

Supplementary Note 1.

AAV9-cTnT-ABEmax-VRQR-h403 N-terminal half

AAV ITR

Cardiac Troponin T promoter

Nuclear Localization Signals (Bipartite NLS)

ABEmax

Linkers

SpCas9-VRQR N-terminal half

Npu N-terminal fragment

WPRES-3 (Woodchuck Hepatitis Virus Posttranscriptional Regulatory Element-3)

bGH poly(A) signal (bovine growth hormone polyadenylation signal)

hU6 promoter-sgRNA scaffold

h403_sgRNA

Highlighted Text (Nuclear localization signals, ABEmax, Linkers, SpCas9-VRQR, Npu N-terminal fragment) encode expressed proteins.

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AAV9-cTnT-ABEmax-VRQR-h403 C-terminal half

AAV ITR

Cardiac Troponin T promoter

Nuclear Localization Signals (Bipartite NLS)

Npu C-terminal fragment

Linkers

SpCas9-VRQR C-terminal half

WPRE-3 (Woodchuck Hepatitis Virus Posttranscriptional Regulatory Element-3)

bGH poly(A) signal (bovine growth hormone polyadenylation signal)

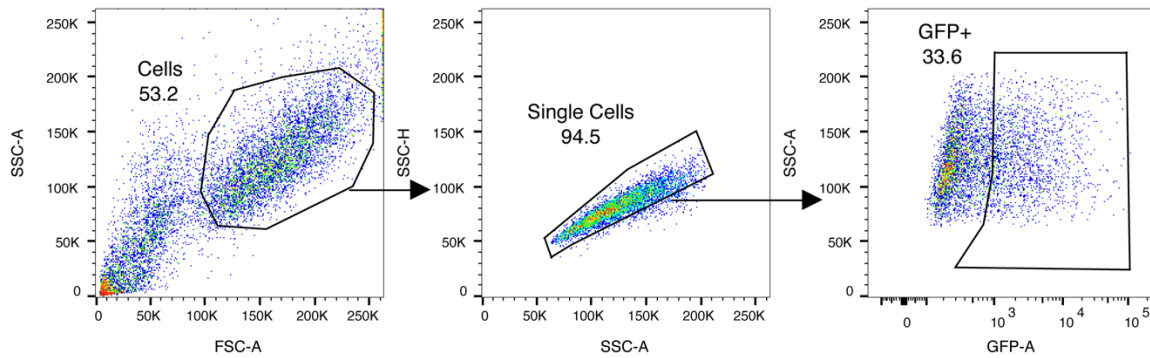
hU6 promoter-sgRNA scaffold

h403_sgRNA

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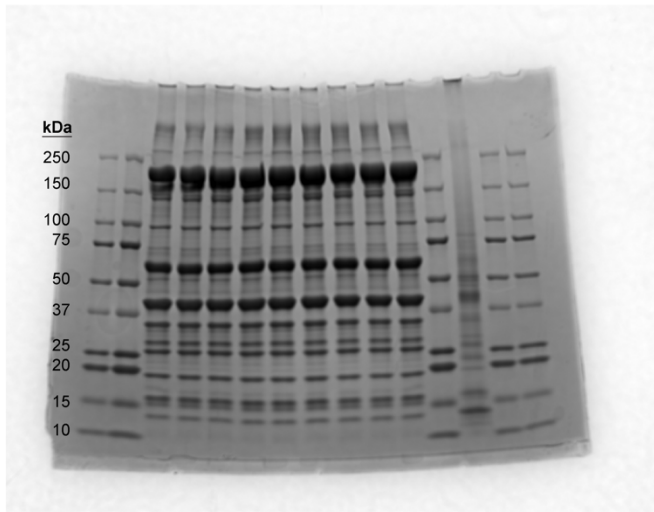


Supplementary Figure 1. Representative flow cytometry gating strategy for GFP+ iPSCs.

For generation of isogenic iPSCs containing the *MYH7* c.1208 G>A (p.R403Q) mutation via homology-directed repair, and for base editing correction of the *MYH7* c.1208 G>A (p.R403Q) mutation, iPSCs were nucleofected with a single plasmid encoding Cas9 nuclease or an adenine base editor linked to GFP via a 2A self-cleaving peptide, and the sgRNA of interest. Cells that were successfully nucleofected with the gene editing components express GFP, and single GFP+ iPSCs were collected.

Whole heart
homogenate control

↓



Supplementary Figure 2. Uncut gels. Full unedited gel for Extended Data Fig 6. Molecular weights for ladder markings are in kDa.

