34 | 2.35 | 7.13 | 4.48 |
| 108 | *C20ORF166* | 7.33 | 2.41 | 2.12 | 1.37 |
| 109 | *CHST1* | 7.33 | 3.21 | 0.97 | 0.91 |
| 110 | *CXCL16* | 7.32 | 3.15 | 10.12 | 6.44 |
| 111 | *FGF3* | 7.28 | 3.92 | 4.72 | 5.14 |
| 112 | *TNNI2* | 7.27 | 2.99 | 1.00 | 2.36 |
| 113 | *NTF3* | 7.23 | 3.29 | 3.69 | 2.45 |
| 114 | *POU3F3* | 7.20 | 3.63 | 3.87 | 3.82 |
| 115 | *SHH* | 7.17 | 4.44 | 7.95 | 7.02 |
| 116 | *GLI3* | 7.17 | 3.02 | 5.52 | 4.06 |
| 117 | *NKX6-1* | 7.17 | 3.32 | 0.79 | 1.21 |
| 118 | *ZIC5* | 7.16 | 3.91 | 7.21 | 8.54 |
| 119 | *WFDC1* | 7.14 | 2.63 | 5.52 | 3.00 |
| 120 | *KCNK16* | 7.11 | 2.96 | 0.78 | 0.73 |
| 121 | *KCNQ1OT1* | 7.07 | 2.47 | 0.38 | 0.56 |
| 122 | *LSP1* | 7.06 | 3.10 | 0.21 | 0.65 |
| 123 | *KRT35* | 7.05 | 3.07 | 0.34 | 0.73 |
| 124 | *MAG* | 7.04 | 2.57 | 4.04 | 2.12 |
| 125 | *ALX4* | 7.03 | 3.48 | 8.11 | 8.59 |
| 126 | *FLT1* | 7.03 | 3.33 | 4.22 | 3.55 |
| 127 | *FLT4* | 7.02 | 2.97 | 12.36 | 9.28 |
| 128 | *FLI1* | 6.99 | 2.67 | 5.01 | 2.62 |
| 129 | *CD300C* | 6.96 | 2.91 | 0.43 | 0.75 |
| 130 | *HMX2* | 6.95 | 3.79 | 6.65 | 5.22 |
| 131 | *MT1M* | 6.93 | 2.69 | 5.43 | 4.01 |
| 132 | *NEUROG3* | 6.91 | 3.22 | 6.19 | 5.08 |
| 133 | *FSCN2* | 6.90 | 3.00 | 3.40 | 2.77 |
| 134 | *EPHA8* | 6.90 | 2.78 | 0.70 | 1.21 |
| 135 | *UTF1* | 6.89 | 2.56 | 8.17 | 7.39 |
| 136 | *MAGEA11* | 6.89 | 3.60 | 2.18 | 0.81 |
| 137 | *HAS1* | 6.87 | 2.15 | 4.46 | 2.36 |
| 138 | *GDF10* | 6.87 | 2.86 | 0.79 | 0.79 |
| 139 | *FOXF2* | 6.86 | 4.29 | 7.84 | 12.04 |
| 140 | *GAD2* | 6.86 | 2.79 | 7.11 | 6.23 |
| 141 | *EPHA2* | 6.86 | 2.80 | 0.52 | 0.79 |
| 142 | *MYH7* | 6.84 | 2.60 | 1.93 | 1.27 |
| 143 | *NEU2* | 6.82 | 3.09 | 3.26 | 1.62 |
| 144 | *CYP11B2* | 6.78 | 2.34 | 5.59 | 2.82 |
| 145 | *UMODL1* | 6.78 | 2.60 | 2.44 | 1.67 |
| 146 | *C21ORF128* | 6.78 | 2.60 | 2.44 | 1.67 |
| 147 | *PAX9* | 6.77 | 4.15 | 5.27 | 5.67 |
| 148 | *FMNL1* | 6.76 | 2.81 | 1.73 | 1.41 |
| 149 | *CLEC10A* | 6.75 | 2.02 | 3.49 | 1.61 |

| # | Gene | **LAN-1 rel AUC H3K27me3 (ranking score)** | LAN-1 rel AUC EZH2 | Kelly rel AUC H3K27me3 | Kelly rel AUC EZH2 |
|---|---|---|---|---|---|
| 150 | *CHRNA4* | 6.72 | 2.30 | 3.34 | 1.93 |
| 151 | *HOXA6* | 6.71 | 3.08 | 7.37 | 8.04 |
| 152 | *HOXA5* | 6.71 | 3.08 | 7.37 | 8.04 |
| 153 | *HOXA7* | 6.71 | 3.08 | 7.37 | 8.04 |
| 154 | *CYP26B1* | 6.69 | 3.95 | 3.81 | 3.22 |
| 155 | *TLX1* | 6.68 | 3.29 | 6.76 | 6.43 |
| 156 | *ETV4* | 6.68 | 2.78 | 2.51 | 1.63 |
| 157 | *DLX3* | 6.67 | 3.13 | 5.68 | 3.88 |
