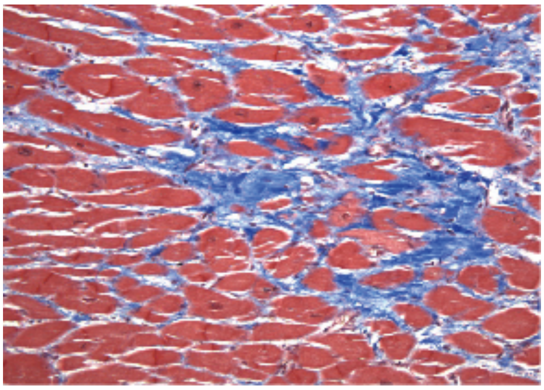
# Supplemental Material

## Supplemental Figures

### Figure S1, Cardiac pathological result of the heart transplantation patient

The sections are Masson trichrome stains from the left ventricle in which muscle is red and diffuse interstitial collagen is blue. The white spaces adjacent to myocytes are an artifact of myocyte shrinkage away from interstitial connective tissue with the formalin fixation and routine processing.



### Figure S2, The genetic structure of the *C10orf71* and its surrounding regions

A, The genes near *C10orf71*. B, Linkage disequilibrium relationship of SNPs within 50 kb of either side of *C10orf71* calculated by Haploview software using CHB data as a reference.

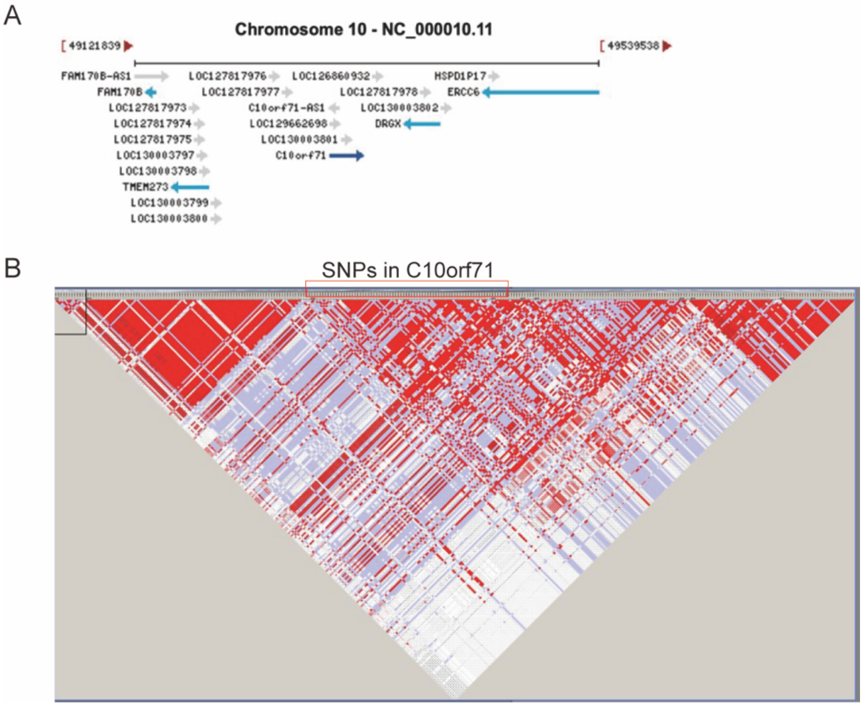


**Figure S3, Truncated C10orf71 proteins expressed by *C10orf71* with frameshift variants**

A, Sequencing validation of expression plasmids for *C10orf71* with variants found in DCM patients. The blue shadows indicate the mutation sites. B, Western blotting using cell lysates of HEK293T cells transfected with *C10orf71* expression plasmids.

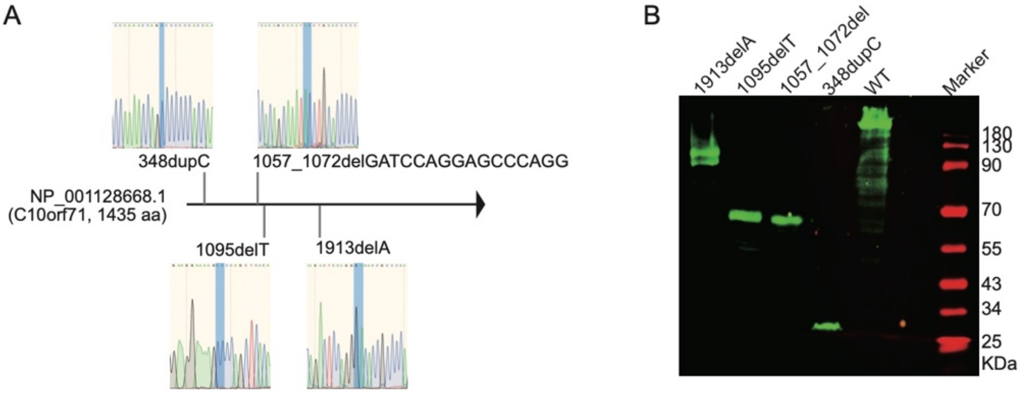


**Figure S4, Construction of *C10orf71* mutant hiPSCs**

A, The gRNA used in the construction. B and C, Sequencing validation of *C10orf71* mutant hiPSCs. The red boxes indicate the positions of the insertion of one base pair (B) and deletion of 11 base pairs (C).

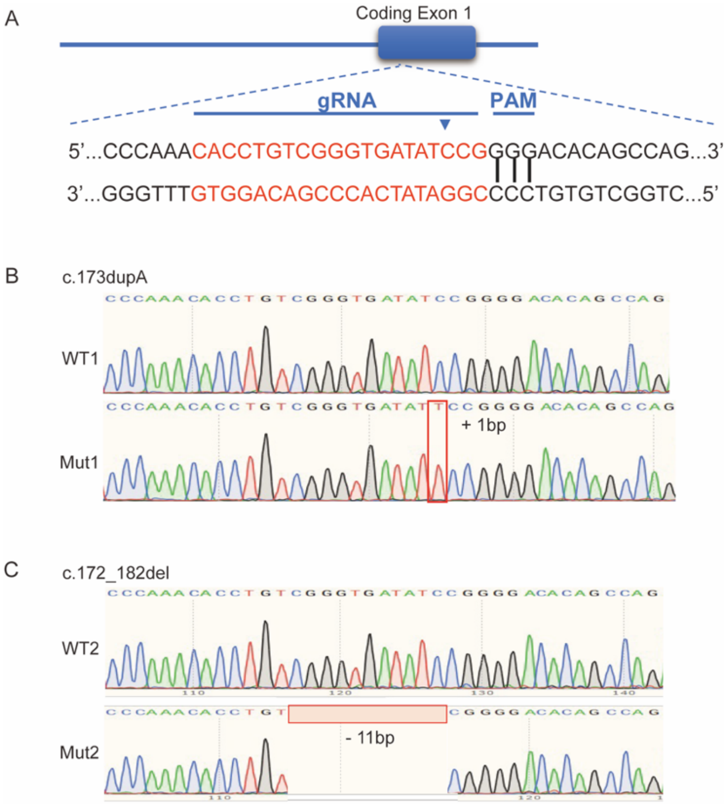


**Figure S5, Quantitative analysis of C10orf71 mRNA with frameshift variant**

The level of frameshift variant mRNA was assessed using qPCR (A) and RNA sequencing (B). Each dot in panel A represents one biological repeat. Data represent means ± SD. *P < 0.05 in Mann-Whitney test. The red box in panel B indicates the C10orf71 protein coding region.

