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Supplemental information

A universal strategy for AAV delivery of base editors to correct genetic point mutations in neonatal PKU mice

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Supplementary information

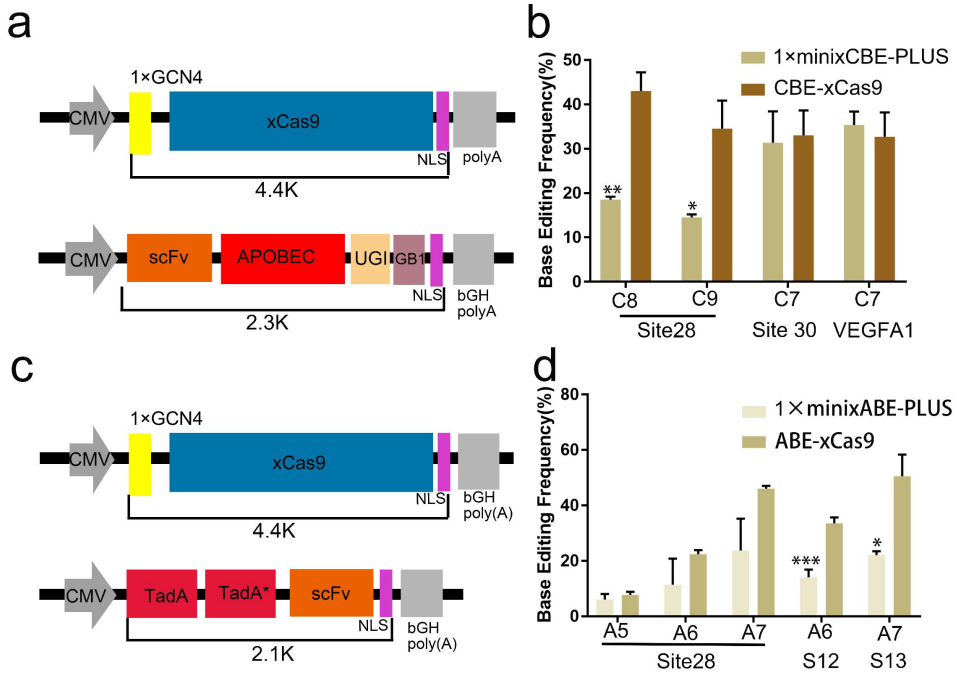

Figure S1. Construction and verification of minixBE-PLUS editing system. (a) Schematic diagram showing the expression cassettes of pCMV-1×GCN4-xCas9, CMV-scFv-CBE. (b) Cytosine base editing of 1×minixCBE-PLUS and CBE-xCas9 at three genomic loci in HEK293T cells. (n = 3 independent experiments). Values represent mean ± SD. Asterisks indicate statistically significant differences in editing efficiencies observed between CBE-xCas9 and 1×minixCBE-PLUS at each site. (c) Schematic diagram showing the expression cassettes of pCMV-1×GCN4-xCas9, pCMV-ABE-scFv. (d) Adenine base editing of 1×minixABE-PLUS and ABE-xCas9 at three genomic loci in HEK293T cells. (n = 3 independent experiments). Values represent mean ± SD. Asterisks indicate statistically significant differences in editing efficiencies observed between ABE-xCas9 and 1×minixABE-PLUS at each site. (abbreviations, CMV(human cytomegalovirus promoter), UGI(Uracil DNA

glycosylase inhibitor), NLS (nuclear localization signal), GB1(G protein B1 domain))

