nature portfolio

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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
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on 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 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)
☐	☒ 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

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	In silico mismatch data was obtained with AstraZeneca proprietary software based on Cas Offinder software (https://github.com/snugel/cas-offinder).
Data analysis	Data visualization and statistical analysis were done with GraphPad Prism 10 (GraphPad Software, Inc.) and R 4.2.3. Amplicon sequencing data was analyzed with a pipeline based on RIMA (DOI: 10.1093/nar/gky653). PASTA translocation analysis used fg-idprimer (https://github.com/fulcrumgenomics/fg-idprimer; -k=6, -K=8, -S=5, --max-mismatch-rate=0.07). Long-read sequencing analysis used the following public tools: minimap2 v2.29 (Li, H. Minimap2: pairwise alignment for nucleotide sequences. Bioinformatics 34, 3094-3100 (2018)), SAMtools v1.22 (Danecek, P. et al. Twelve years of SAMtools and BCFtools. Gigascience 10 (2021)), Sniffles2 v2.6.2 (Smolka, M. et al. Detection of mosaic and population-level structural variants with Sniffles2. Nature Biotechnology 42, 1571-1580 (2024)), VariantAnnotation Bioconductor package (Obenchain, V. et al. VariantAnnotation: a Bioconductor package for exploration and annotation of genetic variants. Bioinformatics 30, 2076-2078 (2014)), rtracklayer package and GenomicRanges (Lawrence, M. et al. Software for computing and annotating genomic ranges. PLoS Comput Biol 9, e1003118 (2013)). scATAC-seq/scRNA-seq analysis used the following public tools: bcl2fastq (v2.20.0.422), 10x Genomics Cellranger (cellranger-arc count v 2.0.2), Signac (1.10.0) (Stuart, T., Srivastava, A., Madad, S., Lareau, C.A. & Satija, R. Single-cell chromatin state analysis with Signac. Nat Methods 18, 1333-1341 (2021)), Seurat (4.3.0.1) (Hao, Y. et al. Integrated analysis of multimodal single-cell data. Cell 184, 3573-3587 e3529 (2021)), MACS2 (2.2.9.1) (Zhang, Y. et al. Model-based analysis of ChIP-Seq (MACS). Genome Biol 9, R137 (2008)). Total RNA-seq used the following public tools: FastQC (v0.12.1) (https://www.bioinformatics.babraham.ac.uk/projects/fastqc/), RNAseQC (2.3.5) (Graubert, A., Aguet, F., Ravi, A., Ardlie, K.G. & Getz, G. RNA-SeQC 2: efficient RNA-seq quality control and quantification for large cohorts. Bioinformatics 37, 3048-3050 (2021)), samtools stats (v1.18) (Li, H. et al. The Sequence Alignment/Map format and SAMtools. Bioinformatics 25, 2078-2079 (2009)), STAR (v2.7.11a) (Dobin, A. et al. STAR: ultrafast universal RNA-seq aligner. Bioinformatics 29, 15-21 (2013)), MultiQC (v1.17) (Ewels, P., Magnusson, M., Lundin, S. & Kaller, M. MultiQC: summarize analysis results for multiple tools and samples in a single report. Bioinformatics 32, 3047-3048 (2016)), FastP (v0.23.4) (Chen, S. Ultrafast one-pass FASTQ data preprocessing, quality

control, and deduplication using fastp. Imeta 2, e107 (2023)), Salmon (v1.10.1) (Patro, R., Duggal, G., Love, M.I., Irizarry, R.A. & Kingsford, C. Salmon provides fast and bias-aware quantification of transcript expression. Nat Methods 14, 417-419 (2017)), Nextflow workflow management system (v23.10) (Di Tommaso, P. et al. Nextflow enables reproducible computational workflows. Nat Biotechnol 35, 316-319 (2017)) and Bioconda software repository (Gruning, B. et al. Bioconda: sustainable and comprehensive software distribution for the life sciences. Nat Methods 15, 475-476 (2018)). DNA methylation analysis was done with BEDTools (Quinlan, A.R. & Hall, I.M. BEDTools: a flexible suite of utilities for comparing genomic features. Bioinformatics 26, 841-842 (2010)).

Translocation analysis based on rhAmpSeq amplicon sequencing was performed using PASTA [https://www.biorxiv.org/content/10.64898/2026.07.23.740402v1]. The custom code for scATAC-seq and RNA-seq experiments to determine % cells with open chromatin peak and % cells expressing gene, and to calculate average methylation around the cleavage sites can be found at [https://github.com/AstraZeneca/Madsen_etal_2026].

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

All details and data to support the findings of this study are part of the manuscript or available in a publicly accessible repository. The sequencing data generated in this study have been deposited in the NCBI Sequence Read Archive database under accession code SRP699144 [https://www.ncbi.nlm.nih.gov/sra/?term=SRP699144]. BioProject number: PRJNA1461838 [https://www.ncbi.nlm.nih.gov/bioproject/PRJNA1461838]. Processed data is provided in the Supplementary Data files. Source data are provided with this paper.

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	Primary HSPCs were acquired from Charles River from both male and female donors. No sex-based analyses have been performed due to the low number of donors (n=3 donors total)
Reporting on race, ethnicity, or other socially relevant groupings	Not collected
Population characteristics	Not collected
Recruitment	N/A
Ethics oversight	AstraZeneca has a governance framework and processes in place to ensure that commercial sources have appropriate patient consent and ethical approval in place for collection of the samples for research purposes including use by for-profit companies.

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

Life sciences study design

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

Sample size	No sample size precalculation was performed. Sample size was determined as generation of at least triple independent samples for comparisons between groups that is sufficient to perform statistical tests.
Data exclusions	Genomic loci with less than 2,000x coverage in rhAmpSeq or less than 10,000x coverage in amplicon sequencing were excluded from the analysis due to the limited sensitivity achieved at this depth. No other data/samples were excluded.

Replication	Experiments producing key data on single-cell editing were repeated by different co-authors. The experimental findings can be reliably reproduced.
Randomization	In vitro experiments were not randomized; mice were randomized into groups based on their sex and age.
Blinding	The Investigators were not blinded to allocation during experiments and outcome assessment.

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
☒	☐ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	C57Bl6/N mESCs were acquired from Primogenix. HSPCs were acquired commercially from Charles River.
Authentication	Cell lines were authenticated by the suppliers prior to shipping.
Mycoplasma contamination	All cell lines tested negative for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	N/A

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	Cryopreserved C57BL6/N mouse zygotes were purchased from Janvier labs (#SE-ZYG-CNG). C57BL/6N mice were bought from Charles River. C57Bl6/N mESCs for generation of transgenic mice were acquired from Primogenix (C57BL/6N-PRX-B6N #1). The two inducible Pcsk9-editing mouse models (doxy-gP and doxy-gMH) were generated by electroporation of Primogenix C57BL6/N (PrX) ES cells with the respective DNA constructs, injection into Balb/cAnCrl blastocysts to generate chimeric mice, and breeding of chimeric males with C57BL/6N Crl females. Transgene presence was verified by genotyping. Wild-type litter mates were used as controls.
Wild animals	N/A
Reporting on sex	All experimental groups consisted of equal numbers of female and male mice (i.e. 2 + 2 animals). No sex-based analyses have been performed due to the low number of animals.
Field-collected samples	N/A
Ethics oversight	All animal experiments were approved by the AstraZeneca internal committee for animal studies as well as the Gothenburg Ethics Committee for Experimental Animals (license number 2194-2019), compliant with EU directives on the protection of animals used for scientific purposes.

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

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A