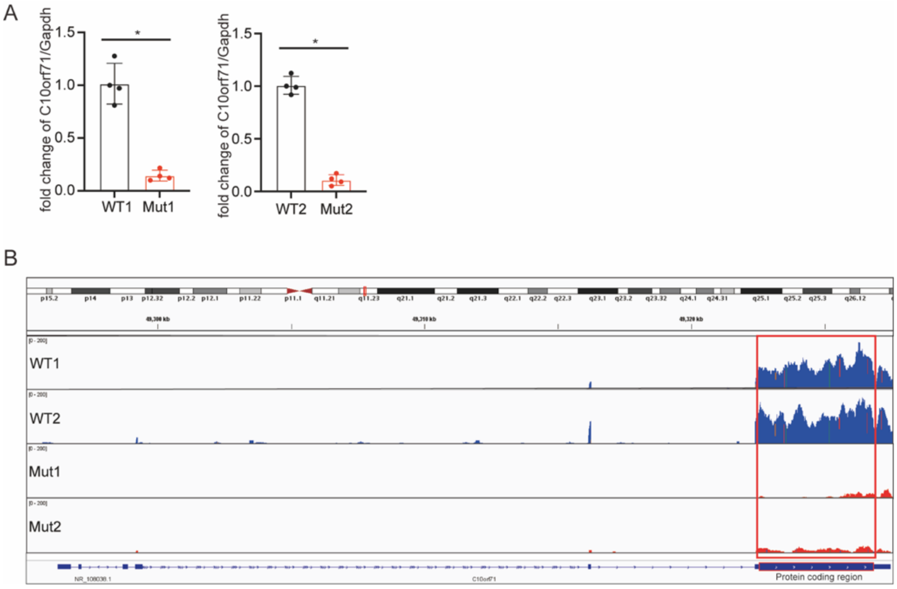


**Figure S6, Structural prediction of C10orf71 protein in different databases**

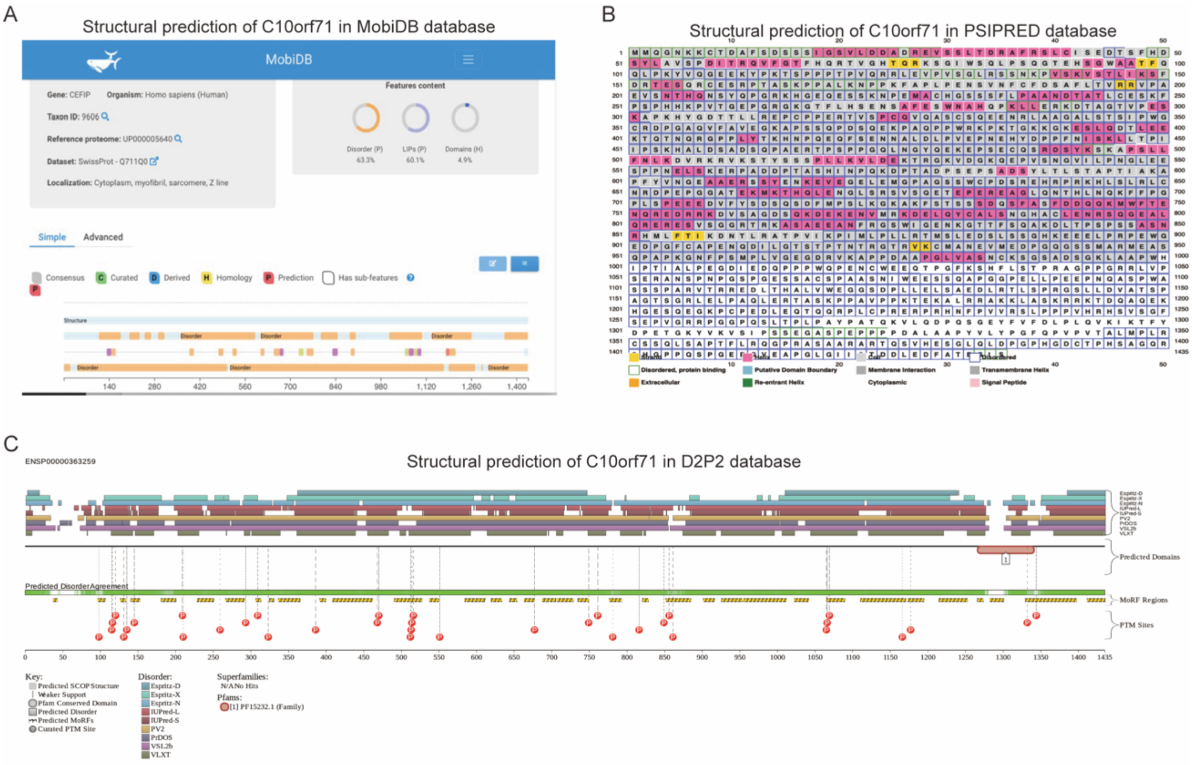
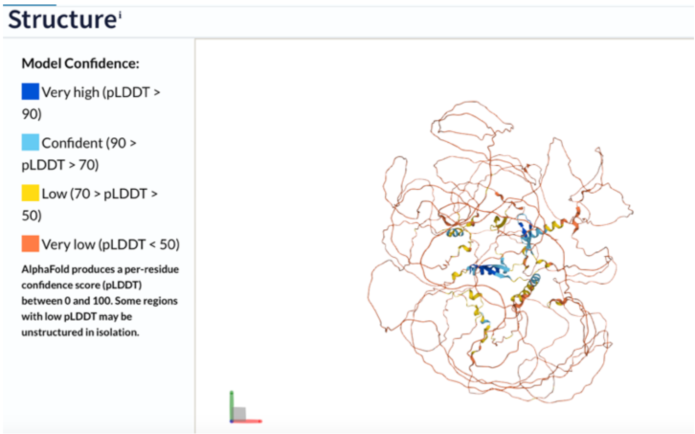


**Figure S7, C10orf71 structure predicted by AlphaFold**



Structure

Model Confidence:

🟦 Very high (pLDDT > 90)

🟦 Confident (90 > pLDDT > 70)

🟨 Low (70 > pLDDT > 50)

🟧 Very low (pLDDT < 50)

AlphaFold produces a per-residue confidence score (pLDDT) between 0 and 100. Some regions with low pLDDT may be unstructured in isolation.

**Figure S8, Hydrophilicity of C10orf71 calculated by ProtScale**

Score < 0 indicates the hydrophilicity.

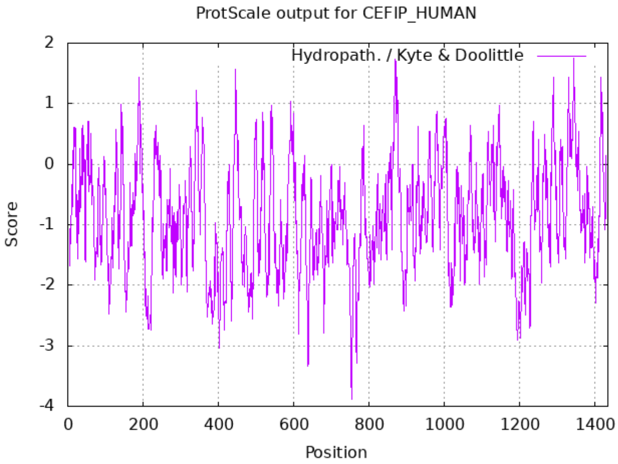


**Figure S9, Expression of *C10orf71* in GTEx Portal**

The red frame indicates the expression of *C10orf71* in heart.

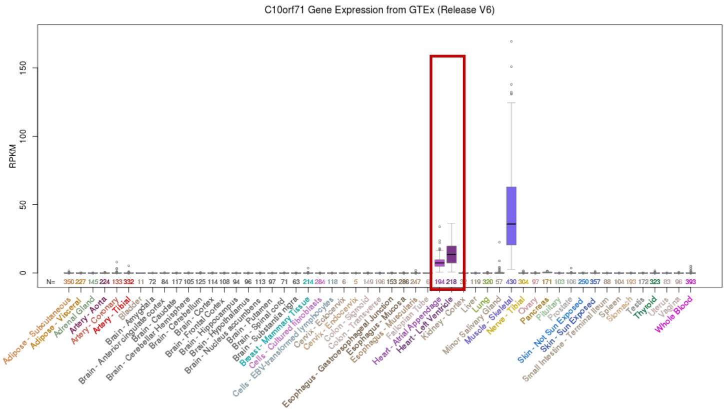


**Figure S10, Expression level of cardiac marker *Tnnt2* during heart development**

Each dot represents one biological repeat. Data represent means ± SD.

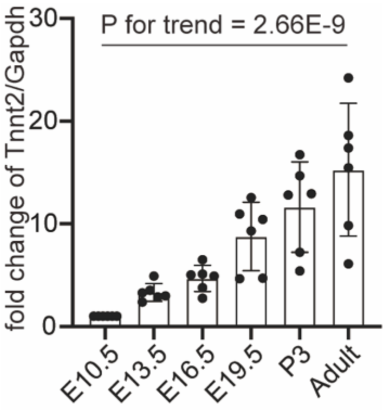


**Figure S11, Expression level of m*C10orf71* during myogenesis**

A, Expression level of *mC10orf71* in a public data from GEO database (GDS587). B, Expression level of *mC10orf71* during myogenesis of C2C12 cells. Each dot represents one biological repeat. Data represent means ± SD.

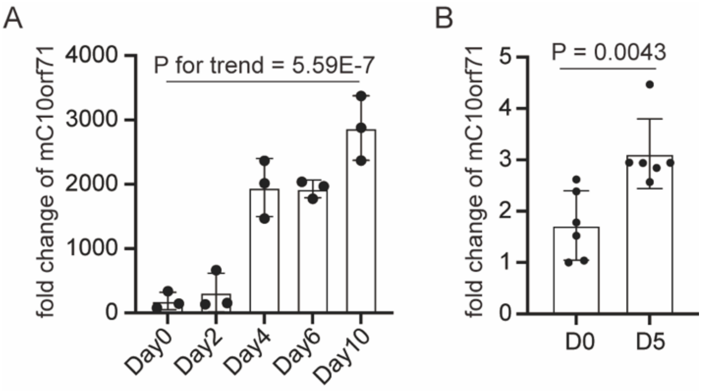


**Figure S12, Expression of *C10orf71* and cardiac markers (*TNNT2* and *MYH7*) in different types of cells in our single nucleus RNA sequencing data of human heart**

The red boxes indicate cardiomyocytes.

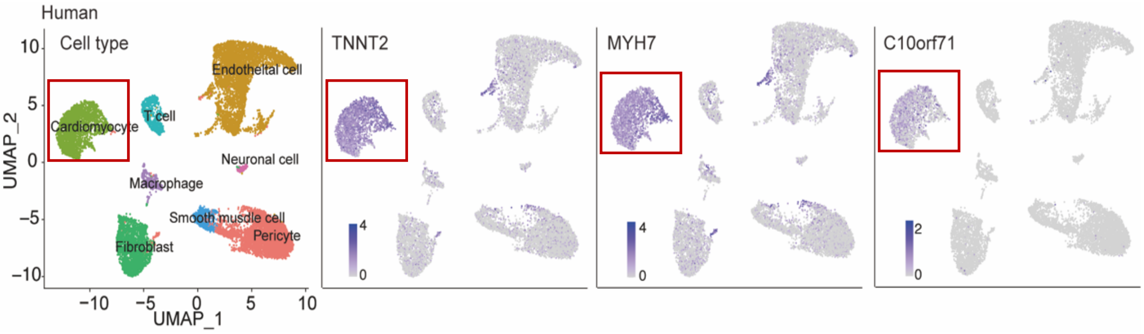


**Figure S13, Expression of *C10orf71* and cardiac markers (*TNNT2* and *MYH7*) in different types of cells in a published single cell sequencing database**

A, UMAP of this data. B, Violin plots of the target genes. The red boxes indicate ventricular-cardiomyocytes.

