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☐ Initial submission ☐ Revised version ☒ Final submission

Life Sciences Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form is intended for publication with all accepted life science papers and provides structure for consistency and transparency in reporting. Every life science submission will use this form; some list items might not apply to an individual manuscript, but all fields must be completed for clarity.

For further information on the points included in this form, see Reporting Life Sciences Research. For further information on Nature Research policies, including our data availability policy, see Authors & Referees and the Editorial Policy Checklist.

Experimental design

1. Sample size

   Describe how sample size was determined.

   Based on past experience, we assumed a coefficient of variance of 30%. For mouse and elecrophysiology experiments we aimed for >80% power for a 1.5% difference. For the two rat experiments we aimed for >80% power for a 1.75% difference.

2. Data exclusions

   Describe any data exclusions.

   No data were excluded, except when animals were determined to be sick, or a sample was an outlier as determined by the Grubbs' test for outliers (alpha=0.05)

3. Replication

   Describe whether the experimental findings were reliably reproduced.

   Data were reliably reproduced.

4. Randomization

   Describe how samples/organisms/participants were allocated into experimental groups.

   Animals were randomly assigned into groups with equal means and standard deviation.

5. Blinding

   Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

   In experiments involving different genotypes, investigators were not blinded. For experiments involving the same genotype, but treatment with r Asprosin, GFP, anti-asprosin mAb, or IgG, animals were randomly assigned into groups with equal mean and standard error, and data were obtained in a blinded fashion. Food intake, energy expenditure, and body composition measures were performed in a blinded fashion, as long as the genotype was not visually obvious (extreme leanness or difference in fur color). Neuronal experiments were performed in an unblinded manner.

Note: all studies involving animals and/or human research participants must disclose whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or in the Methods section if additional space is needed).

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
☐	☒ A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☒	☐ A statement indicating how many times each experiment was replicated
☐	☒ The statistical test(s) used and whether they are one- or two-sided (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section)
☐	☒ A description of any assumptions or corrections, such as an adjustment for multiple comparisons
☐	☒ The test results (e.g. *P* values) given as exact values whenever possible and with confidence intervals noted
☐	☒ A clear description of statistics including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
☐	☒ Clearly defined error bars

See the web collection on statistics for biologists for further resources and guidance.

Software

Policy information about availability of computer code

7. Software

Describe the software used to analyze the data in this study.	Graphpad Prism 6, R

For manuscripts utilizing custom algorithms or software that are central to the paper but not yet described in the published literature, software must be made available to editors and reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). *Nature Methods* guidance for providing algorithms and software for publication provides further information on this topic.

Materials and reagents

Policy information about availability of materials

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a for-profit company.	Fbn1<NPS/+> mice are available on reasonable request.

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	The anti-asprosin monoclonal antibody was validated using ELISA and loss-of-function experiments in vivo and in vitro. In addition the epitope was verified with binding studies, and dilution series and response curves were analyzed.

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.	n/a
b. Describe the method of cell line authentication used.	n/a
c. Report whether the cell lines were tested for mycoplasma contamination.	n/a
d. If any of the cell lines used are listed in the database of commonly misidentified cell lines maintained by ICLAC, provide a scientific rationale for their use.	n/a

Animals and human research participants

Policy information about studies involving animals; when reporting animal research, follow the ARRIVE guidelines

11. Description of research animals

Provide details on animals and/or animal-derived materials used in the study.

Mice: All animals were male and age-matched for single experiments. C57BL/6 (WT), Lepr<db/db>, Lep<ob/ob>, a/a and Ay/a mice were purchased from Jackson Laboratories. Fbn1<NPS/+> mice were created using CRISPR/Cas9 technology at the Baylor College of Medicine Mouse Embryonic Stem Cell Core on a C57BL/6 background. Sprague Dawley rats were used for rat experiments.

Policy information about studies involving human research participants

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.

Since this disease is incredibly rare, two individuals with neonatal progeroid syndrome were recruited for this study.