Supplementary Table 1. Summary of oligos

Oligo Name	Oligo Sequence
sgRNA for HDR Knock-In of MYH7 R403Q	TCATTGCCCACTTTCACCCG
ssODN for HDR Knock-In of MYH7 R403Q	TGCTACTTGCCTTTTCCTTCCAGAGGCTGACAAGTCTGCCTACCTC ATGGGGCTGAACTCAGCCGACCTGCTCAAGGGGCTGTGCCACCCT CAGGTGAAAGTGGGCAATGAGTACGTCACCAAGGGGCAG
Sequencing for hMYH7 F	ACCTCCACATCCTGGGTTCAA
Sequencing for hMYH7 R	GTGGAGGAGAGACCCATATT
Sequencing for hMYH6 F	GGAGGCTGTAGTGAGCCAAG
Sequencing for hMYH6 R	AGGAGCAAGCGAGTGATTGT
h403_sgRNA	CCGCAGGTGAAAGTGGGCAA
HTS ON-Target F	TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGTCCTCTCATACA CTGCCTTGG
HTS ON-Target R	GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGCACCATGCCTG GCTAATTTT
HTS OFF1 F	TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGGGGACAATGAC TGCCTCTGT
HTS OFF1 R	GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGTACCTCATGGG GCTGAACTC
HTS OFF2 F	TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGCAGGTCTCGATT CCAAGGAG
HTS OFF2 R	GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGGCACAACCCA CAAGTTTGTTT
HTS OFF3 F	TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGTTTTCAAATAT TCCTGCTCACT
HTS OFF3 R	GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGAGGCACCTTTC TGTGTGCTT
HTS OFF4 F	TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGATTCTGGATGCA GGATTTGC
HTS OFF4 R	GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGGTGGACAACA GGCCACTCTT
HTS OFF5 F	TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGGGACAATTTGT ATTTTAGCTTATTTTC
HTS OFF5 R	GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGTCCCCTGCTTT TCTCTGTGT
HTS OFF6 F	TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGTGATCCTGAAG ATTAGTGGATGC
HTS OFF6 R	GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGCCATCCTGAG ATAATCCTCCA
HTS OFF7 F	TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGACCTAGGAGGC TGGGATTGT
HTS OFF7 R	GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGCATGACAAGG AGTCCGAGGT
HTS OFF8 F	TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGGCCCTGGTTAC AGCATAAG
HTS OFF8 R	GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGCCACAACCAC TGACTGACTGA
sgRNA for Knock-In of MYH7 R403Q into murine Myh6	TCGTTCCCCACCTTCACCCG

ssODN for Knock-In of MYH7 R403Q into murine Myh6	TGGGACAAAGGAATGGAGGTACTGAAAATGCTTCCCCTCCTTG TCTATCAGATGCTGACAAATCAGCCTACCTCATGGGGCTGAACTC AGCCGACCTGCTCAAGGGGCTGTGCCACCCTCAGGTGAAAGTGG GCAATGAGTACGTCACCAAGGGGCAGAGTGTACAGCAAGTGTAC TAT
Genotyping for Myh6 F	GAGAAGCAGTGGTCATCATC
Genotyping for Myh6 R	GTGAGAAACACGTGGTGTCC
HTS Myh6 On-Target F	TCGTCCGCAGCGTCAGATGTGTATAAGAGACAGGGATCAAGGAC ATGGCAAAT
HTS Myh6 On-Target R	GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGGCTTGGTCTCC AGGGTTG
HTS Myh6 cDNA On-Target F	TCGTCCGCAGCGTCAGATGTGTATAAGAGACAGGATGGCACAGA AGATGCTGA
HTS Myh6 cDNA On-Target R	GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGCGAACATGTG GTGGTTGAAG
Sanger Myh6 cDNA On-Target F	GCTCTTGGCCACTGATAGTGC
Sanger Myh6 cDNA On-Target R	GCTCAAAGCTGTTGAAATCG
VCN N terminal AAV half F	ACCAGAAAGAGCGAGGAAAC
VCN N terminal AAV half R	TCGTTGGGCAGGTTCCTTATC
VCN N terminal AAV Probe	/56-FAM/TTGGTCATC/ZEN/CGCTCGATGAAGCTC/3IABkFQ/
VCN C terminal AAV half F	CCCAAGAGGAACAGCGATAAG
VCN C terminal AAV half R	CCACCACCAGCACAGAATAG
VCN C terminal AAV Probe	/56-FAM/ATCGCCAGA/ZEN/AAGAAGGACTGGGAC/3IABkFQ/