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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 Authors & Referees 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	Sequence data were collected using ABI Prism 3130xl Genetic Analyzer data collection software (version 3.0).
Data analysis	GENETYX genetic information processing software (version 13) was used for sequence alignment. ATGC sequence assembly software (version 7.0) was used for sequence assemblies. Graphpad Prism (version 5) was used for calculating EC50 values. The R statistical package (www.r-project.org) was used for statistical analyses.

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. 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

The data that support the findings of this study are available from the corresponding author upon request. Samples were deposited in the Sequence Read Archive of the NCBI, under project accession PRJNA573567.

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 determine sample size. The sample sizes (n = 3) for the hamster, mouse, and ferret studies were chosen because they have previously been shown to be sufficient to evaluate a significant difference among groups (Belser et al., Nature, 2013; Maines, et al., Science, 2009; Zhang et al., Science, 2013).
Data exclusions	No data were excluded.
Replication	All attempts at replication were successful.
Randomization	No method of randomization was used to determine how the animals were allocated to the experimental groups and processed in this study.
Blinding	No blinding was carried out.

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
☐	☒ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data

Methods

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

Antibodies

Antibodies used	A rabbit polyclonal antibody for influenza A virus nucleoprotein (NP) was prepared in the Department of Pathology, National Institute of Infectious Diseases (Iwasaki et al, Arch Virol, 1999). The antibody was used at a 1:4000 dilution.
Validation	The antibody used for immunohistochemistry (anti-type A influenza NP) was validated in a previous publication (Iwasaki et al., Arch Virol, 1999).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	The hCK cell line was engineered from the MDCK cell line in a previous publication (Takada et al., Nature Microbiology, 2019). The human embryonic kidney (HEK) 293T cell line was obtained from Dr. Tadashi Matsuda.
Authentication	The DNA fingerprinting method was used to show that the hCK and 293T cells have the same origin as the MDCK (CCL-34) and 293T cells (CRL-3216) obtained from ATCC, respectively.
Mycoplasma contamination	All cell lines were regularly tested for mycoplasma contamination by using PCR and were confirmed to be mycoplasma-free.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	Syrian hamsters, BALB/c, and DBA/2 mice were obtained from Japan SLC Inc., Japan. Ferrets were obtained from Wuxi Sangosho Biotechnology Co., Ltd., China. Four- to six-week-old female Syrian hamsters and six-week-old female BALB/c and DBA/2 mice were used in this study. Three- to five-month-old female ferrets were used in this study.
Wild animals	No wild animal was used in this study.
Field-collected samples	This study did not involve samples collected from the field.
Ethics oversight	All experiments with Syrian hamsters, mice, and ferrets were performed in accordance with the University of Tokyo's Regulations for Animal Care and Use and were approved by the Animal Experiment Committee of the Institute of Medical Science, the University of Tokyo.

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	A total of 259 individuals [male/female = 138/121; mean age = 15 years (range: 0–88 years)] were enrolled to this study. Please see Supplementary Tables 1–4.
Recruitment	Patients with influenza-like symptoms were recruited at 8 medical facilities (Clinic Bambini, Hagiwara Clinic, Akebonocho Clinic, Sotobo Children's Clinic, Alpaca Kids Ent Clinic, Wada Pediatric Clinic, IMSUT Hospital of the Institute of Medical Science, and Nezu Clinic) during the 2018–2019 influenza season in Japan regardless of age, sex , gender, race, ethnicity, or other characteristics. Written informed consent was obtained from the patient or patient's guardian before study enrollment.
Ethics oversight	The research protocol was approved by the Research Ethics Review Committee of the Institute of Medical Science of the University of Tokyo (approval no. 26-42-0822).

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