
Efficient in vivo genome editing prevents hypertrophic cardiomyopathy in mice

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Title: *Efficient in vivo Genome Editing Prevents Hypertrophic Cardiomyopathy in Mice*

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Supplementary Information

ABE8e-NG N-terminal vector ORF sequence (NpuN intein fusion at C-terminus):

ATGAAACGGACAGCCGACGGAAGCGAGTTCGAGTCACCAAAGAAGAAGCGGAAAGTCTCT
GAGGTGGAGTTTTCCACGAGTACTGGATGAGACATGCCCTGACCCTGGCCAAGAGGGCA
CGGGATGAGAGGGAGGTGCCTGTGGGAGCCGTGCTGGTGCTGAACAATAGAGTGATCGG
CGAGGGCTGGAACAGAGCCATCGGCCTGCACGACCCAACAGCCCATGCCGAAATTATGG
CCCTGAGACAGGGCGGCCTGGTCATGCAGAACTACAGACTGATTGACGCCACCCTGTACG
TGACATTCGAGCCTTGCGTGATGTGCGCCGGCGCCATGATCCACTCTAGGATCGGCCGCG
TGGTGTTTGGCGTGAGGAACTCAAAAAGAGGCGCCGCGCAGGCTCCCTGATGAACGTGCTGA
ACTACCCCGGCATGAATCACCGCGTCGAAATTACCGAGGGAATCCTGGCAGATGAATGTG
CCGCCCTGCTGTGCGATTTCTATCGGATGCCTAGACAGGTGTTCAATGCTCAGAAGAAGG
CCCAGAGCTCCATCAACTCCGGAGGATCTAGCGGAGGCTCCTCTGGCTCTGAGACACCTG
GCACAAGCGAGAGCGCAACACCTGAAAGCAGCGGGGGCAGCAGCGGGGGGTGAGACAA
GAAGTACAGCATCGGCCTGGCCATCGGCACCAACTCTGTGGGCTGGGCCGTGATCACCG
ACGAGTACAAGGTGCCCAGCAAGAAATTCAAGGTGCTGGGCAACACCGACCGGCACAGCA
TCAAGAAGAACCTGATCGGAGCCCTGCTGTTTCGACAGCGGCGAAACAGCCGAGGCCACC
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GAGTCCTTCCTGGTGGAAAGAGGATAAGAAGCACGAGCGGCACCCCATCTTCGGCAACATC
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GATGGACGGCACCGAGGAACTGCTCGTGAAGCTGAACAGAGAGGACCTGCTGCGGAAGC

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CTGACAGTGGAGTATGGCCTGCTGCCAATCGGCAAGATCGTGGAGAAGAGGATCGAGTGT
ACCGTGTACTCTGTGGATAACAATGGCAACATCTATACAGCCCGTGGCACAGTGGCAC
GATAGGGGAGAGCAGGAGGTGTTTCGAGTATTGCCTGGAGGACGGCAGCCTGATCAGGGC
AACCAAGGACCACAAGTTCATGACAGTGGATGGCCAGATGCTGCCCATCGACGAGATTTT
CGAGCGGGAGCTGGACCTGATGAGAGTGGATAACCTGCCTAATAG

ABE sgRNA sequence (Note: the nucleotide that displaces the disease-causing nucleotide we target for editing is underlined and the scaffold is bolded):

**GCCUCAGGUGAAGGUGGGGAAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCU
AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGC**

ABE8e-NG C-terminal vector ORF sequence (NpuC intein fusion at N-terminus):

ATGAAACGGACAGCCGACGGAAGCGAGTTCGAGTCACCAAAGAAGAAGCGGAAAGTCATC
AAGATTGCTACACGGAATACCTGGGAAAGCAGAACGTGTACGACATCGGCGTGGAGCGG
GATCACAACCTTCGCCCTGAAGAATGGCTTTATCGCCAGCAATTGCTTCGACTCCGTGAAAA
TCTCCGGCGTGGAAGATCGGTTCAACGCCTCCCTGGGCACATACCACGATCTGCTGAAAA
TTATCAAGGACAAGGACTTCCTGGACAATGAGGAAAACGAGGACATTCTGGAAGATATCGT
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GCAGGCTGAGCCGGAAGCTGATCAACGGCATCCGGGACAAGCAGTCCGGCAAGACAATC
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ACAGTGAAGGTGGTGGACGAGCTCGTGAAAGTGATGGGCCGGCACAAGCCCGAGAACAT
CGTGATCGAAATGGCCAGAGAGAACCAGACCACCCAGAAGGGACAGAAGAACAGCCGCG