| 158 | *ESPN* | 6.65 | 2.99 | 7.44 | 6.37 |
| 159 | *MUC2* | 6.64 | 2.27 | 6.12 | 4.58 |
| 160 | *FAM3B* | 6.64 | 2.49 | 5.79 | 2.98 |
| 161 | *GALNT9* | 6.61 | 3.08 | 4.51 | 3.46 |
| 162 | *CCRL2* | 6.61 | 2.24 | 3.25 | 1.39 |
| 163 | *SORCS3* | 6.60 | 3.49 | 11.54 | 12.35 |
| 164 | *CARD10* | 6.60 | 2.75 | 2.76 | 2.39 |
| 165 | *CDKN1C* | 6.60 | 3.70 | 2.21 | 2.03 |
| 166 | *LCN1* | 6.60 | 2.11 | 4.40 | 2.01 |
| 167 | *SFMBT2* | 6.59 | 3.11 | 4.49 | 3.10 |
| 168 | *RASSF5* | 6.59 | 2.79 | 3.13 | 1.98 |
| 169 | *LOC400043* | 6.58 | 2.43 | 0.44 | 1.04 |
| 170 | *GRIK3* | 6.58 | 4.31 | 0.34 | 0.86 |
| 171 | *HOXC5* | 6.56 | 2.26 | 0.32 | 0.71 |
| 172 | *HOXC4* | 6.56 | 2.26 | 0.32 | 0.71 |
| 173 | *HOXC6* | 6.56 | 2.26 | 0.32 | 0.71 |
| 174 | *SLC8A3* | 6.54 | 2.81 | 0.60 | 1.01 |
| 175 | *FGF17* | 6.54 | 2.24 | 0.91 | 0.72 |
| 176 | *AGPAT2* | 6.53 | 2.85 | 0.50 | 1.13 |
| 177 | *IRS4* | 6.51 | 3.62 | 4.81 | 3.31 |
| 178 | *PRDM12* | 6.50 | 5.55 | 8.51 | 15.81 |
| 179 | *FOXL2* | 6.50 | 4.23 | 10.62 | 12.53 |
| 180 | *TAL1* | 6.49 | 3.46 | 3.44 | 3.62 |
| 181 | *C9ORF62* | 6.46 | 2.36 | 0.45 | 0.88 |
| 182 | *MADCAM1* | 6.45 | 4.13 | 4.11 | 3.64 |
| 183 | *SOX13* | 6.43 | 2.61 | 4.80 | 3.72 |
| 184 | *DMRT1* | 6.43 | 2.67 | 4.89 | 3.60 |
| 185 | *HOXC8* | 6.43 | 3.01 | 0.26 | 0.95 |
| 186 | *SLC22A18AS* | 6.41 | 2.89 | 3.26 | 3.98 |
| 187 | *TBX15* | 6.40 | 3.14 | 8.77 | 10.94 |
| 188 | *FEZF2* | 6.40 | 3.51 | 5.55 | 4.82 |
| 189 | *EN1* | 6.39 | 3.19 | 5.66 | 5.94 |
| 190 | *IRF8* | 6.39 | 2.22 | 4.30 | 2.76 |
| 191 | *PDYN* | 6.39 | 2.31 | 3.77 | 1.50 |
| 192 | *BACE2* | 6.38 | 2.44 | 7.57 | 4.22 |
| 193 | *WNT10A* | 6.38 | 2.89 | 0.70 | 1.07 |
| 194 | *BAHCC1* | 6.37 | 4.02 | 0.39 | 1.20 |
| 195 | *HTR5A* | 6.35 | 2.66 | 5.16 | 2.50 |
| 196 | *FOXB1* | 6.34 | 2.70 | 8.62 | 8.04 |
| 197 | *FXYD5* | 6.34 | 2.32 | 5.54 | 2.79 |
| 198 | *IRX2* | 6.33 | 3.54 | 7.85 | 10.20 |
| 199 | *HOXA10* | 6.33 | 2.80 | 6.64 | 5.39 |
| 200 | *PTPN3* | 6.33 | 2.11 | 2.64 | 1.84 |
| 201 | *HOXB3* | 6.31 | 2.82 | 5.69 | 4.42 |
| 202 | *HOXB2* | 6.31 | 2.82 | 5.69 | 4.42 |
| 203 | *CYP26A1* | 6.30 | 2.77 | 5.70 | 4.68 |
| 204 | *CORO2B* | 6.28 | 2.62 | 1.15 | 1.14 |
| 205 | *FZD10* | 6.25 | 2.64 | 6.68 | 5.72 |
| 206 | *ZBTB7C* | 6.23 | 2.42 | 1.52 | 1.23 |
| 207 | *TFAP2A* | 6.21 | 3.45 | 5.83 | 5.75 |
| 208 | *DLX4* | 6.21 | 2.61 | 6.36 | 5.43 |
| 209 | *MMEL1* | 6.20 | 2.77 | 6.59 | 3.84 |
| 210 | *USH1G* | 6.20 | 2.34 | 5.69 | 3.56 |
