

2 **Human heart tissues**

3 All studies are conformed to the Declaration of Helsinki and institutional ethical regulations.
4 All tissues were stored at -80°C until further analyses. Explanted failing hearts were obtained
5 from patients undergoing cardiac transplantation for end-stage cardiac HF secondary to
6 idiopathic dilated cardiomyopathy. Patients were classified as suffering of New York Heart
7 Association (NYHA) Class IV HF, with a mean pretransplant left ventricular ejection fraction
8 of $22\pm 4\%$. None had received chronic intravenous inotropic support over at least 7 days
9 immediately prior to transplantation. Heart failure therapy consisted of angiotensin-
10 converting enzyme inhibitors and diuretics in all patients. Non-failing hearts were obtained
11 from prospective multiorgan donors who had died from head trauma or intracranial bleeding;
12 these hearts were unsuitable for transplantation for technical reasons.

14 **Animal Model**

15 All the animal experiments were approved by the Animal Care and Use Committees of the
16 University of Toulouse. For the determination of sample size, the statistical analysis of the
17 relevant endpoint in relation to the pathological model was performed using a two-tailed
18 unpaired t-test with risks $\alpha=0.05$ and $\beta=0.8$. The primary endpoint was the effect of
19 the experimental intervention on cardiac function (shortening fraction) measured by
20 echocardiography. Only male mice with C57Bl/6j genetic background have been used. The
21 rationale for excluding female mice is based in the protective role of estrogen in cardiac
22 remodeling following heart injuries or stressors, ultimately reducing the risk of heart failure
23 (Iorga et al., 2017). Since the the protein complex described here was not previously studied
24 in the heart, we opted for male mice due to their extensive use as a model organism in cardiac
25 hypertrophy research. Furthermore, previous studies have demonstrated that male mice
26 experience sustained functional decline following transverse aortic constriction (TAC)
27 compared to their female counterparts (Witt et al., 2008).

28 All the animals were purchased from Janvier Labs (Marseille, France). 1 week of habituation
29 time after arrival has been observed for each experiment. Mice were housed in a pathogen-
30 free facility at a constant 22°C temperature on 12 hours of light/dark cycles with free access
31 to food and water. To minimise potential confounders such as cage location, mice were
32 housed in the same rack. Before heart harvesting, an intraperitoneal injection of pentobarbital
33 at a dose of 300 mg/kg has been performed in order to induce anesthesia overdose. CC was
34 aware of the group allocation at the different stages of the experiment. Data acquisition and
35 analysis were performed by investigators who were blinded to the group assignment. All

36 animals except for those died after surgery and one showing necrosed spleen were included in
37 the analyses. Retro-orbital AAV9 injection was performed in 4 weeks old mice, 3 weeks prior
38 to TAC or Sham surgery. Echocardiography was performed 1 and 6 weeks after surgery and
39 then the heart was extracted for anatomical, histological and biochemical analysis (Figure
40 S1G).

41 **Surgical procedure and Echocardiography**

42 Prior to transverse aortic constriction (TAC) surgery, anesthetized with 2–4% isoflurane and
43 endotracheally intubated. Mice were randomly assigned to TAC or Sham. Body temperature
44 was maintained at 37°C using a heating pad and the chest was opened. A curved suture needle
45 with nylon thread was inserted under the aorta. The ligation happened between the truncus
46 brachiocephalicus and the left common carotid artery by tying a nylon suture against a 26-
47 gauge. The needle has been promptly removed. The chest was closed, the pneumothorax was
48 evacuated, and the mice were extubated and allowed to recover from the anesthesia. Sham-
49 operated animals underwent the same surgery except for aortic ligation. Echocardiography
50 was carried out on lightly anesthetized mice (1% isoflurane in air) and placed on a heating
51 pad. The left ventricle dimensions were obtained during TM mode acquisition from the
52 parasternal short axis view at the level of the papillary muscles using a Vivid7 echographer
53 and a 14 MHz transducer (i3L, GEHealthcare). Images were transferred and analyzed off line
54 with EchoPAC (GEHealthcare). All measurements and analyses were performed in blind.

