

Supplementary Materials for

**Human 8-cell embryos enable efficient induction of disease-preventive mutations
without off-target effect by cytosine base editor**

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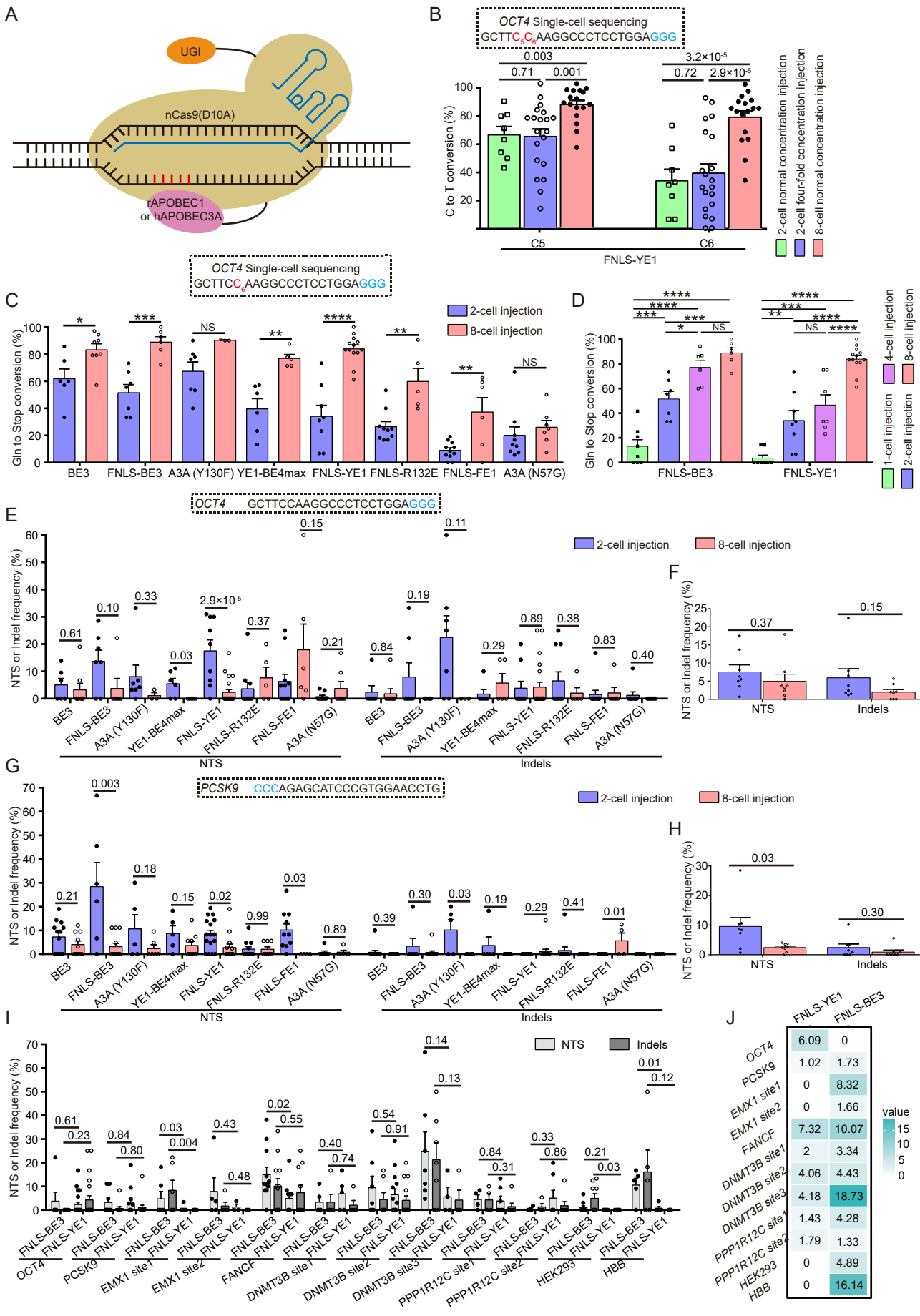
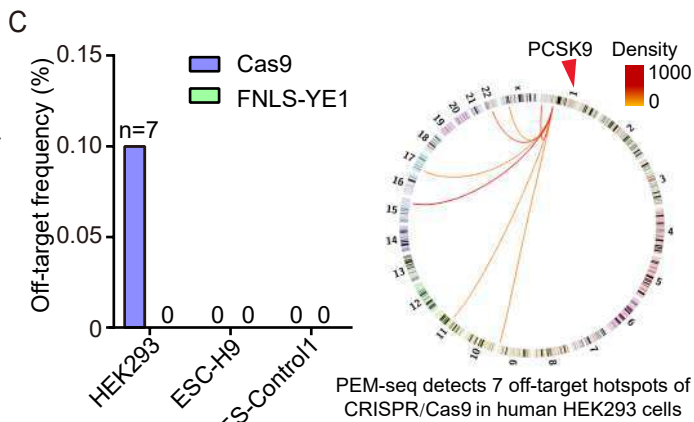
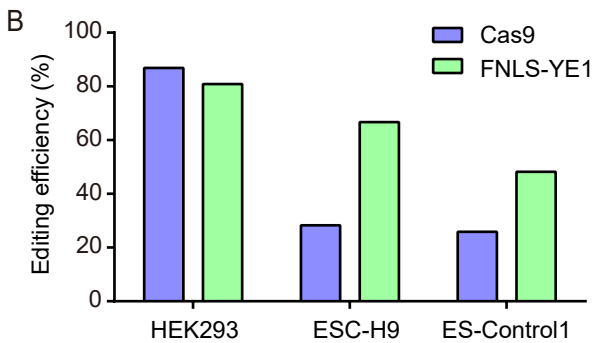
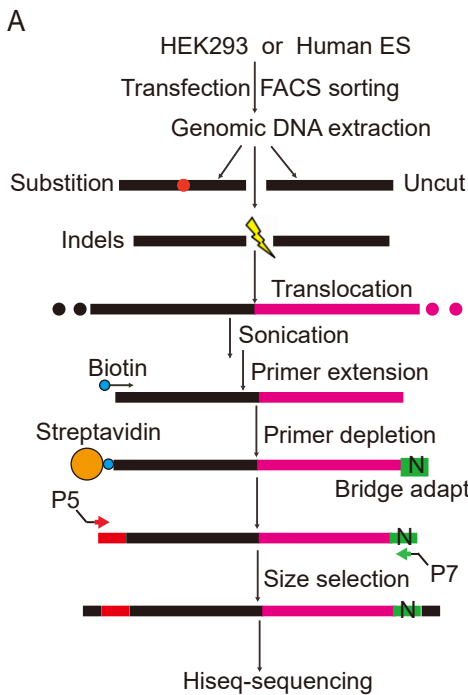


