Supplemental Figures and Tables Captions

Table S1. Recombinant protein composition of human cardiac reconstituted thin filaments. All cTn and RTF utilized in this study were labeled with IAANS at T53C position with the two additional mutations C35S and C84S.

Table S2. Oligonucleotide sequences for sgRNA, ssODN and PCR primers used for hiPSC genome editing.

Table S3. List of 251 transcripts in the customized NanoString codeset.

Figure S1. Sequence alignment of the partial cTnT protein among different species. A multiple sequence alignment of the partial canonical cTnT protein from human (Uniprot ID: P45379), bovine (Uniprot ID: P13789), rabbit (Uniprot ID: P09741), rat (Uniprot ID: P50753), mouse (Uniprot ID: P50752), chicken (Uniprot ID: P02642), and zebrafish (Uniprot ID: Q90Y46) was performed using Clustal Omega. I79 residues are boxed in red and are highly conserved across different species. The human cTnT sequence shown here includes exon 5 which encodes 10 amino acids, which are boxed in blue. Exon 5 is not included in the splice variant normally expressed in the adult heart and so the residue numbers are shifted by ten in this figure.

Figure S2. Genome-editing to create *TNNT2* I79N$^{+/-}$ hiPSC line. Panel A. Genome editing strategy map in which the relevant portion of the TNNT2 nucleotide sequence is shown. Residue 79 is within exon 9 and the annealing position of the designed single guide RNA (sg RNA) is shown in orange and the PAM site (TGG) in pink. The donor DNA or single-stranded oligodeoxynucleotide (ssODN) spanned the region shown by the brown (36 bp PAM distal) and green (91 bp PAM proximal) arrows. Panel B. Sanger sequencing of relevant nucleotides. The gene edited nucleotide is shown by the red arrow in which the codon for Isoleucine (I) ATC was genome edited to AAC (Asparagine (N)) in one allele rendering a I79N heterozygous mutant. The blue arrow indicates the silent mutation (C->G) that was included in the sgRNA target sequence to prevent CRISPR from re-cutting the target sequence once the desired edit was introduced. The top 10 sites that scored high for off target or low for on-target were selected using "Custom Alt-R® CRISPR-Cas9 guide RNA tool" from IDT. The top 10 off target sites were then Sanger sequenced to ensure that the probability of off target mutations was minimized.

Figure S3. The expression of *TNNI3/TNNI1* in WT and I79N$^{+/-}$ hiPSC-CMs.

Figure S4. Heat map and Principal Component Analysis (PCA) of data from NanoString multiplex gene expression analysis. **Panel A**, Heat map of unsupervised hierarchical clustering of all 251 genes. I79N$^{+/-}$ mutation is clustering away from WT with low variability within group. Patterns ofgene expression are evident through the effect of the mutation. **Panel B** PCA of normalized gene expression for I79N$^{+/-}$ (blue) vs WT (black) hiPSC-CMs shows PC1 and PC2 account for 73% and 16% of the variance, respectively. In PCA, I79N$^{+/-}$ samples are clustered away from WT.

Figure S5. NanoString multiplex gene expression functional analysis. Panels A and B. Top 5 functional pathways (i.e., enrichment term) based on adjusted p-value (< 0.05) across six gene set libraries. Enrichment analysis was conducted using the 45 upregulated and 23 downregulated differentially expressed genes (DEG) in I79N$^{+/-}$ hiPSC-CMs compared to WT hiPSC-CMs. **Panels C and D**. Top 5 enriched Gene Ontology (GO) terms sorted by adjusted p-value. X-axis represents the combined score (combination of the p-value and the z-score). Y-axis refers to the namesof pathways terms split by the gene set libraries. Data point size represents the Odds ratio which is the estimate from Fisher's exact test calculated

through Enrichr (Chen et al., 2013; Kuleshov et al., 2016). Color gradient refers to the adjusted p-value of each term. GO_BP: Gene Ontology biological process, GO_CC: Gene Ontology cellular component, GO_MF: Gene Ontology molecular function, Hu_Pheno: human phenotype, Jensen_Diseases: disease database from Jensen Lab, MGI_Pheno: Mammalian Phenotype Ontology. I79N$^{+/-}$ (n=3) to WT (n=4) TNNT2 hiPSC-CMs.

Table S1.

Construct	Gene Name	Description	Length	Molecular Weight (kDa)*	Extinction Coefficient ($M^{-1}cm^{-1}$)*	Uniprot ID
# WT $cTnC^{T53C}$	*TNNC1*	Full length TnC with three mutations (T53C, C35S, C84S) for fluorescence labeling specifically at T53C for functional studies.	161	18	4470	P63316
Troponin I and Troponin T Subunits						
WT cTnI	*TNNI3*	Full length WT cTnI.	211	24	9970	P19429
WT cTnT	*TNNT2*	Full length WT cTnT (isoform 3).	288	35	16960	P45379
I79N cTnT	*TNNT2*	Full length cTnT with I79N mutation.				
Other constructs						
Alpha MAS-Tm	*TPM1*	Full-length Tm with the additional tripeptide (Met-Ala-Ser) to the N-terminus to mimic acetylation process in native Tm and ensure its binding to actin filaments.	287	33	8940	P09493

Both the molecular weight and extinction coefficients were calculated using ProtParam[1].
All cTn and RTF utilized in this study were labeled with IAANS at T53C position with the two additional mutations C35S and C84S.

[1]Gasteiger, E. et al. Protein Identification and Analysis Tools on the ExPASy Server. *The Proteomics Protocols Handbook*, 571 (2005).