| 211 | *KLK2* | 6.20 | 2.21 | 1.17 | 0.96 |
| 212 | *DSCAML1* | 6.18 | 2.71 | 1.98 | 1.50 |
| 213 | *PAX3* | 6.17 | 3.34 | 6.80 | 6.23 |
| 214 | *LOC200772* | 6.17 | 2.27 | 0.31 | 0.98 |
| 215 | *MUC12* | 6.14 | 2.52 | 4.14 | 2.05 |
| 216 | *HOXD11* | 6.12 | 2.55 | 1.78 | 1.35 |
| 217 | *HS3ST4* | 6.12 | 2.20 | 0.85 | 0.72 |
| 218 | *NOG* | 6.11 | 2.74 | 6.75 | 5.15 |
| 219 | *NKD2* | 6.11 | 2.73 | 4.38 | 4.16 |
| 220 | *CYP24A1* | 6.11 | 2.99 | 3.55 | 1.88 |
| 221 | *GPRC5C* | 6.11 | 2.80 | 0.57 | 1.17 |
| 222 | *CDH22* | 6.11 | 2.81 | 1.10 | 1.12 |
| 223 | *TBX5* | 6.09 | 3.10 | 4.34 | 4.26 |
| 224 | *CABP7* | 6.08 | 3.18 | 1.80 | 2.10 |
| 225 | *OVOL1* | 6.07 | 2.62 | 7.78 | 8.56 |

| # | Gene | **LAN-1 rel AUC H3K27me3 (ranking score)** | LAN-1 rel AUC EZH2 | Kelly rel AUC H3K27me3 | Kelly rel AUC EZH2 |
|---|---|---|---|---|---|
| 226 | *GPR101* | 6.05 | 3.11 | 5.63 | 3.80 |
| 227 | *GPC4* | 6.04 | 2.91 | 7.36 | 5.77 |
| 228 | *TFF1* | 6.04 | 2.04 | 2.34 | 1.07 |
| 229 | *BAI1* | 6.02 | 2.77 | 0.19 | 0.95 |
| 230 | *HMHA1* | 5.96 | 2.80 | 5.16 | 4.01 |
| 231 | *UNC93B1* | 5.95 | 2.58 | 1.65 | 1.59 |
| 232 | *PHLDA2* | 5.94 | 2.52 | 3.95 | 4.19 |
| 233 | *KLK13* | 5.93 | 2.22 | 4.58 | 1.73 |
| 234 | *ALOX15* | 5.92 | 2.49 | 4.49 | 2.82 |
| 235 | *NETO1* | 5.92 | 3.18 | 0.41 | 0.89 |
| 236 | *ATP2A3* | 5.91 | 2.13 | 7.38 | 5.66 |
| 237 | *DSP* | 5.91 | 3.27 | 5.78 | 5.53 |
| 238 | *MUC6* | 5.90 | 2.84 | 6.09 | 3.96 |
| 239 | *PVALB* | 5.90 | 2.48 | 7.10 | 3.03 |
| 240 | *DGKG* | 5.88 | 2.65 | 3.38 | 1.93 |
| 241 | *SIM2* | 5.86 | 3.54 | 6.87 | 8.78 |
| 242 | *TTLL10* | 5.85 | 2.62 | 6.47 | 6.57 |
| 243 | *RIPK4* | 5.85 | 2.22 | 7.77 | 4.51 |
| 244 | *CD22* | 5.84 | 2.25 | 3.73 | 1.32 |
| 245 | *FLJ12825* | 5.84 | 2.06 | 0.25 | 0.72 |
| 246 | *GPR123* | 5.83 | 3.10 | 8.41 | 7.18 |
| 247 | *HOXB4* | 5.82 | 2.95 | 7.13 | 6.61 |
| 248 | *KCND3* | 5.82 | 2.76 | 2.43 | 1.56 |
| 249 | *ELN* | 5.82 | 2.63 | 0.37 | 1.24 |
| 250 | *GPR20* | 5.82 | 2.14 | 0.38 | 0.94 |
| 251 | *LMO1* | 5.82 | 2.68 | 0.21 | 0.89 |
| 252 | *OTX2* | 5.81 | 2.81 | 8.40 | 9.36 |
| 253 | *CACNA1A* | 5.81 | 2.62 | 4.23 | 2.94 |
| 254 | *GNGT2* | 5.79 | 2.46 | 6.21 | 2.88 |
| 255 | *CCK* | 5.78 | 2.17 | 3.85 | 2.80 |
| 256 | *SLC13A5* | 5.77 | 2.14 | 3.32 | 1.53 |
| 257 | *TINAGL1* | 5.77 | 2.35 | 0.37 | 1.12 |
| 258 | *COL15A1* | 5.76 | 2.85 | 4.27 | 2.44 |
| 259 | *HOXC11* | 5.74 | 3.26 | 5.50 | 5.67 |
| 260 | *CSMD2* | 5.74 | 2.74 | 8.14 | 5.11 |