Figure S1. Injection of different base editor variants in human 3PN cleavage embryos highly increased base-editing efficiency and decreased NTS or indel frequency. (A) Schematic diagram of cytosine base editor (CBE) system working principle. (B) Comparative analysis of embryos injected with different concentrations of FNLS-YE1 and sgRNA mixtures targeting the *OCT4* locus at the 2-cell and 8-cell stages. (C) Single-cell sequencing analysis of embryos injected with eight CBE variants targeting the *OCT4* locus at the 2-cell and 8-cell stages. Percentage of alleles with targeted conversion of *Gln* codon to stop codon conversion on the *OCT4* locus. (D) Single-cell sequencing analysis of embryos injected with FNLS-BE3 and FNLS-YE1 targeting the *OCT4* locus at the 1-cell, 2-cell, 4-cell, and 8-cell stages. Percentage of alleles with targeted conversion of *Gln* codon to stop codon conversion on the *OCT4* locus. (E-H) Frequency of indel mutations and non-targeted nucleotide substitutions in 2-cell and 8-cell human embryos injected with eight CBE variants targeting *OCT4* (E and F) and *PCSK9* (G and H) loci. Indels, indel mutations; NTS, non-targeted nucleotide substitutions. (I) The NTS or indel frequency of FNLS-BE3 and FNLS-YE1 targeting the 12 endogenous sites at the 8-cell stage. (J) Heatmap showing the indel distribution of embryos injected with FNLS-BE3 and FNLS-YE1 targeting human 12 endogenous sites at the 8-cell stage. Data are presented as the mean \pm SEM. p values were evaluated with unpaired Student's *t*-test. **p* < 0.05, ***p* < 0.01, ****p* < 0.001, *****p* < 0.0001; NS, not significant. Each dot in Figs. S1B-E, G, I and Figs. S1F, H represents an embryo and the base editor tested, respectively.



D PEM-seq detects off-target hotspots of CRISPR/Cas9 in human HEK293 cells

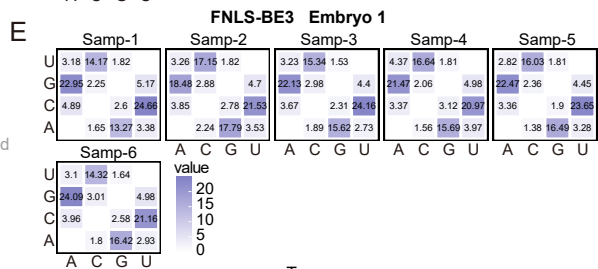
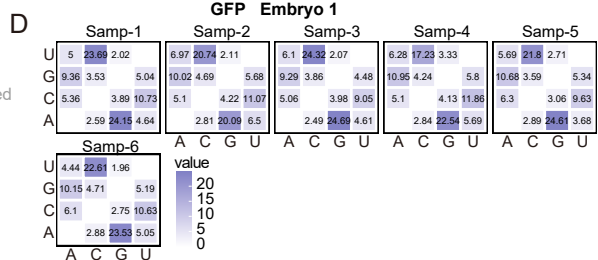
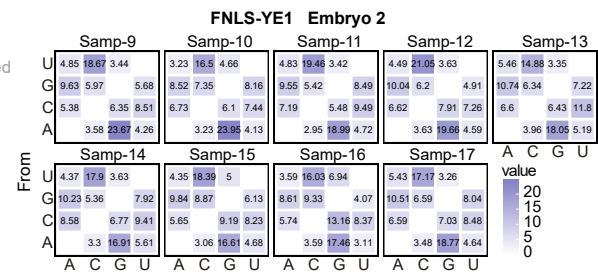
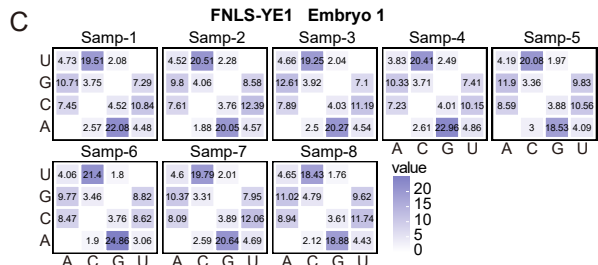
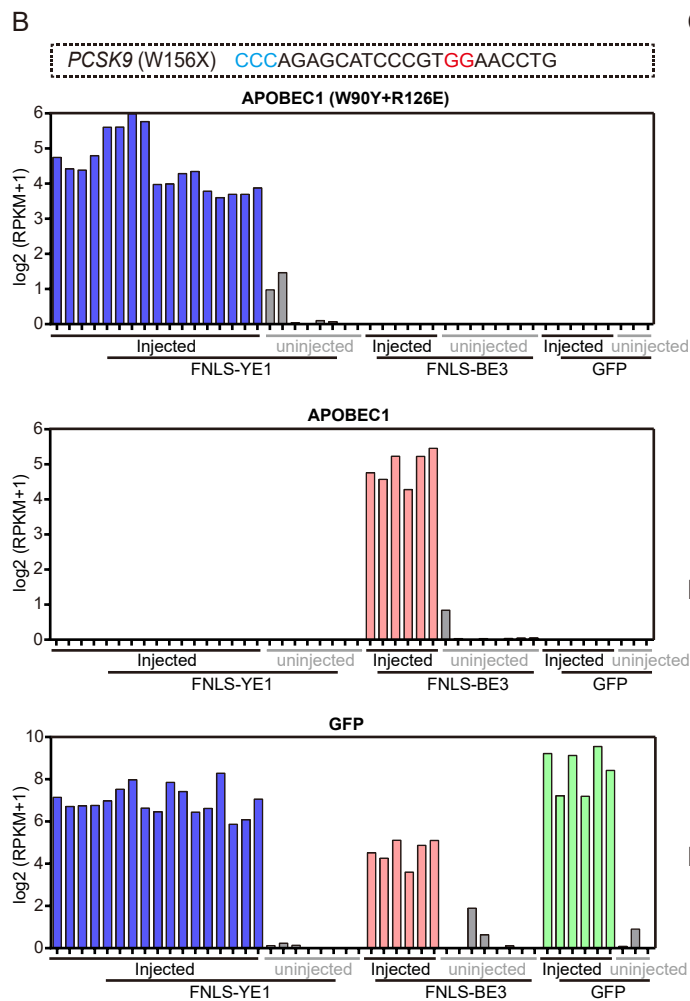
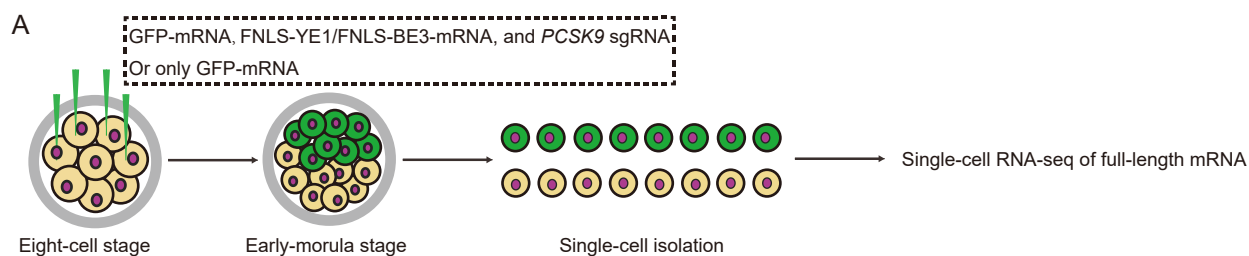
Gene	No.	Target dequence	Genomic location	Direction
<i>PCSK9</i>	OnT	CAGGTTCCACGGGATGCTCTGGG	chr15: 55046575-55046597	-
Intergenic	OT1	CAGTTTCCACGGAATGCTCTGGG	chr15: 84580603-84580625	-
<i>PPM1F</i>	OT2	GCAGGCCCCCGGGATGCTTTGGG	chr22: 21946050-21946072	-
<i>KCNAB2</i>	OT3	CAGGCTCCACAAGATGCCCTGGG	chr1: 21946050-21946072	+
<i>SHANK2</i>	OT4	CCGTTTCTACAGGATGCTCTAGG	chr11: 70520931-70520953	+
Intergenic	OT5	GCAGGACCCAGGATGCCCTGGG	chr9: 137238868-137238890	+
<i>DMD</i>	OT6	CGTGTTCACGGGATGCACTTGG	chrX: 32894602-32894624	+
<i>LRR75A</i>	OT7	ACAGGTCCCTGGCATGCTCTGGG	chr17: 16482410-16482432	+