Table S2. Oligonucleotide sequences for sgRNA, ssODN and PCR primers used for hiPSC genome editing

sgRNA	
I79N - F	5’-CACCGAGTCCACTCTCTCTCCATCG-3’
I79N - R	5’- AAACCGATGGAGAGAGAGTGGACTC-3’
ssODN	
I79N	5’ AGTCCCTGGGTCCAGAATGGGGCTGATGCTGACTATTCCTCTCTCCAACAGGTCGTTCATGCCCAACTTGGTGCCTCCCAAGAATCC CGATGGAGAGAGAGTCGACTTTGATGTAAGCGGTGGCTGT -3’
PCR primers for sequencing	
I79 - F	5’-GCTTCTTTGATTCCAAGTTGTGTG-3’
I79 - R	5’-CCCATCCCACCTATGCTC-3’

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Table S3.

	Gene Name	Accession no.	Probe Position		Gene name	Accession no.	Probe Position
1	ABCC8	NM_000352.4	1761-1860	**33**	CALM3	NM_005184.2	1306-1405
2	ACADM	NM_000016.5	1290-1389	**34**	CALR	NM_004343.2	966-1065
3	ACTA1	NM_001100.3	46-145	**35**	CaMK2A	NM_171825.1	4081-4180
4	B actin	NM_001101.2	1011-1110	**36**	CaMK2B	NM_001220.3	366-465
5	ACTC1	NM_005159.4	2006-2105	**37**	CaMK2D	NM_001221.3	1906-2005
6	ACTN2	NM_001103.2	413-512	**38**	CaMK2G	NM_001222.2	234-333
7	ADRB1	NM_000684.1	796-895	**39**	CASQ2	NM_001232.3	598-697
8	ADRB2	NM_000024.3	1246-1345	**40**	CAV3	NM_001234.3	212-311
9	AKT	NM_0010144	1276-1375	**41**	CER1	NM_005454.2	589-688
10	ALDH1A1	NM_000689.3	12-111	**42**	CHRM2	NM_0010066	1171-1270
11	ALDH1A2	NM_003888.2	3131-3230	**43**	CKB	NM_001823.4	321-420
12	ALDH1A3	NM_000693.2	2281-2380	**44**	CKM	NM_001824.4	136-235
13	CD13	NM_001150.1	2671-2770	**45**	COL1A1	NM_000088.3	5211-5310
14	JCTN or	NM_032466.3	396-495	**46**	COL2A1	NM_001844.4	4746-4845
15	ATP1A2	NM_000702.3	4041-4140	**47**	COL3A1	NM_000090.3	181-280
16	ATP1A3	NM_152296.4	2626-2725	**48**	COL4A2	NM_001846.2	1151-1250
17	ATP2A2	NM_001681.3	1397-1496	**49**	COL4A3	NM_000091.4	1085-1184
18	ATP5F1	NM_001688.4	646-745	**50**	COL9A2	NM_001852.3	2414-2513
19	B2M	NM_004048.2	26-125	**51**	CPT1B	NM_004377.3	1655-1754
20	BMP10	NM_014482.1	441-540	**52**	CRHR2	NM_001883.2	236-335
21	BMP2	NM_001200.2	1516-1615	**53**	CS	NM_004077.2	741-840
22	BMP4	NM_001202.3	660-759	**54**	CTNNB1	NM_0010982	1816-1915
23	BRCA1	NM_007305.2	1276-1375	**55**	CXCR4	NM_003467.2	1336-1435
24	BTAF1	NM_003972.2	1697-1796	**56**	CYP26A1	NM_057157.2	1591-1690
25	BTK	NM_000061.1	571-670	**57**	CYP26B1	NM_019885.2	1806-1905
26	CACNA1C	NM_199460.2	4786-4885	**58**	DKK1	NM_012242.2	76-175
27	CACNA1D	NM_000720.2	5196-5295	**59**	DYNC1I1	NM_0011355	1183-1282
28	CACNA1G	NM_198397.1	1381-1480	**60**	DYNLL2	NM_080677.2	639-738
29	CACNA1H	NM_021098.2	3330-3429	**61**	EMILIN2	NM_032048.2	1446-1545
30	CACNA2D1	NM_000722.2	2909-3008	**62**	ERBB2	NM_0010058	1256-1355
31	CALM1	NM_006888.3	1684-1783	**63**	FGF17	NM_003867.2	280-379
32	CALM2	NM_001743.3	869-968	**64**	FGF19	NM_005117.2	787-886

