nature research

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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 Authors & Referees 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	-qPCR analysis: CFX Maestro™ Software (Bio-rad) -Imaging process for ATAC-See: ZEN imaging software (Zeiss) -Imaging process for kinase array: Image Studio Lite (LI-COR) -Imaging process for immunoblot: Image Lab (Bio-rad) -AmpliSeq Transcriptome analysis: Omics Explorer version 3.2 software (Qlucore) -Ca2+ imaging: NIS Elements AR software
Data analysis	- [RNA-seq] Base quality of raw reads: FastQC 0.11.4 - [RNA-seq] aligned the reads to the human reference genome (hg19): STAR 2.5.1b - [RNA-seq] calculating fragments per kilobase per million aligned reads (FPKM): Cufflinks 2.2.1. - [ATAC-seq] ATAC-seq reads were mapped to hg19 genome: bowtie 2 - [ATAC-seq] Following QC to remove duplicate reads, average read intensities were calculated: deepTools and R/Bioconductor (v.3.2.1) - [ChIP-seq] AQUAS pipeline from the Kundaje lab at Stanford University (https://github.com/kundajelab/chip-seq-pipeline2) - [ChIP-seq] duplicate reads were removed: MarkDuplicates from Picard Tools (v2.17.3) - [ChIP-seq] LMNA data were analyzed: Enriched Domain Detector (v1.0) with an 11 Kb bin size, gap penalty of 5, and FDR significance threshold of 0.05. - [ChIP-seq] LAD gain, loss, and intersection were found: bedtools (v2.27.1)

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/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

GSE118885

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	No statistical methods were used to predetermine sample size. We included all patients who provided consent in our study.
Data exclusions	No data excluded from the analysis.
Replication	For each experiment, all attempts at replication were successful.
Randomization	The experiments were not randomized. We allocated our samples into two groups based on genotype of LMNA gene.
Blinding	The investigators who performed electro-physiological test, Ca2+ imaging analysis and measuring abnormal nuclear structure were blinded to group allocation during experiments and data collection.

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

[SSEA4]
-Company (catalog number): R&D systems (MAB1435)
-Application: Immunostaining
-Source: Monoclonal Mouse IgG3 Clone # MC-813-70
[Oct-3/4]
-Company (catalog number): Santa Cruz Biotechnology (sc-5279)
-Application: Immunostaining
-Source: mouse monoclonal IgG2b # C-10
[NANOG]
-Company (catalog number): Santa Cruz Biotechnology (sc-33760)
-Application: Immunostaining
-Source: rabbit polyclonal IgG # M-149
[SOX2]
-Company (catalog number): R&D systems (MAB2018)