E Information of PEM-seq libraries in *PCSK9* locus in different cell lines

Nuclease	cell line	locus	DNA	Reads	Translocation	Indels	Germline	On-target substitutions	Editing efficiency
Cas9	293T		20µg	325466	20553	262236	37064		86.9%
	ESC-H9	<i>PCSK9</i>	20µg	162249	315	45546	116056		28.3%
	ES-Control1		20µg	115280	288	29544	85156		25.9%
FNLS-YE1	293T		20µg	352378	142	2652	64595	285046	80.9%
	ESC-H9	<i>PCSK9</i>	20µg	250172	15	2267	80894	166932	66.7%
	ES-Control1		20µg	106973	14	1466	53900	51599	48.2%
Control	293T		20µg	478780	32	936	477815		0
	ESC-H9	<i>PCSK9</i>	20µg	115476	6	281	115186		0
	ES-Control1		20µg	311239	23	559	310672		0

Figure S2. Off-target profiling of Cas9 and FNLS-YE1 targeting *PCSK9* by Primer-extension-mediated sequencing (PEM-seq) in HEK293T cells and hESCs.

(A) Schematic diagram of PEM-seq. See “Methods” for details. (B and C) Editing efficiencies (B) and off-target hotspots (C) detected by PEM-seq for Cas9 and FNLS-YE1 targeting *PCSK9* in HEK293T cells and hESCs. (D) List of potential off-target sites captured by PEM-seq. OnT, on-target; OT, off-target. Red letters indicate mismatched nucleotides. (E) Information of PEM-seq libraries for different samples treated with Cas9 or FNLS-YE1 targeting *PCSK9*.

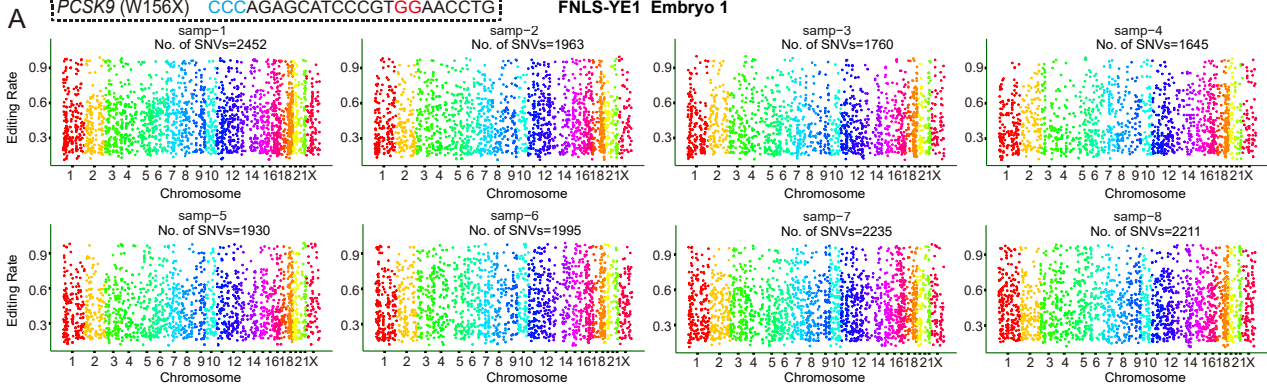


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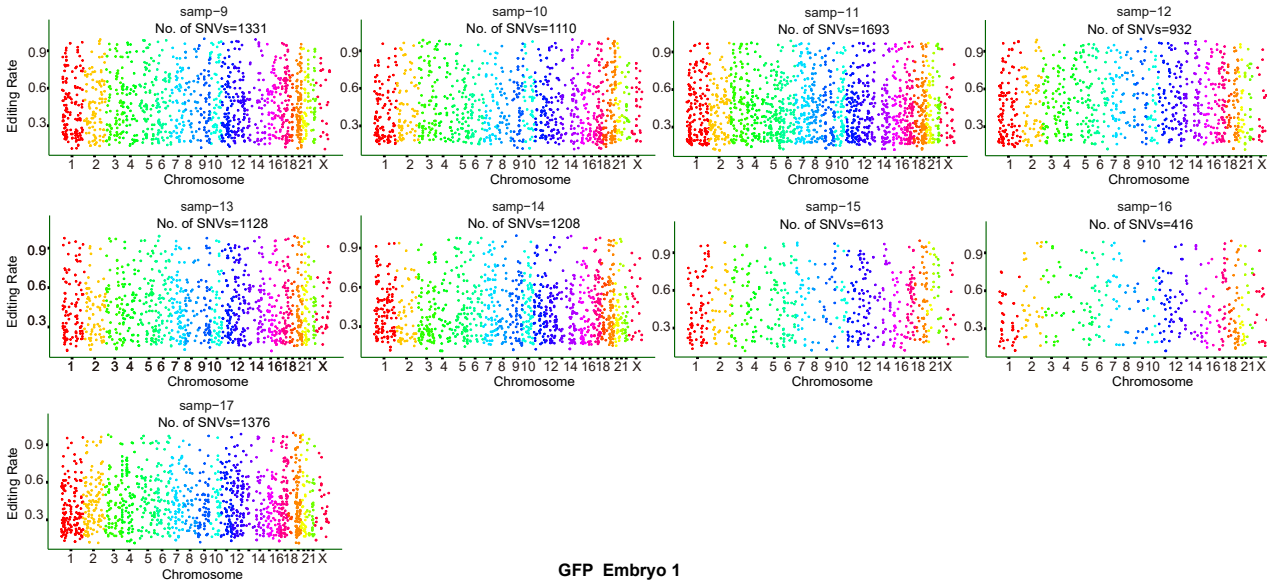
Figure S3. RNA off-target profiling of FNLS-YE1 and FNLS-BE3 targeting *PCSK9* in human 2PN embryos. (A) Schematic of sgRNA-independent RNA off-targeting analyses using RNA sequencing of FNLS-YE1-treated embryos undergoing whole-transcriptome amplification at the single cell level. (B) Expression levels of FNLS-YE1 (APOBEC1-W90Y+R126E), FNLS-BE3 (APOBEC1), and co-injected GFP were quantified in all sequenced single blastomeres of injected embryos. (C-E) Transcriptomic SNVs distribution for different base-conversion types detected in single blastomeres of injected embryos for *PCSK9* editing.

