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Reporting Summary

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Please do not complete any field with "not applicable" or n/a. Refer to the help text for what text to use if an item is not relevant to your study.
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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	
☐	X	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	X	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	X	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.*
x	☐	A description of all covariates tested
☐	X	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	x	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)
☐	x	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.*
x	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
x	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
x	☐	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: Imaging data were collected using Cell Profiler; qPCR dataViiA7 thermocycler or HT7900 (Applied Biosystems).
Membranes were scanned using the Odyssey CLx System (LI-COR). Comparative signal analyses were performed using Image Studio software (LI-COR)
ELISA plate reader: FluoStar Omega microplate reader (BMG Labtech)
cGAS assay: Images were collected using the FLA-5100 imaging system (Fujifilm) and cGAMP accumulation quantified using ImageQuant TL 7.0 (GE Healthcare)

Data analysis: Data were analyzed using Prism 8 (GraphPad, Scientific software). RNA-seq data were analysed using Cutadapt v2.0, HISAT2 v2.1.041, SAMtools v1.6 and DESeq2 v1.24.0. Expression of transposable elements in RNA-Seq data of patient and control fibroblasts was analysed using SQUIRE (as referenced)
CellProfiler (version 2.1.1) and ImageJ (version 1.50i) were used for image analysis. Image studio (form Li-Cor) was used for western blot quantification.

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

RNA-Seq data have been deposited at NCBI GEO (accession number GSE153079). Exome and genome sequencing data is not publicly available due to the possibility of compromising privacy.

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	Statistical methods were not used to determine sample size. Sample size was limited by the number of patients available to us in whom we identified biallelic rare variants in either LSM11 or RNU7-1.
Data exclusions	No data were excluded from the analysis
Replication	Experiments were performed with a minimum of 3 biological and/or technical replicates and were reliably reproduced.
Randomization	No randomisation was used in this study as we were comparing patient and controls.
Blinding	Investigators were not blinded during data collection/analysis. Blinding was not possible because of the need to compare patients and controls

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: anti-cGAS (Cell Signalling Technologies (CST), 15102S, clone D1D3G); anti-cofilin (CST, 5175, clone D3F9); anti-H1.2 (GeneTex, GTX122561, polyclonal); anti-H1.4 (CST, 41328S, clone D4J5Q); anti-H2A (CST, 12349, clone D6O3A); anti-H2B (CST; 12364, clone D2H6); anti-H3 (CST; 4499, clone D1H2); anti-H4 (CST, 13919, clone D2X4V); anti-ISG15 (Abcam, ab14374, polyclonal); anti-laminA/C (CST, 4777, clone 4C11); anti-MX1 (Abcam, ab95926, polyclonal); anti-STING (R&D systems, MAB7169, clone 723505); anti-vinculin (CST, 4650, polyclonal).
Anti-ORF1p was a gift by Oliver Weichenrieder (Max Planck, Tuebingen).
Goat anti-mouse IgG IRDye 800CW (Li-COR, 926-32210); Goat anti-rabbit IgG IRDye 800CW (Li-COR, 926-32211)

Validation

All commercially available antibodies have been validated by the manufacturer with supporting publications found on manufacturer websites. Antibodies were further validated in-house using relevant positive and negative controls.
The human LINE-1 ORF1 antibody was validated in the lab of Oliver Weichenrieder (Max Planck, Tuebingen)