-Application: Immunostaining
-Source: Monoclonal Mouse IgG2A Clone # 245610
[Cardiac troponin T]
-Company (catalog number): Abcam (ab45932)
-Application: Immunostaining
-Source: Rabbit polyclonal IgG
[Cardiac troponin T]
-Company (catalog number): Abcam (ab8295)
-Application: Immunostaining
-Source: Mouse monoclonal [1C11]
[α-Actinin (Sarcomeric)]
-Company (catalog number): Sigma-Aldrich (A7811)
-Application: Immunostaining
-Source: Mouse monoclonal EA-53
[LMNA]
-Company (catalog number): abcam (ab8980)
-Application: Immunoblotting, ChIP-seq
-Source: Mouse monoclonal [133A2]
[LMNA]
-Company (catalog number): Santa Cruz Biotechnology (sc-376248)
-Application: Immunoblotting, Immunostaining, ChIP-seq
-Source: mouse monoclonal IgG1 (E-1)
[LMNA]
-Company (catalog number): abcam (ab8984)
-Application: Immunoblotting
-Source: Mouse monoclonal [131C3]
[LMNB1]
-Company (catalog number): abcam (ab16048)
-Application: Immunostaining
-Source: Rabbit polyclonal
[CaMKII delta]
-Company (catalog number): Abcam (ab181052)
-Application: Immunoblotting
-Source: Mouse monoclonal [EPR13095]
[Phospho-CaMKII delta]
-Company (catalog number): Abcam (ab32678)
-Application: Immunoblotting
-Source: Rabbit polyclonal
[PDGF Receptor beta]
-Company (catalog number): Abcam (ab32570)
-Application: Immunoblotting
-Source: Rabbit monoclonal [Y92]
[Ryanodine Receptor]
-Company (catalog number): Abcam (ab2868)
-Application: Immunoblotting
-Source: Mouse monoclonal [34C]
[SSEA4]
-Ref in manufacturer's web site: Shevinsky, L.H. et al. (1982) Cell 30:697. Kannagi, R. et al. (1983) EMBO J. 2:2355.
[Oct-3/4]
-Ref in manufacturer's web site: PMID: # 27797132, PMID: # 28159471, PMID: # 27876565
[NANOG]
-Ref in manufacturer's web site: PMID: # 24550733, PMID: # 24619130, PMID: # 24380431
[SOX2]
-Ref in manufacturer's web site: Graham, V. et al. (2003) Neuron 39:749., Avilion, A.A. et al. (2003) Genes Dev. 17:126.
[Cardiac troponin T]
-Abcam (ab45932)- Ref in manufacturer's web site: PubMed: 27672365, PubMed: 27226619
-Abcam (ab8295)- -Ref in manufacturer's web site: PubMed: 28487655, PubMed: 28490375.
[α-Actinin (Sarcomeric)]
-Ref in manufacturer's web site: PMID 19668186, PMID 22020047
[LMNA]
-Abcam (ab8980)- Ref in manufacturer's web site: PubMed: 29545600, PubMed: 28737169
-SCBT (sc-376248)- Ref in manufacturer's web site: PMID: # 29684352, PMID: # 29436586
- Abcam (ab8984)- Ref in manufacturer's web site: PubMed: 29580221, PubMed: 29659505
[CaMKII delta]
--Ref in manufacturer's web site: PubMed: 27084844
[Phospho-CaMKII delta]
--Ref in manufacturer's web site: PubMed: 29482582, PubMed: 29593308
[PDGF Receptor beta]
-Ref in manufacturer's web site: PubMed: 28423550, PubMed: 28230073
[Ryanodine Receptor]
-Ref in manufacturer's web site: PubMed: 26301072, PubMed: 25775120
[LMNB1]
-Ref in manufacturer's web site: PubMed: 29308302, PubMed: 29335436
[H3K9me2]
-Company (catalog number): Abcam (ab1220), Active Motif (#39239)

-Application: Immunostaining, ChIP-qPCR
-Ref: PMID 29033129
[H3K9me3]
-Company (catalog number): Active Motif (#61013)
-Application: Immunostaining, ChIP-qPCR
-Ref: PMID:30143619

Validation

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-Application: Immunoblotting
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[PDGF Receptor beta]
-Company (catalog number): Abcam (ab32570)
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[NANOG]
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-Ref: PMID 29033129
[H3K9me3]
-Company (catalog number): Active Motif (#61013)
-Application: Immunostaining, ChIP-qPCR
-Ref: PMID:30143619

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	-We obtained dermal fibroblasts or PBMCs from the patients and generated patient specific iPSC lines using Co-MIPs (doi:10.1038/srep08081) or sendai virus method (ThermoFisher, CytoTune™-iPS 2.0 Sendai Reprogramming Kit; A16517). -H7 hESCs line were obtained from WiCell (WAe007-A). -The iPSC-derived cardiomycytes were generated by previous protocol (doi:10.3791/52628).
Authentication	-Immunofluresence assay of each iPSC line was performed to check the expression of stem cell markers such as NANOG, POU5F1 and SOX2. -SNP karyotyping was tested through HuCytoSNP-12 chip (Illumina), and CNV and SNP visualization was performed using KaryoStudio v1.4 (Illumina).
Mycoplasma contamination	We confirmed that all cell lines were negative for mycoplasma contamination using MycoAlert™ PLUS Mycoplasma Detection Kit (Lonza, LT07-705).
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.