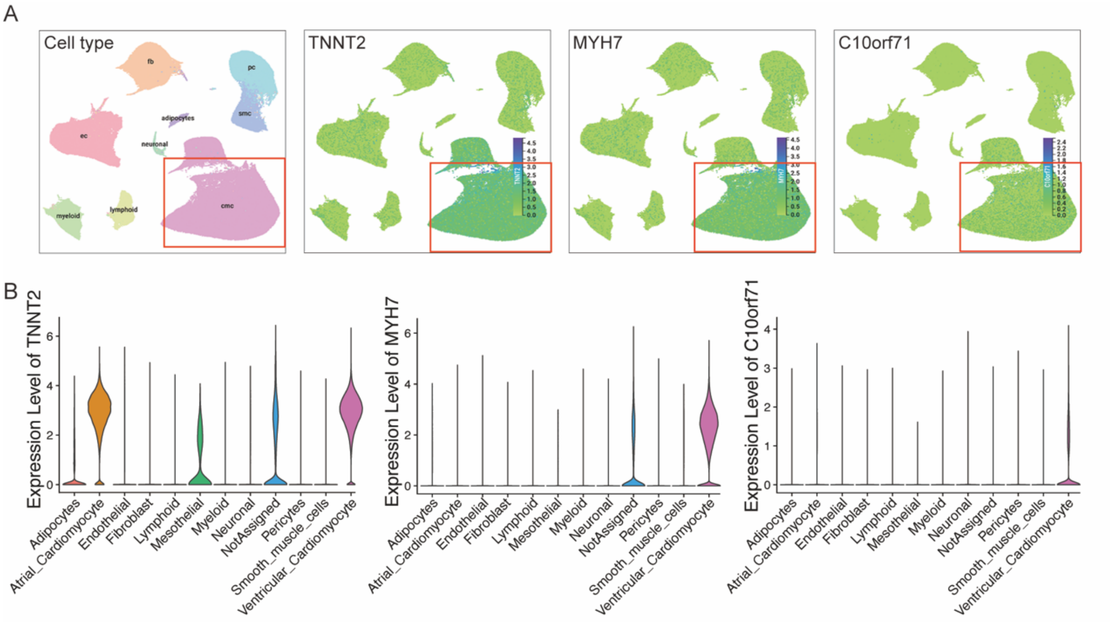


**Figure S14, Construction of *mC10orf71* knockout mice**

*1, gRNA design*

gRNA1 (matching reverse strand of gene): GGTTCTGTGAGATGCCGGTGAGG
gRNA2 (matching forward strand of gene): AGAGAGGGTTTTCCTCGTGGTGG

↓

*2, Cas9 mRNA, gRNA generated by in vitro transcription*

↓

*3, Co-injection into fertilized eggs*

↓

*4, Selection of KO mice by PCR and sequencing*

**PCR Screening:**

PCR Primers (Annealing Temperature 60.0 ºC):
Forward primer (F1): 5'-GCAGCCATTTCGCCATATCC-3'
Reverse primer (R1): 5'-GACTGAGAAAGTACAGGGTAGGG-3'
Targeted allele: 573 bp Wildtype allele: 5490 bp

**Sequencing Confirmation:**

TAACTAACTGGTCATCTCAAAGCCCCACCTTGGGACAGGT--del 4916 bp--CTCCAAAGAAGATCTTCTGATAAAGCAAAAGTTAACATTT

**Figure S15, Efficiency of CRISPR-Cas9 mediated *mC10orf71* knockout**

A, Expression level of m*C10orf71* in hearts of WT and KO mice. B, The statistical results of A. n = 6 per group. Each dot represents one biological repeat. Data represent means ± SD. ***P < 0.001 in Mann-Whitney test.

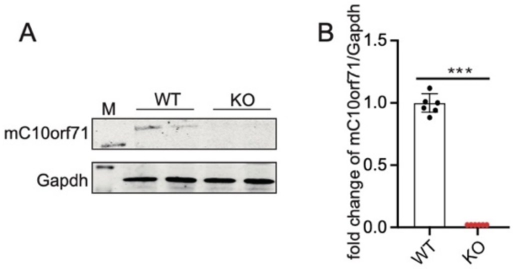


**Figure S16, H&E staining of hearts of mice at different times after birth**

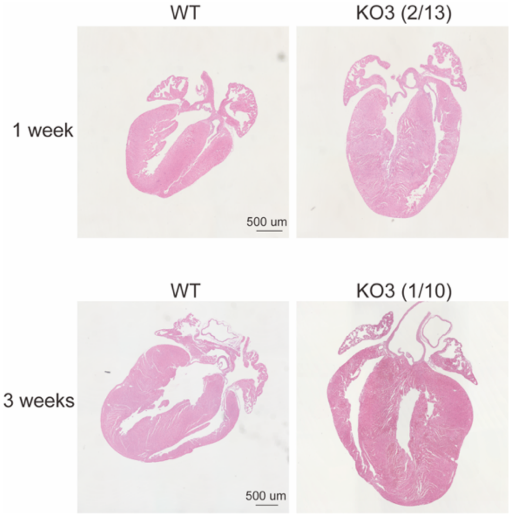


**Figure S17, Heart weight of WT and KO male mice**

Each dot represents one biological repeat. Data represent means ± SD. ***P < 0.001 in t-test. ns, no significance.

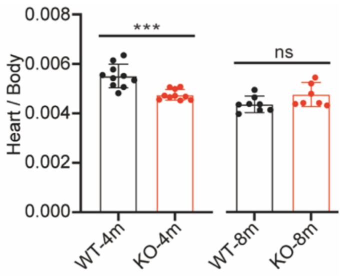


**Figure S18, Echocardiographic parameters of WT and KO male mice**

HR: heart rate. LVVOL-d: left ventricular volume at end-diastole. LVID-d: internal dimension of left ventricle at end-diastole. LVPW-d: left ventricular posterior wall thickness at end-diastole. n = 16 per group at 4 months; n = 7-8 at 8 months. Each dot represents one biological repeat. Data represent means ± SD. *P < 0.05, **P < 0.01 in t-test. ns, no significance.

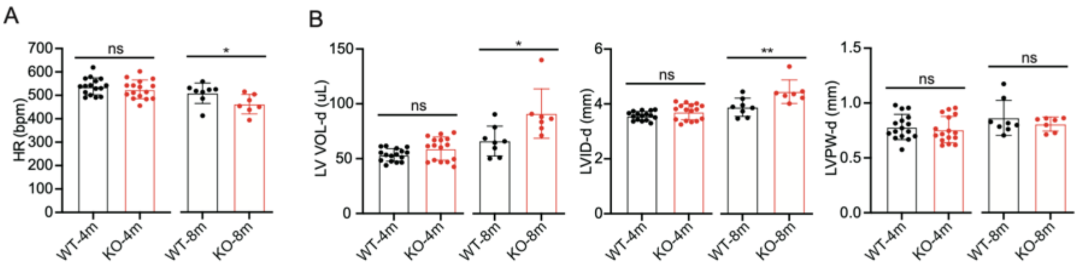


**Figure S19, Echocardiographic parameters of WT and KO male mice aged 53~63 weeks**

n = 5 for WT; n = 8 for KO. Each dot represents one biological repeat. Data represent means ± SD. **P < 0.01 in t-test.

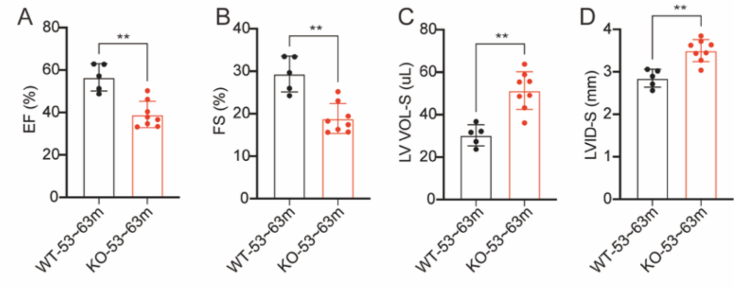


**Figure S20, Myocardial images of WT and KO male mice aged 4 months taken by transmission electron microscopy**

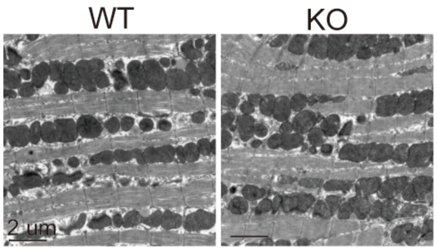


**Figure S21, The heart mass to tibial length and the heart mass to body weight among WT, heterogynous, and homozygous male mice aged 7~8-months**

n = 7-8 per group. Each dot represents one biological repeat. Data represent means ± SD. ns, no significance in one-way ANOVA combined with post hoc Tukey's test.

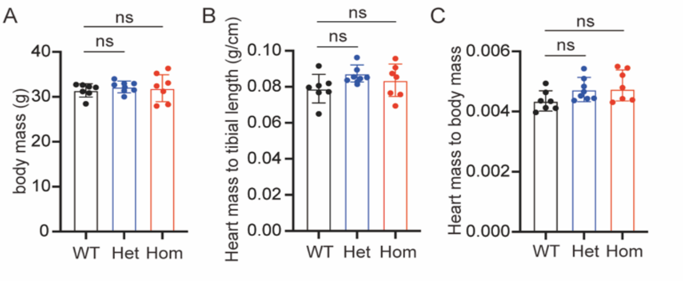


**Figure S22, Cardiac function of WT, heterogynous, and homozygous male mice aged 7~8-months**

A, Representative ultrasound images for hearts with different genotypes. B, Heart rates for hearts with different genotypes. C, Echocardiographic parameters for hearts with different genotypes. n = 7-8 per group. Each dot represents one biological repeat. Data represent means ± SD. *P < 0.05, **P < 0.01, ***P < 0.001 in one-way ANOVA combined with post hoc Tukey's test. ns, no significance.