| 261 | *MT1G* | 5.74 | 1.97 | 6.39 | 4.21 |
| 262 | *FGF4* | 5.74 | 2.42 | 2.80 | 2.60 |
| 263 | *TMPRSS6* | 5.74 | 1.90 | 0.61 | 0.79 |
| 264 | *C1ORF94* | 5.73 | 2.77 | 9.61 | 6.11 |
| 265 | *COMP* | 5.72 | 3.43 | 7.23 | 6.40 |
| 266 | *EMX2OS* | 5.72 | 3.05 | 5.62 | 5.41 |
| 267 | *BMP6* | 5.72 | 2.88 | 5.44 | 4.46 |
| 268 | *ZIC3* | 5.72 | 2.21 | 0.69 | 0.94 |
| 269 | *SLC22A3* | 5.71 | 2.35 | 4.41 | 3.49 |
| 270 | *LOC284379* | 5.71 | 1.53 | 8.07 | 2.84 |
| 271 | *SLC17A7* | 5.71 | 2.66 | 3.17 | 1.85 |
| 272 | *SIRPA* | 5.71 | 2.36 | 0.42 | 0.89 |
| 273 | *CLDN9* | 5.69 | 2.33 | 3.95 | 1.90 |
| 274 | *PTRF* | 5.68 | 3.08 | 6.52 | 5.00 |
| 275 | *WNT2* | 5.67 | 2.48 | 5.52 | 3.24 |
| 276 | *SLC24A3* | 5.65 | 2.76 | 4.32 | 2.61 |
| 277 | *KCNJ5* | 5.63 | 2.30 | 0.42 | 0.74 |
| 278 | *ZFYVE28* | 5.62 | 2.95 | 9.01 | 3.56 |
| 279 | *CACNA1S* | 5.62 | 2.58 | 0.69 | 0.94 |
| 280 | *KRT13* | 5.62 | 1.92 | 0.34 | 0.76 |
| 281 | *ALPI* | 5.61 | 2.07 | 2.78 | 1.31 |
| 282 | *PITPNM3* | 5.61 | 2.68 | 1.85 | 0.99 |
| 283 | *HOXA1* | 5.60 | 2.57 | 5.21 | 3.97 |
| 284 | *VSX1* | 5.60 | 2.45 | 3.81 | 2.71 |
| 285 | *KCNK9* | 5.60 | 3.72 | 2.66 | 2.69 |
| 286 | *FGF6* | 5.57 | 1.75 | 4.21 | 1.76 |
| 287 | *BCL11B* | 5.57 | 3.03 | 1.16 | 1.42 |
| 288 | *CACNA2D3* | 5.57 | 2.50 | 0.46 | 0.73 |
| 289 | *SKAP1* | 5.56 | 1.62 | 4.00 | 1.77 |
| 290 | *WNT3* | 5.56 | 2.78 | 1.27 | 1.25 |
| 291 | *CYP11B1* | 5.55 | 1.96 | 3.05 | 1.57 |
| 292 | *CACNA2D2* | 5.55 | 2.45 | 0.68 | 1.10 |
| 293 | *TMEM115* | 5.55 | 2.45 | 0.68 | 1.10 |
| 294 | *FOXC2* | 5.54 | 2.35 | 6.05 | 6.81 |
| 295 | *SMOC2* | 5.53 | 2.27 | 3.88 | 2.31 |
| 296 | *ITGB4* | 5.52 | 2.05 | 8.19 | 4.94 |
| 297 | *SOX14* | 5.51 | 2.79 | 8.74 | 8.04 |
| 298 | *BTBD11* | 5.51 | 2.41 | 4.06 | 2.31 |
| 299 | *PPP1R1B* | 5.51 | 2.36 | 3.32 | 2.09 |
| 300 | *FGF9* | 5.51 | 2.77 | 0.90 | 0.84 |

**Supplemental Table 4.** Top 60 significant GSEA hits for EZH2 and H3K27me3 ChIP-seq target genes in Kelly and LAN-1 cells using the MSigDB v5.1 c5 collection of 25 Gene Ontology (GO) gene sets related to biological processes. For each gene set hit the table shows if the gene set is related to any of the 15 Neural Development signatures available in the MSigDB c5 collection (1= yes, 0=no), the size of the gene set, the GSEA normalized enrichment score (NES), *P* and false discovery rate (FDR). The significance cut-offs were 0.05 for *P* and 0.25 for FDR. The top 60 gene set hits are ranked in decreasing order based on the NES.