PCSK9 (W156X) CCCAGAGCATCCCCTGGAACCTG

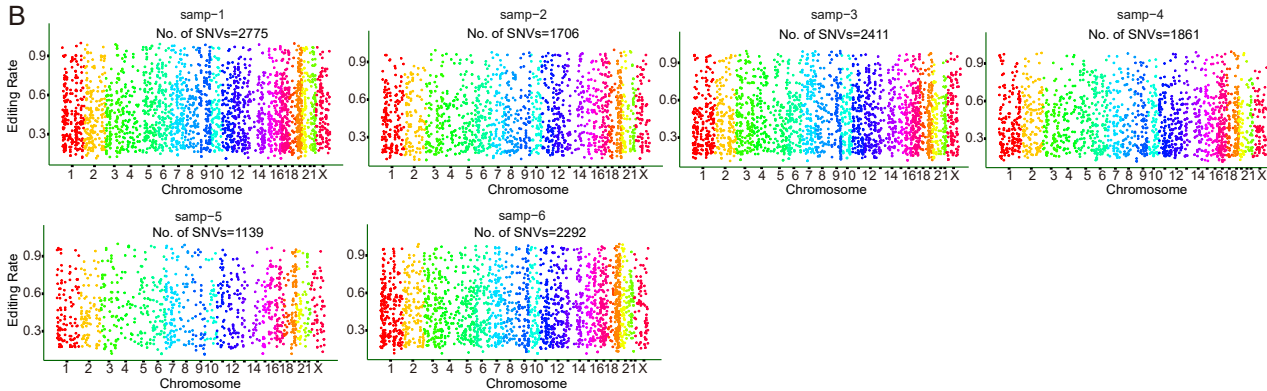
FNLS-YE1 Embryo 1



FNLS-YE1 Embryo 2



GFP Embryo 1



FNLS-BE3 Embryo 1

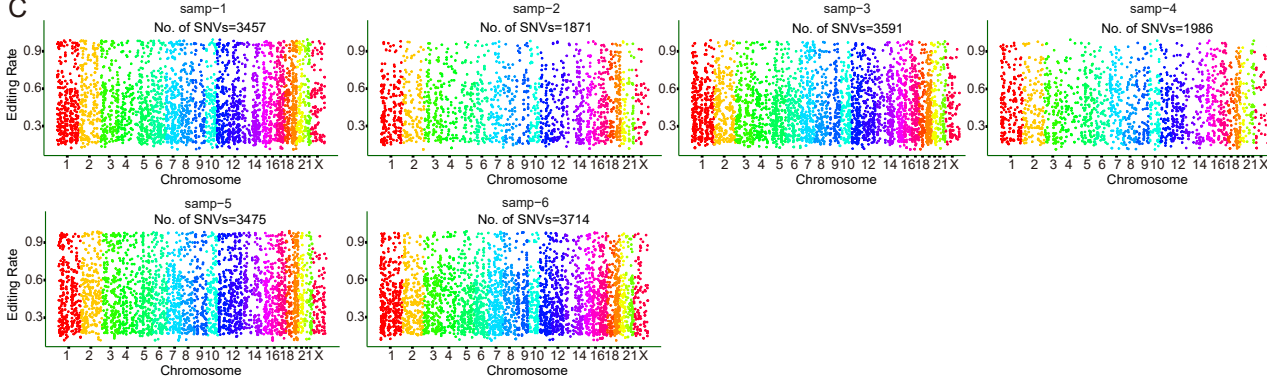


Figure S4. Distribution of off-target RNA SNVs on human chromosomes for all single blastomeres of human 2PN embryos injected with only GFP, FNLS-YE1/sgRNA/GFP, or FNLS-BE3/sgRNA/GFP targeting *PCSK9*. (A) Distribution of off-target RNA SNVs on human chromosomes for FNLS-YE1/sgRNA/GFP mRNA-injected single blastomeres (n = 17 cells, two human 2PN embryos). (B) Distribution of off-target RNA SNVs on human chromosomes for only GFP mRNA-injected single blastomeres (n = 6 cells, one human 2PN embryos). (C) Distribution of off-target RNA SNVs on human chromosomes for FNLS-BE3/sgRNA/GFP mRNA-injected single blastomeres (n = 6 cells, one human 2PN embryo).