55 **AAV9 Production and Administration**

56 The control construct pAAV-shCT has been obtained by Vector Biolabs (#7045). AAV9-
57 TriShMML3 has been constructed from pAAV-shCT. After the removal of the untargeted
58 shRNA, the shRNA sequences sh1, sh3, and sh4 (Supplemental material) from pLKO-
59 shRNAs, (Merck) have been inserted in the BamHI site. Each shRNA is transcribed by the U6
60 promoter. AAV9 production and purification have been performed by the Vectorology
61 Platform Vectoul (www.poletechno-crct.inserm.fr/en/vectorologie). For the injection, mice
62 were randomly assigned to AAV9-shCt or AAV9-shMML3. Mice were lightly anesthetized
63 with 2% isoflurane. 1×10^{12} AAV9 genome copies were injected through the retro-orbital
64 sinus of 4-week-old mice.

66 **Cell culture**

67 **Neonatal rat ventricular myocyte (NRVM) isolation:** Neonatal rats 1–3 days old were
68 euthanized by decapitation. The heart was excised and the atria were removed. Tissues were
69 digested with collagenase A (Roche, #11088793001) and pancreatin (Sigma, #P3292). Cell
70 suspension was purified by centrifugation through a discontinuous Percoll (Cytiva,
71 #17089102) gradient to obtain myocardial cells. Cardiomyocytes were plated at a density of
72 $1-0.5 \times 10^5$ cells/cm² in Dulbecco's modified Eagle's medium (DMEM)/medium 199 (4:1)
73 supplemented with 10% horse serum, 5% fetal bovine serum, glutamine and antibiotics
74 (plating medium), and allowed to attach overnight. Approximately 95% of the cells displayed
75 spontaneous contractile activity in culture and were positive for alpha-actinin staining (Morel
76 et al., 2005).

77 Phenylephrine treatments were performed at 10 μ M for the specified time in NRVMs.
78 Cyclosporin A (CsA) pretreatments were performed at 2 nM for 1 hour prior to phenylephrine
79 treatment. Calyculin pretreatment was performed at 50 nM for 10 min prior to PE treatment.
80 Angiotensin II (1 μ M) treatment was applied for 24 h.

81 **Adult murine cardiomyocyte isolation:**

82 After anesthesia, 7-8 weeks old mouse hearts were quickly isolated in Tyrode buffer (130 mM
83 NaCl, 5.4 mM KCl, 1.4 mM MgCl₂, 0.4 mM NaH₂PO₄, 4.2 mM HEPES, 10 mM glucose,
84 20 mM taurine, 10 mM creatine monohydrate, pH 7.2). The aorta was cannulated for
85 retrograde perfusion in a Langendorff apparatus at a constant rate of 3 mL/min at 37 ° C. The
86 heart was perfused for 5 to 8 min with Tyrode buffer, then with Tyrode supplemented with
87 12.5 μ M CaCl₂ and 0.5 mg/mL Liberase™ (#05401020001 Roche) for 5 to 10 min. Once the
88 enzymatic digestion was complete, the left ventricle was dissected and homogenized with a
89 pipette in Tyrode buffer supplemented with 12.5 μ M CaCl₂ and 5% BSA. The cells were then
90 filtered through a 100 μ m mesh, counted through Malassez chamber and left to sediment by
91 gravity for 10 min.

92
93 **Adult rat cardiomyocyte isolation and culture:**

94 After anesthesia (pentobarbital 60 mg/kg; ip), 12-14 weeks old rats hearts were quickly
95 isolated in Tyrode free Ca²⁺ buffer (in mM: 140 NaCl, 5.37 KCl, 1 MgCl₂, 0.33 NaH₂PO₄, 10
96 HEPES, 11 glucose, pH 7.4). Heart were retrogradely perfused through the aorta in a
97 Langendorff apparatus rinsed 5 min with Tyrode free Ca²⁺. Then, enzymatic digestion was
98 performed by perfusion of 0.15 UI/ml Liberase (Roche) at 37°C in Tyrode buffer (in mM:

99 140 NaCl, 5.37 KCl, 0.025 CaCl₂, 1 MgCl₂, 0.33 NaH₂PO₄, 10 HEPES, 11 glucose, pH 7.4)
00 oxygenated with carbogen. At the end of the enzymatic digestion, left ventricle was kept and
01 gently mechanically dissociated in Tyrode buffer supplemented with 2% BSA. After filtration
02 through 200 µm mesh, cardiomyocytes were then progressively re-exposed to CaCl₂, 0.2 mM
03 then 0.8 mM and finally resuspended in M199 medium supplemented with CCT (2 mM
04 carnitine, 5 mM creatine; 5 mM taurine). Finally, cardiomyocytes were plated on B10 coated
05 with laminin (20 µg/mL). Phenylephrine treatments were performed at 10 µM for the
06 specified time. Cells were lysed in SDS-Free Immunoprecipitation (IP) buffer (20 mM Tris
07 pH 7.5, 150 mM NaCl, 1 mM EDTA, 1% Triton X100), 500 µg to 1 mg of proteins were used
08 for IP.