**(A)** Top 60 GSEA hits for EZH2 ChIP-seq target genes in Kelly cells. Neural Development related gene sets are significantly over-represented in the collection of GSEA hits (odds-ratios = 51.03, $P < 0.001$, according to the two-tailed Fisher exact test).

| Rank | Gene Set | Neural Development | Size | NES | *P* | FDR |
|---|---|---|---|---|---|---|
| 1 | NEURON_DIFFERENTIATION | 1 | 70 | 1.82 | 0.0000 | 0.1167 |
| 2 | GENERATION_OF_NEURONS | 1 | 76 | 1.76 | 0.0000 | 0.1721 |
| 3 | NEURON_DEVELOPMENT | 1 | 57 | 1.75 | 0.0000 | 0.1206 |
| 4 | AXONOGENESIS | 1 | 40 | 1.75 | 0.0013 | 0.0918 |
| 5 | AXON_GUIDANCE | 1 | 20 | 1.75 | 0.0014 | 0.0754 |
| 6 | NEUROGENESIS | 1 | 85 | 1.70 | 0.0000 | 0.1267 |
| 7 | POSITIVE_REGULATION_OF_CELL_DIFFERENTIATION | 0 | 20 | 1.68 | 0.0042 | 0.1369 |
| 8 | NEURITE_DEVELOPMENT | 1 | 49 | 1.67 | 0.0013 | 0.1495 |
| 9 | CELLULAR_MORPHOGENESIS_DURING_DIFFERENTIATION | 0 | 46 | 1.66 | 0.0000 | 0.1403 |
| 10 | HEART_DEVELOPMENT | 0 | 32 | 1.66 | 0.0068 | 0.1326 |
| 11 | REGULATION_OF_BODY_FLUID_LEVELS | 0 | 38 | 1.62 | 0.0066 | 0.2159 |
| 12 | NERVOUS_SYSTEM_DEVELOPMENT | 0 | 348 | 1.58 | 0.0000 | 0.3089 |
| 13 | REGULATION_OF_ANATOMICAL_STRUCTURE_MORPHOGENESIS | 0 | 24 | 1.57 | 0.0182 | 0.3008 |
| 15 | CELL_CELL_SIGNALING | 0 | 292 | 1.51 | 0.0010 | 0.4733 |
| 16 | REGULATION_OF_CELL_DIFFERENTIATION | 0 | 48 | 1.51 | 0.0183 | 0.4455 |
| 17 | ANATOMICAL_STRUCTURE_MORPHOGENESIS | 0 | 302 | 1.51 | 0.0000 | 0.4273 |
| 18 | EXTRACELLULAR_STRUCTURE_ORGANIZATION_AND_BIOGENESIS | 0 | 30 | 1.50 | 0.0240 | 0.4442 |
| 20 | B_CELL_ACTIVATION | 0 | 16 | 1.47 | 0.0476 | 0.5145 |
| 21 | BLOOD_COAGULATION | 0 | 28 | 1.47 | 0.0418 | 0.5062 |
| 22 | ANATOMICAL_STRUCTURE_DEVELOPMENT | 0 | 829 | 1.47 | 0.0000 | 0.4952 |
| 23 | BRAIN_DEVELOPMENT | 1 | 45 | 1.46 | 0.0393 | 0.4949 |
| 24 | SYSTEM_DEVELOPMENT | 0 | 706 | 1.45 | 0.0000 | 0.5227 |
| 25 | CENTRAL_NERVOUS_SYSTEM_DEVELOPMENT | 0 | 107 | 1.45 | 0.0151 | 0.5296 |
| 26 | TISSUE_DEVELOPMENT | 0 | 93 | 1.44 | 0.0233 | 0.5109 |
| 27 | PROTEIN_OLIGOMERIZATION | 0 | 32 | 1.44 | 0.0501 | 0.5167 |
| 28 | REGULATION_OF_ACTION_POTENTIAL | 0 | 16 | 1.43 | 0.0603 | 0.5252 |
| 29 | TUBE_DEVELOPMENT | 0 | 15 | 1.43 | 0.0755 | 0.5241 |
| 30 | COAGULATION | 0 | 29 | 1.43 | 0.0510 | 0.5125 |
| 31 | HUMORAL_IMMUNE_RESPONSE | 0 | 19 | 1.43 | 0.0801 | 0.4969 |
| 32 | SULFUR_COMPOUND_BIOSYNTHETIC_PROCESS | 0 | 18 | 1.43 | 0.0508 | 0.4868 |