		Gene name	Accession number	Probe Position				Gene Name	Accession Number	Probe Position
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66		FGF4	NM_002007.2	689-788		**98**		HRC	NM_002152.2	367-466
67		FGF8	NM_033163.3	545-644		**99**		IPO8	NM_006390.2	861-960
68		PKBP1B or FKBP12.6	NM_000801.4	41-140		**100**		IRX4	NM_016358.2	359-458
69		FLNA	NM_001456.3	7336-7435		**101**		ISL1	NM_002202.2	1376-1475
70		FLNB	NM_001164317.1	2125-2224		**102**		ISL2	NM_145805.1	109-208
71		FOXA1	NM_004496.2	2466-2565		**103**		JAG1	NM_000214.2	916-1015
72		FOXF1	NM_001451.2	1761-1860		**104**		JAK1	NM_002227.1	286-385
73		FOXH1	NM_003923.2	696-795		**105**		JAK2	NM_004972.3	1465-1564
74		GAPDH	NM_001256799.1	387-486		**106**		JAK3	NM_000215.2	1716-1815
75		GATA2	NM_032638.3	1496-1595		**107**		JPH2	NM_020433.4	525-624
76		GATA4	NM_002052.3	2141-2240		**108**		KCNA4	NM_002233.3	657-756
77		GATA6	NM_005257.3	2131-2230		**109**		KCNA5	NM_002234.2	2331-2430
78		GJA1	NM_000165.3	706-805		**110**		KCND3	NM_004980.4	1011-1110
79		GJA5	NM_005266.5	1993-2092		**111**		KCNH2	NM_172057.2	781-880
80		GJC1	NM_001080383.1	811-910		**112**		KCNJ2	NM_000891.2	621-720
81		GNAI1	NM_002069.4	671-770		**113**		KCNJ3	NM_001260508.1	429-528
82		GNAI2	NM_002070.2	1001-1100		**114**		KCNJ5	NM_000890.3	631-730
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85		GNAS	NM_080425.1	1911-2010		**117**		KCNK3	XM_005264293.1	667-766
86		GREM2	NM_022469.3	3006-3105		**118**		KCNK5	NM_003740.3	3616-3715
87		GYPA	NM_002099.4	2312-2411		**119**		KCNN1	NM_002248.3	703-802
88		HAND1	NM_004821.2	1231-1330		**120**		KCNN2	NM_021614.2	1893-1992
89		HAND2	NM_021973.2	1822-1921		**121**		KCNN3	NM_002249.4	2636-2735
90		HAS2	NM_005328.2	961-1060		**122**		KCNQ1	NM_181798.1	836-935
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92		HCN2	NM_001194.3	2075-2174		**124**		KIF20A	NM_005733.2	1210-1309
93		HCN4	NM_005477.2	4911-5010		**125**		KIT	NM_000222.1	6-105
94		HEY1	NM_012258.3	586-685		**126**		KLF4**	NM_004235.4	1981-2080
95		HEY2	NM_012259.2	1576-1675		**127**		KMT2A	NM_005933.2	14001-14100
96		HIF1A	NM_001530.2	1986-2085		**128**		KMT2B	NM_014727.1	7846-7945

