

## Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our [Editorial Policies](#) and the [Editorial Policy Checklist](#).

### Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a Confirmed

- |                                     |                                     |                                                                                                                                                                                                                                                            |
|-------------------------------------|-------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | The exact sample size ( $n$ ) for each experimental group/condition, given as a discrete number and unit of measurement                                                                                                                                    |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly                                                                                                                                    |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | The statistical test(s) used AND whether they are one- or two-sided<br><i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>                                                               |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | A description of all covariates tested                                                                                                                                                                                                                     |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons                                                                                                                                        |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals) |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | For null hypothesis testing, the test statistic (e.g. $F$ , $t$ , $r$ ) with confidence intervals, effect sizes, degrees of freedom and $P$ value noted<br><i>Give <math>P</math> values as exact values whenever suitable.</i>                            |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings                                                                                                                                                           |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes                                                                                                                                     |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | Estimates of effect sizes (e.g. Cohen's $d$ , Pearson's $r$ ), indicating how they were calculated                                                                                                                                                         |

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

### Software and code

Policy information about [availability of computer code](#)

Data collection

The data processing are described in the manuscript and in GEO database description. All software are publicly available to use. BWA(v0.7.17), pairtools (v1.1.3), SAMtools (v1.10), HOMER (v5.1), Juicer (v1.6), Mustache (v1.0.1), bedtool (v2.31.0), ENCODE ATAC-Seq pipeline (v1.0), Picard in GATK (v4.2.3.0), MACS2 (v2.2.7.1), Trimmomatic (v0.39), Bowtie2 (v2.5.0), Seurat (v4.1.2), AtoMx Spatial Information Platform (version 1.3.2), STAR (v2.7.5), salmon (v1.3.0), HTSeq (v0.9.1), DESeq2 (v1.36.0), GSEA (v4.3.2) were used to processing the raw data and collect the processed data, by following the standard workflow of the pipeline. The parameters used were listed in the manuscript to generate the data for further analysis and data interpretation.

Data analysis

Statistical analyses of the data were conducted using Prism 10 version 10.2.3 and R version 4.3.2. Univariate and multivariate logistic regression analyses were performed via IBM SPSS (v26).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

## Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

The Omni-C data for NPE, EBV+NPC, and EBV-NPC cell lines are deposited into the Gene Expression Omnibus database under GEO accession GSE274581 and are available at the following URL [<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE274581>]. The ATAC-seq data for NPE, EBV+NPC, and EBV-NPC cell lines are deposited into the Gene Expression Omnibus database under GEO accession GSE278605 [<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE278605>]. The CUT&RUN-seq data for NPE, EBV+NPC, EBV-NPC cell lines of H3K4me3, CTCF, and H3K27ac for cell lines are deposited into the Gene Expression Omnibus database under GEO accession GSE278605 [<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE278607>]. The Spatial Transcriptome data are deposited into the Gene Expression Omnibus database under GEO accession GSE299776 [<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE299776>]. The GeoMx-DSP data are deposited into the Gene Expression Omnibus database under GEO accession GSE299775 [<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE299775>]. The raw sequence data (WES and bulk RNA-seq) from the clinical samples generated in this study have been deposited in the Genome Sequence Archive (GSA) of the National Genomics Data Center (NGDC), Beijing Institute of Genomics (China National Center for Bioinformation), Chinese Academy of Sciences, under accession number HRA008959 [<https://ngdc.cncb.ac.cn/gsa-human/browse/dac/HDAC004793>]. The raw data are available under controlled access due to data privacy laws related to patient consent for data sharing. The data should be used for research purposes only. According to the guidelines of GSA-human, all non-profit researchers are allowed access to the data, and the Principal Investigator of any research group can apply for the data following the guidelines at the GSA database portal (<https://ngdc.cncb.ac.cn/gsa-human/>). The response time for access requests is approximately 10 working days. Once access has been granted, the data will be available for download within one month. The user can also contact the corresponding author directly for enquiries. The NPC scRNA-Seq publicly available data used in this study are available in the GEO database under accession code GSE150825 [<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE150825>] and GSE162025 [<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE162025>], and from CNGBdb database with accession number CNP0000428 [<https://db.cngb.org/search/project/CNP0000428/>]. Source data are provided with this paper. The remaining data are available within the Article, Supplementary Information or Source Data file.

## Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

### Reporting on sex and gender

Gender was reported in our study and considered in the study design. The findings apply to both genders, as we did not detect difference between genders and our study. In total, 137 male and 40 female NPC patients were included for the multi-omics study.