09 10 **Immunofluorescence and histological studies**

11 For histological analyses, hearts were blocked in diastole by injecting 100 µL KCl 1 M in the
12 left ventricle. Cardiac inclusion in OCT followed. Left ventricles were transversely sectioned
13 at 6 µm thickness and rehydrated in H₂O. Cryoslices and NRVMs, were fixed in 4%
14 paraformaldehyde for 8 min and permeabilised with 0.1% Triton in PBS for 10 min and 5 min,
15 respectively. Non-specific sites were saturated with 3% BSA solution for 1 hour. NRVMs and
16 tissue slices were then incubated respectively with α -sarcomeric actin and vinculin primary
17 antibody (1:100, Supplemental material) at 4°C for 2 hours overnight on rocking plate.
18 Finally, NRVMs and tissues were incubated with a goat anti-mouse secondary antibody
19 coupled to Alexa Fluor® 546 (1: 400) for 1 hour. Controls for background and specificity
20 were conducted by incubating cells and tissue without the primary and secondary antibodies,
21 or without the primary antibody but in the presence of the secondary antibody. For both, cells
22 and tissue, photo acquisition was performed using a Zeiss Observer Z.1 fluorescence
23 microscope with Axio Vision Rel 4.7 software (Carl Zeiss). Average cardiomyocyte area was
24 measured in blind manually on at least two different regions (80-200 cells counted per heart)
25 with ImageJ software. All the representative images in the manuscripts were chosen from
26 those used to quantify and they represent the average result obtained.

27 28 **Yeast two-hybrid screen**

29 The yeast two-hybrid screen has been performed by Hybrigenics
30 (<https://www.hybrigenics.com/>) using a conventional LexA and Gal4 system. The bait
31 fragment consisted of whole human Carabin protein (1-446 aa, hgx4054v1). Human Carabin
32 ORF was cloned into pB27 plasmid for N-terminal LexA DNA binding domain fusion

33 proteins (N-LexA-Carabin-C). The constructs were checked by sequencing and used as baits
34 to screen a random-primed human ventricle and embryo heart RP1 cDNA library constructed
35 into pP6 plasmid for C-terminal Gal4 transcription activating domain fusion proteins. 94
36 million colonies were screened. Positive “prey” clone cDNAs were amplified by PCR and
37 sequenced. The identification of preys was performed by matching with GenBank database
38 using an automated procedure.

40 **Immunoprecipitation**

41 For each immunoprecipitation sample, 3×10^6 NRVMs were lysed in SDS-Free
42 Immunoprecipitation (IP) buffer (20 mM Tris pH 7.5, 150 mM NaCl, 1 mM EDTA, 1%
43 Triton X100). The same buffer was used for mouse heart tissue but lysis was obtained
44 through the use of a potter grinder. Raw lysates were then centrifuged for 20 min at 15,000g
45 at 4°C. Proteins were then quantified by BCA assay. 500 µg to 1 mg of proteins were then
46 incubated overnight on a rotating wheel at 4°C with 8 µg of antibodies targeting the protein of
47 interest.

48 The precipitation of antibody-protein complexes was been performed through 2 h incubation
49 with agarose beads coupled with proteins A/G (Supplemental material) at 4°C. Bead-
50 antibody-protein complexes were washed a first time in IP buffer using a centrifuge cycle of
51 500 g for 5 minutes then three times at 5000 g for 1 minute at 4°C. Proteins were released
52 from beads and denatured adding sample buffer (187.5 mM Tris HCL pH 6.8, 6% SDS, 30%
53 Glycerol, 150 mM DTT, 0.03% Bromophenol blue) and heating at 95°C for 15 min. Finally,
54 samples were centrifuged (15000 g x 5 min, room temperature, RT) and loaded on gel.

