**SUPPLEMENTARY MATERIALS AND METHODS**

*Array-based gene expression profiling*

Sample homogenization in the FastPrep FP120 cell disruptor (Qbiogene, Carlsbad, CA, USA) was followed by total RNA isolation using TRIzol (Invitrogen, Karlsruhe, Germany). RNA integrity was assessed using the 2100 Bioanalyzer (Agilent Technologies, Palo Alto, CA, USA) and only samples with an integrity number >7.5 were further processed. Single-color gene expression profiles were generated as described ([1](#_ENREF_1)) using customized 4 x 44K oligonucleotide microarrays (Agilent Technologies) including all probes represented on the Agilent Whole Human Genome Oligo Microarray complemented with probes from a V2.0 2 x 11K customized microarray ([2](#_ENREF_2)). Labeling and hybridization was performed following the manufacturer’s protocol and data were background corrected using normexp method saddle-point approximation to maximum likelihood ([3](#_ENREF_3)) and normalized using the quantile algorithm from limma ([4](#_ENREF_4)).

*DNA methylation profiling*

DNA was isolated from snap-frozen neuroblastoma tissue. Genome-wide DNA methylation was assessed using the Infinium HumanMethylation450 (450k) BeadChip (Illumina) according to manufacturer’s instructions. Analyses did not include data from probes if (i) the proportion of non-detectable beta values was >0.3 (n=379), (ii) a single nucleotide polymorphism at/near the targeted CpG site was detected according to R-Forge package IMA (<https://rforge.net/IMA/> )   (n=92,600), (iii) probes were controls (n=65) or (iv) probes mapped to the X or Y chromosome (n=10,351). Data from a total of 382,182 probes were kept for further analyses. The k-nearest neighbors method ([5](#_ENREF_5)) was used to impute missing values. Subset quantile normalization was applied according to Touleimat and Tost ([6](#_ENREF_6)).

*Chromatin immunoprecipitation DNA-sequencing (ChIP-seq)*

Cell preparation for ChIP-seq including cross-linking of cells, cell lysis, sonication, chromatin immunoprecipitation procedure and library preparation were performed as previously described ([7](#_ENREF_7)) with the following changes. Cross-linking was done with 4 x 106 cells. Direct cell lysis was achieved by incubating 30 min in 950µL RIPA I (10 mM Tris-HCl pH 8.0, 1 mM EDTA pH 8.0, 140 mM NaCl, 0.2% SDS, 0.1% DOC) on ice. The Sonication Bioruptor Plus with automated cooling to 4°C was used for high intensity sonication for 60 min (SH-SY5Y) or 30 min (Be(2)-C) with 30 s on / 30 s off intervals. Tumor material (30 mg) was disrupted fixed and sonicated as described previously ([8](#_ENREF_8)). All subsequent steps were performed analogous to cell line experiments. Antibodies against H3K4me1 (ab8895, Abcam, Cambridge, UK), H3K27ac (ab4729), H3K4me3 (ab8580, Abcam) and H3K27me3 (ab6002, Abcam) were used for precipitation. Library preparation was performed using the NEBNext Ultra DNA Library Prep Kit for Illumina (New England BioLabs, Ipswich, MA, US) according to the manufacturer’s protocol. Pools containing ChIP-seq libraries were sequenced (50 bases single-end) on the Illumina sequencing platform (German Cancer Research Center Core facility).

*RNA-sequencing (RNA-seq)*

Total RNA was isolated using the miRNeasy Mini Kit (Qiagen) according to the manufacturer's protocol. RNA was depleted from ribosomal RNAs using the Ribo-Zero rRNA Removal Kit (Illumina) according to the manufacturer's protocol. RNA libraries were prepared using the NEBNext Ultra Directional RNA Library Prep Kit for Illumina (New England BioLabs) according to the manufacturer's protocol with the following changes: RNA was fragmented for 20 min at 94°C followed by first strand cDNA synthesis for 10 min at 25°C, 50 min at 42°C and 15 min at 70°C. Size selection of adapter-ligated DNA was done with a bead:DNA ratio of 0.4 (AMPure XP beads, Beckman Coulter) removing index primer and short fragments. Quality, quantity and sizing (approximately 320 bp) of the RNA Library were analyzed using a DNA High Sensitivity DNA chip run on a 2100 Bioanalyzer (Agilent Technologies). Libraries were sequenced (50 bases single-end) on the Illumina sequencing platform (German Cancer Research Center Core facility).

