

## 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 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                                                                                                                                                                                                                                                                                      |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> The exact sample size ( $n$ ) for each experimental group/condition, given as a discrete number and unit of measurement                                                                                                                                    |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly                                                                                                                                    |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> The statistical test(s) used AND whether they are one- or two-sided<br><i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>                                                               |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> A description of all covariates tested                                                                                                                                                                                                                     |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons                                                                                                                                        |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> 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) |
| <input type="checkbox"/>            | <input type="checkbox"/> For null hypothesis testing, the test statistic (e.g. $F$ , $t$ , $r$ ) with confidence intervals, effect sizes, degrees of freedom and $P$ value noted<br><i>Give <math>P</math> values as exact values whenever suitable.</i>                                       |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings                                                                                                                                                                      |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes                                                                                                                                                |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> 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 *LabChart Reader, Biotek Cytation 5, PCLAMP 8 software.*

Data analysis *Zen5 Imaging software, Image Studio Lite (version5.2.5), Adobe Photoshop CC 2019, Fiji (version 2.0), GraphPad Prism (version8.2.1), Ingenuity pathway analysis software, Aperio Image Scope software (version12.3.2.8013), vivo strain software (version3.1.1).*

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 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

All data are available in NCBI's GEO and accession code is GSE168487 [<https://www.ncbi.nlm.nih.gov/ezproxy.u-pec.fr/geo/query/acc.cgi?acc=GSE168487>].

## 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 n=3 mice were used for AAV injection, cellular studies fibrosis analysis and imaging studies. n=4 were used for RNA sequencing studies and n=6 mice were used for echocardiography and western blot studies given it's the standard practice.

Data exclusions No data was excluded except 1 WT sample was removed initially in RNA sequencing analysis due to poor RNA quality.

Replication All studies have biological and technical (n=3) replicates with follow-up validation. The results were consistent across the replicates.

Randomization Mice were randomly chosen based on their genotype.

Blinding Samples were blinded during AAV9 injections and during analysis of results (including echocardiography analysis, western blot quantification, calcium transients, fibrosis analysis, etc.)

## 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                                           |
|-------------------------------------|-----------------------------------------------------------------|
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Antibodies                  |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Eukaryotic cell lines                  |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Palaeontology and archaeology          |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Animals and other organisms |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Human research participants            |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Clinical data                          |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Dual use research of concern           |

### Methods

| n/a                                 | Involved in the study                           |
|-------------------------------------|-------------------------------------------------|
| <input checked="" type="checkbox"/> | <input type="checkbox"/> ChIP-seq               |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Flow cytometry         |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> MRI-based neuroimaging |

## Antibodies

### Antibodies used

Western blot-Antibodies  
 Voltage-dependent anion-selective channel protein 2 (VDAC2) 9412S Cell Signaling Technology  
 Voltage-dependent anion-selective channel protein 1 (VDAC1) ab14734 Abcam  
 Voltage-dependent anion-selective channel protein 3 (VDAC3) ab130561 Abcam  
 Vinculin 13901S Cell Signaling Technology  
 Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) 5174S Cell Signaling Technology  
 Transketolase (TKT) 8616S Cell Signaling Technology  
 Methylene-tetrahydrofolate dehydrogenase 1 (MTHFD1) sc-271412 Santa Cruz Biotech  
 Aldolase B (ALDOB) sc-365449 Santa Cruz Biotech  
 Serine hydroxymethyltransferase 1 (SHMT1) 8071S Cell Signaling Technology  
 Isocitrate dehydrogenase (IDH1/2) sc-373816 Santa Cruz Biotech  
 Phosphofructokinase 1 (PFK1) sc-166722 Santa Cruz Biotech  
 Pyruvate carboxylase (PC) NBP1-49536 Novus Bio  
 Pyruvate dehydrogenase (PDH) 3205S Cell Signaling Technology  
 Lactate dehydrogenase (LDH) 3582S Cell Signaling Technology  
 Hexokinase 1 (HK1) 2024S Cell Signaling Technology  
 Calsequestrin 2 (CASQ2) ab3516 Abcam  
 Citrate synthase (CS) 14309S Cell Signaling Technology  
 Succinyl Co-A synthetase (SUCLG2) 8071S Cell Signaling Technology  
 Succinate dehydrogenase A (SDHA) 5839S Cell Signaling Technology  
 Sodium-calcium exchanger 1 (NCX1) ab151608 Abcam  
 Sarcoplasmic endoplasmic reticular calcium ATPase 2 (SERCA2) 4388S Cell Signaling Technology  
 Ryanodine Receptor 2 (RYR2) MA3-916 Thermofisher Scientific  
 Phospholamban (PLN) 14562S Cell Signaling Technology  
 Phospho-Phospholamban (pPLN) 8496S Cell Signaling Technology

Protein kinase A (PKA) SAB4502337 Sigma Aldrich  
 Phospho-Protein kinase A (pPKA) SAB4503969 Sigma Aldrich  
 Mitochondrial calcium uniporter (MCU) 149975 Cell Signaling Technology  
 Mitochondrial sodium calcium exchanger (NCLX) SAB2102181 Sigma Aldrich  
 Dynamin related protein 1 (DRP1) 146475 Cell Signaling Technology  
 Oxidative phosphorylation (OXPHOS) ab110413 Abcam  
 IRDye 680RD Donkey anti-Mouse Secondary 926-68072 LI-COR Biosciences  
 IRDye 800CW Donkey anti-Rabbit Secondary 926-32212 LI-COR Biosciences  
 Co-Immunoprecipitation-Antibodies  
 Voltage-dependent anion-selective channel protein 2 (VDAC2) PA5-28106 Thermofisher Scientific  
 Immunoglobulin G (IgG) AC005 AbClonal  
 Immunofluorescence/Proximity ligation assay-Antibodies/Stain  
 4',6-diamidino-2-phenylindole (DAPI) D3571 Thermofisher Scientific  
 Voltage-dependent anion-selective channel protein 2 (VDAC2) 66388-1-IG Thermofisher Scientific  
 Sodium-calcium exchanger 1 (NCX1) ab151608 Abcam  
 Sarcoplasmic endoplasmic reticular calcium ATPase 2 (SERCA2) 43885 Cell Signaling Technology  
 Ryanodine Receptor 2 (RYR2) MA3-916 Thermofisher Scientific  
 Quantitative Reverse transcription-PCR-Primers  
 Voltage-dependent anion-selective channel protein 2 (VDAC2) Mm00834279\_m1 Thermofisher Scientific  
 Vinculin Mm00447745\_m1 Thermofisher Scientific

## Validation

All antibodies were previously tested by the company and used in other publications. A separate file title "Antibody list and validation" includes information from the website and relevant publications for each of the antibody.

## Animals and other organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research

|                         |                                                                                                                                                                                                                                                                          |
|-------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Laboratory animals      | C57BL6J mice strain and both male and female mouse were used for all experiments. Echocardiography was performed on mice starting from embryonic day 18.5 until 16-weeks post-natal. Calcium transients were performed on 16-week old mice and co-IP on 8-week old mice. |
| Wild animals            | Study did not involve wild animals                                                                                                                                                                                                                                       |
| Field-collected samples | Study did not involve samples collected from the field                                                                                                                                                                                                                   |
| Ethics oversight        | Studies were performed following guidelines established by IACUC, University of Utah.                                                                                                                                                                                    |

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