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130		KMT2D	NM_003482.3	6071-6170		**162**		NR2F2	NM_021005.2	1531-1630
131		LDHA	NM_001165414.1	1691-1790		**163**		ORAI1	NM_032790.3	911-1010
132		LEFTY1	NM_020997.2	1406-1505		**164**		PDGFRA	NM_006206.3	1926-2025
133		LIN28	NM_024674.4	1961-2060		**165**		PDK2	NM_002611.3	436-535
134		JNK3	NM_138981.2	451-550		**166**		PDK4	NM_002612.3	1676-1775
135		JNK1-alpha	NM_002750.2	946-1045		**167**		p110a	NM_006218.2	2446-2545
136		JNK2-alpha	XM_005265940.1	164-263		**168**		PITX2	NM_000325.5	1382-1481
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156		NOTCH2	NM_024408.3	2843-2942		**188**		PRKAR1A	NM_212472.1	368-467
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195		PKG1	NM_006258.3	995-1094		**227**		CD90	NM_006288.2	136-235
196		PTGS2	NM_000963.1	496-595		**228**		TNNI1	NM_003281.3	976-1075
197		RARA	NM_001033603.1	1191-1290		**229**		TNNI3	NM_000363.4	226-325
198		RARB	NM_000965.3	2756-2855		**230**		TNNT2 exon 5	NM_000364.3	132-231
199		RARG	NM_000966.3	1541-1640		**231**		TNNT2	NM_001276346.1	797-896
200		RBM20	NM_001134363.1	6943-7042		**232**		TOP2A	NM_001067.3	3564-3663
201		ROR2	NM_004560.2	736-835		**233**		TPM1	NM_000366.5	843-942
202		RPS13	NM_001017.2	332-431		**234**		TRDN	NM_001251987.1	297-396
203		RYR2	NM_001035.2	1184-1283		**235**		TRH	NM_007117.2	1883-1982
204		SCN4A	NM_000334.4	6787-6886		**236**		TRPC1	NM_003304.4	991-1090
205		SCN5A	NM_198056.2	8341-8440		**237**		TRPC2	NR_002720.2	561-660
206		SGK1	NM_005627.2	1791-1890		**238**		TRPC3	NM_001130698.1	1479-1578
207		SHOX2	NM_003030.3	830-929		**239**		TRPC4	NM_001135956.1	2436-2535