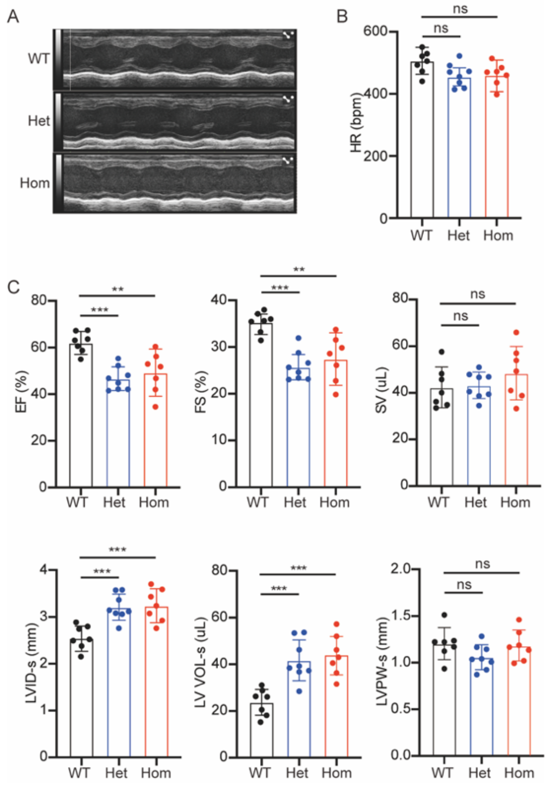


**Figure S23, Cardiac function of WT, heterogynous, and homozygous female mice aged 4~8-months**

Each dot represents one biological repeat. Data represent means ± SD. *P < 0.05, **P < 0.01 in one-way ANOVA combined with post hoc Tukey's test.

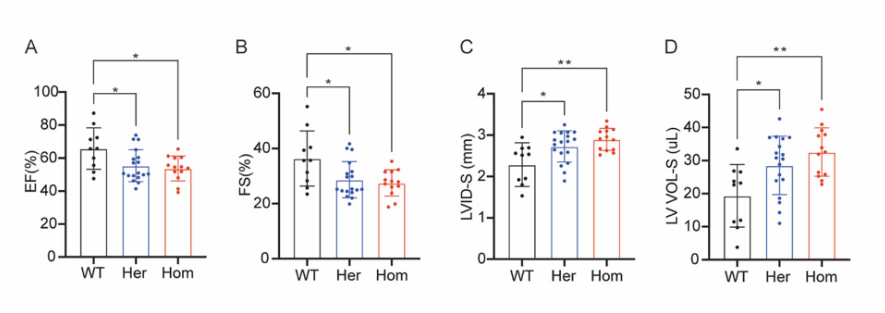


**Figure S24, Expression level for genes related to heart contraction and RNA splicing in adult WT and KO mice**

A-B Heatmap of genes related to heart contraction (A) and RNA splicing (B). Red arrows indicate the known DCM genes. C, qPCR validation of expressional changes of Rbm24, Nexn, Chrm2, Dsg2, Pln, and Sgcb in adult WT and KO mice (n = 12-14). Each dot represents one biological repeat. Data represent means ± SD. ***P < 0.001 in t-test.

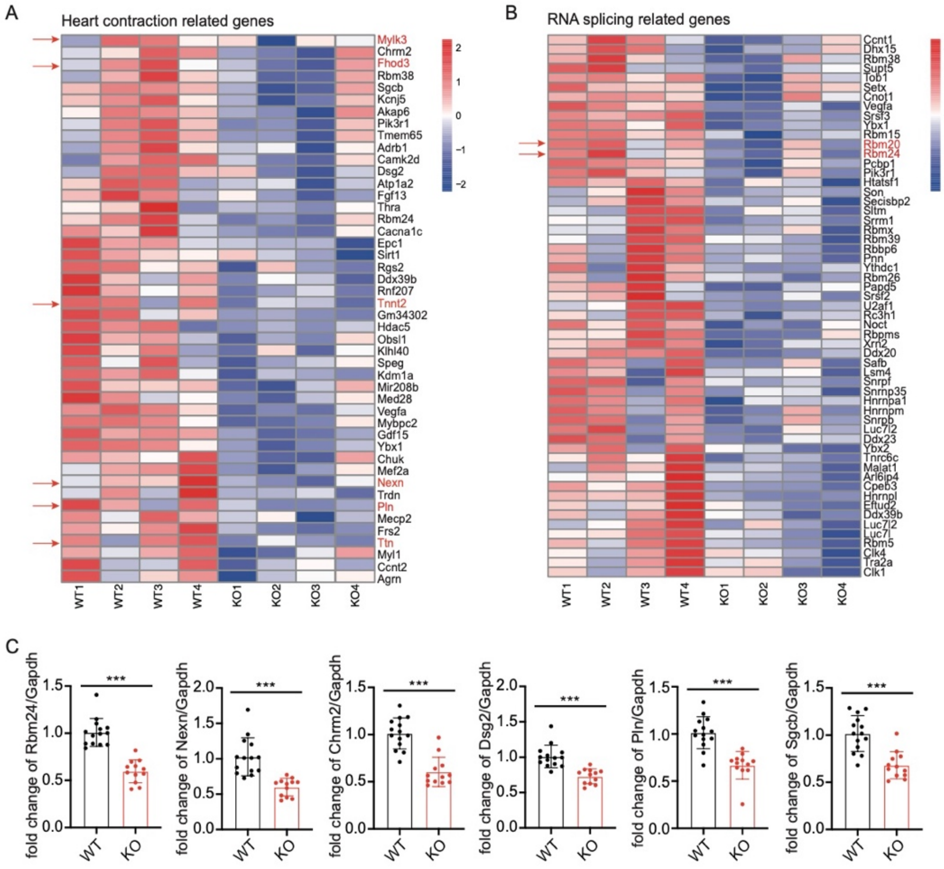


**Figure S25, The proportion of alternative splicing types in response to mC10orf71 knockout**

A3SS: alternative 3′-acceptor sites. A5SS, alternative 5′-donor sites. AltEnd: alternative last exon. AltStart: alternative first exon. CE: cassette exon. IR: intron retention. MXE: mutually exclusive exons.

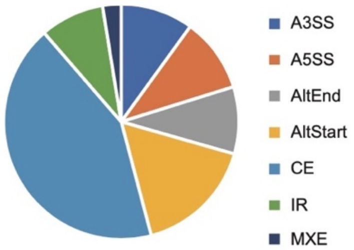


**Figure S26, Splicing changes of *Tnnt2* in KO mice at E18.5**

IGV view showing reads mapping to *Tnnt2*. Due to significant differences in the transcription levels between exons in front and in back of the gene, the results are presented in two parts.

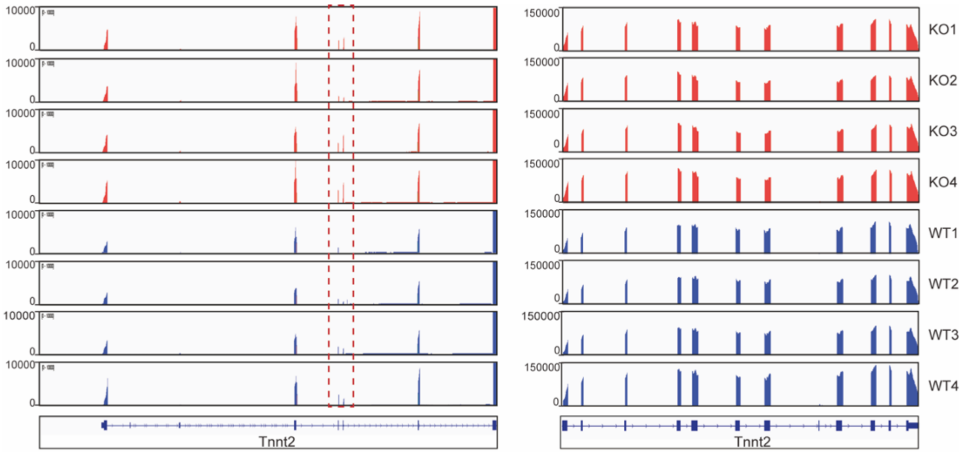


**Figure S27, Heatmap of expression values for genes related to extracellular matrix**

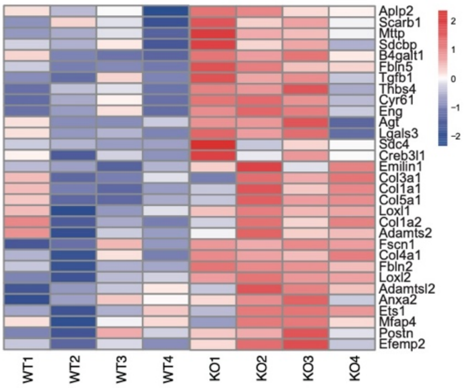


**Figure S28, Heatmap of expression values for candidate genes**

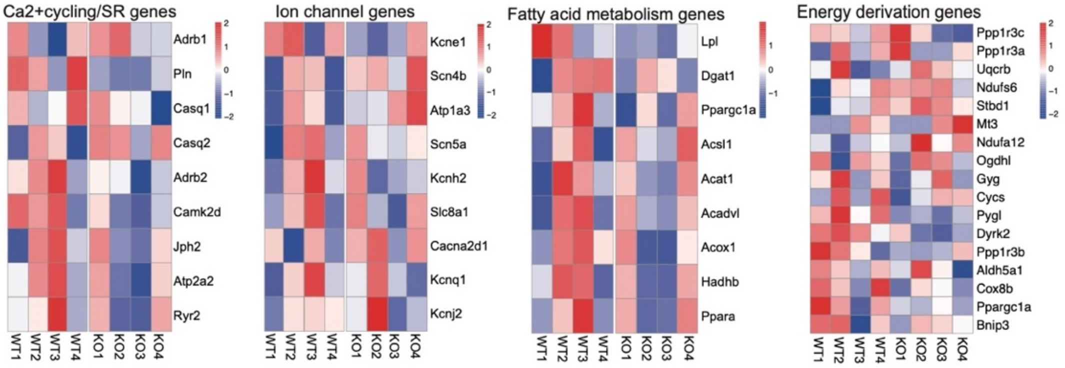


**Figure S29, Quantification of parameters obtained in IonOptix measurements**

Each dot represents one biological repeat. Data represent means ± SD. *P < 0.05 in t-test. ns, no significance.