| 33 | REGULATION_OF_HEART_CONTRACTION | 0 | 21 | 1.42 | 0.0655 | 0.4787 |
| 34 | CELL_CELL_ADHESION | 0 | 64 | 1.42 | 0.0369 | 0.4749 |
| 35 | ADENYLATE_CYCLASE_ACTIVATION | 0 | 15 | 1.42 | 0.0854 | 0.4786 |
| 36 | MULTICELLULAR_ORGANISMAL_DEVELOPMENT | 0 | 857 | 1.42 | 0.0000 | 0.4744 |
| 37 | PROTEOGLYCAN_METABOLIC_PROCESS | 0 | 19 | 1.41 | 0.0922 | 0.4960 |
| 38 | SKELETAL_DEVELOPMENT | 0 | 83 | 1.40 | 0.0244 | 0.5066 |
| 39 | EMBRYONIC_DEVELOPMENT | 0 | 46 | 1.40 | 0.0459 | 0.5057 |
| 40 | SYNAPTIC_TRANSMISSION | 0 | 144 | 1.39 | 0.0209 | 0.5058 |
| 41 | G_PROTEIN_SIGNALING_ADENYLATE_CYCLASE_ACTIVATING_PATHWAY | 0 | 17 | 1.39 | 0.0938 | 0.4999 |
| 42 | POTASSIUM_ION_TRANSPORT | 0 | 49 | 1.39 | 0.0462 | 0.5050 |
| 43 | TRANSMISSION_OF_NERVE_IMPULSE | 0 | 158 | 1.38 | 0.0132 | 0.5073 |
| 44 | ORGAN_DEVELOPMENT | 0 | 445 | 1.38 | 0.0000 | 0.4994 |
| 45 | RESPONSE_TO_EXTERNAL_STIMULUS | 0 | 202 | 1.38 | 0.0075 | 0.5024 |
| 46 | REGULATION_OF_RAS_PROTEIN_SIGNAL_TRANSDUCTION | 0 | 17 | 1.38 | 0.0844 | 0.4986 |
| 47 | RECEPTOR_MEDIATED_ENDOCYTOSIS | 0 | 30 | 1.38 | 0.0727 | 0.4887 |
| 48 | POSITIVE_REGULATION_OF_RESPONSE_TO_STIMULUS | 0 | 28 | 1.38 | 0.0856 | 0.4850 |
| 49 | ANION_TRANSPORT | 0 | 22 | 1.37 | 0.0924 | 0.4845 |
| 50 | SYNAPSE_ORGANIZATION_AND_BIOGENESIS | 0 | 22 | 1.37 | 0.0952 | 0.4949 |
| 51 | ACTIN_POLYMERIZATION_AND_OR_DEPOLYMERIZATION | 0 | 22 | 1.35 | 0.1029 | 0.5372 |
| 53 | CELL_MIGRATION | 0 | 78 | 1.35 | 0.0585 | 0.5391 |
| 54 | PROTEIN_POLYMERIZATION | 0 | 18 | 1.34 | 0.1196 | 0.5672 |
| 55 | NEUROLOGICAL_SYSTEM_PROCESS | 1 | 293 | 1.33 | 0.0125 | 0.5795 |
| 56 | MESODERM_DEVELOPMENT | 0 | 15 | 1.33 | 0.1245 | 0.5707 |
| 57 | EMBRYONIC_MORPHOGENESIS | 0 | 15 | 1.33 | 0.1393 | 0.5658 |
| 58 | METAL_ION_TRANSPORT | 0 | 98 | 1.33 | 0.0596 | 0.5590 |
| 59 | CATION_TRANSPORT | 0 | 121 | 1.33 | 0.0454 | 0.5527 |
| 60 | HEMOSTASIS | 0 | 32 | 1.33 | 0.1148 | 0.5495 |
| 61 | MEISSNER_NPC_HCP_WITH_H3K4ME3_AND_H3K27ME3 | 1 | 139 | 2.21 | 0.0000 | 0.0242 |
| 62 | YAO_TEMPORAL_RESPONSE_TO_PROGESTERONE_CLUSTER_4 | 0 | 15 | 2.20 | 0.0000 | 0.0286 |
| 63 | MEISSNER_NPC_HCP_WITH_H3_UNMETHYLATED | 1 | 505 | 2.19 | 0.0000 | 0.0301 |

**Supplemental Table 4. (B)** Top 60 GSEA hits for EZH2 ChIP-seq target genes in LAN-1 cells. Neural Development related gene sets are significantly over-represented in the collection of GSEA hits (odds-ratios = 39.73, $P < 0.001$, according to the two-tailed Fisher exact test).