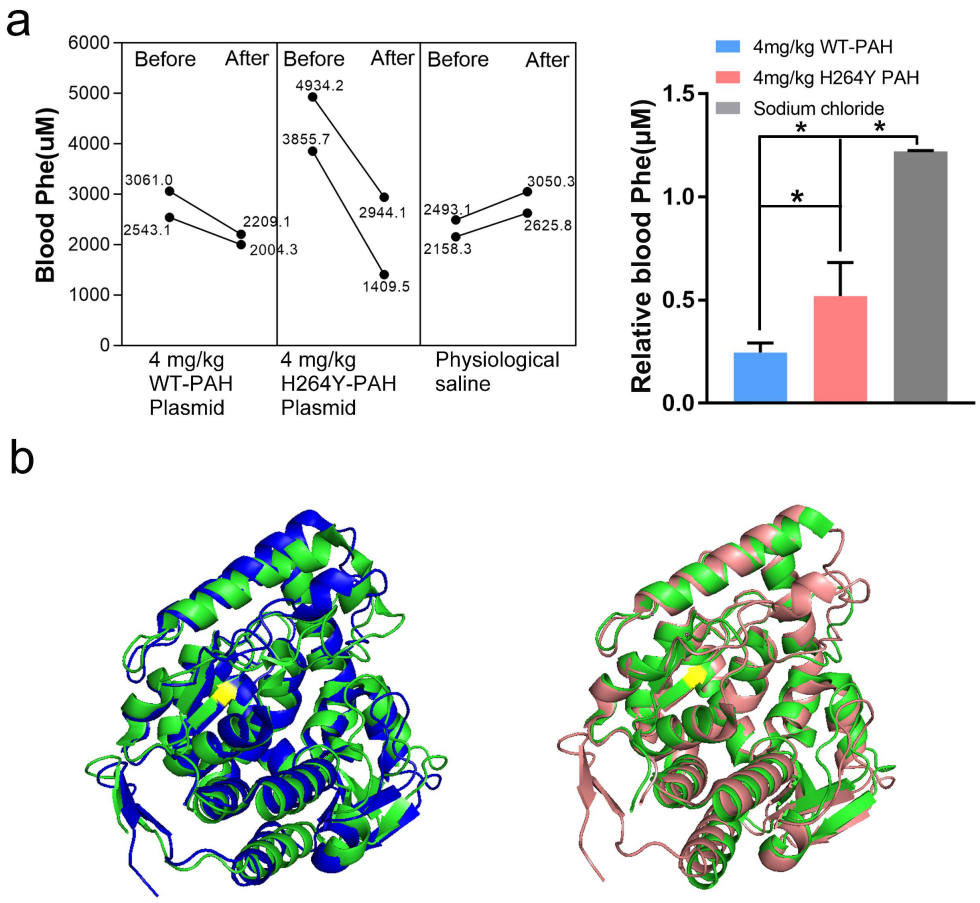

Figure S2. PAH activity evaluation. (a) H264Y-Pah enzyme activity verification. Changes of blood Phe in mice after plasmid injection (left panel). The relative changes of Phe in mice blood after plasmid injection (right panel) (n = 2 or 3 independent experiments). Values represent mean ± SD. Asterisks indicate statistically significant differences in functional editing efficiencies observed between WT-PAH or H254Y-PAH plasmid injected mice and sodium chloride injected mice. (b) Comparison of protein structure between phenylalanine hydroxylase monomer (PDB, 6hpo) (green) and tyrosine hydroxylase monomer (blue) (PDB, 3hfb), or

tryptophan hydroxylase monomer(pink) (PDB, 13e2t). position F264 of phenylalanine hydroxylase is marked in yellow.

