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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 *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 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 *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

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	Data collection was conducted using the following instruments and software: Amersham Imager 600 (GE Healthcare Life Sciences), Synergy HTX Multimode Reader (Agilent BioTek) with Gen5 software version 2.07, NanoZoomer 2.0-HT Slide Scanner (Hamamatsu Photonics), and Zeiss Axio Observer 7 microscope. Electron microscopy was performed using a Morgagni 268D electron microscope (FEI) with Mega View III camera (Soft Imaging System), and a Philips CM12 electron microscope with Gatan OneView Camera. Additional tools included the Complete1300A mouse test system (Aurora Scientific), Natus Mag2Health electromyograph, QX200 Droplet Digital PCR System (Bio-Rad), Roche LightCycler 480 Software version 1.2.9.11, and Precellys® Evolution Touch tissue homogenizer (Bertin Technologies).
Data analysis	The data analysis tools used in this study include CellPose version 1.0, Fiji (ImageJ) version 1.54f, QuPath version 0.3.2, PyMOL version 2.3.2, AxonDeepSeg version 4.1.0, and GraphPad Prism version 9.5.1.

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

The data that support the findings of this study are available in the Source Data file.

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	Sample sizes were determined based on prior studies using comparable methodologies and mouse models, specifically Pereira J et al., 2020 and Muñoz X et al., 2020. For the in vitro experiments, n=3–22 samples were used. In the 8-week mouse cohort, sample sizes ranged from n=6–23 for in vivo phenotyping, n=6–17 for functional muscle assessments, n=3–7 for nerve and muscle histology, n=2–4 for electron microscopy, and n=5–8 for molecular analyses. In the 52-week cohort, we used n=4–18 for in vivo phenotyping, n=3–14 for functional tests, and n=3–6 for histological analyses. These numbers reflect practical considerations and variability in the specific outcomes measured. Individual data points are provided in the figures and Supplementary Data. For GTPase activity assay with recombinant protein, results were confirmed with at least two different batch of protein production. For pull-downs and liposome-binding assays technical triplicates were performed. The number of independent repetitions was determined from previous publications with similar methodologies (Narayan, K. & Lemmon, M. A., 2006)(Wang, L., et al., 2010)(Gómez-Oca, R., et al., 2022). The exact n number of all the experiments was provided in the figure, figure legends and Supplementary Data 1.
Data exclusions	Mice were excluded from specific analyses only when data points were suspected to result from technical errors. In such cases, an outlier test (ROUT, Q=0.1%) was performed in GraphPad Prism. Exclusion occurred only if the data point was identified as an outlier. Relevant tests are listed in Supplementary Data 1.
Replication	For all animal studies, mice used were coming from at least 3 independent litters. Mice with the genotype of interest were analyzed together with at least one control littermate. Each 'n' in a figure represents a unique individual mouse. For western blots, mouse samples were randomly distributed, ensuring 2-4 samples per group including controls groups are running in parallel in the same blot. Some western blots were similarly repeated in a different day and result was replicated. For GTPase activity assay on recombinant proteins, results were confirmed with at least two different batch of protein production. Technical triplicates were performed for liposomes binding assays and pull-downs.
Randomization	Randomization: for all experiments, group allocation was primarily determined by genotype, as predefined by the study design. Although group assignment was not randomized, within each group, mouse samples were randomly selected for downstream analyses such as RT-qPCR, Western blotting, and imaging. Covariates: mice were of the same age. Sex was matched across groups when applicable, and if not, no significant sex-related differences were observed. Data from some experiments were normalized to body weight. Experimental handling and conditions were standardized to minimize other potential sources of bias. For in vitro experiments, randomization was not applied, as protein samples from each production batch were systematically allocated to multiple assays conducted in parallel. Experimental procedures were performed under consistent conditions to ensure comparability across assays.
Blinding	Experimenters were blinded regarding mice genotypes during data collection. For data analyses, such as histopathological assessments, blinding was ensured using the mouse ID number.

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

Commercial antibodies used:
- Integrin β1 (1:250, Sigma-Aldrich MAB1997, lot #3956934)
- GARat Alexa 488 (goat polyclonal, 1:250, Thermo Scientific A-11006, lot #2480078)
- Desmin (rabbit polyclonal, 1:250, Abcam AB15200, lot #1077918-1)
- GAR Alexa 555 (goat polyclonal, 1:250, Invitrogen A32732, lot #WL332194)
- Collagen VI (rabbit polyclonal, 1:250, Novus Biologicals NB120-6588)
- GAR Alexa 488 (goat polyclonal, 1:250, Thermo Scientific A-11008, lot #2018309)
- DAPI (1:1000)
- His (mouse monoclonal, 1:1000, Thermo Scientific MA1-21315-HRP, lot #YK382778)
- Flag (mouse monoclonal, 1:1000, Thermo Scientific MA1-91878-HRP, lot #YG377536)
- GAR perox (goat polyclonal, 1:10000, Jackson Immunoresearch 111-036-045, lot #111806)
- S6RP (rabbit monoclonal, 1:1000, Cell Signaling #2217, lot #10)
- p-S6RP (rabbit polyclonal, 1:1000, Cell Signaling #2211, lot #25)
- Cullin3 (rabbit polyclonal, 1:500, Thermo Scientific PA5-17397, lot #WG3333458)
- SQSTM1/P62 (mouse monoclonal, 1:1000, Thermo Scientific H00008878-M01, lot #I9131-2c11)
- LC3B (rabbit polyclonal, 1:1000, Cell Signaling CS2775, lot #14)
- Cytochrome C (rabbit polyclonal, 1:1000, Cell Signaling #4272)
- GAPDH (mouse monoclonal, 1:1000, Sigma-Aldrich MAB374, lot #4134614)
- GAM perox (goat polyclonal, 1:10000, Jackson Immunoresearch 115-036-068, lot #172700)
- GAR perox (goat polyclonal, 1:10000, Jackson Immunoresearch 111-036-045, lot #111806)