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 ACCATATCGTGCCTCAGAGCTTTCTGAAGGACGACTCCATCGACAACAAGGTGCTGACCA
 GAAGCGACAAGAACCGGGGCAAGAGCGACAACGTGCCCTCCGAAGAGGTCGTGAAGAAG
 ATGAAGAATACTGGCGGCAGCTGCTGAACGCCAAGCTGATTACCCAGAGAAAGTTTCGAC
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 ACAAATACTACCACACGCCACGACGCCTACCTGAACGCCGTCTGTGGGAACCGCCCTGATC
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 TACAGCAACATCATGAACTTTTTCAAGACCGAGATTACCCTGGCCAACGGCGAGATCCGGA
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 GATTTTGCCACCGTGCGGAAAGTGCTGAGCATGCCCAAGTGAATATCGTGAAAAAGACC
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 GAGCCCCCTCGGGCCTTCAAGTACTTTGACACCACCATCGACCGGAAGGTGTACCGGAGCA
 CCAAAGAGGTGCTGGACGCCACCCTGATCCACCAGAGCATCACCGGCCTGTACGAGACAC
 GGATCGACCTGTCTCAGCTGGGAGGTGACTCTGGCGGCTCAAAAAGAACCGCCGACGGC
 AGCGAATTCGAGCCCAAGAAGAAGAGGAAAGTCTAA

SaCas9 nuclease sgRNA sequence (Note: the allele-specific nucleotide is underlined and the scaffold is bolded):

GUACUCAUUGCCCACUUUCACCUGUUUUAGUACUCUGUAAUGAAAAUUACAGAAUCUA
CUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUUU

SaCas9 nuclease ORF sequence:

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GGAGAACAATGAGGGCCGGAGATCCAAGAGGGGAGCAAGGCGCCTGAAGCGGAGAAGG
CGCCACAGAATCCAGAGAGTGAAGAAGCTGCTGTTTCGATTACAACCTGCTGACCGACCAC
TCCGAGCTGTCTGGCATCAATCCTTATGAGGCCAGAGTGAAGGGCCTGTCCCAGAAGCTG
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CGTGAATGAGGTGGAGGAGGACACCGGCAACGAGCTGTCCACAAAGGAGCAGATCAGCC
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AGTATCTGGAGAACATGAATGATAAGAGGCCCCCTCGCATCATCAAGACCATCGCCTCTAA
GACACAGAGCATCAAGAAGTACAGCACAGACATCCTGGGGAACCTGTATGAAGTCAAGAG
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CAGCGAATTCGAGCCCAAGAAGAAGAGGAAAGTCTAAA

SpCas9-NG nuclease ORF Sequence:

ATGGGCAGCAGTCATCATCATCACCATCACGACAAGAAGTACAGCATCGGCCTGG
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CCTGATCGGAGCCCTGCTGTTCGACAGCGGCGAAACAGCCGAGGCCACCCGGCT
GAAGAGAACCGCCAGAAGAAGATACACCAGACGGAAGAACCGGATCTGCTATCTG
CAAGAGATCTTCAGCAACGAGATGGCCAAGGTGGACGACAGCTTCTTCCACAGAC
TGGAAGAGTCCTTCCTGGTGGGAAGAGGATAAGAAGCACGAGCGGCACCCCATCTT

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CAGCTGAAGCGGCGGAGATACACCGGCTGGGGCAGGCTGAGCCGGAAGCTGATC
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GTCCAAGCTGGTGTCCGATTTCCGGAAGGATTTCCAGTTTTACAAAGTGCGCGAGA
TCAACAACCTACCACCACGCCCCACGACGCCTACCTGAACGCCGTCGTGGGAACCGC
CCTGATCAAAAAGTACCCTAAGCTGGAAAGCGAGTTCGTGTACGGCGACTACAAG
GTGTACGACGTGCGGAAGATGATCGCCAAGAGCGAGCAGGAAATCGGCAAGGCT
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TCTCAGCTGGGAGGTGACTCTGGCGGCTCAAAAAGAACCGCCGACGGCAGCGAA
TTCGAGCCCAAGAAGAAGAGGAAAGTCTAA

Supplementary Table 1. AAV expression in cardiomyocytes by region and in other cell types of the left ventricle. The fraction of cardiomyocytes within the LVs, RVs, LAs, and RAs from 4 male SvEv mice that express ABE transcripts following one dose of AAV treatment. In LVs, the expression transcripts found in additional cell types is quantified.

Supplementary Table 2. Mouse serum analyses. Markers for liver toxicity are quantified from serum obtained after treating SvEV (one dose; n=3 males) and SvEv/S4 (two doses; n=3 males) mice with dual-AAV9 carrying ABE. Serum data are shown for SvEv/S4 mice treated with low (n=1 male, 2 females), medium (n=3 females) and high (n=2 females) doses of Cas9KD. For comparison serum from SvEv WT (n=3 males) and untreated 403 SvEV (n=3 males) are shown.

Supplementary Table 3. RNAseq of untreated and base edited HCM model mice. The mean expression $\pm$ SD of genes related to hypertrophy, the sarcomere, the cytoskeleton, calcium signaling, the extracellular matrix, and metabolism are quantified in untreated R403Q-129SvEv/S4 mice and those treated with two doses of ABE.

Supplementary Table 4. Summary of off-target sites 1-16. The genomic coordinates, alignment to the target site, nearest genes, and primers used to amplify each of the 16 tested off-target sites are provided.

Supplementary Table 5. Genomic off-target sites nominated by CIRCLE-seq. A list of all off-target coordinates and alignments to the mm10 mouse genome nominated by CIRCLE-seq.