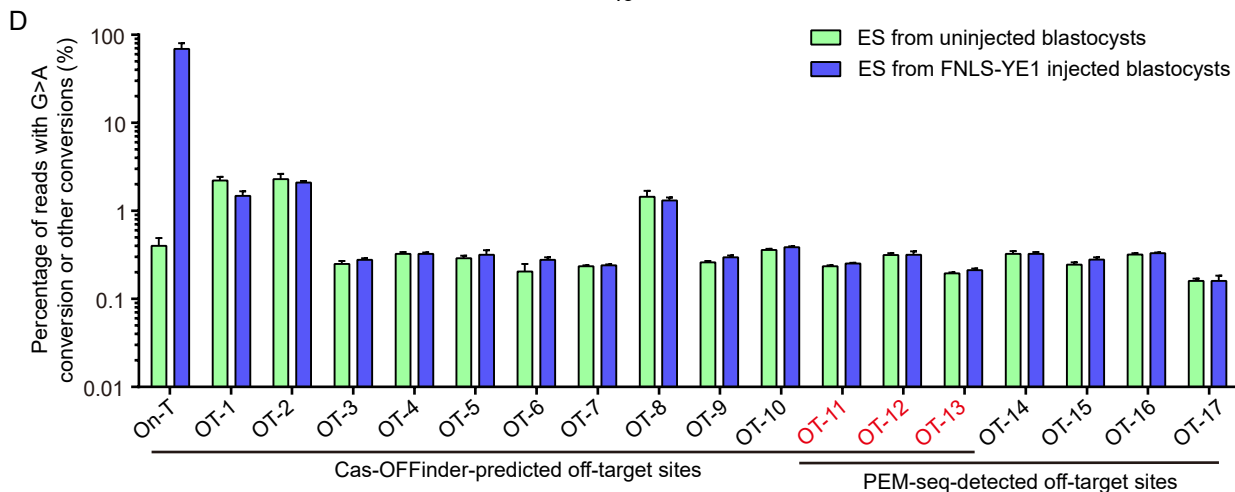
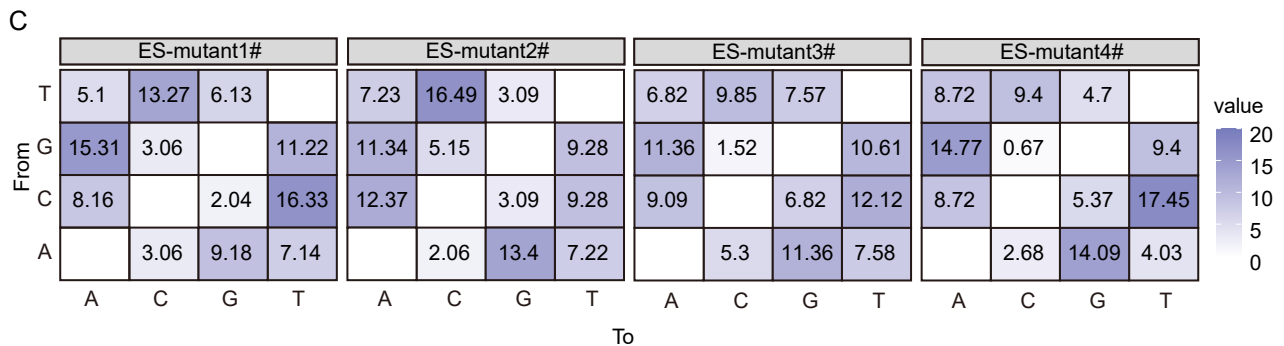
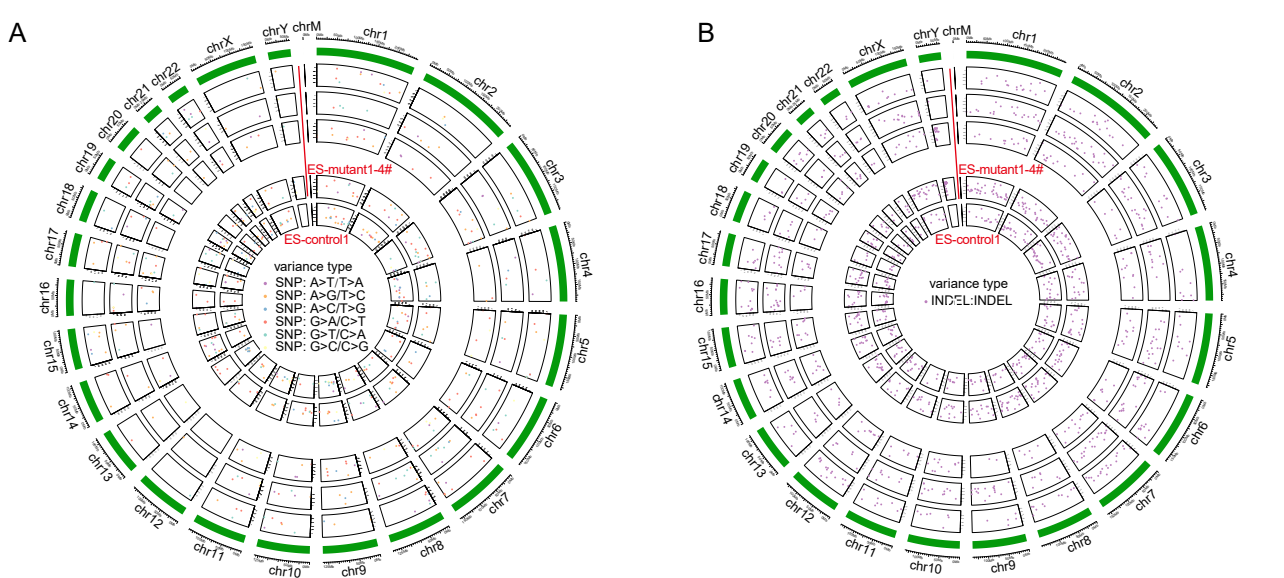


Figure S5. DNA off-target profiling of FNLS-YE1 targeting *PCSK9* in hESCs derived from non-edited and edited embryos by WGS. (A and B) Distribution of SNVs (A) and indels (B) in the human genome for control and *PCSK9*-edited hESCs. hESCs from outer circle to inner circle were ES-mutant1-4# and ES-control1. (C) Distribution frequency of SNV mutation types for *PCSK9*-edited hESCs. The number in each cell indicates the proportion of a certain type of mutation among all SNV mutations. (D) Editing rate for on-target and off-target sites in human embryonic stem cells derived from control and FNLS-YE1-treated embryos. Data are presented as the mean \pm SEM.

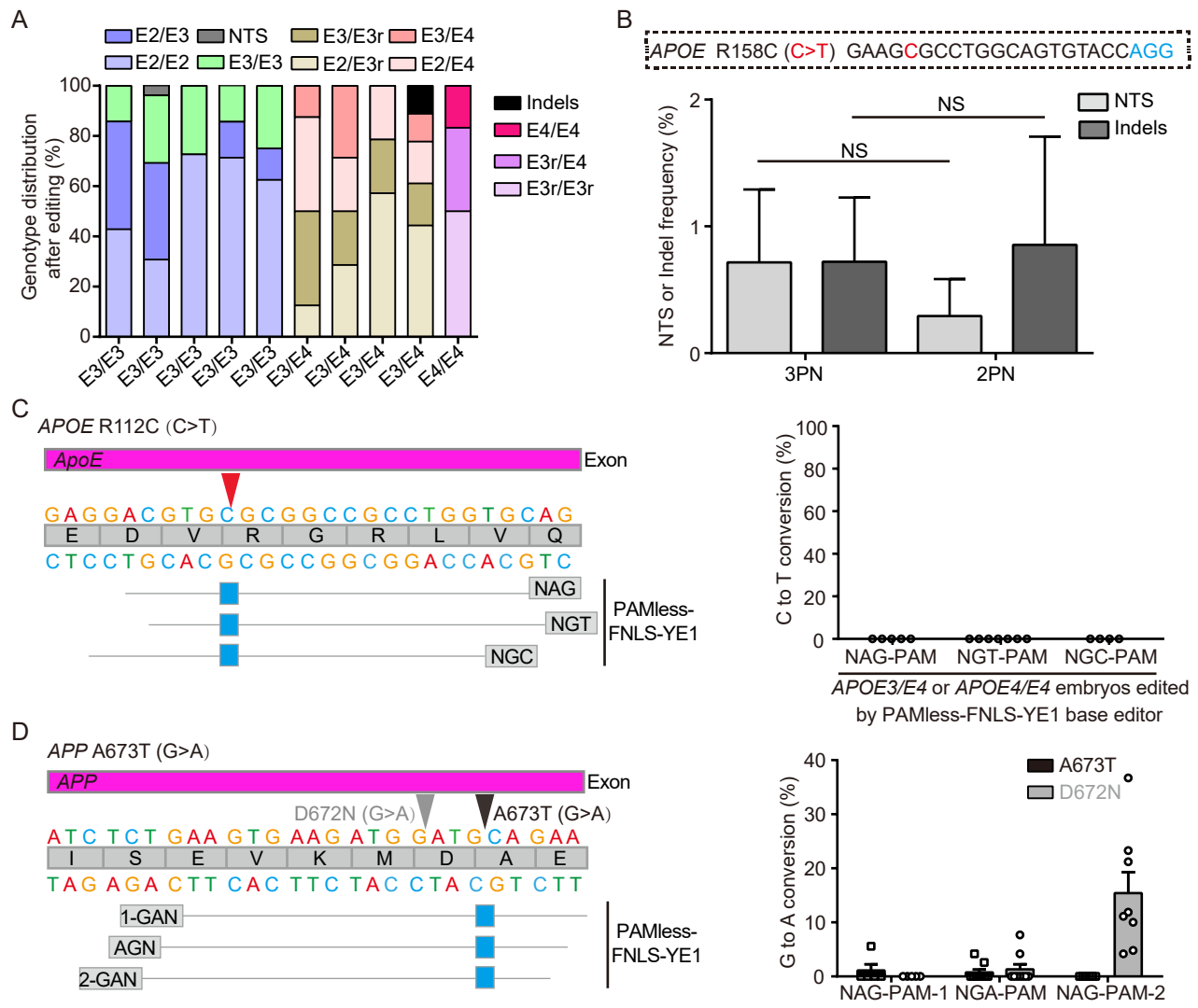
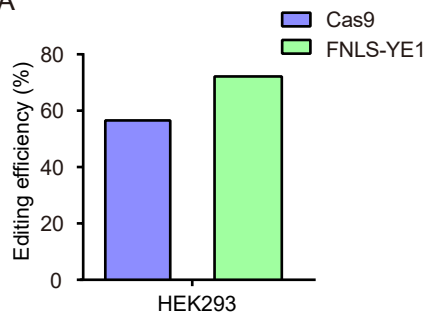
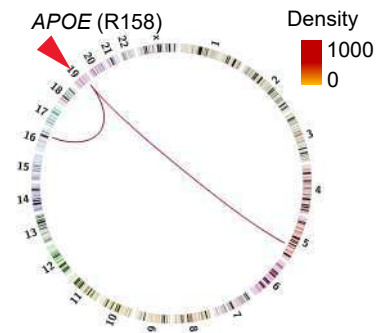
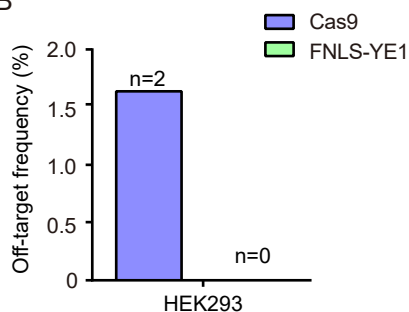


