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Reporting Summary

Nature Research 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 Research policies, see Authors & Referees and the Editorial Policy Checklist.

Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. figure legend, table legend, main text, or Methods section).

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	An indication of whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐	A description of all covariates tested
☒	☐	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☒	☐	A full description of the statistics 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)
☒	☐	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	No custom code was used for data collection
Data analysis	5C sequencing data was processed using 5C-Pro (https://github.com/bioinfo-pf-curie/5C-Pro), quality controls were performed using the HiTC BioConductor package, noisy interactions were excluded using "neighborhood coefficient of variation" (https://github.com/zhanyinx/Coefficient_Variation). Capture-C sequencing reads were trimmed using the Trim Galore! pipeline (http://www.bioinformatics.babraham.ac.uk/projects/trim_galore/), processed using the HiC-Pro pipeline (v2.8.0) and informative interactions were selected using the makeViewpoint HiC-Pro utility. RNA sequencing reads were aligned using the STAR mapper (v2.5.2b) and the GENCODE (vM1) annotations, reads counts per gene were generated with STAR. Read counts were normalized and analyzed for differential expression using the EdgeR package. RAP sequencing reads were aligned using BWA version 0.5.9, and filtered using Picard.

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/reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research 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 list of figures that have associated raw data
- A description of any restrictions on data availability

Data has been deposited in the NCBI GEO under the accession number GSE111205. This data is associated to main Figures 1, 2, 3 and 4, and to Supplementary Figures 2, 3, 4, 5 and 6.

Field-specific reporting

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

☒ Life sciences ☐ Behavioural & social sciences

For a reference copy of the document with all sections, see nature.com/authors/policies/ReportingSummary-flat.pdf

Life sciences

Study design

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

Sample size	No sample-size calculation was performed. Sample size for one biological replicate for DNA or RNA FISH experiments presented in this study was usually n>100. These numbers for single cell quantitative or qualitative analysis are common in the field.
Data exclusions	Based on our previous experiments (Nora et al 2012), inefficient primers in the 5C analysis were discarded prior to downstream analysis.
Replication	All experiments have been replicated at least twice, and all attempts of replication were successful. Replicates were performed by using an independently generated cell line and/or by repeating the experiment on the same cell line. Replicates on the same cell line were performed on independently cultured cell passages. Specifics for each experiment have been detailed in text and figure legends, in short: 5C experiments were performed twice for each cell line (replicates were pooled) with two cell lines for each genomic alteration, except for cell line 13b and D7 for which 5C was performed once; Capture-C experiments were performed once for each independent cell line; RNAseq was performed twice for each cell line, with two cell lines for each inversion; RAP was performed twice for each cell line, with one cell line for each inversion; FISH was performed at least twice for each cell line, with two cell lines for each male inversion and one for each female; nCounter analysis was performed twice for each cell line, with two cell lines for each male inversion and one for each female inversion; Pyrosequencing was performed twice on each cell line, with one cell line for each female.
Randomization	Not relevant, since experimental groups were based on genotypes.
Blinding	For key conclusions, counting of RNA FISH images was repeated blindly by an another person.

Materials & experimental systems

Policy information about availability of materials

n/a	Involved in the study
☒	☐ Unique materials
☒	☐ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Research animals
☒	☐ Human research participants

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Parental wildtype male mESCs, E14Tg2a.4, were obtained from Sanger. E14Tg2a.4 is a subclone of E14Tg2a. E14Tg2a cells were derived from the 129P2 mouse strain and Hprt mutated (Doetschman et al. Nature, 1987). Female mESCs, Pgk#106, were derived from Pgk12.1 and contain a heterozygote tetO knock-in allele (Masui et al. Cell, 2011). Pgk12.1 originates from Norris et al. Cell, 1994.
Authentication	No authentication performed on source cell lines. Cell lines generated in this study were validated using PCR and Sanger sequencing.

Mycoplasma contamination	All cell lines tested negative for Mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	None of the cell lines used are listed in the ICLAC database.

Method-specific reporting

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ Magnetic resonance imaging