56 **Western blot**

57 For protein quantification from heart, about 20 mg of tissue have been used. Protein were
58 extracted using ceramic beads in Precellys® mill/homogenizer (Bertin Technologies) in Tris-
59 SDS buffer (50 mM Tris pH 6.0, 1% SDS and protease inhibitors, Supplemental material).
60 Protein extraction *in vitro*, has been performed harvesting at least 1×10^6 cells with the same
61 lysis buffer. Tissue and cell lysates were then centrifuged at 4°C with 15,000 g speed for 20
62 and 10 minutes, respectively. Protein content in the supernatant was quantified by BCA
63 method. Samples were added with Laemmli Buffer 4X (187.5 mM Tris HCL pH 6.8, 6% SDS,
64 30% glycerol, 150 mM β-mercaptoethanol, 0.03% Bromophenol blue) and denatured 5 min at
65 95°C. 5 to 25 µg of proteins were loaded and separated in SDS-PAGE. Proteins were

66 transferred onto activated nitrocellulose membrane using TransBlot semi-dry apparatus
67 (#1704150, BioRad) following manufacturer's program for 1.5 mm gels. If the analysis
68 involved proteins with MW>150 kDa, Criterion TGX precast gels (#5671084, BioRad) and
69 wet transfer (Tris 250 mM, Glycine 0.4 M, 10% V/V Methanol and 0.01% W/V SDS) for 2 h
70 at 380 mA were used. The membrane was blocked in TBST-BSA 3% for 1 hour at RT. After
71 overnight incubation with primary antibodies at 4°C, membranes were incubated with
72 secondary antibodies (1 hour at RT) or G protein coupled to peroxidase (HRP) for
73 immunoprecipitated samples (90 minutes at RT). Membranes were revealed by
74 chemiluminescence using ECL Prime Kit (Supplemental material) and read with the
75 BioradChemiDoc™ XRS+. Quantification was carried out using ImageLab software.

76 77 **Size-exclusion chromatography (SEC)**

78 Cytosolic and nuclear separation was performed on 30×10^6 cells prior to SEC. 1 mg of
79 nuclear proteins was then injected using an AKTA purifier 25 (#29018224, GE Life Science)
80 onto a Superose 6 10/300GL column (GE Life Sciences) conditioned with IP Buffer (pH 7.5).
81 The flow rate was 0.2 mL/min, and 40x400 μ L fractions were collected using a low protein
82 binding 96-deep-well plate. The system was previously calibrated with high molecular weight
83 markers (GE Life Science). Protein elution was monitored through a spectrophotometer
84 detector set on wavelengths of 280 nm and 254 nm. On the basis of the chromatogram
85 obtained, fractions were pulled and tested in western blot.

86 87 **RNA extraction, cDNA synthesis and RT-qPCR experiment**

88 Extraction of RNA from tissue and cells was performed using QIAGEN RNeasy Mini Kit
89 (Supplemental material) following manufacturer's instructions. In case of tissue, at least
90 15 mg of mouse or human heart were used. The mechanical liberation of mRNA was obtained
91 using ceramic beads in a refrigerated Precellys® mill/homogenizer. After RNA extraction,
92 quantification was performed using DropSense 16 (Unchained Labs) or Nanodrop (Thermo
93 Fisher) and cDNA was using iScript cDNA Synthesis Kit (Supplemental material).
94 Quantitative PCR was performed with the SsoFast™ EvaGreen Supermix (Supplemental
95 material) using Viia7 Real-Time PCR System or StepOne Plus Real-Time PCR System
96 (ThermoFisher).

97 98 **Plasmid constructs and siRNA transfection**

99 PcDNA3.1 construct was purchased from ThermoFisher (V79020). PcDNA3.1-c-myc
00 Carabin was cloned by insertion of myc-Carabin ORF in EcoRI cloning site of pcDNA3.1.
01 All plasmids constructs were verified by DNA sequencing. Transient transfection experiments
02 of NRVMs were performed using Lipofectamine 2000 (#12566014, ThermoFisher) in
03 Optimem medium in absence of antibiotic following manufacturer instructions. After 4 hours,
04 cells were rinsed with PBS and put in serum-free J1 medium. NRVM transfections with
05 siRNAs against Rat MLL3 (#502710, Dharmacon), Carabin (#4390816, Ambion), STK24
06 (#M-087854-01-0020, Dharmacon), Calcineurin ($\text{A}\alpha$:#24674, Dharmacon ; $\text{A}\beta$:#25675,
07 Dharmacon) and control siRNAs (#D-001206-14-20) were performed using Dharmafect Duo
08 (#T-2010-03, Dharmacon) in Optimem medium for 24 h followed by 24 h in serum-free J1
09 culture medium before treatment following manufacturer's instructions.

