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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	For all data collection, instrument data was obtained using the manufacturer recommended software
Data analysis	The Grace plotting program and customized scripts written in Perl were used to analyze aggregation kinetic data as described in Materials and Methods. InCell Developer software(GE Healthcare) was used to process images from cellular assays. NMR spectra were processed/analyzed using Topspin and Sparky as decscribed in Material and Methods. Images from immunohistochemistry stained human patient samples were analyzed with NIH ImageJ. ITC data processed using Origin 7.0 software. Statistical analyses performed with Prism (GraphPad software)

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 datasets generated and analyzed in the current study are available from the corresponding author upon reasonable 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

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	No sample size calculation was performed for aggregation screens however, reproducibility between replicates and individual experiments was verified during the optimization of the technique (see supplementary data).
Data exclusions	No data was excluded from analysis
Replication	All attempts at replication were successful. Experiments were also replicated with different batches of reagents (e.g. aggregation inducers), protein preparations (e.g. Hsc70, DNAJA2), and cell line stocks (e.g. clone 1 cells)
Randomization	Samples were from protein preparations (verified by SDS-PAGE). Sample groups divided according to protein identity.
Blinding	Investigators were not blinded to group allocation

Materials & experimental systems

Policy information about availability of materials

n/a	Involved in the study
☐	☒ Unique materials
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Research animals
☒	☐ Human research participants

Unique materials

Obtaining unique materials	Protein expression constructs or purified proteins used in the study are available from the authors. The clone 1 cell line is available with permission from Marc Diamond (UT Southwestern). Human patient samples were received from William W. Seeley and the UCSF Neurodegenerative Disease Brain Bank.

Antibodies

Antibodies used	Detailed information regarding antibodies used in the study are provided in the Materials and Methods.
Validation	DnaJA2 antibody (Origene) was tested for specificity against a panel of other Hsp40 family members by dot immunoblot in this study. The DnaJB4 antibody (Atlas Antibodies) was used in the Human Protein Atlas Project. Hsc70 and Hsp72 antibody (Enzo) checked for cross reactivity by immunoblot. According to the manufacturer, Hsp27 antibody (StressMarq) has been used for IHC/IF in Unger et al (2017), Kotter et al. 2014, Periera et al 2018. The AT8 antibody (Pierce/ThermoFisher) has been used for IHC/IF staining results in over >250 publications as referenced on the manufacturer's product webpage.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	The clone 1 cell line was obtained from Marc Diamond (UT Southwestern)

Authentication	The cell line was authenticated through replication of results in phenotypic assays developed for the cell line by the laboratory of Marc Diamond (UT Southwestern).
Mycoplasma contamination	Original cell line stock tested negative for myocplasma using commercial kit (Mycoalert, Lonza)
Commonly misidentified lines (See ICLAC register)	N/A

Method-specific reporting

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ Magnetic resonance imaging