208		SIRPA	NM_080792.2	3116-3215		**240**		TRPC5	NM_012471.2	3686-3785
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212		SLC8A1	NM_021097.1	441-540		**244**		SSEA5	NM_001270483.1	1007-1106
213		SLN	NM_003063.2	376-475		**245**		TTN b	NM_003319.4	1805-1904
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215		SPCS1	NM_014041.3	611-710		**247**		VCAM-1	NM_001078.3	2536-2635
216		STIM1	NM_003156.3	3101-3200		**248**		VEGFA	NM_001025366.1	1326-1425
217		TACR1	NM_015727.1	856-955		**249**		WNT3	NM_030753.3	1336-1435
218		TACR3	NM_001059.1	471-570		**250**		WNT3A	NM_033131.2	699-798
219		TBX1	NM_080646.1	541-640		**251**		ZFP42 (or REX1)	NM_174900.3	946-1045
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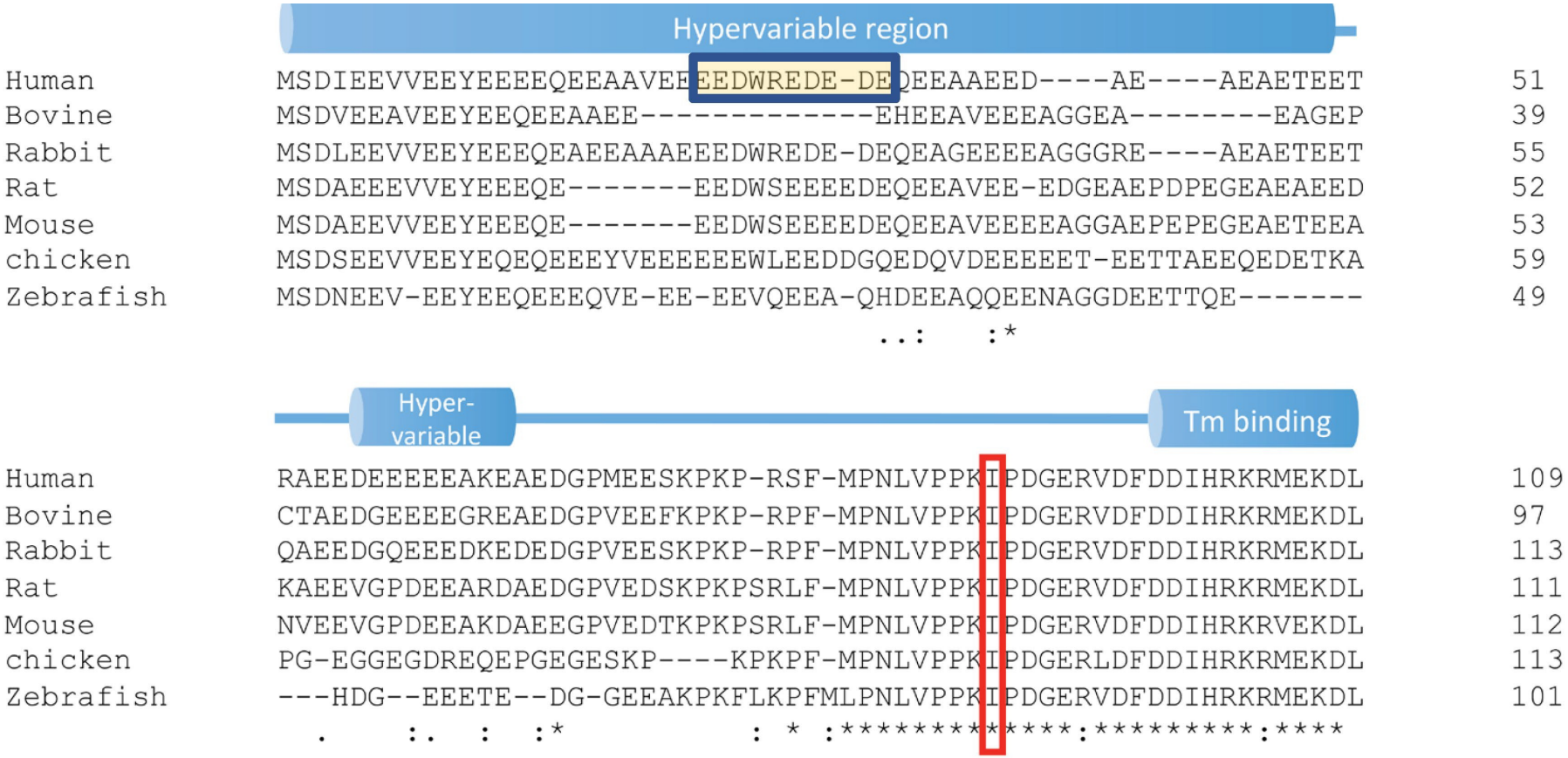
Figure S1.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Zebrafish MSDNEEV-EEYEEQEEEQVE-EE-EEVQEEA-QHDEEAQQEENAGGDEETTQE------- 49
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Hyper-variable
Tm binding
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Rabbit QAEEDGQEEEDKEDEDGPVEESKPKP-RPF-MPNLVPPKIPDGERVDFDDIHRKRMEKDL 113
Rat KAEEVGPDEEARDAEDGPVEDSKPKPSRLF-MPNLVPPKIPDGERVDFDDIHRKRMEKDL 111
Mouse NVEEVGPDEEAKDAEEGPVEDTKPKPSRLF-MPNLVPPKIPDGERVDFDDIHRKRVEKDL 112
chicken PG-EGGEGDREQEPGEGESKP----KPKPF-MPNLVPPKIPDGERLDFDDIHRKRMEKDL 113
Zebrafish ---HDG--EEETE--DG-GEEAKPKFLKPFMLPNLVPPKIPDGERVDFDDIHRKRMEKDL 101
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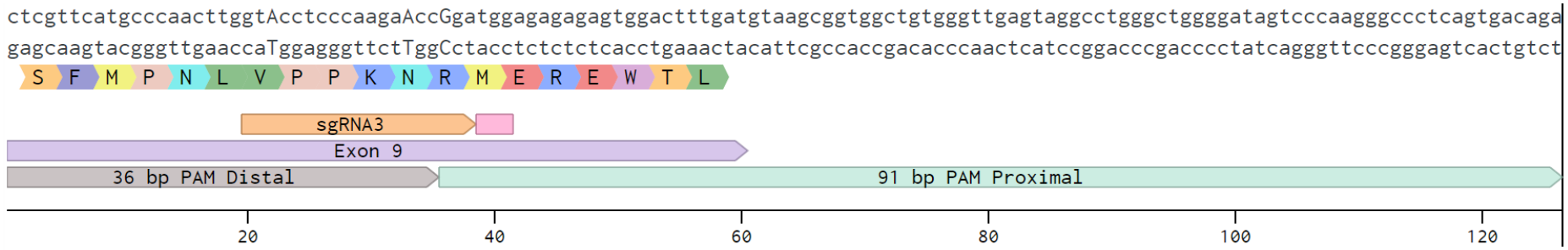
Figure S2.

A.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S F M P N L V P P K N R M E R E W T L
sgRNA3
Exon 9
36 bp PAM Distal
91 bp PAM Proximal
20
40
60
80
100
120

B.