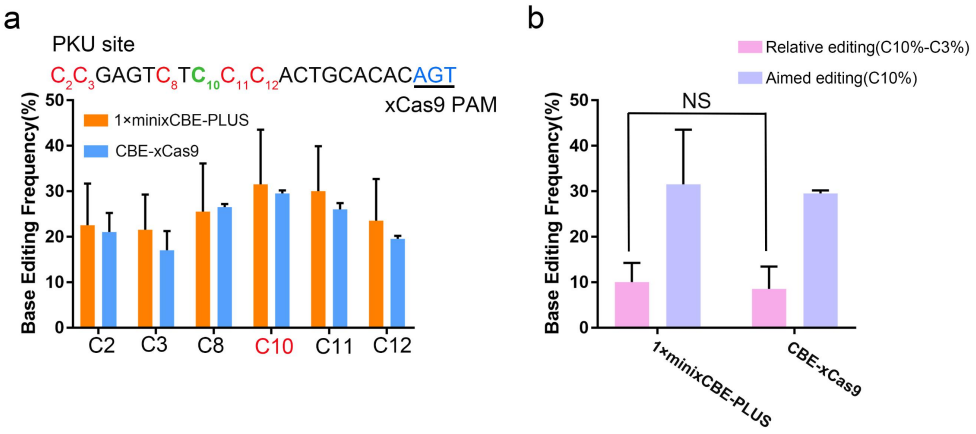

Figure S3. *In vitro* base editing of mouse PKU site by 1×minixCBE-PLUS. (a) The editing of 1×minixCBE-PLUS, and CBE-xCas9 with the sgRNA on PKU site of each c (n = 3 independent experiments). The aimed cytosine (C10, i.e. C835) was shown in green, and the bystanders were shown in red. (b) The relative editing efficiency (C10%-C3%) of 1×minixCBE-PLUS, and CBE-xCas9 (n = 3 independent experiments). Values represent mean ± SD. Asterisks indicate statistically significant differences in functional editing efficiencies observed between CBE-xCas9 and 1×minixCBE-PLUS at PKU site .

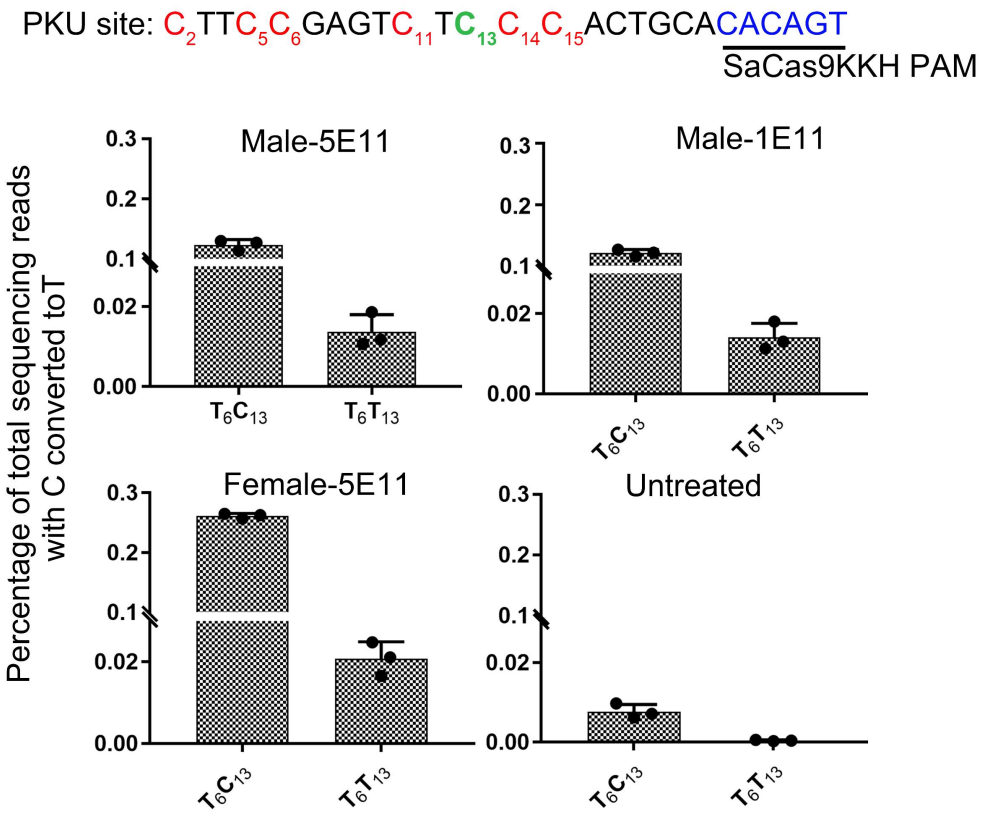

Figure S4. AAV8-miniSaCBE-PLUS-PKU produced minus non-sense edits *in vivo*. HTS of high-dose (5E11-PKU) male, low-dose (1E11-PKU) male, high-dose (5E11-PKU) female, untreated mice liver DNA revealed that AAV8-miniSaCBE-PLUS-PKU only produced minus non-sense edits *in vivo*.