Figure S6. Blastomere genotyping and base conversion results from human embryos injected with FNLS-YE1 targeting *APOE4*, *APOE3*, and *APP* loci. (A) Genotype distribution after editing by FNLS-YE1 in single blastomere from human 2PN embryos carrying *APOE3/E3*, *APOE3/E4*, and *APOE4/E4*. (B) Frequency of NTS/indel formation in 3PN and 2PN embryos treated with FNLS-YE1. (C) Base conversion rate on *APOE* (R112C) locus using PAMless-FNLS-YE1. (D) Base conversion rate on *APP* (A673T) locus using PAMless-FNLS-YE1. Data are presented as the mean \pm SEM. p values were evaluated with unpaired Student's *t*-test. NS, not significant. Each dot in Figs. S6C and S6D represents an embryo.

A



B



C

PEM-seq detects off-target hotspots of CRISPR/Cas9 in human HEK293 cells

Gene	No.	Target dequence	Genomic location	Direction
<i>APOE</i> (R158)	OnT	GAAGCGCCTGGCAGTGTACCAGG	chr19: 44908818-44908840	+
LOC105379198	OT1	AAAGCACCTAGCAGAGTACCTGG	chr5: 127219661-127219683	+
<i>SLC9A5</i>	OT2	AAAGTGCCTAGCAGAGTACCTGG	chr16: 67259439-67259461	+

D

Information of PEM-seq libraries in *APOE* (R158) locus in HEK293 cells

Nuclease	cell line	locus	DNA	Reads	Translocation	Indels	Germline	On-target substitutions	Editing efficiency
Cas9	293T	<i>APOE</i>	20μg	12090	1650	5190	4420		56.6%
FNLS-YE1	293T	<i>APOE</i>	20μg	20280	40	120	14880	14640	72.2%
Control	293T	<i>APOE</i>	20μg	19250	0	80	19100		0

Figure S7. DNA off-target profiling of Cas9 and FNLS-YE1 targeting *APOE* (158R) by PEM-seq in HEK293T cells. (A and B) Editing efficiencies (A) and off-target hotspots (B) detected by PEM-seq for Cas9 and FNLS-YE1 targeting *APOE* (158R) in HEK293T cells. (C) List of potential off-target sites captured by PEM-seq. OnT, on-target; OT, off-target. Red letters indicate mismatched nucleotides. (D) Information of PEM-seq libraries for different samples treated with Cas9 or FNLS-YE1 targeting *APOE* (158R).