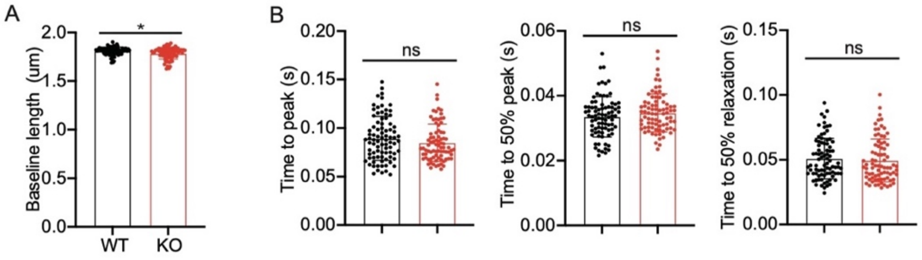


**Figure S30, Phenotype of hiPSC-CMs with homozygous c.172_182del mutation**

A, Relative mRNA levels of *C10orf71* in WT2 hiPSCs and WT2 hiPSC-CMs after 40 days of differentiation (n = four independent differentiations). *P < 0.05 in Mann-Whitney test. B, Representative images for WT2 and Mut2 monolayer hiPSC-CMs sheets. C, Relative mRNA levels of *TTN, TNNT2, MYH7,* and *ACTN2* in WT2 and Mut2 hiPSC-CMs at day 40 (n = four independent differentiations). *P < 0.05 in Mann-Whitney test. D, MEA parameters for WT2 and Mut2 hiPSC-CMs, including beat amplitude, beat period, and excitation-contraction delay (n = 8 per group). **P < 0.01, ***P < 0.001 in t-test. ns, no significance. Each dot represents one biological repeat. Data represent mean ± SD.

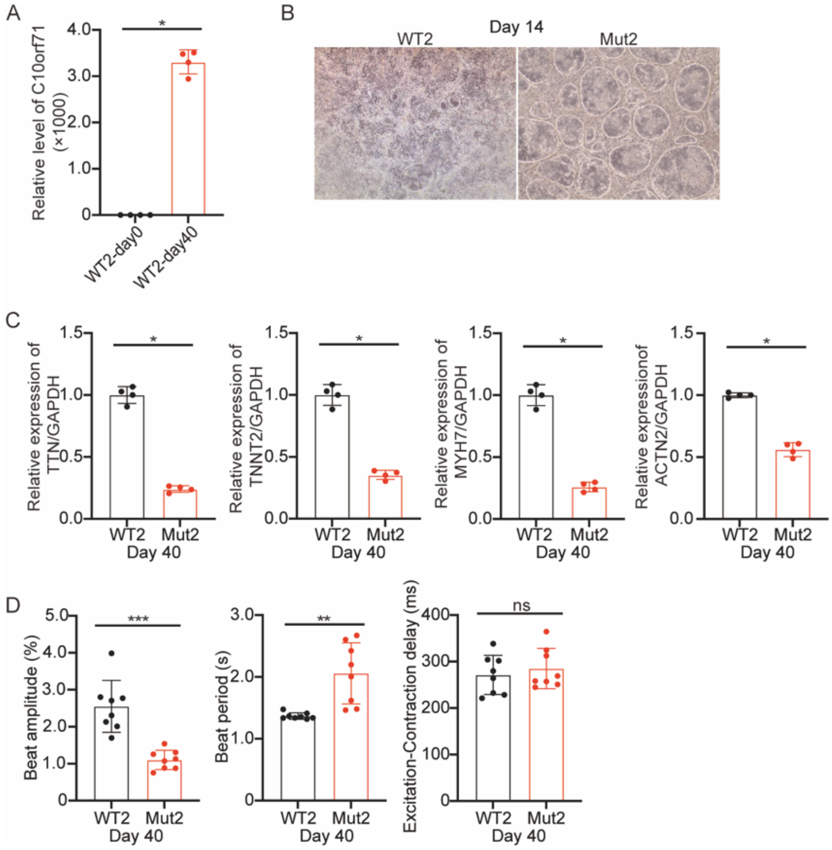


**Figure S31, Pluripotent markers (NANOG and SSEA4) in WT1 and c.173dupA mutant hiPSCs**

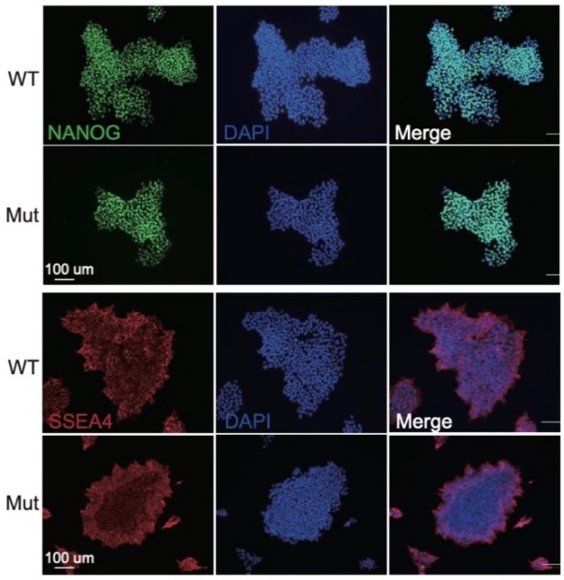


**Figure S32, Phenotype of hiPSC-CMs with heterozygous c. 164_173del mutation**

A, Sequencing results of WT1 and Mut3 hiPSCs. B, Relative mRNA levels of *TTN, TNNT2, MYH7,* and *ACTN2* in WT1 and Mut3 hiPSC-CMs at day 40 (n = four independent differentiations). *P < 0.05 in Mann-Whitney test. C, MEA parameters for WT1 and Mut3 hiPSC-CMs, including beat amplitude, beat period, and excitation-contraction delay (n = 8 per group). ***P < 0.001 in t-test. ns, no significance. Each dot represents one biological repeat. Data represent mean ± SD.

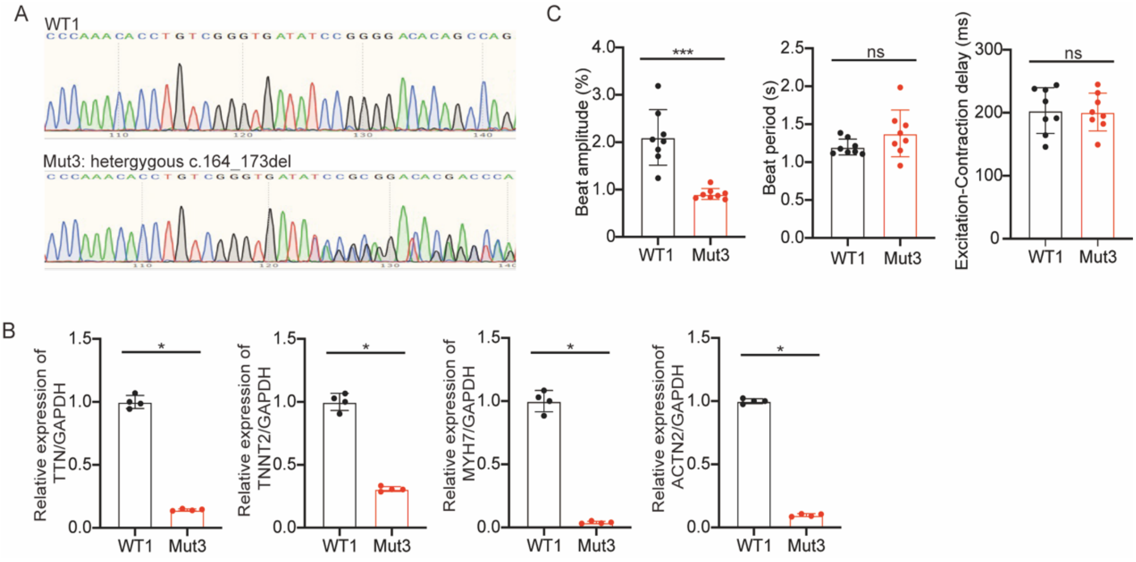


**Figure S33, Immunofluorescence for hiPSC-HOs**

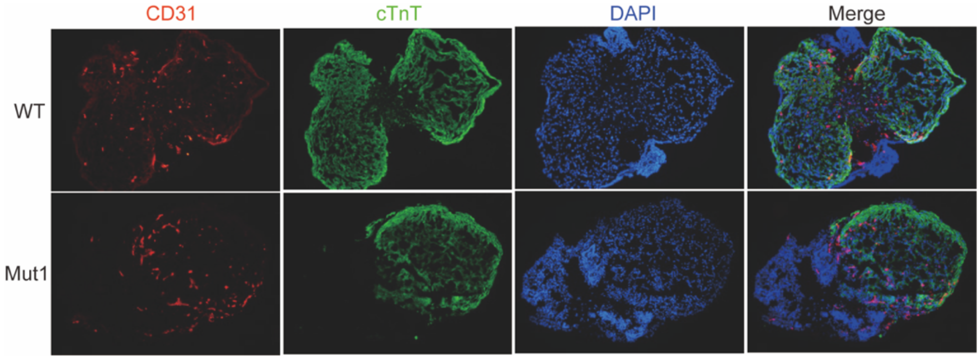


**Figure S34, Contractility of WT and heterozygous mutant hiPSC-HOs**

Contractility was assessed based on dynamic morphological information. Each dot represents one biological repeat. Data represent means ± SD. **P < 0.01 in t-test.