	Phe										Weigh									
	Male					Female					Male					Female				
Groups \ Weeks	8w	12w	16w	20w	24w	8w	12w	16w	20w	24w	8w	12w	16w	20w	24w	8w	12w	16w	20w	24w
WT or PKU heterozygote vs 5E11 AAV8-miniSaCBE-PLUS-PKU	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	**	*	ns	ns	ns
WT or PKU heterozygote vs 1E11 AAV8-miniSaCBE-PLUS-PKU	****	*	ns	ns	ns						**	ns	ns	ns	ns					
WT or PKU heterozygote vs 5E11 AAV8-miniSaCBE-PLUS-ctrl	****	****	****	****	****	****	****	****	****	****	****	****	**	***	****	****	****	***	**	***
WT or PKU heterozygote vs PKU untreated	****	****	****	****	****	****	****	****	****	****	***	**	ns	*	**	****	****	****	****	****
5E11 AAV8-miniSaCBE-PLUS-PKU vs 1E11 AAV8-miniSaCBE-PLUS-PKU	****	*	ns	ns	ns						*	ns	ns	ns	ns					
5E11 AAV8-miniSaCBE-PLUS-PKU vs 5E11 AAV8-miniSaCBE-PLUS-ctrl	****	****	****	****	****	****	****	****	****	****	****	**	ns	ns	ns	**	***	***	***	***
5E11 AAV8-miniSaCBE-PLUS-PKU vs PKU untreated	****	****	****	****	****	****	****	****	****	****	**	ns	ns	ns	ns	ns	**	****	****	****
1E11 AAV8-miniSaCBE-PLUS-PKU vs 5E11 AAV8-miniSaCBE-PLUS-ctrl	ns	ns	**	****	****						ns	ns	*	*	*					
1E11 AAV8-miniSaCBE-PLUS-PKU vs PKU untreated	ns	****	***	****	****						ns	ns	ns	ns	ns					
5E11 AAV8-miniSaCBE-PLUS-ctrl vs PKU untreated	ns	****	ns	ns	ns	ns	ns	*	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns

Figure S5. The results of *ANOVA* analysis between the mutiple groups in

Figure 4e and Figure 4f. Asterisks indicate statistically significant differences in phe level and weigh of tested mice between multiple groups.

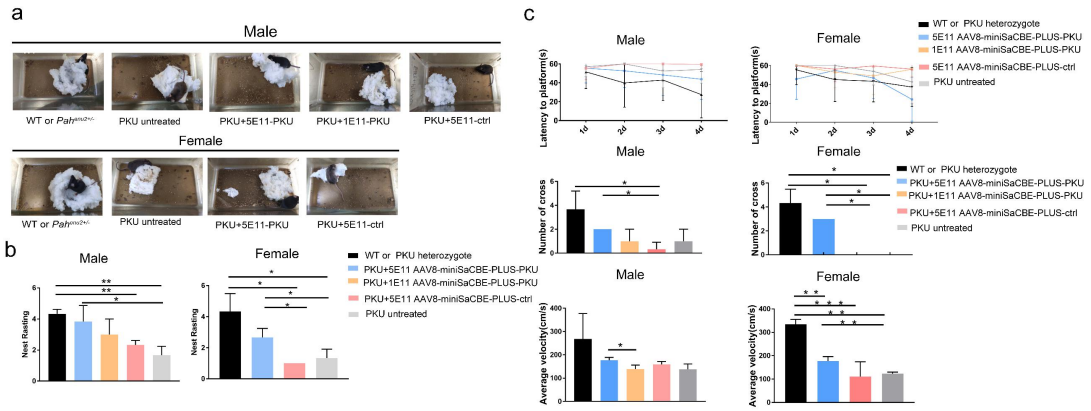

Figure S6. Behavioral analysis. (a) Photos of male and female mice' nesting situation. (b) Rating assessment of mice's nesting ability. n=3 mice for each group. Values represent mean ± SD. Asterisks indicate statistically significant differences between each group. (c) Performance in the water maze is presented with male and female respectively. The results are shown in top latency to the target platform (seconds), middle number of crosses, bottom average velocity (cm/s). n=3 mice for each group. Values represent mean ± SD. Asterisks indicate statistically significant differences between each group.