### Reporting on race, ethnicity, or other socially relevant groupings

No socially relevant categorized variables were used in the study.

### Population characteristics

if patients fulfilled the following criteria: a pathological diagnosis of nasopharyngeal undifferentiated nonkeratinising carcinoma; availability of prospectively collected clinical data; and availability of qualified samples from primary nasopharyngeal foci. All the enrolled patients had received first-line treatments according to NCCN guidelines and were followed through medical visits and telephone interviews. Cancer progression was confirmed by histopathological examination or at least two other tests, including cytopathologic diagnosis, computed tomography, magnetic resonance imaging, positron emission tomography, single-photon emission computed tomography, ultrasound examination, and endoscopy. Patients with any confirmed distant site were diagnosed with distant metastasis. The clinical characteristics of the human research participants including age and TNM stage were summarized in Table 1 in the manuscript. In the HK cohort, the median age at diagnosis is 51y with range of 31y to 81y. In the GZ cohort, the median age is 42y with range of 8y to 77y.

### Recruitment

NPC patients were recruited in Hong Kong (HK) and Guangzhou (GZ), respectively, and classified into two groups (MET-NPC and nonMET-NPC) based on distant metastasis-free survival (DMFS) in this study. The MET-NPC group had early development of distant metastasis with DMFS of less than three years after treatment, while the nonMET-NPC group had DMFS longer than three years or no distant metastasis in five-year follow-up time after treatment.

### Ethics oversight

Informed consent for sample collection was written and obtained from patients, and samples were collected according to protocols approved by the Institutional Review Board of the University of Hong Kong (UW 09-251) and Hong Kong Clinical Research Ethics Committee (HKECREC-2021-078) for the HK cohort and the Institutional Review Board of Sun Yat-Sen University Cancer Center (G2021-110-01) for the GZ cohort.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

## Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

- ☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see [nature.com/documents/nr-reporting-summary-flat.pdf](https://www.nature.com/documents/nr-reporting-summary-flat.pdf)

# Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

|                 |                                                                                                                                                                                                                                                                                                                                                                                          |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sample size     | The sample size for the multi-centre study was estimated by R package pwr (version 1.3-0). With effect size of 0.8 and a significant level of 0.05, we required at least 25 and 33 patients in each group with an analysis power of 80% and 90%, respectively. Therefore, we included 39 MET and 38 nonMET patients in the HK cohort and 36 MET and 64 nonMET patients in the GZ cohort. |
| Data exclusions | All the data passed the quality control and thus were included in the study.                                                                                                                                                                                                                                                                                                             |
| Replication     | We used the duplicates to verify the robustness of the modified Hi-C data, and utilized the multi-centre study to confirm the association between the EBVIR-enhancer-KDM5B signature with distant metastasis. The findings can be replicated in two independent patient cohorts.                                                                                                         |
| Randomization   | No randomization was used based on our research aim to compare two groups of patients with and without distant metastasis. We used the multivariable logistic regression analysis to control the covariates, such as overall stage and plasma EBV DNA copies, to evaluate the association of KDM5B pathway activities with metastasis.                                                   |
| Blinding        | The investigators were not blinded for patient group, as a group comparison is needed for the study.                                                                                                                                                                                                                                                                                     |

## Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

### Materials & experimental systems

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| n/a                                 | Involved in the study                                           |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Antibodies                  |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Eukaryotic cell lines       |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Palaeontology and archaeology          |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Animals and other organisms |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Clinical data                          |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Dual use research of concern           |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Plants                                 |

### Methods

|                                     |                                                 |
|-------------------------------------|-------------------------------------------------|
| n/a                                 | Involved in the study                           |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> ChIP-seq    |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Flow cytometry         |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> MRI-based neuroimaging |