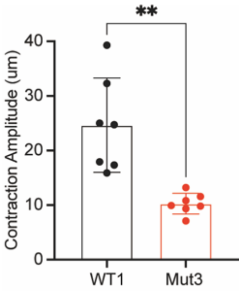


**Figure S35, The effect of OM treatment on heterozygous mice**

Each dot represents one biological repeat. Data represent means ± SD. *P < 0.05, **P < 0.01, ***P < 0.001 in t-test. ns, no significance.

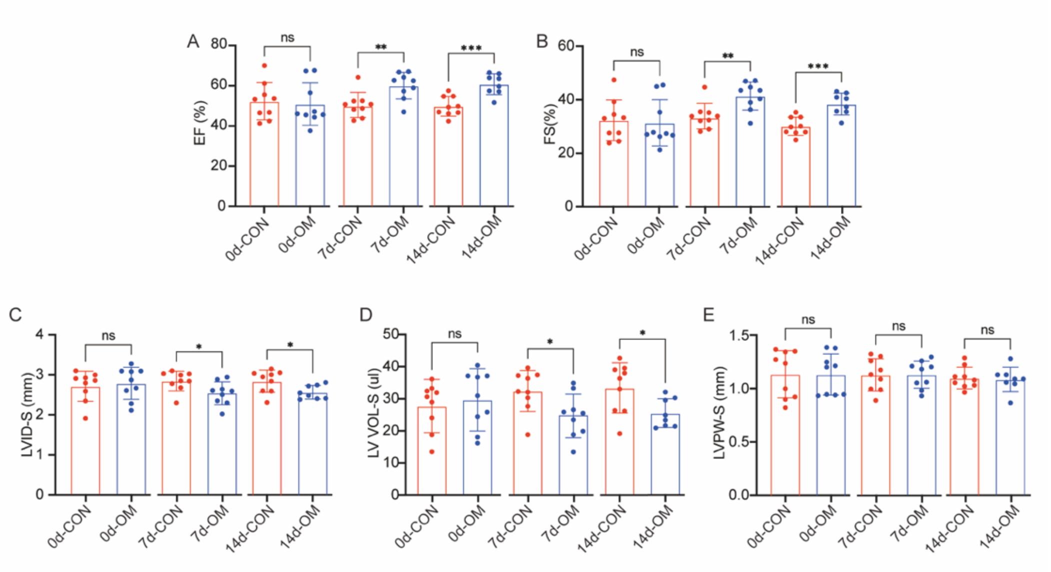
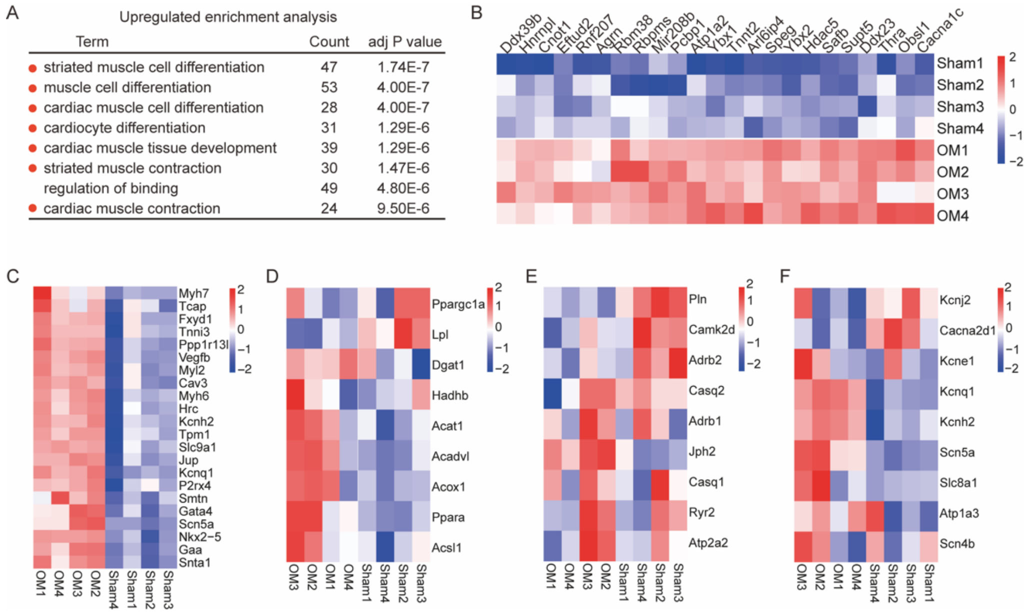


**Figure S36, Upregulated GO terms after OM treatment**

(A) GO enrichment analysis of up-regulated genes after OM treatment (n = 4 per group). The top eight terms are listed. The red dots indicate the terms associated with CM differentiation and contraction. (B) Heatmap of expression values for contractile genes down-regulated in KO heart and up-regulated by OM treatment. (C) Heatmap of expression values for up-regulated contractile genes apart from genes in B. (D-F) Heatmap of expression values for genes related to fatty acid metabolism (D), $Ca^{2+}$cycling/SR (E), and ion channels (F).

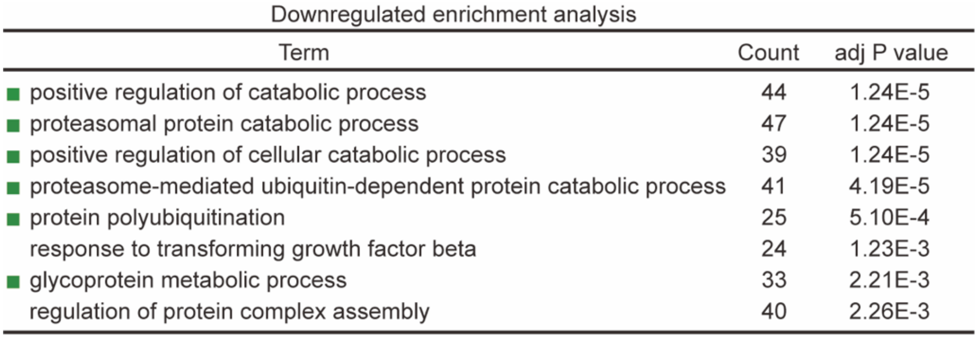


Upregulated enrichment analysis

| Term | Count | adj P value |
|---|---|---|
| ● striated muscle cell differentiation | 47 | 1.74E-7 |
| ● muscle cell differentiation | 53 | 4.00E-7 |
| ● cardiac muscle cell differentiation | 28 | 4.00E-7 |
| ● cardiocyte differentiation | 31 | 1.29E-6 |
| ● cardiac muscle tissue development | 39 | 1.29E-6 |
| ● striated muscle contraction | 30 | 1.47E-6 |
| regulation of binding | 49 | 4.80E-6 |
| ● cardiac muscle contraction | 24 | 9.50E-6 |

**Figure S37, Downregulated GO terms after OM treatment**

The top eight terms are listed. The green squares indicate the terms associated with catabolic process (n = 4 per group).



Downregulated enrichment analysis

| Term | Count | adj P value |
|---|---|---|
| 🟩 positive regulation of catabolic process | 44 | 1.24E-5 |
| 🟩 proteasomal protein catabolic process | 47 | 1.24E-5 |
| 🟩 positive regulation of cellular catabolic process | 39 | 1.24E-5 |
| 🟩 proteasome-mediated ubiquitin-dependent protein catabolic process | 41 | 4.19E-5 |
| 🟩 protein polyubiquitination | 25 | 5.10E-4 |
| response to transforming growth factor beta | 24 | 1.23E-3 |
| 🟩 glycoprotein metabolic process | 33 | 2.21E-3 |
| regulation of protein complex assembly | 40 | 2.26E-3 |

**Table S1 Clinical characteristics of sporadic DCM cohort from Beijing Anzhen Hospital**

| **Onset age** | **< 6 m** | **6 m ~ 1 y** | **1 y ~3 y** | **3 y ~6 y** | **6 y ~9 y** | **9 y ~12 y** | **12 y ~18 y** | **Adult** |
|---|---|---|---|---|---|---|---|---|
| **Number of cases** | 3 | 19 | 20 | 25 | 16 | 14 | 9 | 114 |
| **DCM/enlarged heart*** | 2/1 | 6/13 | 5/15 | 7/18 | 7/9 | 6/8 | 4/5 | 114/0 |
| **Onset age** | 146 days | 11±2 months | 26±7 months | 4.7±0.8 years | 7.3±0.9 years | 10.0±0.8 years | 14.2±1.7 years | 46 ±11 years |
| **Gender (male/female)** | 2/1 | 13/6 | 11/9 | 15/10 | 6/10 | 8/6 | 3/6 | 93/21 |
| **LVIDd (mm)** | 38.00±9.64 | 40.00±5.77 | 40.94±10.29 | 44.39±5.58 | 46.77±8.18 | 48.80±9.35 | 56.63±8.19 | 68.61±12.55 |
| **LVIDd-standard (mm)** | 21.18±1.51 | 24.12±2.08 | 29.44±2.10 | 32.96±2.21 | 36.63±2.09 | 39.42±2.72 | 40.94±1.89 | 45-55mm for male, and 35-50mm for female |
| **LVIDs (mm)** | 28.17±5.25 | 28.71±8.18 | 28.82±10.03 | 30.06±7.87 | 33.38±6.74 | 35.80±7.97 | 40.63±10.68 | 58.51±11.91 |
| **LVIDs-standard (mm)** | 12.72±1.20 | 14.77±1.95 | 18.10±1.82 | 20.40±1.94 | 23.16±2.16 | 24.89±2.57 | 25.79±2.73 | 25-37mm for male, and 20-35mm for female |
| **EF (%)** | 47±16 | 55±20 | 59±12 | 59±13 | 59±6 | 55±8 | 54±16 | 30±11 |

m, month; y, year.