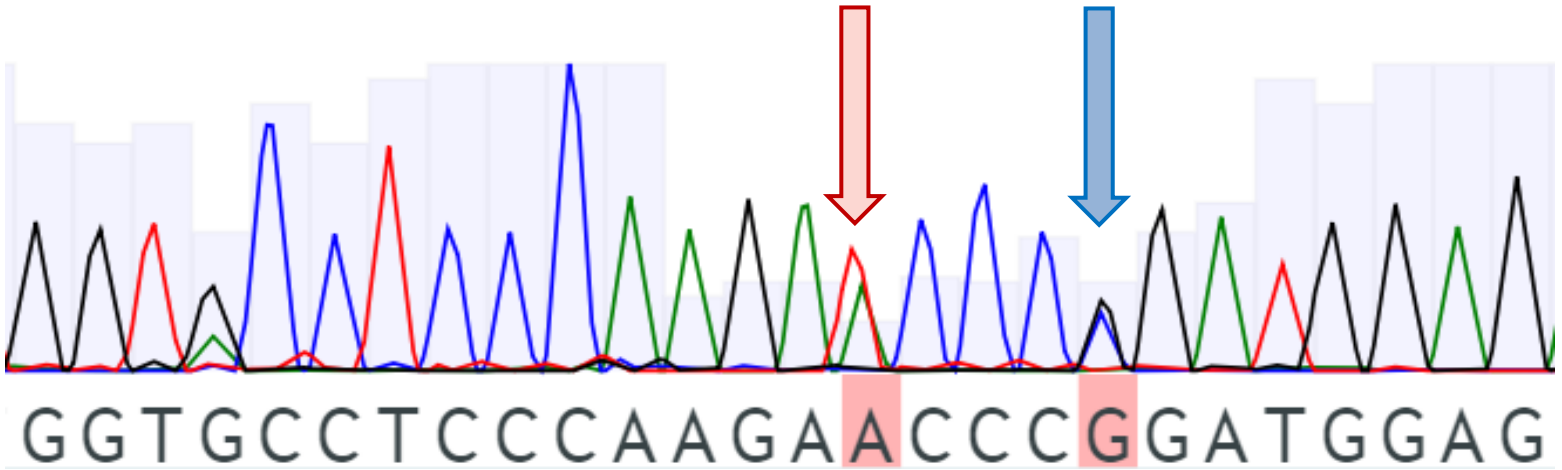

GGTGCCTCCCAAGAACCCGGATGGAG

Figure S3.

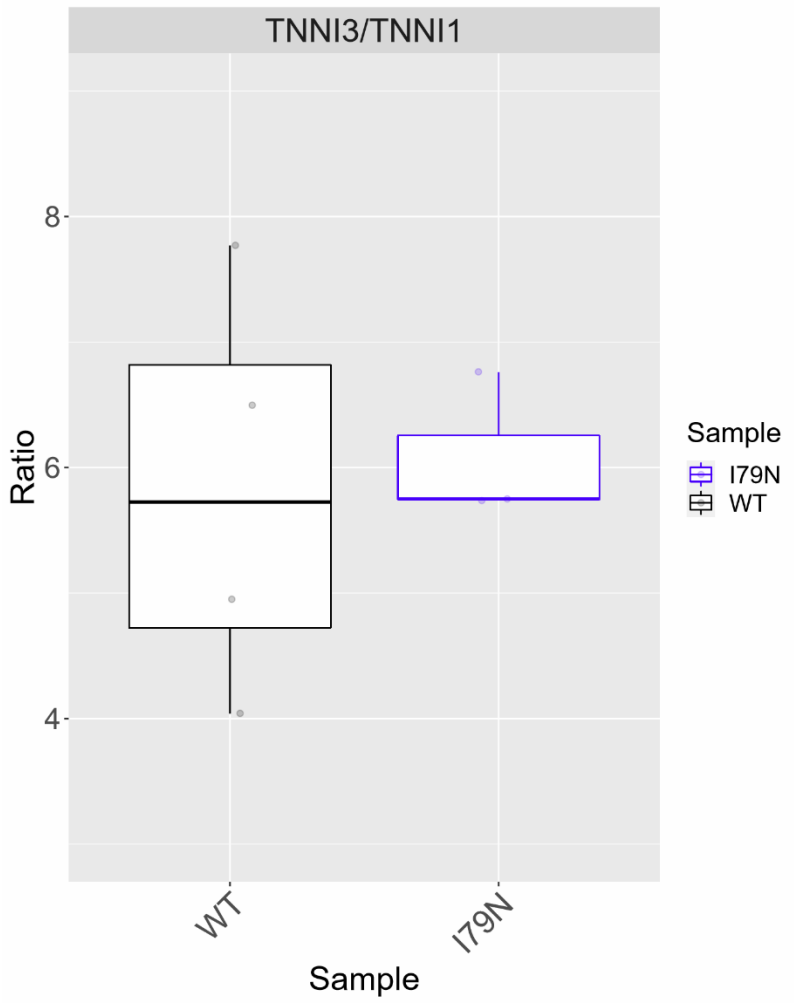
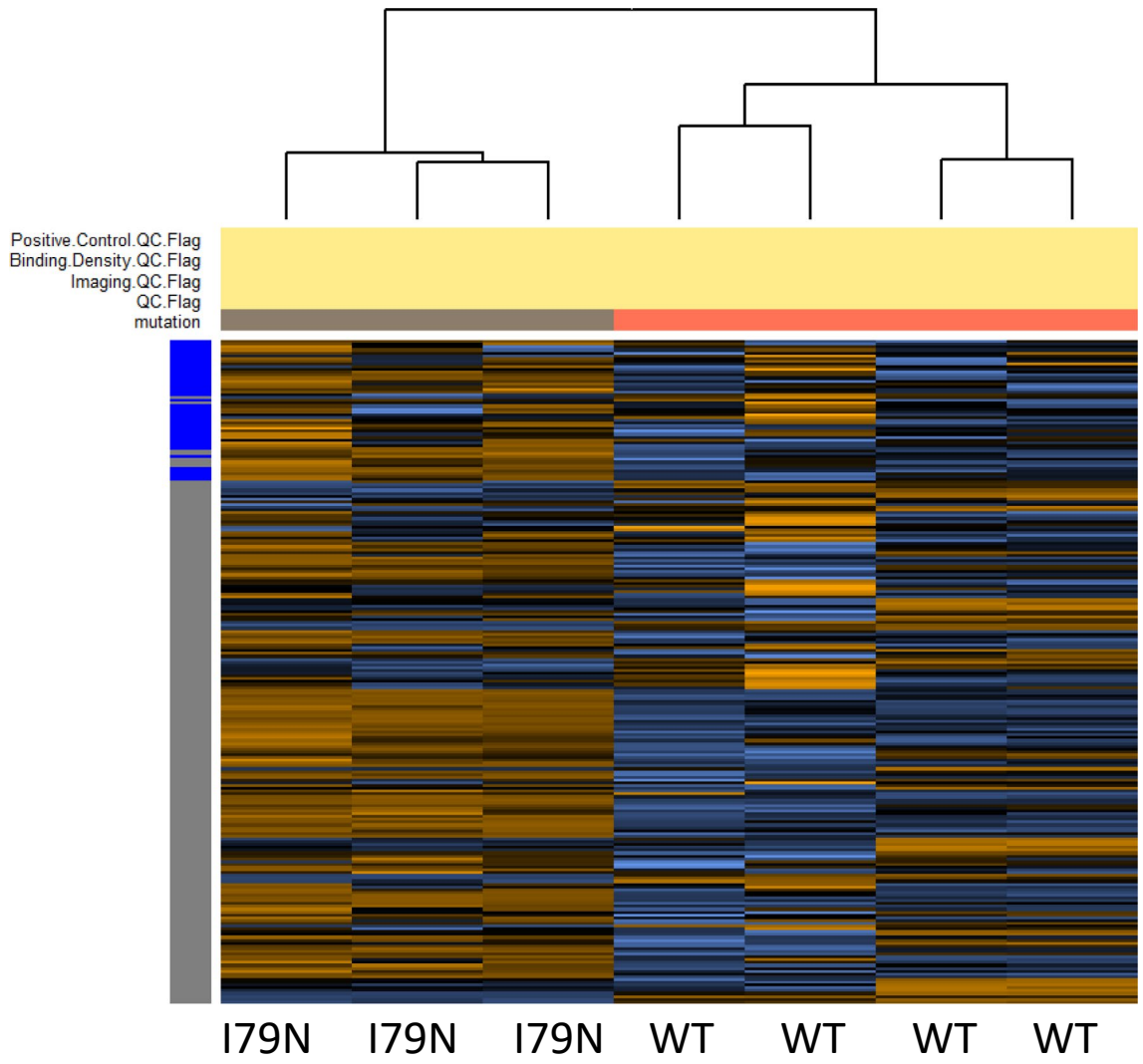


