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Reporting Summary

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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	Confocal Images were captured by Zen Software (Carl Zeiss Zen 2009) (Zeiss, Pleasanton, CA, USA). Image Lab 4.1 Software were used to acquire Immunoblots, and Step One Softwere v2.2.2 were used for qPCR acquisition. Correlation analysis was conducted in R and heatmaps generated with the pheatmap package. Subread filtering was performed using the SMRT analysis software (v2.2) of Pacific Biosciences. The mass spectrometer was operated in the data-dependent acquisition mode using Xcalibur2.1.3.
Data analysis	Circular consensus (CCS) reads in FASTQ format were mapped to CaMKII-δ gene loci from all sample species, using GMAP (version 2014-09-29). The RNA-seq reads were mapped using TopHat-2.0.8 with default parameters. Mass spectrometry peptides were identified using Proteome Discoverer Software (version 1.4.1.14, Thermo) suited with Mascot software (version 2.3.01, Matrix Science). Comet Assay Software Project (v1.2.3b1), and ImageJ (1.40g) for western blot analysis. Echocardiographic analysis using a Vevo2100 digital imaging system (Vevo LAB Workstation vevo2100 1.6.0) . Statistical analysis was performed with GraphPad Prism version 5.01 (GraphPad Software, Inc.) and the SPSS 18.0 software package (SPSS Inc.).

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. 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 the sequencing data in this study have been deposited in the NCBI with the accession numbers PRJNA381326, PRJNA381328, and PRJNA381329, and have been open to public. All the data supporting the findings of this study are available from the corresponding author on reasonable request.

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 size was chosen based on previous experience and standards in the field. All of the experiments were repeated at least 3 times. The sample sizes for in vitro (n>=3) and in vivo (n >=5-6) are typical of the field. All Sample sizes are listed in the corresponding figure legend and Supplemental Table 5 ("Statistics Source Data"). No statistical method was used to predetermine sample size.
Data exclusions	No non-inclusion or exclusion parameters were used in our studies.
Replication	Figs. 1b,c and Supplementary Figs. 2b, 3g,l, 4a,b,f, 7a were independently repeated 3 times, and Fig. 6g and Supplementary Figs. 6a,g were independently repeated 6 times. All the other experiments were independently repeated 4 times. All the experimental findings were reliably reproduced.These was included in the "Statistics and Reproducibility" section of the Methods.
Randomization	All the samples, organisms and participants were randomly allocated into different experimental groups.
Blinding	Investigators were not blinded to treatments, but no subjective assessments were made.

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
☐	☒ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data

Methods

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

Antibodies

Antibodies used	Antibodies against the following proteins were used: rat/human UBE2T and p-threonine (Cell Signaling Technology, 12992 (Lot#: 1; 1:1000) and 9381 (Lot#: 22; 1:1000)); mouse UBE2T (Aviva Systems Biology, ARP-43145_P050 (Lot#: QC13585-40506; 1:1000)); p-CaMKII (Thermo, MA1-047 (Lot#: QC207772; 1:1000)), t-CaMKII-δ (GeneTex, GTX111401 (Lot#: 40058; 1:1000)), Myc and Flag (Sigma, SAB4700447 (Lot#: 522137; 1:5000 for western blots, 1:200 for immunohistochemistry), and F1804 (Lot#: SLBR7936V; 1:5000 for western blots, 1:200 for immunohistochemistry)), γH2AX, p-serine, and ox-CaMKII (Millipore, 05-636, clone JBW301 (Lot#: 2884537; 1:1000 for western blots, 1:200 for immunohistochemistry), 05-1000, clone 4A4 (Lot#: 2691195; 1:1000) and 07-1387 (Lot#: 2739150; 1:1,000)), COX-2, HA, and lamin A/C (Santa Cruz, sc-1747 (Lot#: H1911; 1:1000), sc-7392 (Lot#: L1115; 1:1000 for western blots, 1:200 for immunohistochemistry) and sc-6215 (Lot#: J2615; 1:1000)), PAI-2 (Bioworld, BS3702 (Lot#: CA36131; 1:1000)), β-actin (EARTHOX, E021070-01 (Lot#:0a1401, 1:100 for immunohistochemistry)), FANCD2 and FANCI (abcam, ab108928 (Lot#: GR130039-32; 1:1000) and ab74332 (Lot#: GR251812-8; 1:1000)), and GAPDH (EASYBIO,

BE0023, clone 2B8 (1:10000)).

The antibodies against exon 16 and exon 21 of CaMKII-? were produced in rabbits by Abcam, USA with antigenic epitopes comprised the following amino-acid sequences: PPCIPNGKENFSGGTSLW corresponding to exon 21, the C terminus unique for a subclass of splice variants of CaMKII-δ?, and CEPQTTVIHNPDGNK corresponding to exon 16 of CaMKII-δ?. When used, the antibodies were diluted 1:1000 for western blots, 1:200 for immunohistochemistry.