*DNA methylation-based cluster analysis*

Patients were clustered based on DNA methylation data (m-values) of the 1000 most variable CpGs using hierarchical clustering with average linkage and non-centralized correlation distance function. In an additional approach, only DNA methylation data from 119 CpGs in the gene bodies of the protocadherin beta family members *PCDHB2-18* were used for clustering. To assess uncertainty in hierarchical cluster analysis we used multiscale bootstrap resampling obtaining approximately unbiased p-values. Cluster analyses were carried out using R package pvclust. The Kaplan-Meier method was used to estimate overall survival curves of patient subclusters. Cox regression was used to investigate the prognostic power of DNA methylation-based clustering adjusting for established prognostic variables. Variance inflation factors were calculated to estimate collinearity in the model. To investigate MYC(N) deregulation independent of genomic amplification, we estimated a MYC(N) activity score for each tumor using the median expression of a set of 155 previously identified MYC(N) target genes ([9](#_ENREF_9)). For testing the association between MYC(N) activity score and patient subclusters, the Wilcoxon rank-sum test was used. *MYC(N)* expression in relation to methylation-based clustering was estimated by averaging signals from Agilent probes A\_23\_P215956, A\_24\_P178011, A\_24\_P38363 and A\_32\_P60687 for MYC, and A\_23\_P303390 and A\_24\_P94402 for MYCN.

Accession codes

RNA-seq, ChIP-seq as well as expression and methylation array data were deposited in Gene Expression Omnibus (GEO) under accession numbers GSE73518, GSE80197, GSE80397, GSE79859**,** GSE80243 and GSE80445. ChIP-seq data from primary tumors were deposited at the DKFZ data management platform and may be accessed upon request. Public expression data submitted under GEO accessions GSE35218 and GSE62564 as well as ArrayExpress accession E-MTAB- 2691 were used. UCSC accession IDs for ENCODE ChIP-seq tracks from the neuroblastoma cell line SK-N-SH were: wgEncodeEH003373 (Mx1), wgEncodeEH003393 (p300, SC-584), wgEncodeEH003227 (TCF12), wgEncodeEH003249 (GATA3), wgEncodeEH003302 (RXRA), wgEncodeEH003237 (NFIC), wgEncodeEH003226 (JunD), wgEncodeEH003297 (FOSL2), wgEncodeEH003243 (FOXM1), wgEncodeEH003298 (MEF2A), wgEncodeEH003286 (TEAD4), wgEncodeEH003270 (p300, SC-585), wgEncodeEH003261 (ZBTB33), wgEncodeEH003242 (ELF1), wgEncodeEH002269 (NRSF), wgEncodeEH003375 (RFX5), wgEncodeEH003300 (Pbx3), wgEncodeEH003376 (Rad21), wgEncodeEH003377 (SMC3), wgEncodeEH003269 (USF-1), wgEncodeEH003371 (CTCF), wgEncodeEH003374 (Nrf1), wgEncodeEH003228 (YY1), wgEncodeEH003248 (GABP), wgEncodeEH002271 (Sin3Ak-20), wgEncodeEH002270 (Pol2), wgEncodeEH002301 (TAF1) and wgEncodeEH003299 (Max). UCSC accession IDs for ENCODE ChIP-seq tracks from the neuroblastoma cell line SH-SY5Y were: wgEncodeEH002031 (GATA3, SC269) and wgEncodeEH001770 (GATA2).

