nature research

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# Life Sciences Reporting Summary

Nature Research wishes to improve the reproducibility of the work we publish. This form is published with all life science papers and is intended to promote consistency and transparency in reporting. All life sciences submissions use this form; while some list items might not apply to an individual manuscript, all fields must be completed for clarity.

For further information on the points included in this form, see Reporting Life Sciences Research. For further information on Nature Research policies, including our data availability policy, see Authors & Referees and the Editorial Policy Checklist.

## Experimental design

1. Sample size

Describe how sample size was determined.

No statistical methods were used to determine the samples sizes. Samples sizes were determined by the amount of biological material available. For each experiment two or more biological replicates are presented. Reduced sample sizes were sufficient in cases where a marked contrast between the control and experimental samples was observed together with low variance between different replicates.

2. Data exclusions

Describe any data exclusions.

One of the eight sets of TAIL-seq spike-ins was excluded from the spike-in recovery analysis because it was behaving as a clear outlier.

3. Replication

Describe whether the experimental findings were reliably reproduced.

All attempts at replication were successful

4. Randomization

Describe how samples/organisms/participants were allocated into experimental groups.

Samples were allocated to groups according to genotype. In order to control for covariates, control and experimental samples were always processed in parallel.

5. Blinding

Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

No blinding was used during data acquisition and analysis. Data blinding was not used due to the small number of samples processed at any one time.

Note: all studies involving animals and/or human research participants must disclose whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or the Methods section if additional space is needed).

| n/a | Confirmed | |
|---|---|---|
| ☐ | ☒ | The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.) |
| ☐ | ☒ | A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly. |
| ☐ | ☒ | A statement indicating how many times each experiment was replicated |
| ☐ | ☒ | The statistical test(s) used and whether they are one- or two-sided (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section) |
| ☐ | ☒ | A description of any assumptions or corrections, such as an adjustment for multiple comparisons |
| ☐ | ☒ | The test results (e.g. *p* values) given as exact values whenever possible and with confidence intervals noted |
| ☐ | ☒ | A summary of the descriptive statistics, including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range) |
| ☐ | ☒ | Clearly defined error bars |

*See the web collection on statistics for biologists for further resources and guidance.*

## Software

Policy information about availability of computer code

7. Software

| | |
|---|---|
| Describe the software used to analyze the data in this study. | In this study we used the TAIL-seq software obtained from Prof. Narry Kim's group. Scripts used to further process the TAIL-seq data output will be made available in GitHub, https://github.com/marcosmorgan/TAIL-seq. |

For all studies, we encourage code deposition in a community repository (e.g. GitHub). Authors must make computer code available to editors and reviewers upon request. The *Nature Methods* guidance for providing algorithms and software for publication may be useful for any submission.

## Materials and reagents

Policy information about availability of materials

8. Materials availability

| | |
|---|---|
| Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a for-profit company. | All mice, cell lines and materials generated in this study are readily available from the authors or from standard commercial sources. |

9. Antibodies

| | |
|---|---|
| Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species). | The following antibodies were used: anti-TUT4 (Proteintech, 18980-1-AP), anti-AGO2 (O'Carroll lab), anti-HA (Covance, MMS-101P) and anti-α-tubulin (Sigma, T9026), anti-TUT7 (a gift from R. Pillai, University of Geneva) and anti-SMC1α (Bethyl, A300-055A). |

10. Eukaryotic cell lines

| | |
|---|---|
| a. State the source of each eukaryotic cell line used. | Mouse embryonic fibroblasts and embryonic stem cells were derived from mice generated in the laboratory. |
| b. Describe the method of cell line authentication used. | After derivation of the cell lines used no further verification was performed. |
| c. Report whether the cell lines were tested for mycoplasma contamination. | All cell lines were tested negative for mycoplasma. |
| d. If any of the cell lines used in the paper are listed in the database of commonly misidentified cell lines maintained by ICLAC, provide a scientific rationale for their use. | No commonly misidentified cell lines were used. |

## Animals and human research participants

Policy information about studies involving animals; when reporting animal research, follow the ARRIVE guidelines

11. Description of research animals

| | |
|---|---|
| Provide details on animals and/or animal-derived materials used in the study. | The animals and the alleles used in this study are described in the methods section. For each experiment the sex and age of the animals are reported in the corresponding method section. |

Policy information about studies involving human research participants

12. Description of human research participants

| | |
|---|---|
| Describe the covariate-relevant population characteristics of the human research participants. | The study did not involve human research participants. |