11 **ChIP-Seq**

12 *Adult mouse cardiomyocyte fixation & Chromatin Immunoprecipitation*

13 Isolated adult mouse cardiomyocytes were fixed in 20 mL of Minimal Essential Medium
14 Eagle (#M0894, Merck) supplemented with 1% formaldehyde at RT for 10 min. After
15 centrifugation (500 g x 7min), supernatant was discarded and 0,125 M Glycine in PBS
16 solution was added for 5 min at RT. Cells were washed twice with cold PBS, then PMSF and
17 Protease inhibitors were added before snap-freezed in liquid nitrogen.

18 For chromatin immunoprecipitation, 3×10^6 isolated adult cardiomyocytes from at least three
19 1-week Sham or 1-week TAC mice were resuspended in 600 μL of Lysis Buffer from ChIP-
20 IT Express kit (Supplemental material). Cell suspension were then transferred in a Potter
21 dounce and incubated in ice for 30 minutes. Nuclear liberation was then performed using the
22 homogenizer and monitored by microscopy. The nuclei suspension was transferred in a 1.5
23 mL siliconized Eppendorf and centrifuged for 10 min with a speed of 3000 g at 4°C. After
24 discarding the supernatant, nuclei were resuspended in 300 μL of Shearing Buffer following
25 the manufacturer's instructions and chromatin liberation was achieved using a smaller potter
26 dounce. Nuclear lysates were then transferred in bioruptor tubes (#C30010016, Diagenode).
27 Sonication was performed using Bioruptor pico® sonication device (#B01060010,
28 Diagenode) and consisted in 7 cycles 30 sec on/30 sec off. The sheared chromatin was then
29 transferred into new tubes and centrifuged (15000 g x 10 min, 4°C). Supernatants were
30 collected. DNA concentration was measured by NanoDrop (ThermoFisher) and 1 μg
31 chromatin was collected for input. ChIP reaction were realised on 30 μg of chromatin and

32 3 µg antibody. The antibodies used for this step are reported in Supplemental material. ChIP
33 reaction tubes were incubated on rocking wheel at 4°C overnight. Washing and decrosslink
34 steps were performed as indicated in kit's manual. Immunoprecipitated DNA was recovered
35 using Chromatin IP DNA Purification kit (Supplemental material).

36 ***Library Preparation & Next-Generation Sequencing***

37 Samples quality controls and library preparation were performed at the GeT-Sante facility
38 (<https://get.genotoul.fr/la-plateforme/get-sante/>). dsDNA quantity was determined using the
39 Qubit dsDNA HS Assay Kit (Q32851, ThermoFisher Scientific). Shearing profile of input
40 sample was checked with Fragment Analyzer® (M5310AA, Agilent Technologies), using the
41 NGS High Sensitivity Kit (#DNF474, Agilent Technologies). ChIP-seq paired-end libraries
42 have been prepared according to Active Motif's protocol, using the Next Gen DNA Library
43 Kit (#53216, Active Motif), working from 988-1200 pg of dsDNA. Illumina compatible
44 adaptors were ligated, allowing the barcoding of the samples with single indices, and the
45 addition of molecular identifiers. The libraries were amplified using 12 cycles of PCR, and an
46 additional 2-sides purification step was finally performed, allowing to obtain 300-700 bp
47 fragments.

48 Libraries quality was assessed using the NGS High Sensitivity Kit on the Fragment Analyzer.
49 Libraries quantification and sequencing were performed at the GeT-PlaGe core facility
50 (INRAE, Toulouse). Libraries were quantified by qPCR using the KAPA Library
51 Quantification Kit. Libraries were equimolarly pooled and DNA sequencing was then
52 performed on one lane of the Illumina HiSeq 3000 instrument (Illumina), using a paired-end
53 read length of 2x150 bp with the Illumina HiSeq3000 Reagent Kits.