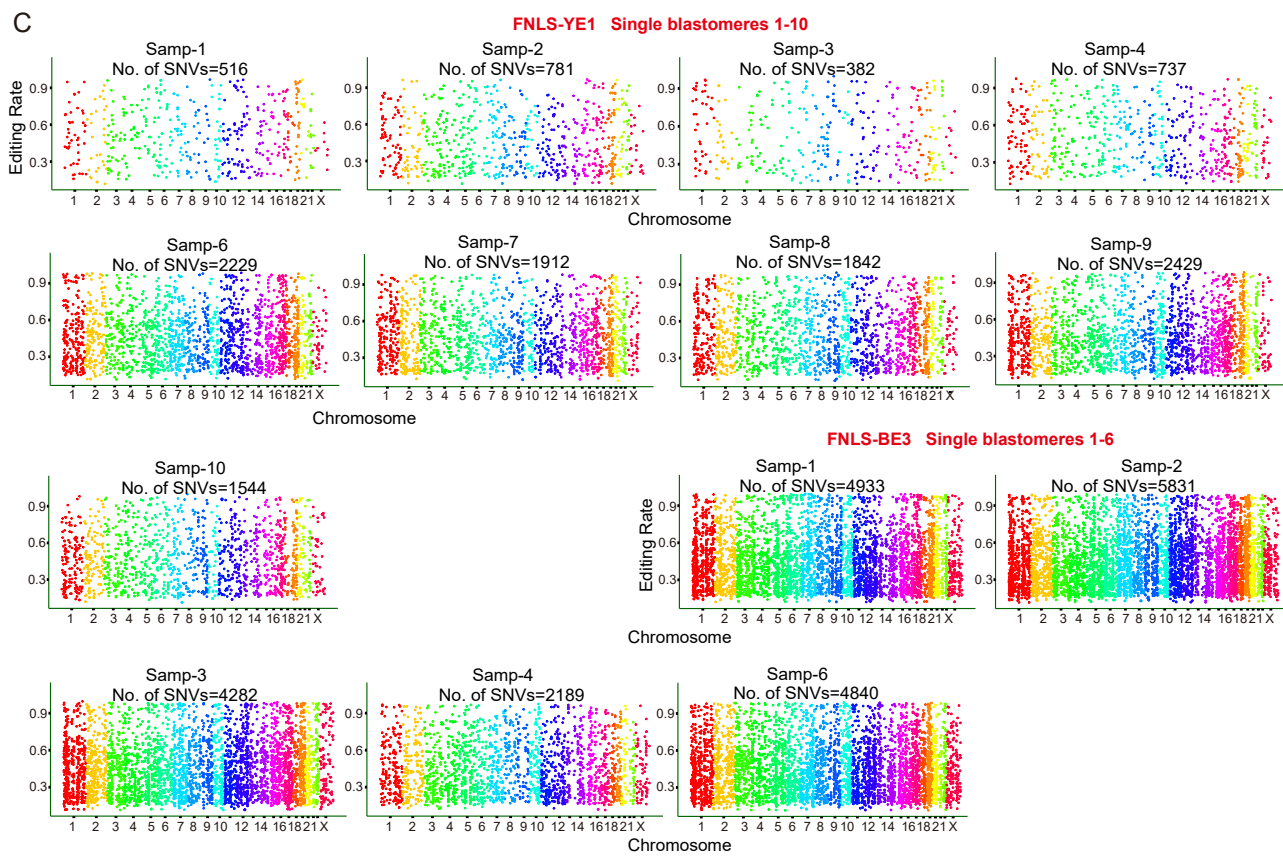
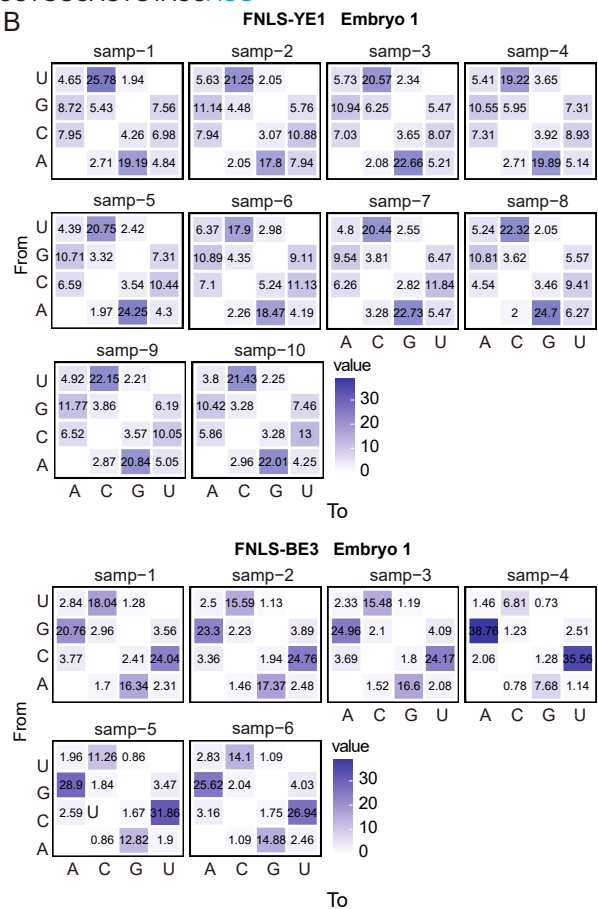
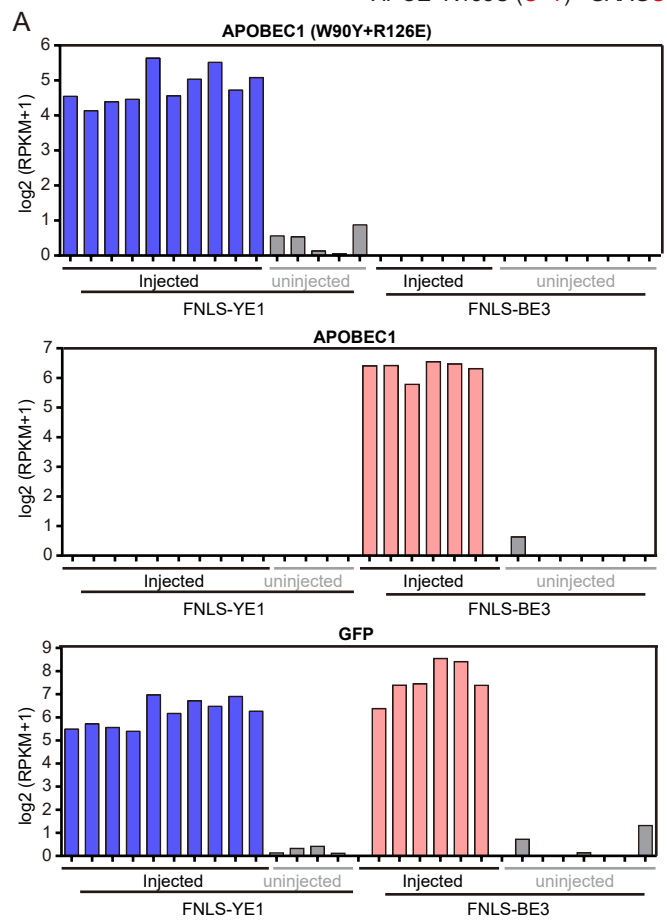


Figure S8. RNA off-target profiling of FNLS-YE1 targeting *APOE* (158R) in human 2PN embryos. (A) Expression levels of FNLS-YE1 (APOBEC1-W90Y+R126E), FNLS-BE3 (APOBEC1), and co-injected GFP were quantified in all sequenced single blastomeres of injected embryos for *APOE* (158R) editing. (B) Transcriptomic SNVs distribution for different base-conversion types detected in single blastomere of injected embryos for *APOE* (158R) editing. (C) Distribution of off-target RNA SNVs on human chromosomes for FNLS-YE1/sgRNA/GFP mRNA-injected (n = 10 cells, one human 2PN embryo) and FNLS-BE3/sgRNA/GFP mRNA-injected (n = 6 cells, one human 2PN embryos) single blastomeres.