Summary of commercially available antibodies:
anti-cGAS - Cell Signalling Technologies (CST), 15102S
Species: Human
Application: Western Blot

anti-cofilin - CST, 5175
Species: Human, Mouse, Rat, Monkey, Dog
Application: Western Blot, Immunofluorescence

anti-H1.2 - GeneTex, GTX122561
Species: Human
Application: Western Blot, Immunofluorescence, Immunohistochemistry (Paraffin)

anti-H1.4 - CST, 41328S
Species: Human, Monkey
Application: Western Blot, Chromatin Immunoprecipitation

anti-H2A - CST, 12349
Species: Human, Monkey, Mouse, Rat, Zebrafish
Application: Western Blot, Immunofluorescence, Chromatin Immunoprecipitation

anti-H2B - CST; 12364
Species: Human, Mouse, Rat, Monkey
Application: Western Blot, Immunohistochemistry, Chromatin Immunoprecipitation

anti-H3 - CST; 4499
Species: Human, Mouse, Rat, Monkey
Application: Western Blot, Immunohistochemistry, Immunofluorescence, Flow cytometry

anti-H4 - CST, 13919
Species: Human, Mouse, Rat, Monkey
Application: Western Blot, Immunohistochemistry, Immunofluorescence

anti-ISG15 - Abcam, ab14374
Species: Human
Application: Western Blot, ELISA

anti-laminA/C - CST, 4777
Species: Human, Mouse, Rat, Monkey
Application: Western Blot, Immunoprecipitation, Immunohistochemistry, Immunofluorescence, Flow cytometry
anti-MX1 - Abcam, ab95926
Species: Human, Monkey
Application: Western Blot, Immunohistochemistry (Paraffin)

anti-phospho-STING (CST, 19781S)
Species: Human
Application: Western Blot

anti-vinculin - CST, 4650
Species: Human, Mouse, Rat, Monkey, Dog
Application: Western Blot

Goat anti-mouse IgG IRDye 800CW (Li-COR, 926-32210)
Based on ELISA and flow cytometry, this antibody reacts with the heavy and light chains of mouse IgG1, IgG2a, IgG2b, and IgG3, and with the light chains of mouse IgM and IgA. This antibody was tested by dot blot and and/or solid-phase adsorbed for minimal cross-reactivity with human, rabbit, goat, rat, and horse serum proteins, but may cross-react with immunoglobulins from other species. The conjugate has been specifically tested and qualified for Western blot applications.

Goat anti-rabbit IgG IRDye 800CW (Li-COR, 926-32211)
Based on ELISA and flow cytometry, this antibody reacts with the heavy and light chains of rabbit IgG, and with the light chains of rabbit IgM and IgA. This antibody was tested by dot blot and and/or solid-phase adsorbed for minimal cross-reactivity with human, mouse, rat, sheep, and chicken serum proteins, but may cross-react with immunoglobulins from other species. The conjugate has been specifically tested and qualified for Western blot and In-Cell Western™ assay applications.

Eukaryotic cell lines

Cell line source(s)	Cell lines were from: Bj-5ta (ATCC, ref. CRL-4001); HEK293 (Invitrogen, ref. R78007); 293FT (Invitrogen, ref. R70007); THP1 STING KO (Invitrogen, ref. thpd-kostg); cGAS KO (Invitrogen, ref. thpd-kocgas); THP1 WT and MAVS KO were a gift from Jan Rehwinkel; HCT116 and PA-1 were provided by Duncan Sproul and by Jose L Garcia-Perez respectively.
Authentication	Cell lines were not authenticated
Mycoplasma contamination	All cell lines tested negative for mycoplasma
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	18 patients from 11 families, 11 males, 7 females, first presenting in early childhood and demonstrating a clinical phenotype consistent with a diagnosis of Aicardi-Goutières syndrome.
Recruitment	Patients conforming to a clinical diagnosis of Aicardi-Goutières syndrome were recruited through the physician responsible for their care.
Ethics oversight	Comité de Protection des Personnes (ID-RCB/EUDRACT: 2014-A01017-40) in France, and the Leeds (East) Research Ethics Committee (REC reference: 10/H1307/2; IRAS project ID: 62971) in the UK.

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

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	not a clinical trial
Study protocol	*Note where the full trial protocol can be accessed OR if not available, explain why.*
Data collection	*Describe the settings and locales of data collection, noting the time periods of recruitment and data collection.*
Outcomes	*Describe how you pre-defined primary and secondary outcome measures and how you assessed these measures.*