Validation

All commercial antibodies were validated by the manufacturer for the species and application used in this study.
1. Rat/human UBE2T and p-threonine (Cell Signaling Technology, 12992 (https://www.cellsignal.com/products/primary-antibodies/ube2t-d2l7h-rabbit-mab/12992) and 9381 (https://www.cellsignal.com/products/primary-antibodies/phospho-threonine-antibody-p-thr-polyclonal/9381));
2. Mouse UBE2T (Aviva Systems Biology, ARP-43145_P050 (https://www.avivasysbio.com/ube2t-antibody-n-terminal-region-arp43145-p050.html);
3. p-CaMKII (Thermo, MA1-047 (https://www.thermofisher.com/antibody/product/Phospho-CaMKII-alpha-Thr286-Antibody-clone-22B1-Monoclonal/MA1-047));
4. t-CaMKII-δ (GeneTex, GTX111401 (https://www.genetex.com/Product/Detail/CaMKII-delta-antibody/GTX111401));
5. Myc and Flag (Sigma, SAB4700447 (https://www.sigmaaldrich.com/catalog/product/sigma/sab4700447?lang=en&region=US), and F1804 (https://www.sigmaaldrich.com/catalog/product/sigma/f1804?lang=en&region=US);
6. γH2AX, p-serine, and ox-CaMKII (Millipore, 05-636, clone JBW301 (http://www.emdmillipore.com/US/en/product/Anti-phospho-Histone-H2A.X-Ser139-Antibody-clone-JBW301,MM_NF-05-636?bd=1), 05-1000, clone 4A4 (http://www.emdmillipore.com/US/en/product/Anti-Phosphoserine-Antibody-clone-4A4-mouse-IgG1,MM_NF-05-1000) and 07-1387 (http://www.emdmillipore.com/US/en/product/Anti-oxidized-CaM-Kinase-II-Met281-282-Antibody,MM_NF-07-1387);
7. COX-2, HA, and lamin A/C (Santa Cruz, sc-1747 (https://www.scbt.com/scbt/product/cox-2-antibody-m-19?productCanUrl=cox-2-antibody-m-19&_requestid=17106856), sc-7392 (https://www.scbt.com/scbt/product/ha-probe-antibody-f-7?requestFrom=search) and sc-6215 https://www.scbt.com/scbt/product/lamin-a-c-antibody-n-18?requestFrom=search);
8. PAI-2 (Bioworld, BS3702 (https://www.bioworlde.com/PAI-2-(V307)-polyclonal-antibody(discontinued)(BS3702).html);
9. β-actin (EARTHOX, E021070-01 (https://www.earthox.net/anti-actin-rabbit-polyclonal-antibody/);
10. FANCD2 and FANCI (abcam, ab108928 (https://www.abcam.com/fancd2-antibody-epr2302-ab108928.html) and ab74332 (https://www.abcam.com/fanci-antibody-ab74332.html);
11. GAPDH (Signalway Antibody, BE0023, clone 2B8 (https://www.sabbiotech.com/g-17686-GAPDH-Monoclonal-Antibody(2B8)-44031.html)).

The home-made antibodies were validated using in vivo (mouse) and in vitro (neonatal rat ventricular cardiomyocytes) models with overexpression and knockdown of the targeted proteins, together with the epitope competition experiments (Fig. 4a,i, Supplemental Fig. 2b,c,d, Supplemental Fig. 6h).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	We used human embryonic kidney (HEK) 293 cells (ATCC, Cat# CRL-1573) in our study.
Authentication	We authenticated our HEK293 cell by STR test.
Mycoplasma contamination	We have tested the HEK293 cells for mycoplasma contamination with Macgene kit (COK001) , and the results were negative.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.

Animals and other organisms

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

Laboratory animals	C57BL/6 mice (8-12 weeks of age) and Sprague-Dawley rats (8-10 weeks of age) were used in the current study without otherwise indicated. For TAC surtery, 6-week-old C57BL/6 mice were used. NRVMs were isolated from 1-day-old Sprague-Dawley rats (male and female). Rhesus monkeys (18-28 years of age) were from our in-house cohort as previously reported (Circulation 2011: 124, 77-86). Only males were used unless otherwise indicated.
Wild animals	Our study did not involve wild animals.
Field-collected samples	Our study did not involve samples collected from the field.
Ethics oversight	All procedures involving experimental animals (mice, rats, and rhesus monkeys) followed protocols approved by the Committee for Animal Research of Peking University and conformed to the Guide for the Care and Use of Laboratory Animals.

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	The normal human tissue was obtained from the NIH NeuroBioBank at the University of Maryland, Baltimore, MD. Human ventricular tissue from patients with hypertrophic cardiomyopathy was obtained during hypertrophic ventricular septum myectomy surgery in Fuwai Hospital. The HCM patients were diagnosed according to symptoms, echocardiography and serum NTproBNP by the experienced surgeons. The information was as follows: Fig. 1a (all males, died of multiple injuries, 22, 40 and 42 years of age), Fig. 1h (Normal (died of multiple injuries, 22 (male), 40 (male), 42 (male), 28 (male), 42 (female), 48 (female) and 31 (female) years of age); HCM (38 (male), 48 (male), 50 (male), 26 (male), 37 (female), and 42 (female) years of age)), and Fig. 6a-c (Normal (died of multiple injuries, 22 (male), 40 (male), 42 (male), and 31 (female) years of age); HCM (38 (male), 48 (male), 50 (male), 26 (male), 50 (male), 37 (female), 33 (female) and 42 (female) years of age)).
Recruitment	The normal human tissue and information were offered by the NIH NeuroBioBank at the University of Maryland, Baltimore, MD. Human ventricular tissue from patients with hypertrophic cardiomyopathy was obtained during hypertrophic ventricular septum myectomy surgery in Fuwai Hospital between 2013 and 2015, and offered by the surgeons with any self-selection. All the samples were randomly selected for our analysis
Ethics oversight	Human protocol was approved by the Ethics Committee of Fuwai Hospital, the Chinese Academy of Medical Sciences, and Peking Union Medical College.

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