Table S1. List of sgRNAs and Oligos sequence

sgRNA	target sequence	Oligo F	Oligo R
FANCF site1	GATGTTCCAATCAGTACGCAGAGAGT	CACCGATGTTCCAATCAGTACGCA	AAACTGCGTACTGATTGGAACATC
CYP4V2 site4	TGCCTTAGATATCATCTGTGAGAAT	CACCGTGCCTTAGATATCATCTGTG	AAACCACAGATGATATCTAAGGCAC
HEK3-1	TCTGCTTCTCCAGCCCTGGCCTGGGT	CACCGTCTGCTTCTCCAGCCCTGGC	AAACGCCAGGGCTGGAGAAGCAGAC
HEK293 site4-4	CTTTAACCCCCACCTCCAGCCGCAGT	CACCGCTTTAACCCCCACCTCCAGC	AAACGCTGGAGGTGGGGGTTAAAGC
EMX1	CCTCCCTCCCTGGCCCAGGTGAAGGT	CACCGCCTCCCTCCCTGGCCCAGGT	AAACACCTGGGCCAGGGAGGGAGGC
FANCF site2	GCCGTCTCCAAGGTGAAAGCGGAAGT	CACCGCCGTCTCCAAGGTGAAAGC	AAACGCTTTCACCTTGGAGACGGC
Sa site6	GATGTTCCAATCAGTACGCAGAGAGT	CACCGATGTTCCAATCAGTACGCA	AAACTGCGTACTGATTGGAACATCC
VEGFA site11	GCTCCATTCACCCAGCTTCCCTGTGGT	CACCGCTCCATTCACCCAGCTTCC	AAACGGGAAGCTGGGTGAATGGAGC
RUNX1 4	GTACTCACCTCTCATGAAGCACTGTGGGT	CACCGTACTCACCTCTCATGAAGC	AAACAGTGCTTCATGAGAGGTGAGTAC
EMX1 #6	GCAACCACAAACCCACGAGGGCAGAGT	CACCGCAACCACAAACCCACGAGG	AAACCCCTCGTGGGTTTGTGGTTGC
Sa site1	CTGAATAGCTGCAAACAAGTGCAGAAT	CACCGCTGAATAGCTGCAAACAAG	AAACCACTTGTTTGCAGCTATTCAGC
Sa site11	GCTGTTGCATGAGGAAAGGGACTAGAGT	CACCGCTGTTGCATGAGGAAAGG	AAACGTCCCTTTCCTCATGCAACAGC
Site28	GACAAACCAGAAGCCGCTCCTGG	CACCGACAAACCAGAAGCCGCTCC	AAACGGAGCGGCTTCTGGTTTGTCC
Site30	GAACACAAAGCATAGACTGCGGG	CACCGAACACAAAGCATAGACTGC	AAACGCAGTCTATGCTTTGTGTTCC

VEGFA 1	GATGTCTGCAG GCCAGATGA **GGG**	CACCGATGTCTG CAGGCCAGATGA	AAACTCATCTGGCCT GCAGACATC
S12	GCAGACGGCAG TCACTAGGG **GGC**	CACCGCAGACGG CAGTCACTAGGG	AAACCCCTAGTGACT GCCGTCTGC
S13	GTCGCAGGACA GCTTTTCCT **AGA**	CACCGTCGCAGG ACAGCTTTTCCT	AAACAGGAAAAGCTG TCCTGCGAC
18-PKU-sgRNA	TCCGAGTCTCC CACTGCA **CACAGT**	CACCGTCCGAGT CTTCCACTGCA	AAACTGCAGGGGAAG ACTGGAC
19-PKU-sgRNA	TTCCGAGTCTCC CACTGCA **CACAGT**	CACCGTTCCGAG TCTTCCACTGCA	AAACTGCAGGGGAAG ACTGGAAC
20-PKU-sgRNA	CTTCCGAGTCTC CCACTGCA **CACAGT**	CACCGCTTCCGA GTCTTCCACTGC A	AAACTGCAGGGGAAG ACTGGAAGC
21-PKU-sgRNA	CCTTCCGAGTCT TCCACTGCA **CACAGT**	CACCGCCTTCCG AGTCTTCCACTG CA	AAACTGCAGTGGAAG ACTGGAAGGC