*Partial patients under the age of 18 did not reach the standard for systolic dysfunction, which is defined as enlarged heart rather than DCM.

**Table S2 Genotype of mice at weaning**

| | **WT** | **Het** | **Hom** | **P** |
|---|---|---|---|---|
| **Expected** | 81.5 | 163 | 81.5 | 2.64E-9 |
| | 25% | 50% | 25% | |
| **Actual** | 157 | 125 | 44 | |
| | 48.2% | 38.3% | 13.5% | |

**Table S3 Echocardiography data at 4 months, 8 months as well as 53-63 weeks**

| | **4 months** | | **8 months** | | **53-63 weeks** | |
|---|---|---|---|---|---|---|
| | WT | KO | WT | KO | WT | KO |
| EF (%) | 64±9 | 51±7 | 63±5 | 53±8 | 57±6 | 39±5 |
| FS (%) | 34±7 | 26±4 | 34±4 | 27±5 | 29±4 | 19±3 |
| LVID-s (mm) | 2.35±0.31 | 2.77±0.33 | 2.55±0.24 | 3.24±0.36 | 2.85±0.21 | 3.58±0.23 |
| LVVOL-s (uL) | 19.72±5.93 | 29.53±8.37 | 23.73±5.52 | 42.72±11.87 | 30.29±4.96 | 54.02±8.17 |

## Table S4 Contractile genes exhibiting a lower open chromatin positioning on their promoter regions

| Gene | Transcript Id | Chromosome | Peak start | Peak end | P value | annotation | Gene strand |
|---|---|---|---|---|---|---|---|
| Nedd4l | ENSMUST00000236764 | 18 | 65208890 | 65209641 | 0.00462574 | Promoter (<=1kb) | 1 |
| Edn1 | ENSMUST00000021796 | 13 | 42454624 | 42455284 | 0.01008322 | Promoter (<=1kb) | 1 |
| Ttn | ENSMUST00000011934 | 2 | 76812055 | 76812454 | 0.02007142 | Promoter (<=1kb) | 2 |
| Tnni1 | ENSMUST00000152208 | 1 | 135726935 | 135727322 | 0.00495353 | Promoter (<=1kb) | 1 |
| Ank2 | ENSMUST00000238781 | 3 | 126916945 | 126918692 | 0.03195264 | Promoter (<=1kb) | 2 |
| Myl2 | ENSMUST00000014080 | 5 | 122238696 | 122239328 | 0.00177765 | Promoter (<=1kb) | 1 |
| Flna | ENSMUST00000144429 | X | 73289267 | 73290784 | 0.04323042 | Promoter (<=1kb) | 2 |
| Thra | ENSMUST00000124072 | 11 | 98645509 | 98646004 | 0.0256838 | Promoter (1-2kb) | 1 |
| Myh7 | ENSMUST00000149852 | 14 | 55225899 | 55226657 | 0.03061676 | Promoter (1-2kb) | 2 |

## Table S5 Alternative splicing events found in contractile genes in adult KO mice

| Gene | Location | Exon | KO_Junc_Inclusive::Exclusive | WT_Junc_Inclusive::Exclusive | KO_Exp_Inclusive::Exclusive | WT_Exp_Inclusive::Exclusive | delta_PSI | P-Value | FDR | Splicing Type |
|---|---|---|---|---|---|---|---|---|---|---|
| Tnnt2 | 1:135842015-135842026 | 4 | 2238::17 | 375::305 | 904::9761 | 169::8983 | 0.44099061 | 2.32E-78 | 5.64E-75 | CE |
| Actc1 | 2:114047544-114047577 | 7 | 93805::4 | 86718::20 | 49485::31759 | 45604::35012 | 1.88E-04 | 2.87E-47 | 3.50E-44 | IR |
| Pln | 10:53344672-53344767 | 3 | 9057::56 | 6100::50 | 5074::9598 | 3424::9511 | 0.00198501 | 2.63E-41 | 2.14E-38 | IR |
| Myh6 | 14:54944427-54944470 | 36 | 92695::0 | 113753::23 | 38220::38938 | 48904::56368 | 2.08E-04 | 5.65E-26 | 2.50E-23 | IR |
| Tnnt2 | 1:135843778-135843814 | 5 | 93::352 | 44::0 | 31::8533 | 37::7851 | -0.7914019 | 1.58E-23 | 5.90E-21 | CE |
| Atp2a2 | 5:122489017-122489097 | 5--6 | 42::1612 | 91::339 | 44::1639 | 100::366 | -0.1862349 | 3.13E-23 | 9.61E-21 | AltEnd |
| Tnnt2 | 1:135852160-135852214 | 16 | 56074::10 | 81898::9 | 28588::38811 | 41197::49449 | -6.84E-05 | 2.69E-19 | 7.71E-17 | IR |
| Myh6 | 14:54942466-54942484 | 38 | 0::16 | 460::0 | 43085::32315 | 79187::57575 | -1 | 3.04E-19 | 8.21E-17 | A3SS |
| Myh6 | 14:54943180-54943249 | 37 | 21::1 | 27::635 | 42152::44487 | 77265::82915 | 0.91379074 | 2.82E-18 | 7.23E-16 | A3SS |
| Casq2 | 3:102145235- | 12 | 3592::10 | 1973::0 | 1969::2423 | 1098::1978 | -0.0027762 | 2.10E- | 3.93E- | IR |

|  |  |  |  |  |  |  |  |  |  |  |
|---|---|---|---|---|---|---|---|---|---|---|
|  | 102145365 |  |  |  |  |  |  | 13 | 11 |  |
| Tnnt2 | 1:135845555-135845566 | 6 | 2283::211 | 700::0 | 4257::10882 | 3239::9972 | -0.0849088 | 6.93E-12 | 1.25E-09 | A3SS |
| Myh6 | 14:54944722-54944763 | 35 | 62541::0 | 98816::19 | 31532::30027 | 27906::29927 | 1.94E-04 | 1.28E-11 | 2.22E-09 | IR |
| Myh7 | 14:54990742-54990760 | 10 | 25::5 | 7::54 | 32::43 | 67::114 | 0.71857923 | 1.77E-09 | 2.33E-07 | A5SS |
| Myh7 | 14:54975879-54976025 | 31 | 554::2 | 146::27 | 122::99 | 173::193 | 0.1524744 | 9.80E-09 | 1.11E-06 | A5SS |
| Atp2a2 | 5:122456511-122457303 | 20 | 1320::205 | 1272::91 | 684::3240 | 634::2135 | -0.0676617 | 2.43E-08 | 2.58E-06 | IR |
| Myh7 | 14:54978987-54978993 | 29 | 108::43 | 99::167 | 106::137 | 171::221 | 0.34305134 | 8.87E-08 | 8.63E-06 | A3SS |
| Myh7 | 14:54986460-54986547 | 19 | 84::33 | 88::135 | 19::78 | 36::204 | 0.32349412 | 1.27E-06 | 9.23E-05 | CE |
| Atp2a2 | 5:122501090-122501170 | 1--2 | 1::868 | 9::318 | 6::690 | 31::264 | -0.0263722 | 2.11E-06 | 1.43E-04 | AltStart |
| Pkp2 | 16:16246538-16246618 | 5--6 | 9::209 | 21::74 | 9::146 | 23::69 | -0.1797682 | 4.72E-06 | 2.84E-04 | AltStart |
| Tnnt2 | 1:135838127-135838179 | 1--2 | 234::639 | 113::631 | 69::573 | 38::467 | 0.11615952 | 5.80E-06 | 3.44E-04 | CE |
| Smtn | 11:3521457- | 22-23 | 5::319 | 33::325 | 9::372 | 34::379 | -0.0767467 | 1.27E- | 6.24E- | CE |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 3521514 | | | | | | | 05 | 04 | |
| Myh7 | 14:54975387-54975417 | 32 | 113::2 | 144::20 | 110::333 | 215::334 | 0.10455992 | 5.53E-05 | 0.00202332 | A3SS |
| Pln | 10:53341982-53342108 | 2 | 415::37 | 195::15 | 364::117 | 191::174 | -0.0104298 | 5.76E-05 | 0.00204887 | MXE |
| Myl1 | 1:66937443-66937523 | 1--2 | 1::14 | 31::20 | 1::8 | 28::11 | -0.5411765 | 8.04E-05 | 0.00262642 | AltStart |
| Tnni3 | 7:4519429-4519518 | 7 | 81087::0 | 129301::19 | 39693::21610 | 67332::35265 | 1.48E-04 | 2.25E-04 | 0.0055747 | IR |
| Flna | X:74232967-74232990 | 29 | 43::111 | 51::46 | 20::106 | 25::75 | -0.2465524 | 2.87E-04 | 0.0068446 | CE |
| Myl3 | 9:110769416-110769426 | 6 | 9::16 | 14::0 | 24185::31769 | 35526::47012 | -0.64 | 3.49E-04 | 0.00793019 | A3SS |
| Dsc2 | 18:20032490-20032535 | 17 | 67::6 | 12::9 | 31::47 | 10::39 | 0.34637965 | 6.86E-04 | 0.01304864 | CE |
| Cav1 | 6:17327238-17327362 | 2--3 | 29::845 | 2::405 | 18::947 | 1::860 | 0.02826677 | 0.00190263 | 0.02543552 | CE |
| Tnnc1 | 14:31210133-31210179 | 3 | 54798::7 | 46982::4 | 27982::22133 | 22990::17068 | -4.26E-05 | 0.00351733 | 0.03756553 | IR |
| Atp1a2 | 1:172273971-172274000 | 23 | 970::23 | 1417::31 | 512::458 | 738::499 | -0.0017533 | 0.00352616 | 0.03756553 | IR |
| Tnnt2 | 1:135848811- | 11 | 11::9 | 33::5 | 28615::27225 | 27123::32839 | -0.322389 | 0.0043 | 0.0437 | MXE |