Figure S4.

A.


Positive.Control.QC.Flag
Binding.Density.QC.Flag
Imaging.QC.Flag
QC.Flag
mutation
I79N
I79N
I79N
WT
WT
WT
WT

B.

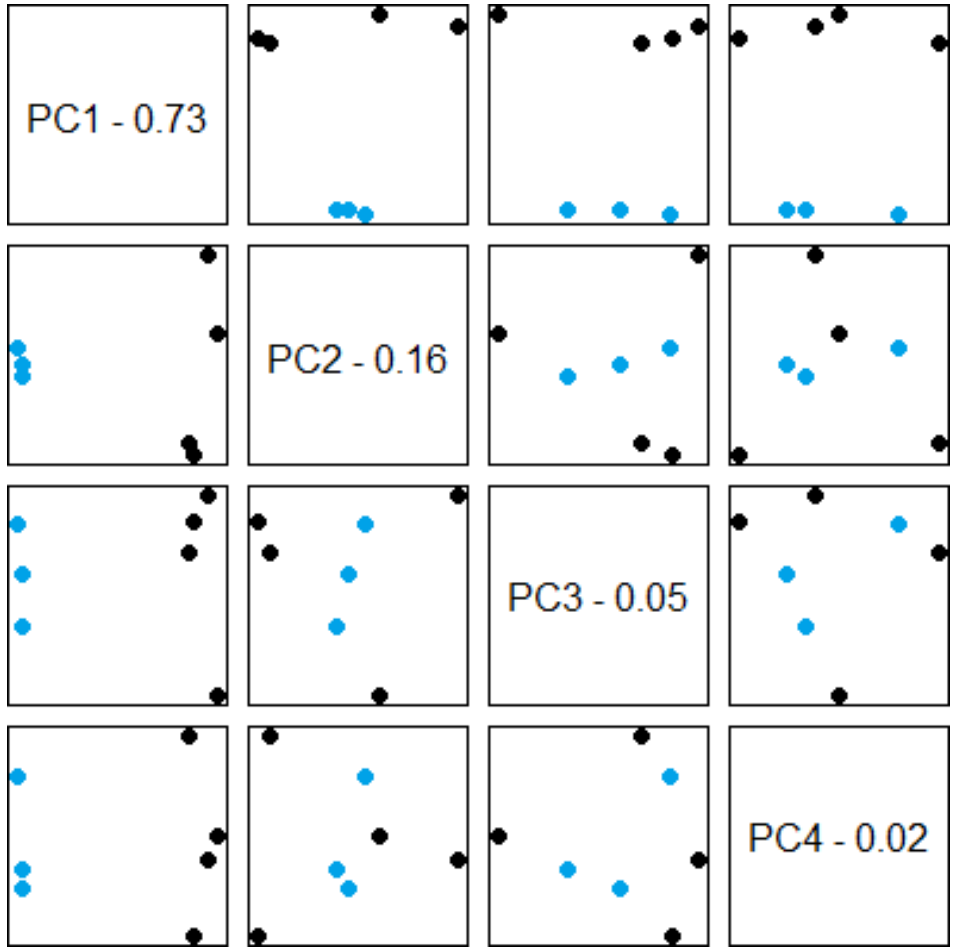
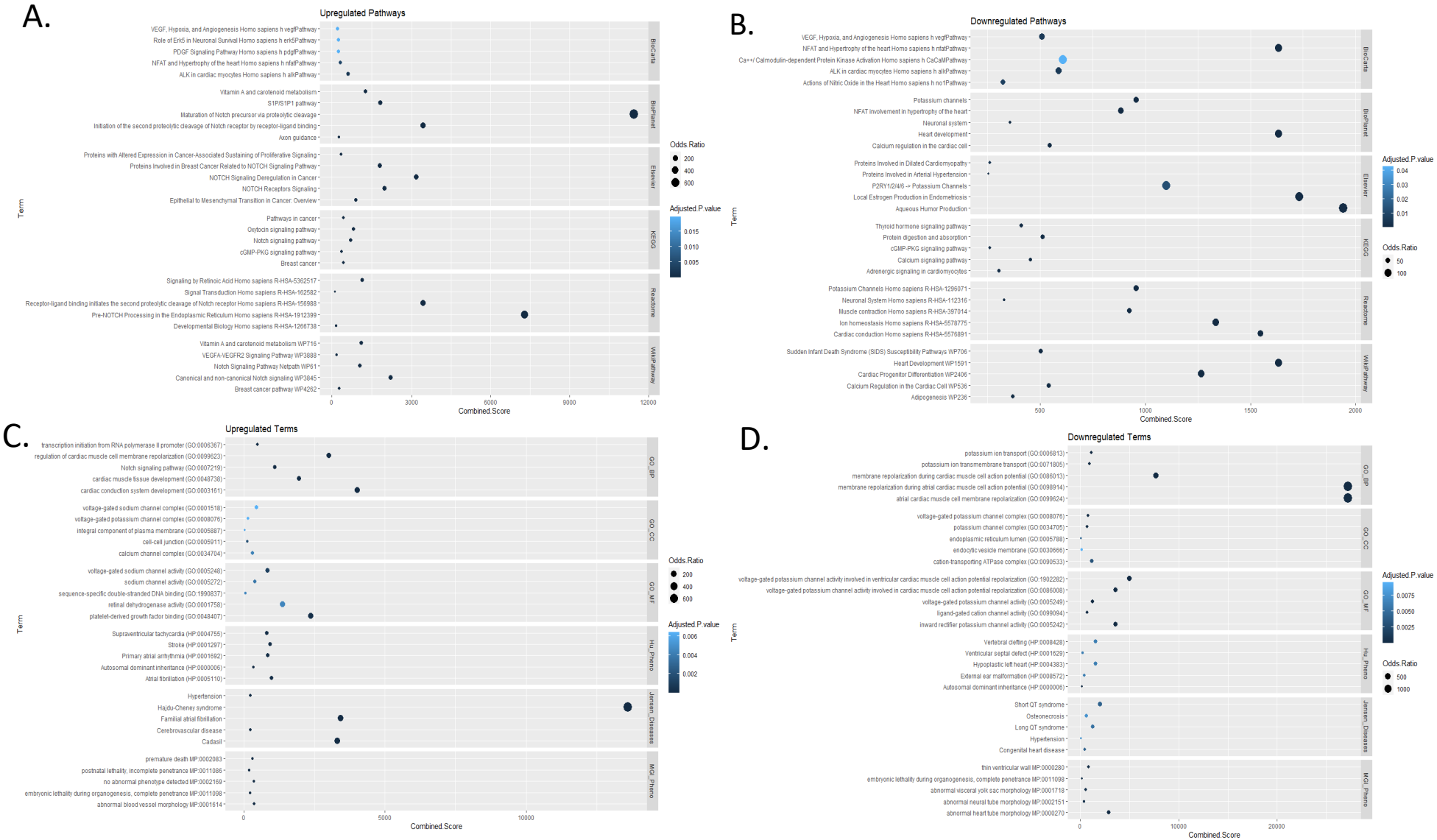