| Rank | Gene Set | Neural Development | Size | NES | *P* | FDR |
|---|---|---|---|---|---|---|
| 1 | SKELETAL_DEVELOPMENT | 0 | 83 | 1.87 | 0.0000 | 0.1256 |
| 2 | ION_TRANSPORT | 0 | 150 | 1.82 | 0.0000 | 0.1276 |
| 3 | ANION_TRANSPORT | 0 | 22 | 1.81 | 0.0017 | 0.0899 |
| 4 | NEURON_DIFFERENTIATION | 1 | 70 | 1.78 | 0.0000 | 0.1125 |
| 5 | GENERATION_OF_NEURONS | 1 | 76 | 1.77 | 0.0000 | 0.1053 |
| 6 | SYSTEM_DEVELOPMENT | 0 | 706 | 1.76 | 0.0000 | 0.0948 |
| 7 | MONOVALENT_INORGANIC_CATION_TRANSPORT | 0 | 78 | 1.75 | 0.0000 | 0.0878 |
| 8 | NEURON_DEVELOPMENT | 1 | 57 | 1.73 | 0.0000 | 0.1125 |
| 9 | POTASSIUM_ION_TRANSPORT | 0 | 49 | 1.72 | 0.0016 | 0.1116 |
| 10 | ANATOMICAL_STRUCTURE_DEVELOPMENT | 0 | 829 | 1.72 | 0.0000 | 0.1019 |
| 11 | NEURITE_DEVELOPMENT | 1 | 49 | 1.71 | 0.0000 | 0.0936 |
| 12 | REGULATION_OF_HEART_CONTRACTION | 0 | 21 | 1.71 | 0.0072 | 0.0942 |
| 13 | ORGAN_DEVELOPMENT | 0 | 445 | 1.71 | 0.0000 | 0.0876 |
| 14 | MULTICELLULAR_ORGANISMAL_DEVELOPMENT | 0 | 857 | 1.70 | 0.0000 | 0.0860 |
| 15 | NERVOUS_SYSTEM_DEVELOPMENT | 0 | 348 | 1.70 | 0.0000 | 0.0852 |
| 16 | LIPID_TRANSPORT | 0 | 21 | 1.69 | 0.0114 | 0.0836 |
| 17 | METAL_ION_TRANSPORT | 0 | 98 | 1.64 | 0.0015 | 0.1565 |
| 18 | CATION_TRANSPORT | 0 | 121 | 1.61 | 0.0029 | 0.2012 |
| 19 | NEUROGENESIS | 1 | 85 | 1.60 | 0.0015 | 0.2087 |
| 20 | ECTODERM_DEVELOPMENT | 0 | 54 | 1.59 | 0.0093 | 0.2001 |
| 21 | MUSCLE_DEVELOPMENT | 0 | 83 | 1.59 | 0.0031 | 0.2038 |
| 22 | EPIDERMIS_DEVELOPMENT | 0 | 47 | 1.55 | 0.0227 | 0.2680 |
| 23 | SYSTEM_PROCESS | 0 | 440 | 1.55 | 0.0000 | 0.2598 |
| 24 | HUMORAL_IMMUNE_RESPONSE | 0 | 19 | 1.55 | 0.0297 | 0.2621 |
| 25 | CELLULAR_MORPHOGENESIS_DURING_DIFFERENTIATION | 0 | 46 | 1.54 | 0.0182 | 0.2590 |
| 26 | RESPONSE_TO_EXTERNAL_STIMULUS | 0 | 202 | 1.52 | 0.0027 | 0.2952 |
| 27 | AXONOGENESIS | 1 | 40 | 1.51 | 0.0190 | 0.3104 |
| 28 | INSULIN_RECEPTOR_SIGNALING_PATHWAY | 0 | 18 | 1.51 | 0.0374 | 0.3019 |
| 29 | TRANSMEMBRANE_RECEPTOR_PROTEIN_TYROSINE_KINASE_SIGN | 0 | 74 | 1.51 | 0.0201 | 0.3050 |
| 30 | CELL_CELL_SIGNALING | 0 | 292 | 1.50 | 0.0013 | 0.3118 |
| 31 | NEUROLOGICAL_SYSTEM_PROCESS | 1 | 293 | 1.50 | 0.0000 | 0.3042 |
| 32 | ORGAN_MORPHOGENESIS | 0 | 112 | 1.49 | 0.0124 | 0.3167 |
| 33 | ANATOMICAL_STRUCTURE_MORPHOGENESIS | 0 | 302 | 1.49 | 0.0013 | 0.3083 |
| 34 | TISSUE_DEVELOPMENT | 0 | 93 | 1.48 | 0.0118 | 0.3359 |
| 35 | WOUND_HEALING | 0 | 36 | 1.47 | 0.0378 | 0.3569 |
| 36 | RESPONSE_TO_NUTRIENT | 0 | 16 | 1.46 | 0.0673 | 0.3492 |
| 37 | PROTEOGLYCAN_METABOLIC_PROCESS | 0 | 19 | 1.46 | 0.0506 | 0.3408 |
