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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.

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	*Provide a description of all commercial, open source and custom code used to collect the data in this study, specifying the version used OR state that no software was used.*
Data analysis	The results of the the raw mass spectrometry data were matched to the Protein Prospector algorithm (http://prospector.ucsf.edu/prospector/mshome.htm) and data were searched against the SwissProt Human protein sequence database (downloaded March 6, 2012). Interactor scoring was determined using the MiST (https://github.com/kr oganlab/mist) and compPASS algorithms (http://bioplex.hms.ha rvard.edu/download Comppass.php). The WNV-host protein-protein interaction network was generated using Cytoscape (version 2.8.3, Smoot et al., 2011) and host protein complexes were derived using CORUM (http://mips.helmholtz-muenchen.de/corum/). Heat maps depicting Gene Ontology terms and associated significance values were analyzed and visualized using Metascape (http://metascape.org/gp/index.html#/main/step1). The heat map generated from siRNA screening data was visualized and analyzed using Morpheus (https://software.broadinstitute.org/morpheus/).

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

The raw mass spectrometry data has been submitted to PRIDE (Project accession: PXD011728). A complete list of all MiST and compPASS scores for interacting host proteins are provided in Table S1 and the interactors that are above our designated threshold are in Table S2. All Gene Ontology enrichment analyses and associated significance values are provided in Tables S3, S6 and S7. Overlap with previous proteomic and genetic studies with associated PMIDs are provided in Table S4. The overlap of flavivirus capsid interactors, including MiST and compPASS scores for DENV and ZIKV-interacting host proteins that are above our designated threshold are in Table S5. Interactors selected for RNAi screening and all screening data is provided in Table S8. All siRNA and primer sequences used in this study are provided in Tables S9 and S10. Any additional data related to this manuscript will be provided upon request.

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	Sample size was determined using classical statistical methods for calculations of mean and significance.
Data exclusions	No data was excluded from analysis.
Replication	All experimental findings were reliably reproduced.
Randomization	Not relevant to this study
Blinding	Not relevant to this study

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	All unique materials used in this study are readily available upon request.

Antibodies

Antibodies used	All antibodies used in the this study are commercially available. The supplier and catalog numbers are provided in the methods section of the text.

Validation	Validation of all antibodies provided by the manufacturer as indicated in the text.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	ATCC
Authentication	Cell lines were obtained from ATCC without independent validation.
Mycoplasma contamination	All cell lines were negative for Mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	None used