Homemade antibodies used (produced at IGBMC, Illkirch, France):
- DNM2 (rabbit polyclonal, 1:1000, Homemade #2865)

Validation

Primary antibodies were used as recommended by the manufacturers. For immunofluorescence (IF), negative controls (no primary antibody) were included to ensure specificity. All antibodies were further validated in control (wild-type) mouse tissues for IF and Western blot, as well as by previous publications. The validation of commercial antibodies is available on the manufacturer's websites and in relevant publications:

Immunofluorescence=
- Integrin β1 (Sigma-Aldrich MAB1997, manufacturer website:"immunohistochemistry: suitable", used in mouse muscles in Lionello V et al., 2019 and Goret et al., 2025).
- Desmin (Abcam AB15200, manufacturer website:"Used in Desmin IHC, ICC/IF", used in mouse muscles in Gineste et al., 2023 and Goret et al., 2025).
- Collagen VI (Novus Biologicals NB120-6588, manufacturer webste:" Applications/dilutions: Immunocytochemistry/ Immunofluorescence 1:10-1:500").

Western blot=
- His (Thermo Scientific MA1-21315-HRP, manufacturer website : "Applications : Western Blot (WB) 1:500").
- Flag (Thermo Scientific MA1-91878-HRP, manufacturer website : "Applications : Western Blot (WB) 1:1000").
- S6RP (Cell Signaling #2217, manufacturer website : "Application : Western Blotting 1:1000", used in mouse tissues in Giraud et al., 2023).
- p-S6RP (Cell Signaling #2211, manufacturer website : "Application : Western Blotting 1:1000", used in mouse tissues in Giraud et al., 2023).
- Cullin3 (Thermo Scientific PA5-17397, manufacturer website : "Applications : Western Blot (WB) 1:1000", used in mouse tissues in Gineste et al., 2023).
- SQSTM1/P62 (Thermo Scientific H00008878-M01, manufacturer website : "Applications : Western Blot (WB) 1-5µg/mL", used in mouse tissues in Gineste et al., 2023).
- LC3B (Cell Signaling CS2775, manufacturer website : "Application : Western Blotting 1:1000").
- Cytochrome C (Cell Signaling #4272, manufacturer website : "Application : Western Blotting 1:1000").
- GAPDH (Sigma-Aldrich MAB374, manufacturer website : "western blot: suitable").

The homemade DNM2 antibody was produced on site at IGBMC and was validated in several publications (e.g. Cowling B et al., 2011, Gomez-Oca R et al., 2019, Goret M et al., 2025).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

- Sf21 cells were originally obtained from the laboratory of Imre Berger at EMBL Grenoble in 2010. These cells were initially sourced from Invitrogen™ (catalog number B82101).

Authentication

The cells were maintained in-house. They were dentified and verified by their characteristic morphology and ability to grow in suspension in serum-free medium.

Mycoplasma contamination

Mycoplasma testing at EMBL confirmed the cells were contamination-free.

Commonly misidentified lines (See ICLAC register)	Sf21 cells are not listed in the ICLAC Register of Misidentified Cell Lines.

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	All animal experiments were conducted following protocols approved by the institutional ethical committee Com'Eth IGBMC-ICS (Illkirch, France) under the APAFIS project numbers #33314-2021092710329260 and #34674-2022011417453821. Mice were housed in cages with access to food ad libitum in a temperature-controlled room (19°C to 22°C) with a 12:12-hour light/dark cycle. The ambient humidity was maintained between 40-60%, and the room was ventilated with 100% fresh, non-recirculated air, with 15 air changes per hour. The pressure in the housing room was positive (0.5 to 2.5 Pa relative to the corridor).For the breeding and maintenance of animals, we used standard laboratory diets: SAFE®D03 during breeding and weaning and SAFE®D04 after weaning. Two mouse models were used and crossed in the study: - The Dnm2S619L/+ mouse line (background C57BL6N) previously generated at the Institut Clinique de la Souris (ICS) and characterized (Munoz X et al., 2020) - The Dnm2K562E/+ mouse line (background C57BL6J) previously generated at the Institut Clinique de la Sourice (ICS) and characterized (Pereira J et al., 2020) Mice resulting from the crossing were phenotyped, both sexes, at the ages of 8 and 52-66 weeks as specify in the text and in main and supplementary figures.
Wild animals	The study did not involve wild animals.
Field-collected samples	The study did not involve field-collected samples.
Ethics oversight	All animal experiments in this study were conducted in compliance with relevant ethical regulations and approved by the institutional ethical committee Com'Eth IGBMC-ICS (Illkirch, France), under the APAFIS project numbers 33314-2021092710329260 and 34674-2022011417453821. Mice were housed in ventilated cages with ad libitum access to food and water, in temperature-controlled rooms with a 12:12-hour light/dark cycle. Animals were monitored at least once a week to assess general health and well-being, including signs of distress or abnormal behavior. Euthanasia was performed by cervical dislocation when required, in accordance with national and European regulations on animal experimentation.

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