| 38 | REGULATION_OF_G_PROTEIN_COUPLED_RECEPTOR_PROTEIN_SIG | 0 | 22 | 1.46 | 0.0565 | 0.3467 |
| 39 | SULFUR_METABOLIC_PROCESS | 0 | 36 | 1.46 | 0.0571 | 0.3412 |
| 40 | RESPONSE_TO_CHEMICAL_STIMULUS | 0 | 232 | 1.46 | 0.0054 | 0.3336 |
| 41 | SYNAPTIC_TRANSMISSION | 0 | 144 | 1.45 | 0.0099 | 0.3425 |
| 42 | HEART_DEVELOPMENT | 0 | 32 | 1.45 | 0.0570 | 0.3401 |
| 43 | BLOOD_COAGULATION | 0 | 28 | 1.45 | 0.0600 | 0.3365 |
| 44 | DEVELOPMENTAL_MATURATION | 0 | 16 | 1.44 | 0.0584 | 0.3450 |
| 45 | PATTERN_SPECIFICATION_PROCESS | 0 | 25 | 1.43 | 0.0637 | 0.3595 |
| 46 | CELL_SURFACE_RECEPTOR_LINKED_SIGNAL_TRANSDUCTION_GO | 0 | 481 | 1.42 | 0.0000 | 0.3716 |
| 47 | TRANSMISSION_OF_NERVE_IMPULSE | 0 | 158 | 1.41 | 0.0240 | 0.3921 |
| 48 | SYNAPTOGENESIS | 0 | 18 | 1.41 | 0.0829 | 0.4007 |
| 49 | PROTEIN_AMINO_ACID_DEPHOSPHORYLATION | 0 | 59 | 1.41 | 0.0579 | 0.3940 |
| 50 | EXOCYTOSIS | 0 | 20 | 1.40 | 0.0786 | 0.3917 |
| 51 | G_PROTEIN_COUPLED_RECEPTOR_PROTEIN_SIGNALING_PATHWA | 0 | 238 | 1.40 | 0.0067 | 0.3917 |
| 52 | RESPONSE_TO_EXTRACELLULAR_STIMULUS | 0 | 30 | 1.40 | 0.0759 | 0.3890 |
| 53 | RESPONSE_TO_WOUNDING | 0 | 116 | 1.39 | 0.0377 | 0.4037 |
| 54 | DEPHOSPHORYLATION | 0 | 66 | 1.39 | 0.0402 | 0.3965 |
| 55 | SODIUM_ION_TRANSPORT | 0 | 16 | 1.38 | 0.0904 | 0.4093 |
| 56 | STEROID_METABOLIC_PROCESS | 0 | 48 | 1.38 | 0.0648 | 0.4057 |
| 57 | NEGATIVE_REGULATION_OF_MAP_KINASE_ACTIVITY | 0 | 16 | 1.38 | 0.1082 | 0.4007 |
| 58 | COAGULATION | 0 | 29 | 1.38 | 0.0935 | 0.3954 |
| 59 | HEMOSTASIS | 0 | 32 | 1.37 | 0.0880 | 0.4081 |
| 60 | SENSORY_PERCEPTION | 0 | 135 | 1.37 | 0.0188 | 0.4154 |

**Supplemental Table 5.** The shRNA sequences and the CRISPR-Cas9 sgRNA sequences targeting *MYCN* and *EZH2* that were used in this study.

| # | Designation | Clone ID | Clone Name | Target Sequence |
|---|---|---|---|---|
| 1 | shNT | | | CCTAAGGTTAAGTCGCCCTCGC |
| 2 | sh*LUC* | | | CTTCGAAATGTCCGTTCGGTT |
| 3 | sh*MYCN*1 | TRCN0000020694 | NM_005378.3-2000s1c1 | GCCAGTATTAGACTGGAAGTT |
| 4 | sh*MYCN*3 | TRCN0000020696 | NM_005378.3-230s1c1 | CGGACGAAGATGACTTCTACT |
| 5 | sh*MYCN*5 | TRCN0000020698 | NM_005378.3-919s1c1 | CTGAGCGATTCAGATGATGAA |
| 6 | sh*EZH2*-4 | TRCN0000040073 | NM_004456.3-2582s1c1 | CGGAAATCTTAAACCAAGAAT |
| 7 | sh*EZH2*-5 | TRCN0000040076 | NM_004456.3-324s1c1 | TATTGCCTTCTCACCAGCTGC |
| 8 | sgNT | | | TAGCGAACGTGTCCGGCGT |
| 9 | sg*EZH2*-1 | | | TTATCAGAAGGAAATTTCCG |
| 10 | sg*EZH2*-2 | | | TTATGATGGGAAAGTACACG |
| 11 | sg*EZH2*-3 | | | AGAAGGGACCAGTTTGTTGG |
| 12 | sg*EZH2*-4 | | | CTGCTGCTCTCACCGCTGAG |