PC1 - 0.73
PC2 - 0.16
PC3 - 0.05
PC4 - 0.02

Figure S5


A.
Upregulated Pathways
VEGF, Hypoxia, and Angiogenesis Homo sapiens h vegfPathway
Role of Erk5 in Neuronal Survival Homo sapiens h erk5Pathway
PDGF Signaling Pathway Homo sapiens h pdgfPathway
NFAT and Hypertrophy of the heart Homo sapiens h nfatPathway
ALK in cardiac myocytes Homo sapiens h alkPathway
BioCarta
Vitamin A and carotenoid metabolism
S1P/S1P1 pathway
Maturation of Notch precursor via proteolytic cleavage
Initiation of the second proteolytic cleavage of Notch receptor by receptor-ligand binding
Axon guidance
BioPlanet
Proteins with Altered Expression in Cancer-Associated Sustaining of Proliferative Signaling
Proteins Involved in Breast Cancer Related to NOTCH Signaling Pathway
NOTCH Signaling Deregulation in Cancer
NOTCH Receptors Signaling
Epithelial to Mesenchymal Transition in Cancer: Overview
Elsevier
Pathways in cancer
Oxytocin signaling pathway
Notch signaling pathway
cGMP-PKG signaling pathway
Breast cancer
KEGG
Signaling by Retinoic Acid Homo sapiens R-HSA-5362517
Signal Transduction Homo sapiens R-HSA-162582
Receptor-ligand binding initiates the second proteolytic cleavage of Notch receptor Homo sapiens R-HSA-156988
Pre-NOTCH Processing in the Endoplasmic Reticulum Homo sapiens R-HSA-1912399
Developmental Biology Homo sapiens R-HSA-1266738
Reactome
Vitamin A and carotenoid metabolism WP716
VEGFA-VEGFR2 Signaling Pathway WP3888
Notch Signaling Pathway Netpath WP61
Canonical and non-canonical Notch signaling WP3845
Breast cancer pathway WP4262
WikiPathway
Term
0
3000
6000
9000
12000
Combined.Score
Odds.Ratio
200
400
600
Adjusted.P.value
0.015
0.010
0.005
B.
Downregulated Pathways
VEGF, Hypoxia, and Angiogenesis Homo sapiens h vegfPathway
NFAT and Hypertrophy of the heart Homo sapiens h nfatPathway
Ca++/ Calmodulin-dependent Protein Kinase Activation Homo sapiens h CaCaMPathway
ALK in cardiac myocytes Homo sapiens h alkPathway
Actions of Nitric Oxide in the Heart Homo sapiens h no1Pathway
BioCarta
Potassium channels
NFAT involvement in hypertrophy of the heart
Neuronal system
Heart development
Calcium regulation in the cardiac cell
BioPlanet
Proteins Involved in Dilated Cardiomyopathy
Proteins Involved in Arterial Hypertension
P2RY1/2/4/6 -> Potassium Channels
Local Estrogen Production in Endometriosis
Aqueous Humor Production
Elsevier
Thyroid hormone signaling pathway
Protein digestion and absorption
cGMP-PKG signaling pathway
Calcium signaling pathway
Adrenergic signaling in cardiomyocytes
KEGG
Potassium Channels Homo sapiens R-HSA-1296071
Neuronal System Homo sapiens R-HSA-112316
Muscle contraction Homo sapiens R-HSA-397014
Ion homeostasis Homo sapiens R-HSA-5578775
Cardiac conduction Homo sapiens R-HSA-5576891
Reactome
Sudden Infant Death Syndrome (SIDS) Susceptibility Pathways WP706
Heart Development WP1591
Cardiac Progenitor Differentiation WP2406
Calcium Regulation in the Cardiac Cell WP536
Adipogenesis WP236
WikiPathway
Term
500
1000
1500
2000
Combined.Score
Adjusted.P.value
0.04
0.03
0.02
0.01
Odds.Ratio
50
100
C.
Upregulated Terms
transcription initiation from RNA polymerase II promoter (GO:0006367)
regulation of cardiac muscle cell membrane repolarization (GO:0099623)
Notch signaling pathway (GO:0007219)
cardiac muscle tissue development (GO:0048738)
cardiac conduction system development (GO:0003161)
GO_BP
voltage-gated sodium channel complex (GO:0001518)
voltage-gated potassium channel complex (GO:0008076)
integral component of plasma membrane (GO:0005887)
cell-cell junction (GO:0005911)
calcium channel complex (GO:0034704)
GO_CC
voltage-gated sodium channel activity (GO:0005248)
sodium channel activity (GO:0005272)
sequence-specific double-stranded DNA binding (GO:1990837)
retinal dehydrogenase activity (GO:0001758)
platelet-derived growth factor binding (GO:0048407)
GO_MF
Supraventricular tachycardia (HP:0004755)
Stroke (HP:0001297)
Primary atrial arrhythmia (HP:0001692)
Autosomal dominant inheritance (HP:0000006)
Atrial fibrillation (HP:0005110)
HU_Pheno
Hypertension
Hajdu-Cheney syndrome
Familial atrial fibrillation
Cerebrovascular disease
Cadasil
Jensen_Diseases
premature death MP:0002083
postnatal lethality, incomplete penetrance MP:0011086
no abnormal phenotype detected MP:0002169
embryonic lethality during organogenesis, complete penetrance MP:0011098
abnormal blood vessel morphology MP:0001614
MGI_Pheno
Term
0
5000
10000
Combined.Score
Odds.Ratio
200
400
600
Adjusted.P.value
0.006
0.004
0.002
D.
Downregulated Terms
potassium ion transport (GO:0006813)
potassium ion transmembrane transport (GO:0071805)
membrane repolarization during cardiac muscle cell action potential (GO:0086013)
membrane repolarization during atrial cardiac muscle cell action potential (GO:0098914)
atrial cardiac muscle cell membrane repolarization (GO:0099624)
GO_BP
voltage-gated potassium channel complex (GO:0008076)
potassium channel complex (GO:0034705)
endoplasmic reticulum lumen (GO:0005788)
endocytic vesicle membrane (GO:0030666)
cation-transporting ATPase complex (GO:0090533)
GO_CC
voltage-gated potassium channel activity involved in ventricular cardiac muscle cell action potential repolarization (GO:1902282)
voltage-gated potassium channel activity involved in cardiac muscle cell action potential repolarization (GO:0086008)
voltage-gated potassium channel activity (GO:0005249)
ligand-gated cation channel activity (GO:0099094)
inward rectifier potassium channel activity (GO:0005242)
GO_MF
Vertebral clefting (HP:0008428)
Ventricular septal defect (HP:0001629)
Hypoplastic left heart (HP:0004383)
External ear malformation (HP:0008572)
Autosomal dominant inheritance (HP:0000006)
HU_Pheno
Short QT syndrome
Osteonecrosis
Long QT syndrome
Hypertension
Congenital heart disease
Jensen_Diseases
thin ventricular wall MP:0000280
embryonic lethality during organogenesis, complete penetrance MP:0011098
abnormal visceral yolk sac morphology MP:0001718
abnormal neural tube morphology MP:0002151
abnormal heart tube morphology MP:0000270
MGI_Pheno
Term
0
10000
20000
Combined.Score
Adjusted.P.value
0.0075
0.0050
0.0025
Odds.Ratio
500
1000