## Antibodies

|                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antibodies used | <p>A volume of 1µL of CTCF (Millipore, Cat# 07-729), H3K4me3 (EpiCypher Cat# 13-0041), H3K27ac (Abclonal, Cat# A7253), H3K27me3 (Invitrogen, Cat# MA5-11198), and IgG (EpiCypher Cat# 13-0042) antibodies were used for CUT&amp;RUN experiment.</p> <p>anti-KDM5B (dilution 1:400, Cat# HPA027179, Sigma-Aldrich) was used for immunohistochemical (IHC) staining and western blot experiment.</p> <p>CD20 (NanoString Technologies, clone ID: IGEL/773), CD45 (NanoString Technologies, clone ID: D9M8I), PanCK (NanoString Technologies, clone ID: AE-1/AE-3), as well as the secondary antibody (ThermoFisher Goat Anti-rabbit, A-11012) were used for GeoMx Digital Spatial Profiler (DSP).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Validation      | <p>The antibodies were validated by the manufacture.</p> <p>For CUT&amp;RUN-seq in methods,</p> <p>CTCF (Millipore, Cat# 07-729)<br/> <a href="https://www.merckmillipore.com/HK/en/product/Anti-CTCF-Antibody,MM_NF-07-729">https://www.merckmillipore.com/HK/en/product/Anti-CTCF-Antibody,MM_NF-07-729</a></p> <p>H3K4me3 (EpiCypher Cat# 13-0041),<br/> <a href="https://www.epicypher.com/products/antibodies/snap-chip-certified-antibodies/histone-h3k4me3-antibody-snap-chip-certified-cutana-cut-run-compatible">https://www.epicypher.com/products/antibodies/snap-chip-certified-antibodies/histone-h3k4me3-antibody-snap-chip-certified-cutana-cut-run-compatible</a></p> <p>H3K27ac (Abclonal, Cat# A7253),<br/> <a href="https://www.abclonal.co.kr/catalog-antibodies/AcetylHistoneH3K27RabbitpAb/A7253">https://www.abclonal.co.kr/catalog-antibodies/AcetylHistoneH3K27RabbitpAb/A7253</a></p> <p>H3K27me3 (Invitrogen, Cat# MA5-11198) <a href="https://www.thermoFisher.com/antibody/product/H3K27me3-Antibody-clone-G-299-10-Monoclonal/MA5-11198">https://www.thermoFisher.com/antibody/product/H3K27me3-Antibody-clone-G-299-10-Monoclonal/MA5-11198</a></p> <p>IgG (EpiCypher Cat# 13-0042)<br/> <a href="https://www.epicypher.com/products/nucleosomes/snap-cutana-spike-in-controls/cutana-igg-negative-control-antibody-for-cut-run-and-cut-tag">https://www.epicypher.com/products/nucleosomes/snap-cutana-spike-in-controls/cutana-igg-negative-control-antibody-for-cut-run-and-cut-tag</a></p> <p>For immunohistochemical (IHC) staining and western blot experiment, anti-KDM5B (dilution 1:400, Cat# HPA027179, Sigma-Aldrich)<br/> <a href="https://www.sigmaaldrich.com/HK/en/product/sigma/hpa027179?srltid=AfmBOoqdm8DjoQjYasLCbuXdhIntiAYcX9nwrldWPBZcCTA0DV_Punt">https://www.sigmaaldrich.com/HK/en/product/sigma/hpa027179?srltid=AfmBOoqdm8DjoQjYasLCbuXdhIntiAYcX9nwrldWPBZcCTA0DV_Punt</a></p> <p>For GeoMx Digital Spatial Profiler (DSP),<br/> CD20 (NanoString Technologies, clone ID: IGEL/773)<br/> <a href="https://nanosttring.com/wp-content/uploads/CD20_IGEL773_AF647_Hs.pdf">https://nanosttring.com/wp-content/uploads/CD20_IGEL773_AF647_Hs.pdf</a></p> |

CD45 (NanoString Technologies, clone ID: D9M8I)  
<https://www.cellsignal.com/products/primary-antibodies/cd45-intracellular-domain-d9m8i-xp-rabbit-mab-bsa-and-azide-free/47937>  
 PanCK (NanoString Technologies, clone ID: AE-1/AE-3)  
[https://nanosttring.com/wp-content/uploads/2022/07/KRTpan\\_AE1AE3\\_AF594\\_Hs\\_FrF.pdf](https://nanosttring.com/wp-content/uploads/2022/07/KRTpan_AE1AE3_AF594_Hs_FrF.pdf)  
 secondary antibody (Thermofisher Goat Anti-rabbit, A-11012)  
<https://www.thermofisher.com/antibody/product/Goat-anti-Rabbit-IgG-H-L-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-11012>

## Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

|                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cell line source(s)                                               | Two nasopharynx-derived normal immortalised squamous epithelial cell lines, NP69SV40T (NP69, RRID: CVCL_F755) and NP460-tert (NP460, RRID: CVCL_X205), were used in this study. The EBV+ NPC cell lines used included C17 (RRID: CVCL_VT47), C666-1 (RRID: CVCL_M597), and NPC43 (RRID: CVCL_UH64). The EBV- NPC cell lines used included NPC53 (RRID: CVCL_UH65) and NPC38 (RRID: CVCL_UH63). These cell lines were sourced from the NPC tissue bank at the University of Hong Kong. NPC43noEBV, HK1, and HK1EBV cells were kindly provided by Dr. Anna Tsang from The Chinese University of Hong Kong. NPC43noEBV cells originated from the EBV+ NPC43 cell line with undetectable EBV DNA. HK1EBV cells were infected with EGFP-neo-resistant EBV-infected Akata cells, and G418 was used for EBV+ cell selection. Namalwa cells (RRID:CVCL_1841) was obtained from the NPC tissue bank at the University of Hong Kong. The EBV+ PDXs were established previously and provided by Professor George Tsao's laboratory, including C15, Xeno23, Xeno32, Xeno47, Xeno76 and NPC113 |
| Authentication                                                    | DNA sample from cells were extracted for STR profiling for cell line authentication.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Mycoplasma contamination                                          | Mycoplasma contamination is regularly checked, which is free from contamination.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Commonly misidentified lines (See <a href="#">ICLAC</a> register) | Not applicable                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

## Animals and other research organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research, and [Sex and Gender in Research](#)

|                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Laboratory animals      | NOD/SCID mice were used to to obtain patient-derived xenografts (PDXs). NOD/SCID mice were obtained from The Centre for Comparative Medicine Research (CCMR), which is an AAALAC International accredited service centre of the Faculty of Medicine in The University of Hong Kong.                                                                                                                                                                                                                     |
| Wild animals            | NOD.Cg-Prkdcscid/J, Strain #:001303, RRID:IMSR_JAX:001303. Inbred NOD.CB17-Prkdcscid/J (NOD/SCID) from The Jackson Laboratory, USA feeding with LabDiet® 5LG4 (Breeding Diet), LabDiet® 5053 (Maintenance Diet) were used.                                                                                                                                                                                                                                                                              |
| Reporting on sex        | Male mice were used in in this study.                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Field-collected samples | Animals and the equipment used on animals are under routine monitoring with up to the performance standards as listed by the Guide for the Care and Use of Laboratory Animals, 8th Edition, National Research Council. Animals were housed in individually ventilated cages under a 12:12 dark light cycle within environmentally controlled rooms and were fed ad libitum with laboratory diet manufactured by LabDiet, USA. Temperature regulated at 16-26 oC with relative humidity range of 30–70%. |
| Ethics oversight        | All animal care and experimental procedures were approved by by the Committee on on the Use of of Live Animals in in Teaching and Research at at University of of Hong Kong. Animals and the equipment used on animals are under routine monitoring with up to the performance standards as listed by the Guide for the Care and Use of Laboratory Animals, 8th Edition, National Research Council.                                                                                                     |

Note that full information on the approval of the study protocol must also be provided in the manuscript.

## Plants

|                       |                |
|-----------------------|----------------|
| Seed stocks           | Not applicable |
| Novel plant genotypes | Not applicable |
| Authentication        | Not applicable |

## Data deposition

- ☒ Confirm that both raw and final processed data have been deposited in a public database such as [GEO](#).
- ☒ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

## Data access links

May remain private before publication.

The CUT&RUN-seq data for NPE, EBV+NPC, EBV-NPC cell lines of H3K4me3, CTCF, and H3K27ac for cell lines has been included and is deposited with GEO accession GSE278605 [<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE278607>].

## Files in database submission

fastq, bam, narrowpeak files are provided.

Genome browser session  
(e.g. [UCSC](#))

IGV browser or UCSC genome browser

## Methodology

## Replicates

one repeat per cell line. Control sample has been evaluated for the reproducibility. Spike-in positive control and IgG control are included to monitor the performance of the data.

## Sequencing depth

20 million 150bp paired-end sequencing under NovaSeq6000 platform.

## Antibodies

CTCF (Millipore, Cat# 07-729), H3K4me3 (EpiCypher Cat# 13-0041), H3K27ac (Abclonal, Cat# A7253), H3K27me3 (Invitrogen, Cat# MA5-11198), and IgG (EpiCypher Cat# 13-0042) antibodies.

## Peak calling parameters

Peak calling with matched control IgG was performed for each sample at -q 0.05.

## Data quality

SNAP-CUTANA™ K-MetStat Panel (EpiCypher Cat# 19-1002) spike-in controls with mono-, di-, and trimethylation at H3K4, H3K9, H3K27, H3K36, and H4K20 and unmodified controls were spiked into positive control (H3K4me3) and negative control (IgG) antibodies to monitor assay success.

## Software

Trimmomatic (v0.39), Bowtie2 (v2.5.0), Picard in GATK (v4.2.3.0), MACS2 (v2.2.7.1)