54 ***ChIP-seq Data Analysis***

55 The 150-nucleotides sequence reads generated by Illumina sequencing were trimmed with
56 SICKLE (<https://github.com/najoshi/sickle>) and mapped to the mouse musculus mm10
57 genome using the BOWTIE2 algorithm with default settings (Langmead & Salzberg, 2012).
58 Only reads that align without mismatches uniquely to the genome were used in the
59 subsequent analysis. In addition, duplicate reads were removed using PICARD
60 (<https://broadinstitute.github.io/picard/>). The peak callings were performed with MACS2
61 (Zhang et al., 2008) to look for significant enrichment ($p < 0,001$) in the ChIP/IP data file when
62 compared to the Input data file. Peaks showing at least a two-fold enrichment to Input were
63 kept for further analysis. To visualize the distribution of peak occupancy across features of the
64 mm10 genome, ChIPseeker (Yu et al., 2015) was used. ChIPpeakAnno (Zhu et al., 2010) was

65 used for venn diagrams and density plots. EnrichedHeatmap (Gu et al., 2018) and Diffbind
66 (<http://bioconductor.org/packages/release/bioc/vignettes/DiffBind/inst/doc/DiffBind.pdf>)
67 were used to generate heatmaps and hierarchical heatmaps, respectively. EnrichR (Kuleshov
68 et al., 2016) and ClusterProfiler (Luo & Brouwer, 2013) were used for Gene Ontology
69 analysis. Motif analysis were performed using MEME-ChIP (Machanick & Bailey, 2011).

71 *ATAC-seq Data Analysis*

72 ATAC-seq sequence reads extracted from GEO Database (GSE154521) were aligned to the
73 mm10 reference mouse genome using the BWA-MEM (Li, 2013). Duplicates were removed
74 using PICARD (<https://broadinstitute.github.io/picard/>). The peak callings were performed
75 using Genrich (<https://github.com/jsh58/Genrich>) and the overlappings of ChIP- and ATAC-
76 seq data were performed with ChIPpeakAnno (Zhu et al., 2010). Ggplot2 package (Wickham,
77 2009) was used to create heatmaps.

79 *RNA-seq Data Analysis*

80 RNA-seq sequence reads extracted from ENA Database (PRJNA229481) were trimmed with
81 Trim-Galore (https://www.bioinformatics.babraham.ac.uk/projects/trim_galore) and aligned
82 using STAR (Dobin et al., 2013). Transcript analysis and quantification were performed with
83 StringTie (Pertea et al., 2015) and ChIP- and RNA-seq data were overlapped with
84 ChIPpeakAnno (Zhu et al., 2010). Ggplot2 package (Wickham, 2009) was used to create
85 heatmaps.

88 **Statistical analysis**

89 No data points were removed or disregarded during the analysis process. The number of
90 experimental biological replicates per group was chosen based on our experience in previous
91 experiments.

92 The statistical analyses were performed with GraphPad Prism 9.5. Results were expressed as
93 mean±SEM. Statistical analyses are described in Supplemental Table 3 and in the legends of
94 each figure and table. The adjusted p-values are indicated on each graph and Table. P-values
95 less than 0.05 were considered significant.

96 Normality of the residues was checked by Anderson-Darling, D'Agostino-Pearson, Shapiro-
97 Wilk, Kolmogorov-Smirnov tests and variance equality was evaluated using Brown-
98 Forsythe's and Barlett's tests.

99 Non-parametric tests were employed to assess group differences in experiments with fewer
00 than 10 biological replicates or those not meeting the assumptions of normality or
01 homoscedasticity. The Mann-Whitney test was used to compare 2 conditions while
02 comparisons of more than two conditions were performed with the Kruskal-Wallis test for
03 paired data and the Friedman test for unpaired data. Both were corrected by multiple
04 comparisons of all conditions by controlling the False Discovery Rate using the two-stage
05 linear step-up procedure of Benjamini, Krieger and Yekutieli.

06 For samples >10 that complied with the normality of the residues and homoscedasticity,
07 ordinary one-way ANOVA tests corrected with Sidak's or Tukey's multiple comparisons test
08 were performed for the analysis of more than 2 independent groups.

09 To address dependency in Figures 2D and 3A, a hierarchical analysis was performed using
10 nested one-way ANOVA corrected with Tukey's multiple comparisons test.

11 For the ChIP-, ATAC- and RNA-seq data, statistical analyses were performed using the
12 permTest function of the RegioneR package (Gel et al., 2016), the hypergeometric tests were
13 performed using the R function phyper.

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