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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	Graphad Prism v8 and v9 were used to produce figures. Mafft v7.475 was used for multiple sequence alignments. IQTREE and ModelFinder v2.1.2 was used to infer maximum-likelihood phylogenies. Figtree v1.4.4 was used to annotate and manipulate phylogeny trees. NextClade server v0.9 and Pangolin v2.12 were used to assign lineages to sequences.
Data analysis	Software versions and parameters used for sequence conservation analysis are reported in methods. For in-depth variant analyses, the SAMFIRE package v1.06 was used (https://github.com/cjri/samfire/). To validate frequency variants, custom code was used as part of the package AnCovMutlti (github.com/PollockLaboratory/AnCovMulti).

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

Sequences fro SARS-CoV-2 were obtained from GISAID database (https://gisaid.org/) using the filters and search parameters defined in the methods section.

Structural models were obtained from the Protein Data Bank (PDB) https://www.rcsb.org/.
Long-read sequencing data that support the findings of this study have been deposited in the NCBI SRA database with the accession codes SAMN16976824 - SAMN16976846 under BioProject PRJNA682013 (https://www.ncbi.nlm.nih.gov/bioproject/PRJNA682013). Short-read and consensus fasta files have been deposited and are available to view and download on GitHub (https://github.com/Steven-Kemp/sequence_files). Raw data used to create figures are available to view and download on GitHub (https://github.com/Steven-Kemp/sequence_files/tree/main/figure_data).

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 formal sample size calculation was undertaken as this case study report focused only on a single patient. By definition n=1
Data exclusions	No data were excluded.
Replication	All experimental data were reproducible and we have shown data representative of at least two independent experiments
Randomization	not applicable as this is a descriptive study of one patient
Blinding	not applicable as this is a descriptive study of one patient and blinding was not appropriate

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	Panel of non-commercially available antibodies fully described in Science: DOI: 10.1126/science.abc5902. were provided by Brouwer et al at request. All antibiodies were diluted to a starting concentration of 10 ug/ml and then titrated 5-fold, except for COVA1-18 which was at a starting concentration of 1 ug/ml and COVA2-02 at a starting assay concentration of 30 ug/ml due to their different neutralization potency. Spike S2 antibody (Invitrogen,, Cat no: Pa1-41165), p24 antibody (NIH AIDS Reagents cat no: ARP465). Anti-CD3 antibody (MEM57, Abcam, 200 ng/ml, 1:1000, Cat no Ab8090)
Validation	Validated by providing lab: see supplementary: https://science.sciencemag.org/content/sci/suppl/2020/06/15/science.abc5902.DC1/abc5902-Brouwer-SM.pdf

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	HeLa cells were donated by kind request from James Voss as noted in the acknowledgments section. HEK 293T cells from ATCC were used for transfection work.
Authentication	None of the cell lines used were authenticated.

Mycoplasma contamination	All cell lines used were tested a(by PCR) and were mycoplasma free.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified lines were used in this study.

Human research participants

Policy information about studies involving human research participants

Population characteristics	A single septuagenarian male was treated at a local Cambridge hospital for COVID-19 symptoms.
Recruitment	As part of routine testing, nose + throat samples and endotracheal aspirates were collected from the patient at 23 time-points.
Ethics oversight	*Identify the organization(s) that approved the study protocol.*

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