**SUPPLEMENTARY FIGURE LEGENDS**

**Figure S1. Dendrogram and probability values for hierarchical clustering of 105 neuroblastomas based on genome-wide DNA methylation.**

Red values at each knot represent approximately unbiased p-values (x100) from multiscale bootstrap resampling. Cluster p-values indicate how strong the respective cluster is supported by data. Based on hierarchical clustering with average linkage and non-centralized correlation distance function using the 1,000 most variable probes.

**Figure S2.** **Genome-wide DNA methylation patterns in neuroblastomas are associated with patient outcome.**

Kaplan-Meier estimates of overall survival for DNA methylation subgroup 2s versus the remaining cluster 2 patients and cluster 1 patients. Based on hierarchical clustering with average linkage and non-centralized correlation distance function using the 1,000 most variable probes.

**Figure S3. Genes whose hypermethylation and downregulation are associated with neuroblastoma high-risk disease (HyperDownHR) are induced during neuronal differentiation of neuroblastoma cells.**

Time-dependent mean fold induction of 341 HyperDownHR genes in differentiating Be(2)-C cells after all-trans retinoic acid (ATRA) treatment. Time points were 6h, 12h, 24h, 48h, 96h and 144h. Expression was measured using 44k arrays. Reference for fold induction was solvent (ethanol) control at the respective time points.

**Figure S4. Examples for genes whose hypermethylation and downregulation are associated with neuroblastoma high-risk disease (HyperDownHR) and that are marked by both H3K27me3 and DNA methylation at putative regulatory regions in Be(2)-C cells.**

Gene locus plots show input normalized H3K27me3, H3K4me3, H3K27ac and H3K4me1 ChIP-seq profiles, putative Be(2)-C enhancers (defined in Materials and Methods) and DNA methylation levels at 450k methylation array probes as represented with the color scale depicted. H3K27me3 coverage is associated with promoter methylation of **(A)** *HENMT1* and intragenic enhancer methylation of **(B)** *SPOCK2* and **(C)** *SLC18A2*.

**Figure S5. MYCN deregulation is associated with activation of PRC2 components.**

**(A)** Hierarchical clustering of 498 neuroblastomas by average linkage and Euclidian distance function based on expression of PRC2 core component encoding genes (RNA-seq, z-scores). MYCN status is indicated for each sample (red: MYCN-amplified, green: MYCN-nonamplified, white: unknown). Expression levels of individual genes are represented with the color scale depicted. Average PRC2 component expression is represented by a red-white-blue scale with red indicating highest and blue lowest expression. **(B)** Expression of the PRC2 core component encoding genes *RBBP7*, *EZH2*, and *EED* in 493 primary neuroblastomas dependent on *MYCN* status (RNA-seq). P-values were calculated by ANOVA tests. **(C)** Expression of the PRC2 core component encoding genes *RBBP7*, *EZH2*, and *EED* in synchronized *MYCN-*amplified IMR5-75 cells with and without shRNA-mediated MYCN knockdown (MYCN high vs. MYCN low). The predominant cell cycle phase after thymidine block release is given. Arrows depict diverging predominant cell cycle phases in MYCN high vs. MYCN low. Adjusted p-values were calculated by likelihood ratio test.

**Figure S6. Genes whose hypermethylation and downregulation are associated with high-risk disease (HyperDownHR) are H3K27me3-marked in a MYCN-dependent fashion.**

Composite H3K27me3 profile of HyperDownHR genes vs. genome-wide gene-associated H3K27me3 occupancy in *MYCN*-amplified IMR5-75 cells with and without shRNA-mediated MYCN knockdown (MYCN high vs. MYCN low) with respect to transcription start site (TSS) and transcription termination site (TTS).

**Figure S7. Example for genes whose hypermethylation and downregulation are associated with neuroblastoma high-risk disease (HyperDownHR) that significantly lost H3K27me3 and DNA methylation at putative regulatory regions upon treatment with DAC and EPZ-6438 in Be(2)-C cells.**

Gene locus plot for *DPP6*, which is significantly induced upon DAC/EPZ-6438 combination treatment (p=0.025). Input normalized H3K27me3 ChIP-seq profiles, putative Be(2)-C enhancers (defined in Materials and Methods) and DNA methylation levels at 450k methylation array probes as represented with the color scale are depicted. Only 450k methylation array probes representing differential methylation are shown.

**Figure S8. Genes whose hypermethylation and downregulation are associated with high-risk disease (HyperDownHR) are preferentially induced upon DAC/TSA treatment.** **(bottom)** graphical representation of moderated t-statistics for differential gene expression upon DAC / trichostatin A (TSA) treatment across 17 neuroblastoma cell lines (Duijkers et al., 2013). Positive values indicate induction upon treatment, negative values indicate repression. Black lines indicate moderated t-statistics for HyperDownHR genes within the range of moderated t-statistics for all genes represented on the array (grey). **(top)** Smoothed local frequency graph illustrating enrichment of the HyperDownHR gene set among DAC/TSA-induced genes (camera procedure: p=0.039). For moderated t-statistics of individual genes see Table S8.