nature research

Corresponding author(s): Hayden C. Metsky

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	We downloaded sequences from NCBI GenBank, using the Entrez module in Biopython (v1.66), and other resources. Details are given in the Methods section. See Supplementary Table 1 for links to downloaded accessions.
Data analysis	We used the publicly available software package viral-ngs v1.17.0 (http://viral-ngs.readthedocs.io/en/latest/) to analyze all sequencing data including demultiplexing of sequencing runs, viral genome assembly, taxonomic read classification, alignment to viral genomes, and detection of intra-host variants. Additional custom scripts specific to our compute environment were used for generating plots and parsing output.

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

Sequences used as input for probe design (Supplementary Table 1) are available in the repository at <https://github.com/broadinstitute/catch>. Sequences of the probe designs are available at <https://github.com/broadinstitute/catch/tree/cf500c6/probe-designs>. Viral genomes sequenced as part of this study will be deposited in NCBI GenBank(Clark et al. 2016) prior to publication under BioProject accession PRJNA431306 (PRJNA436552 for the 2018 Lassa virus genomes).

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 ☐ Ecological, evolutionary & environmental 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	We performed experimental testing of CATCH using a total of 68 patient and environmental samples (30 samples for validation, 23 samples for 2018 Lassa virus sequencing, and 15 pools of samples with uncharacterized contents). Predetermining sample size is not applicable here as no statistical tests were performed.
Data exclusions	No data were excluded from the analyses, except for samples with too few raw sequencing reads (explained in Methods and highlighted in Supplementary Table 3). These limits were determined prior to data analysis based on total sequencing output.
Replication	Replication in this study was evaluated via the inclusion of multiple samples containing the same known virus. For evaluating within-host variants (Fig. 3d), we used multiple sequencing replicates and saw high concordance. For assessing sensitivity in a dilution series, we used two replicates (Fig. 3a) and saw high concordance.
Randomization	No randomization was performed. Randomization was not applicable as we do not make statistical claims based on this data.
Blinding	Investigators were not blinded to the identities of samples containing known viruses. However, the 15 sample pools for which microbial content was uncharacterized prior to testing serve as a form of blinded evaluation since no pathogen in these samples were known to the investigator.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☐	☒ Unique biological materials
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☐	☒ Human research participants

Methods

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

Unique biological materials

Policy information about availability of materials

Obtaining unique materials	Unique materials are not available from commercial sources nor from the authors. All materials included in this study were collected for research purposes and included in this study with full ethical approvals. Materials are limited in volume and subject

to ethical and institutional restrictions on their use due to sample provenance.

Human research participants

Policy information about studies involving human research participants

Population characteristics	Population characteristics are not relevant as only viral genetic material detected within human-derived samples was analysed in this study.
Recruitment	Samples from human subjects included in this study were obtained from numerous studies that had been evaluated and approved by the relevant Institutional Review Boards (IRBs) or Ethics Committees. All studies recruited individuals presenting at respective recruitment locations based on study-specific inclusion and exclusion criteria. There are no relevant biases as the study focuses on viral infections present in these human-derived samples.