|  |  |  |
|---|---|---|
| 135848888 | 629 | 8191 |

**Table S6 Alternative splicing events found in contractile genes in KO mice at E18.5**

| Gene | Location | Exon | KO_Junc_Inclusive::Exclusive | WT_Junc_Inclusive::Exclusive | KO_Exp_Inclusive::Exclusive | WT_Exp_Inclusive::Exclusive | delta_PSI | P-Value | FDR | Splicing Type |
|---|---|---|---|---|---|---|---|---|---|---|
| Tnnt2 | 1:135841901-135841911 | 4 | 0::3667 | 3394::2478 | 1::14590 | 778::14568 | -0.5780691 | 2.28E-117 | 1.85E-114 | CE |
| Cav1 | 6:17339475-17340098 | 7 | 544::34 | 2469::92 | 236::1774 | 1214::2038 | -0.0229001 | 5.37E-84 | 3.06E-81 | IR |
| Actc1 | 2:114050439-114050558 | 4 | 109097::0 | 257203::43 | 59977::60657 | 142620::124816 | 1.70E-04 | 2.39E-65 | 1.05E-62 | IR |
| Myh6 | 14:54943180-54943239 | 38 | 482::400 | 141::1642 | 48177::45420 | 31989::28313 | 0.46749473 | 2.52E-53 | 7.57E-51 | A3SS |
| Tnnt2 | 1:135842026-135843785 | 4 | 4083::0 | 3124::867 | 36::168 | 188::293 | 0.21739312 | 1.84E-50 | 4.99E-48 | IR |
| Pln | 10:53343718-53343828 | 3 | 17202::29 | 18214::18 | 8983::13500 | 10063::11331 | -6.96E-04 | 2.18E-42 | 4.28E-40 | IR |
| Tnnt2 | 1:135842009-135842031 | 5 | 942::3113 | 0::2390 | 954::4082 | 521::3820 | 0.23227715 | 3.88E-40 | 7.37E-38 | MXE |
| Actc1 | 2:114047544-114047577 | 8 | 342097::64 | 260285::27 | 183480::124510 | 139163::86767 | -8.33E-05 | 6.08E-34 | 1.05E-31 | IR |
| Myh7 | 14:54980411-54982166 | 26 | 179::3087 | 136::19612 | 31::2651 | 81::14136 | 0.04792033 | 1.32E-13 | 6.59E-12 | IR |
| Myh7 | 14:54980411- | 26 | 179::3087 | 136::19612 | 31::795 | 81::4224 | 0.04792033 | 1.34E- | 6.59E- | IR |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 54982166 | | | | | | | 13 | 12 | |
| Tnni3 | 7:4519429-4519518 | 9 | 233955::156 | 89883::5 | 119388::35388 | 45223::14188 | -6.08E-04 | 6.83E-10 | 2.28E-08 | IR |
| Tnnt2 | 1:135848002-135848057 | 13 | 204477::45 | 169050::0 | 93387::87981 | 75688::71018 | -2.22E-04 | 1.30E-08 | 3.54E-07 | IR |
| Atp2a2 | 5:122488882-122489097 | 6 | 8::156 | 10::3175 | 18::159 | 8::3093 | 0.04564077 | 1.75E-08 | 4.68E-07 | AltEnd |
| Tnnt2 | 1:135850738-135850769 | 17 | 253357::38 | 172754::0 | 121329::133829 | 80998::88125 | -1.51E-04 | 4.83E-07 | 9.45E-06 | IR |
| Tnnc1 | 14:31210133-31210179 | 3 | 204546::6 | 98353::7 | 98516::68485 | 46428::34129 | 4.69E-05 | 2.49E-05 | 3.28E-04 | IR |
| Myh6 | 14:54948124-54948176 | 33 | 17282::12 | 38358::0 | 7583::8210 | 16250::17745 | -7.23E-04 | 9.38E-05 | 0.00106709 | IR |
| Myh7 | 14:54973094-54973125 | 37 | 66087::50 | 63310::14 | 28813::27433 | 28464::27954 | -5.35E-04 | 1.33E-04 | 0.00143428 | IR |
| Tnni3 | 7:4521902-4522070 | 4 | 2284::83422 | 1521::49570 | 2720::20806 | 1663::11402 | -0.003121 | 9.74E-04 | 0.00749704 | IR |

## Table S7 Primers used in this study

| **Primer** | **Sequence（5' - 3'）** | **Primer** | **Sequence（5' - 3'）** |
|---|---|---|---|
| c10-348-pf | CCGGATATCACCCGACAGGT | human-TNNT2-rt-pf | TTCACCAAAGATCTGCTCCTCGCT |
| c10-348-pr | GTGTTGATACTTTGGAGACAGGC | human-TNNT2-rt-pr | TTATTACTGGTGTGGAGTGGGTGTGG |
| c10-1057-pf | CCAGCTGCAGTCAGGAAGAG | mouse-Ttn-rt-pf | GGAGGGTAGTACCGCAACCT |
| c10-1057-pr | CAGGCAGGTCAAGAGCATTGT | mouse-Ttn-rt-pr | CGCTAAAGGAGATCTGCACGC |
| c10-1095-pf | CCAGCTGCAGTCAGGAAGAG | human-TTN-rt-pf | CCCCATCGCCCATAAGACAC |
| c10-1095-pr | CAGGCAGGTCAAGAGCATTGT | human-TTN-rt-pr | CCACGTAGCCCTCTTGCTTC |
| c10-1913-pf | GAGAACAAGGAGGTGGAAGGAG | human-MYBPC3-rt-F | CAAGGTCTATCTGTTCGAGCTG |
| c10-1913-pr | CACAGATCTGGAGAGCCCATT | huamn-MYBPC3-rt-R | AGAATCCCAGTGTCCTCATGG |
| c10-348-mut-pf | AAAGTACCCCAAAACCAGCCCCCCCACCAACGCC | human-ACTN2-rt-F | CAAACCTGACCGGGGAAAAAT |
| c10-348-mut-pr | GCTGGTTTTGGGGTACTTTTCCTCTCCCTGAACG | human-ACTN2-rt-R | CTGAATAGCAAAGCGAAGGATGA |
| c10-1057-mut-pf | CTATACCCTGGGGGTGCAGGTATTTGCTGTGGAAGGAAAAG | human-MYH7-rt-F | GGCAAGACAGTGACCGTGAAG |
| c10-1057-mut-pr | CTTTTCCTTCCACAGCAAATACCTGCACCCCCAGGGTATAG | humna-MYH7-rt-R | CGTAGCGATCCTTGAGGTTGTA |
| c10-1095-mut-pf | GCTGTGGAAGGAAAAGCCCCAGCTCACAACCT | mouse-Chrm2-rt-pf | GCTACTGGCCTTTGGGACCT |
| c10-1095-mut-pr | GCTTTTCCTTCCACAGCAAATACCTGGGCTCC | mouse-Chrm2-rt-pr | GTCCGCTTAACTGGGTAGGTT |
| c10-1913-mut-pf | GTGTCCAGACTCCAGGGACACCGCCCCAGG | mouse-Dsg2-rt-pf | GACAACGAGCCAGTGTTCAC |
| c10-1913-mut-pr | CCCTGGAGTCTGGACACCAGCTGGATCCG | mouse-Dsg2-rt-pr | GTCTCCGGGTCATCTGCATC |
| mouse-C10orf71-rt-pf | GTTCAGTGATACCTCCAGCAT | mouse-Nexn-rt-pf | GAAGGCGGCATTTGCTGAAG |

| | | | |
|---|---|---|---|
| mouse-C10orf71-rt-pr | GACACCTGGCTGGTGACATC | mouse-Nexn-rt-pr | GTTCTTCCTCTGTTCGTCGTCT |
| human-C10orf71-rt-pf | GGGAGGCTGCTGAGAGAAGC | mouse-Pln-rt-pf | GTGCAATACCTCACTCGCTCG |
| human-C10orf71-rt-pr | GAGCCCATTCTCTAGCTGGT | mouse-Pln-rt-pr | GATGCAGATCAGCAGCAGACAT |
| mouse-Gapdh-rt-pf | GTGAAGGTCGGTGTGAACGG | mouse-Rbm20-rt-pf | CAGCTTCCTCTGGGACAAGT |
| mouse-Gapdh-rt-pr | GGTCAATGAAGGGGTCGTTG | mouse-Rbm20-rt-pr | CAGCCCCAGGTTAATGACGT |
| human-GAPDH-rt-pf | CGGGAAGCTTGTCATCAATGG | mouse-Rbm24-rt-pf | GGCCAATGTGAATCTGGCATAC |
| human-GAPDH-rt-pr | GGCAGAGATGATGACCCTTT | mouse-Rbm24-rt-pr | GCCTGCGGGTAGACGTAGT |
| mouse-Tnnt2-rt-pf | GAGACAGAGGAGGCCAACGT | mouse-Sgcb-rt-pf | GCCATCTGCGTGATCGTCCT |
| mouse-Tnnt2-rt-pr | GTGGCACCAAGTTGGGCAT | mouse-Sgcb-rt-pr | CCGCTCTCGTGGAACTCCAT |