

Reporting Summary

Nature Portfolio 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 Portfolio 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
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☒ | ☐ | 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
<i>Give P values as exact values whenever suitable.</i> |
| ☒ | ☐ | 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	Image Studio 5.2, MicroCal PEAQ-ITC Control Software 1.41, Fida 1 Instrument Software 2.42, SparkControl Magellan 3.0, LightCYcler 480 Software release 1.5.0
Data analysis	Image Studio 5.2, GraphPad Prism 8.0.2, Excel 2016, NITPIC 2.1.0, SEDPHAT 15.2b, GUSI 2.1.0, Fida Analysis Software 2.32, Pymol 3.0, PowerPoint 2016, LightCYcler 480 Software release 1.5.0, AlphaFold 2.2, ColabFold 1.3, AlphaFill, PLIP 2.3.0, SpotOn webserver (no version number, accessed September 2023), MMseqs2 webserver (version 2)

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 Portfolio [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 description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

All data supporting the findings of this study are included in the article and its Supplementary Information files.

Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

Reporting on sex and gender

Reporting on race, ethnicity, or other socially relevant groupings

Population characteristics

Recruitment

Ethics oversight

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

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](https://www.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	For in vitro studies, sample sizes were determined based on the specific standard deviation of each type of experiment. Experiments were repeated at least 3 times and up to 6 times in some cases, as indicated, to obtain standard deviations small enough to allow the observation of significant differences between signals. For in vivo experiments on <i>Drosophila</i> , sample size was determined based on previous experiments by our lab and others. For survival assays, a mean number of 335 animals was used per condition for Fig. 5d, of 146 for Extended Fig. 6c and of 115 for Extended Fig. 6d-e. Power analysis was conducted and we provide the precise number of flies for each tested condition and the p-values of logrank tests in Extended Table 4.
Data exclusions	no data were excluded
Replication	For in vitro studies, experiments were repeated at least 3 times and up to 6 times in some cases, as indicated. All attempts at replication were successful. For in vivo studies, increased survival associated with Fdx1 inactivation in frataxin-deficient flies was observed in four independent longevity experiments.
Randomization	No randomization needed for the in vitro studies. For in vivo survival experiments (Fig. 5c-d and Extended Fig. 6c-d-e) and RT-qPCR (Fig. 5c), experimental groups are male flies of the same genotype affected randomly to various doses of RU-486 treatments. Other qRT-PCR experiments (Fig. 5b and Extended Fig. 6a-b) are performed on males of different genotypes that were age-matched and handled in parallel.
Blinding	No blinding needed for the in vitro studies. For in vivo survival experiments, experimental groups are flies of the same genotype submitted to various concentrations of RU-486 treatments during developmental and adult stages. Counting of dead flies were done simultaneously with the transfer of flies on fresh medium containing the appropriate RU-486 dosage so blinding was not applicable.

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
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

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

Animals and other research organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research, and [Sex and Gender in Research](#)

Laboratory animals	The following Drosophila lines were used in this study: fh-GAAs and daGS (generated by our team and already published), w1118 (vdrc), UAS-Fdx1 RNAi (vdrc) and daGAL4 (BDSC). All experiments were performed on males. RT-qPCR were performed on third instar larvae or 3 days old adult, as specified in the legends of Figure 5 and Extended Fig 6.
Wild animals	None
Reporting on sex	Since the fh gene is located on the X chromosome, all experiments were performed on males. This allowed to perform the studies on frataxin-deficient hemizygous fh-GAAs/Y males obtained by single crosses between fh-GAAs females and males carrying transgenes of interest on autosomes.
Field-collected samples	None
Ethics oversight	No ethical approval required for studies on Drosophila

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

Plants

Seed stocks	no plant used
Novel plant genotypes	no plant used
Authentication	no plant used