Table S2. Primers used to amplify each target regions for sanger sequencing

Target site	chrom	Forward primer	Reverse primer
FANCF site1	Chr11	CGACGAGACAAAGGCGGCT	TCACTGTGACGTCCTGCTCT
CYP4V2 site4	Chr4	TGAAGAAACTTCGGTATCTG	TATGGAAGCCCATGCAGGCG
HEK3-1	Chr9	AGAATGGGTCACAGTGGCAA	TAGGAAAAGCTGTCCTGCGA
HEK293 site4-4	Chr20	CTGCTGAGGGCGGCTTCTC	TGAAATCGCTCGGAGCCTC
EMX1	Chr2	TCTCTCTGGCCCACTGTGTC	CCATTGGCCTGCTTCGTG
FANCF site2	Chr11	CGACGAGACAAAGGCGGCT	TCACTGTGACGTCCTGCTCT
Sa site6	Chr11	ATGACTGGCATCATCTCGCA	GGTGCTGACGTAGGTAGTGC
VEGFA11	Chr6	GGAACAAGGGCCTCTGTCTG	GCCGTTCCCTCTTTGCTAGG
RUNX14	Chr2	GTTCTCACGCACCGACT	GAGTCCCAGAGGTATCC

	1	GAA	AGC
EMX1 #6	Chr2	TCTCTCTGGCCCACTGTGTC	CCATTGGCCTGCTTCGTG
Sa site1	Chr5	AAGTTACTGCAGCCCAAG	CAAGCAGGTGATTACAGG
Sa site11	Chr1	GCAGAAACCACAGTGTGT	CACTACCCCTGTTCCTAAAG
Site28	Chr3	GGCACAAAGGATGAAGGCT	GCTCAGTCTTGCATGAAACAC
Site30	Chr5	ACAGGCTACCCCCTAAGT	TCCCAAGTGAGAAGCCAGTG
VEGFA site1	Chr6	GGAACAAGGGCCTCTGTCTG	GCCGTTCCCTCTTTGCTAGG
S12	Chr6	CACAGCTTCCCGTTCTCAGC	AGGGACACACAGATCTATT
S13	Chr9	ATGTGGGCTGCCTAGAAAGG	CCCAGCCAAACTTGTCAACC
PKU-sgRNA		CCTTGGGGAGTCATACCTCA	ATAAAGCAGGCAGTGGATCA
BGH_PA_qPCR		GCCAGCCATCTGTTGT	GGAGTGGCACCTTCCA
BGH_PA_qPCR_Probe		TCCCCCGTGCCTTCCTTGACC	

Table S3. HTS Primers used for on-target sequence amplification.

Primer name	Forward primer	Reverse primer
1-Bar-DNA-OT	aagcgtg CCTTGGGGAGTCATACCTCA	GTTCAGGTG
2-Bar-DNA-OT	attctcg CCTTGGGGAGTCATACCTCA	TGTACATGG
3-Bar-DNA-OT	attgctc CCTTGGGGAGTCATACCTCA	
4-Bar-DNA-OT	atcaagc CCTTGGGGAGTCATACCTCA	
5-Bar-DNA-OT	atccgga CCTTGGGGAGTCATACCTCA	
6-Bar-DNA-OT	atcgaag CCTTGGGGAGTCATACCTCAA	
7-Bar-DNA-OT	atcgtcc CCTTGGGGAGTCATACCTCA	
8-Bar-DNA-OT	atgcttc CCTTGGGGAGTCATACCTCA	
9-Bar-DNA-OT	atggcga CCTTGGGGAGTCATACCTCA	
10-Bar-DNA-OT	acttagc CCTTGGGGAGTCATACCTCA	
S99-Bar-DNA-OT	tgtgtca CCTTGGGGAGTCATACCTCA	
S38-Bar-DNA-OT	caactgt CCTTGGGGAGTCATACCTCA	
1-RNA-pku-ontargetF	catcgac GACAACATCCCGCAGCT	GTTCAGGTG
2-RNA-pku-ontargetF	catgatc GACAACATCCCGCAGCT	TGTACATGG
3-RNA-pku-ontargetF	catgcaa GACAACATCCCGCAGCT	
4-RNA-pku-ontargetF	cagttac GACAACATCCCGCAGCT	

