

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 (<i>n</i>) 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
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☐ | ☒ 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. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted
<i>Give P values as exact values whenever suitable.</i> |
| ☒ | ☐ 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 <i>d</i> , Pearson's <i>r</i>), 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	Sequencing data were collected using Illumina FASTQ Generation version 1.0.0 for NextSeq 2000 runs and Oxford Nanopore MinKNOW version 25.09.16 for PromethION runs. Oxford Nanopore runs used Bream version 8.8.3, Configuration version 6.8.9 and MinKNOW Core version 6.8.11, and were basecalled using Dorado version 7.11.2.
Data analysis	Illumina and Oxford Nanopore sequencing reads were processed and analyzed using custom Python scripts available at https://github.com/Shipman-Lab/Detectron . Custom scripts were used to demultiplex reads, count barcode sequences, and calculate barcode enrichment or fold-change values.

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](#)

Sequencing data associated with this study are available in the NCBI Sequence Read Archive (Bioproject PRJNA1366125). Source data underlying the figures are provided in Source Data file 1. Complete variant, plasmid, primer and statistical summary information are provided in the Supplementary Tables.

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	n/a
Reporting on race, ethnicity, or other socially relevant groupings	n/a
Population characteristics	n/a
Recruitment	n/a
Ethics oversight	n/a

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	No statistical method was used to predetermine sample size. Quantitative experiments were performed with at least three independent biological replicates unless otherwise stated, consistent with standard practice for molecular biology and synthetic biology assays. The ratiometric host-susceptibility was performed with nine matched biological replicates. For the variant library and machine-learning analyses, sample size was determined by the number of successfully recovered variants after applying the predefined exclusion criterion, yielding 7,814 variants. No statistical testing was performed until all biological replicates had been collected.
Data exclusions	Variants in the Detectron variant library were excluded using a predefined variance-based criterion: SEM greater than 50% of the corresponding mean across biological replicates. This excluded 26 of 7,840 variants, leaving 7,814 variants for analysis. No other data were excluded.
Replication	All experiments were performed with biological replicates as indicated in the figure legends. Quantitative experiments were performed using independent biological replicates, and all replicate values are shown where applicable. All attempts at replication were successful.
Randomization	Random allocation was not applicable because experimental groups were defined by predetermined plasmid constructs, bacterial strains, phage treatments, barcode identities or RNA inputs. Samples were processed in parallel under matched experimental conditions, and relevant technical covariates were controlled through predefined normalization strategies, including plasmid normalization, WT barcode normalization or strain-matched reference barcode normalization.
Blinding	Blinding was not relevant because the study used predefined bacterial strains, plasmid constructs, phage treatments and DNA barcode identities, and the primary measurements were objective molecular readouts from qPCR, sequencing or PAGE analysis. Group identities were required for experimental setup, barcode demultiplexing and normalization, and no subjective outcome scoring was performed.

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

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	No laboratory animals were used. This study used bacterial strains and bacteriophages, as described in the Methods.
Wild animals	This study did not involve wild animals.
Reporting on sex	Sex-based analysis was not applicable because this study used bacterial strains and bacteriophages.
Field-collected samples	This study did not involve field-collected samples.
Ethics oversight	No ethical approval was required because this study did not involve humans, human samples, vertebrate animals or regulated animal research.

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