Human research participants

Policy information about studies involving human research participants

Population characteristics	The detail information of patients was described in Extended Data Figure 1b. Patients III-1, III-3, and III-9 (age 57, 60, and 67, respectively) carried the c.349_350insG frame shift mutation on LMNA gene initially presented with atrial fibrillation that progressed to atrioventricular block and ventricular tachycardia. These patients eventually required implantable cardioverter defibrillators (ICDs) and later developed DCM. The other two carriers (III-15 and III-17; ages 38 and 45, respectively) were younger and had exhibited paroxysmal atrial fibrillation prior to the beginning of the study. III-1, III-3, III-9, IV-1, and IV-2 individuals are male. III-15 and III-17 individuals are female.
Recruitment	The fibroblasts, PBMCs, and heart tissues were obtained from patients using IRB-approved protocol at Stanford University (Protocol ID 17576 and 29904). Informed consents were obtained from all patients who were included in our study.
Ethics oversight	IRB-approved protocols at Stanford University (Protocol ID 17576 and 29904)

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

ChIP-seq

Data deposition

☒ Confirm that both raw and final processed data have been deposited in a public database such as GEO.

☒ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links
May remain private before publication.

Gene Expression Omnibus (GEO): GSE118885

Files in database submission

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RNA_PT3WT_Rep1Aligned.out.sorted.q255.bw
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PT3WT_EDD_SCLMNA_vs_Input_peaks.bed
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SC_6_USPD16084632_HJ3FYBBXX_L2_2.fq.gz

Genome browser session
(e.g. UCSC)

Provide a link to an anonymized genome browser session for "Initial submission" and "Revised version" documents only, to enable peer review. Write "no longer applicable" for "Final submission" documents.

Methodology

Replicates

Two parental hiPSCs lines (III-3; WT/MT, IV-1; WT/WT), and two isogeneic lines (III-3; WT/Corr-WT, IV-1; WT/Ins-MT).
Two different antibodies were used for LMNA ChIP-seq. ab8984 and sc-376248

Sequencing depth

Raw_Reads Clean_Reads Raw_Base(G) Clean_Base(G) Effective_Rate(%) Error_Rate(%) Q20(%) Q30(%) GC_Content(%) Paired-End
H3K4_pt3WT 54856219 42145611 16.5 12.6 76.83 0.02 95.06 88.98 56.01 Yes
H3K4_pt3MT 59207590 39834003 17.8 12 67.28 0.01 95.73 90.23 57.05 Yes
H3K27_pt3WT 41638326 31134930 12.5 9.3 74.77 0.01 95.98 90.68 46.75 Yes
H3K27_pt3MT 53964775 40732993 16.2 12.2 75.48 0.01 96.2 91.15 47.07 Yes
ab_pt3WT 53766870 43207940 16.1 13 80.36 0.02 95.93 90.19 40.85 Yes
ab_pt3MT 47369372 41177310 14.2 12.4 86.93 0.02 95.56 89.41 41.44 Yes
SC_pt3WT 57419745 51251376 17.2 15.4 89.26 0.02 95.63 89.53 40.58 Yes
SC_pt3MT 50700560 48187024 15.2 14.5 95.04 0.02 95.45 89.2 40.92 Yes

Antibodies

Santa Cruz Biotechnology sc-2025: IgG
Active Motif 39159: H3K4me3
Active Motif 39155: H3K27me3
Abcam ab8984: LMNA
Santa Cruz Biotechnology sc-376248: LMNA

Peak calling parameters

Enriched Domain Detector (v1.0) with an 11 Kb bin size, gap penalty of 5, and FDR significance threshold of 0.05.

Data quality

LMNA-sc-376248: EDD peaks (pt3WT; 587, pt3MT; 614)
LMNA-ab8974: EDD peaks (pt3WT; 585, pt3MT; 615)

Software

- [ChIP-seq] AQUAS pipeline from the Kundaje lab at Stanford University (https://github.com/kundajelab/chip-seq-pipeline2)
- [ChIP-seq] duplicate reads were removed: MarkDuplicates from Picard Tools (v2.17.3)
- [ChIP-seq] LMNA data were analyzed: Enriched Domain Detector (v1.0) with an 11 Kb bin size, gap penalty of 5, and FDR significance threshold of 0.05.
- [ChIP-seq] LAD gain, loss, and intersection were found: bedtools (v2.27.1)