5-RNA-pku-ontargetF	ctatggt GACAACATCCCGCAGCT
6-RNA-pku-ontargetF	ctacaag GACAACATCCCGCAGCT
7-RNA-pku-ontargetF	ctacgtc GACAACATCCCGCAGCT
8-RNA-pku-ontargetF	ctagcac GACAACATCCCGCAGCT
9-RNA-pku-ontargetF	cttagct GACAACATCCCGCAGCT
10-RNA-pku-ontargetF	cttggag GACAACATCCCGCAGCT
11-RNA-pku-ontargetF	ctgctaa GACAACATCCCGCAGCT
12-RNA-pku-ontargetF	ctcgtat GACAACATCCCGCAGCT
13-RNA-pku-ontargetF	gaactac GACAACATCCGCAGCT
14-RNA-pku-ontargetF	gaaccta GACAACATCCCGCAGCT
15-RNA-pku-ontargetF	gaaggtc GACAACATCCCGCAGCT
16-RNA-pku-ontargetF	gattctg GACAACATCCCGCAGCT
17-RNA-pku-ontargetF	gattgct GACAACATCCCGCAGCT
18-RNA-pku-ontargetF	gatgacg GACAACATCCCGCAGCT
19-RNA-pku-ontargetF	gatgtgc GACAACATCCCGCAGCT
20-RNA-pku-ontargetF	gaccatc GACAACATCCCGCAGCT
21-RNA-pku-ontargetF	gacgaat GACAACATCCCGCAGCT

Table S4. Off-target sequence

Target site	sequence	chrom	strand
OT1	ACTTCAGACTCTCTCACTGCAACTGGT	Chr14	-
OT2	ATTTCCAAGTCTCCCACTGCTGTGAGT	Chr10	+
OT3	CCTCCCCAGTCTCCCACTGCTGACAAT	Chr11	-
OT4	CCTACAGAGTATTCCACTGCACCCAGT	Chr10	-
OT5	CCTTTCGAGTCTTTCACTGCACTCAGT	Chr7	-
OT6	TCTTCCTAGGCTCCCACAGCAATGAGT	Chr11	-
OT7	CATTCCCAGTGTACCACTGCAGTCAGT	Chr4	+
OT8	TCTTCAGAGTCTTCCTCTGCATCCGAT	ChrX	+

Table S5. Off-target Primers for amplification

off-target site	Forward primer	Reverse primer
OT1	gctgtaa GCATTTCTCAGATCTAATCTTCTGA	TGAGCATATGTGACCT GAGGA
OT2	gcctcta GAAACAGTTTGCACCCCCTA	CCCCAGGTTCATCAGT TCAC
OT3	gcgagtt CTTAGCGCCGCTGACTCT	TCCCTCTCCTTTTGCTT CCT
OT4	aactagg GACTGCAATACTCACGGTTCC	TGAGCCCAAGAGACTT CCTG
OT5	aacctag GCCATTTGATGAATGAATAGCA	GGTTTTCCATCCGTCC TGT

OT6	aagatgc AGGATGAGACCCAGGACCA	CCTGCAAGCTTTCCAC TCAT
OT7	ctggatg GCTGGGGCTATACAAAATTCC	CAGTAGTTCCAGTCAC GGTTG
OT8	ccaatga AAAAATATGCCCGTGTCATTG	TGCTGCTGTTGGAATC TGAG

Note1：

Plasmid sequences (CDS)

4×GCN4-SaCas9KKH

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