*Gene set analysis*

Genes whose GpG methylation levels were significantly associated with both expression and high-risk disease were investigated for GO term and Reactome pathway enrichment using the Database for Annotation, Visualization and integrated Discovery tool (DAVID) ([10](#_ENREF_10)). Enrichment of chromosomal positions and genes targeted by PRC2 in embryonic stem cells (ESCs) ([11](#_ENREF_11)) was identified and tested for using the “compute overlaps” tool of the Molecular Signatures Database (MSigDB, Broad institute, collections C1 and C2). Global expression and DNA methylation data were derived from a study treating 17 neuroblastoma cell lines with an epigenetic drug combination ([12](#_ENREF_12)). To select optimal gene expression probe sets (Affymetrix HU133plus2.0) from this dataset, the jetset algorithm was applied ([13](#_ENREF_13)). The camera gene set test procedure was used to test whether genes from gene sets of interest were highly ranked in terms of differential expression relative to genes not in the gene set ([14](#_ENREF_14)). Statistical analyses were performed using the R / Bioconductor software environment.

**SUPPLEMENTARY REFERENCES**

1. Oberthuer A, Juraeva D, Li L, Kahlert Y, Westermann F, Eils R, et al. Comparison of performance of one-color and two-color gene-expression analyses in predicting clinical endpoints of neuroblastoma patients. Pharmacogenomics J. 2010;10:258-66.

2. Oberthuer A, Berthold F, Warnat P, Hero B, Kahlert Y, Spitz R, et al. Customized oligonucleotide microarray gene expression-based classification of neuroblastoma patients outperforms current clinical risk stratification. J Clin Oncol. 2006;24:5070-8.

3. Silver JD, Ritchie ME, Smyth GK. Microarray background correction: maximum likelihood estimation for the normal-exponential convolution. Biostatistics. 2009;10:352-63.

4. Smyth GK. Limma: linear models for microarray data. In: Gentleman R, Carey V, Dudoit S, Irizarry RA, Huber W, editors. Bioinformatics and Computational Biology Solutions using R and Bioconductor. New York: Springer; 2005. p. 397-420.

5. Troyanskaya O, Cantor M, Sherlock G, Brown P, Hastie T, Tibshirani R, et al. Missing value estimation methods for DNA microarrays. Bioinformatics. 2001;17:520-5.

6. Touleimat N, Tost J. Complete pipeline for Infinium((R)) Human Methylation 450K BeadChip data processing using subset quantile normalization for accurate DNA methylation estimation. Epigenomics. 2012;4:325-41.

7. Blecher-Gonen R, Barnett-Itzhaki Z, Jaitin D, Amann-Zalcenstein D, Lara-Astiaso D, Amit I. High-throughput chromatin immunoprecipitation for genome-wide mapping of in vivo protein-DNA interactions and epigenomic states. Nature protocols. 2013;8:539-54.

8. Dahl JA, Collas P. A rapid micro chromatin immunoprecipitation assay (microChIP). Nature protocols. 2008;3:1032-45.

9. Westermann F, Muth D, Benner A, Bauer T, Henrich KO, Oberthuer A, et al. Distinct transcriptional MYCN/c-MYC activities are associated with spontaneous regression or malignant progression in neuroblastomas. Genome Biol. 2008;9:R150.

10. Huang da W, Sherman BT, Lempicki RA. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nature protocols. 2009;4:44-57.

11. Ben-Porath I, Thomson MW, Carey VJ, Ge R, Bell GW, Regev A, et al. An embryonic stem cell-like gene expression signature in poorly differentiated aggressive human tumors. Nature genetics. 2008;40:499-507.

12. Duijkers FA, de Menezes RX, Goossens-Beumer IJ, Stumpel DJ, Admiraal P, Pieters R, et al. Epigenetic drug combination induces genome-wide demethylation and altered gene expression in neuro-ectodermal tumor-derived cell lines. Cellular oncology. 2013;36:351-62.

13. Li Q, Birkbak NJ, Gyorffy B, Szallasi Z, Eklund AC. Jetset: selecting the optimal microarray probe set to represent a gene. BMC bioinformatics. 2011;12:474.

14. Wu D, Smyth GK. Camera: a competitive gene set test accounting for inter-gene correlation. Nucleic acids research. 2012;40:e133.