nature research

Corresponding author(s): Feixiong Cheng and Haiyuan Yu

Last updated by author(s): Aug 4, 2022

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 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	No software was used for data collection.
Data analysis	Empirical Bayes estimation of prior variance was calculated using limma package v3.46.0 in R platform v4.0.3. All other statistical analyses were conducted using MatchIt package v4.0.0 in R platform v4.1.0. A sigmoid fit was used to extract EC50 values using MATLAB (2020b). All networks were visualized using Cytoscape v3.8.0. Code availability: https://github.com/ChengF-Lab/COVID-19_Map

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 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

GTEx v8 data was downloaded from https://gtexportal.org/home/

ENCODE ZNF579 ChIP-seq is available under accession no. ENCSR018MQH.

RNA-seq of human bronchial epithelial cells infected with SARS-CoV-2 is available under accession no. GSE147507.
RNA-seq of upper airway from COVID-19 patients vs. non-COVID-19 patients is available under accession no. GSE156063.
RNA-seq of peripheral blood mononuclear cells isolated from COVID-19 patients vs. non-COVID-19 patients is available under accession no. GSE157103.

Mass spectrometry proteomics data have been deposited to the ProteomeXchange Consortium via the PRIDE partner repository with the dataset identifier PXD035805.

Human protein-protein interactome and drug-target network are available at https://github.com/ChengF-Lab/COVID-19_Map
An interactive version of Fig. 1b is available at https://github.com/ChengF-Lab/COVID-19_PPI

Unaltered scans used to generate Fig. 2b-c and Fig. 2f-h are available in the Source Data file.

All other data are available in the supplementary tables.

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 statistical method was used to predetermine sample size. Sample size was determined by sample and data availability. All available samples and data were used in our experiments and analyses. Specifically, for our interactome screens, we tested all available viral and human proteins in our clone libraries, and for our analyses, we used all available data.
Data exclusions	No data were excluded from our results or analyses.
Replication	Quantification data represent mean ± SD of three independent experiments for in vitro assays. All attempts at replication were successful.
Randomization	Not applicable as all experiments and analyses were performed using all available samples.
Blinding	Not applicable as all experiments and analyses were performed using all available samples.

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
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Antibodies

Antibodies used

V5 tag monoclonal antibody (NA) (catalog no. R960-25; Invitrogen)
c-Myc monoclonal antibody (9E10) (catalog no. 13-2500; Invitrogen)
Anti-FLAG monoclonal antibody (M2) (catalog no. Fl804; Sigma-Aldrich)
ZNF579 polyclonal antibody (NA) (catalog no. A303-275A; Bethyl Laboratories)
Anti-SARS-CoV-2-spike antibody (1A9) (catalog no. GTX632604; GeneTex)

Validation

All manufacturers showed validation data for antibodies on their websites (including WB, IF, IHC, etc.)

V5 tag monoclonal antibody (NA) (catalog no. R960-25; Invitrogen) was verified by relative expression to ensure that the antibody binds to the antigen stated. (https://www.thermofisher.com/antibody/product/V5-Tag-Antibody-Monoclonal/R960-25)
c-Myc monoclonal antibody (9E10) (catalog no. 13-2500; Invitrogen) was verified by relative expression to ensure that the antibody binds to the antigen stated. (https://www.thermofisher.com/antibody/product/c-Myc-Antibody-clone-9E10-Monoclonal/13-2500)
Anti-FLAG monoclonal antibody (M2) (catalog no. Fl804; Sigma-Aldrich) (https://www.sigmaaldrich.com/US/en/product/sigma/f1804)
ZNF579 polyclonal antibody (NA) (catalog no. A303-275A; Bethyl Laboratories) (https://www.thermofisher.com/antibody/product/ZNF579-Antibody-Polyclonal/A303-275A)
Anti-SARS-CoV-2-spike antibody (1A9) (catalog no. GTX632604; GeneTex) (https://www.genetex.com/Product/Detail/SARS-CoV-SARS-CoV-2-COVID-19-spike-antibody-1A9/GTX632604)

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

Caco-2 (HTB-37) cells were purchased from ATCC.
HEK 293T (CRL-3216) cells were purchased from ATCC.
A549 (CCL-185; ATCC) cells exogenously expressing angiotensin-converting enzyme 2 (ACE2) (A549-ACE2) were a gift from Benjamin R. Tenoever, Icahn School of Medicine at Mount Sinai.

Authentication

A549-ACE2 cells were authenticated by the Tenoever Lab, Icahn School of Medicine at Mount Sinai.

All other cell lines were not further authenticated.

Mycoplasma contamination

No mycoplasma contamination was detected via PCR.

Commonly misidentified lines
(See ICLAC register)

No commonly misidentified cell lines were used in this study.