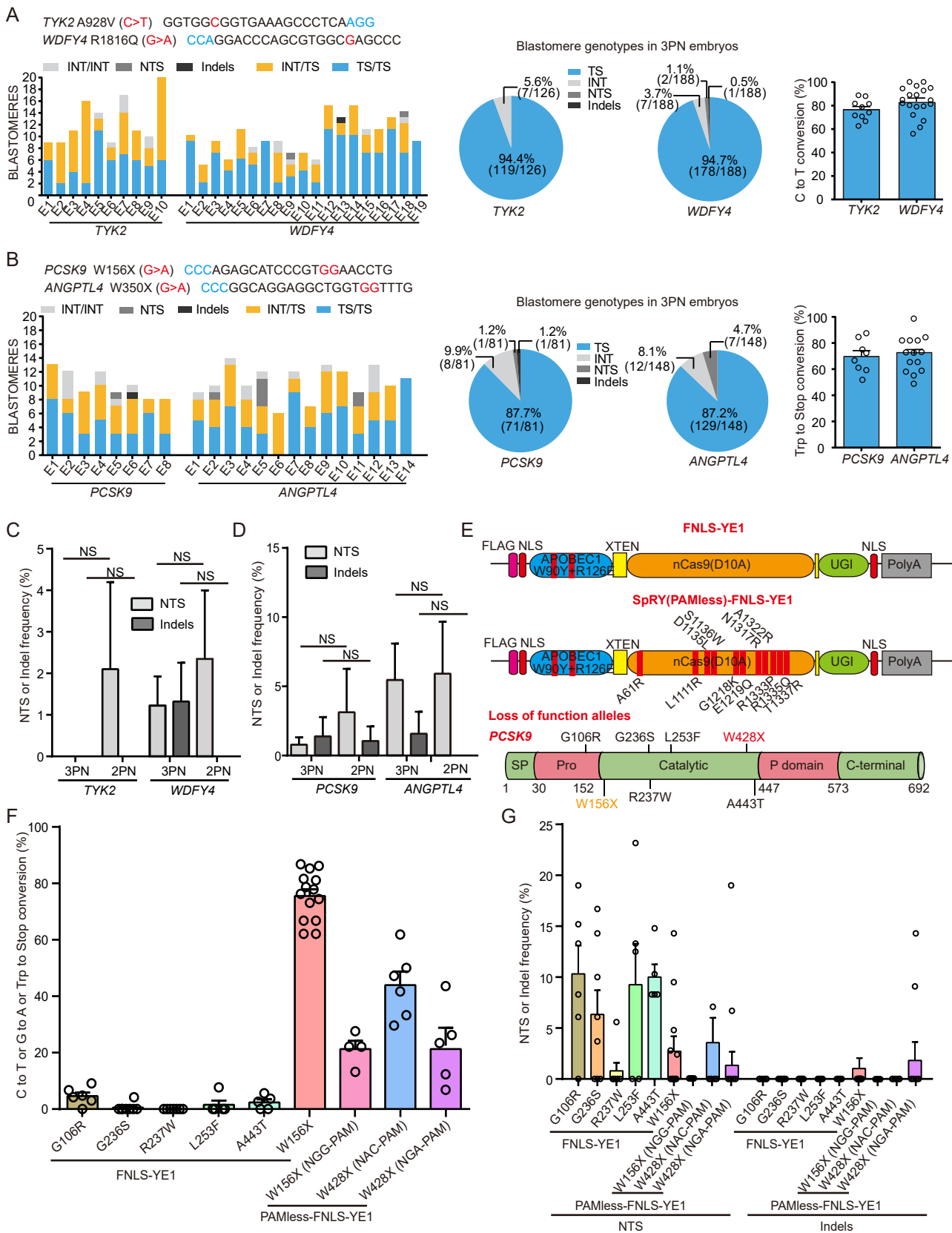
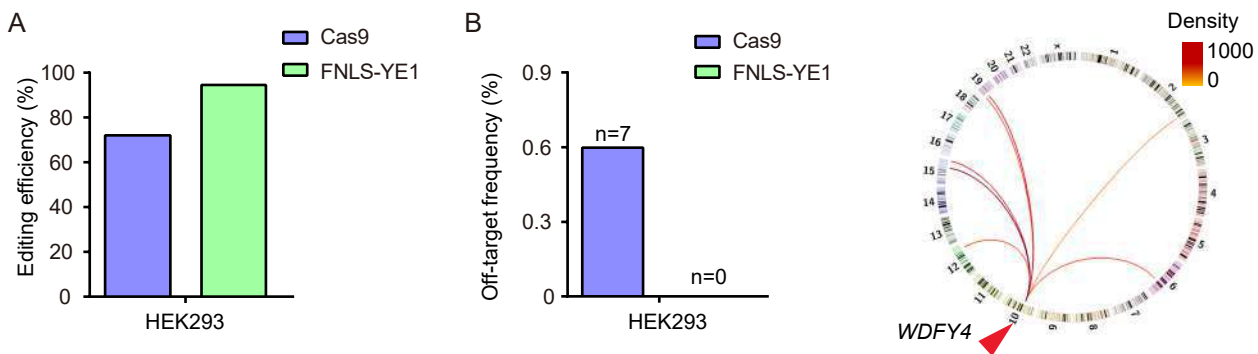


Figure S9. Efficient induction of protective mutation for systemic lupus erythematosus and familial hypercholesterolemia in human 3PN embryos. (A) Single blastomere genotyping analysis of human 3PN embryos for the induction of protective mutations on *TYK2* and *WDFY4* with FNLS-YE1 at 8-cell stage. (B) Single blastomere genotyping results of human 3PN embryos injected with FNLS-YE1 for the induction of protective mutations on *PCSK9* and *ANGPTL4* loci at 8-cell stage. (C and D) Frequency of NTS/indels formation in human 3PN embryos for *TYK2* (C), *WDFY4* (C), *PCSK9* (D), and *ANGPTL4* (D) editing with FNLS-YE1. (E) Schematics of PAMless-FNLS-YE1 and illustration of clinically *PCSK9*-related loss-of-function alleles. (F) Induction efficiency of *PCSK9*-related protective mutations in human 3PN embryos injected by FNLS-YE1 or PAMless-FNLS-YE1. (G) NTS or indels frequency of *PCSK9*-related protective mutations in human 3PN embryos injected by FNLS-YE1 and PAMless-FNLS-YE1. TS, targeted substitution; NTS, non-targeted nucleotide substitution; INT, intact; Indels, indel mutations. Data are presented as the mean \pm SEM. p values were evaluated with unpaired student's t test. Each dot in Figure S9 represents an embryo.



C PEM-seq detects off-target hotspots of CRISPR/Cas9 in human HEK293 cells

Gene	No.	Target dequence	Genomic location	Direction
<i>WDFY4</i>	OnT	GGGCTCGCCACGCTGGGTCTGG	chr10: 48817334-48817356	-
<i>PIAS1</i>	OT1	GGGCAGGCCACGCTGGGCACCAGG	chr15: 68198295-68198317	-
Intergenic	OT2	GAGCTCCAACGCTGGGTCCAGG	chr19: 17794029-17794051	+
<i>RASAL1</i>	OT3	GGGCTCAGCACGTTGGGTCCAGG	chr12: 113113220-113113242	-
<i>AL078600.1</i>	OT4	AGGCTAGCCACTCTGGGTCTGG	chr11: 70520931-70520953	-
<i>CHRNA1</i>	OT5	GGGCTGGCGCCGCTGGGTCCAGG	chr2: 232542925-232542947	-
<i>SYNM</i>	OT6	AGGCATGTACGCTGGGTCCCGG	chr15: 99131874-99131896	+
<i>REXO1</i>	OT7	GAGCTCGCCACGCTGGGAGTAGG	chr19: 1826364-1826386	+

D Information of PEM-seq libraries in *WDFY4* locus in HEK293 cells

Nuclease	cell line	locus	DNA	Reads	Translocation	Indels	Germline	On-target substitutions	Editing efficiency
Cas9	293T	<i>WDFY4</i>	20µg	163040	4763	112614	44785		72.0%
FNLS-YE1	293T	<i>WDFY4</i>	20µg	64679	18	355	62255	61153	94.5%
Control	293T	<i>WDFY4</i>	20µg	313183	24	1198	311945		0

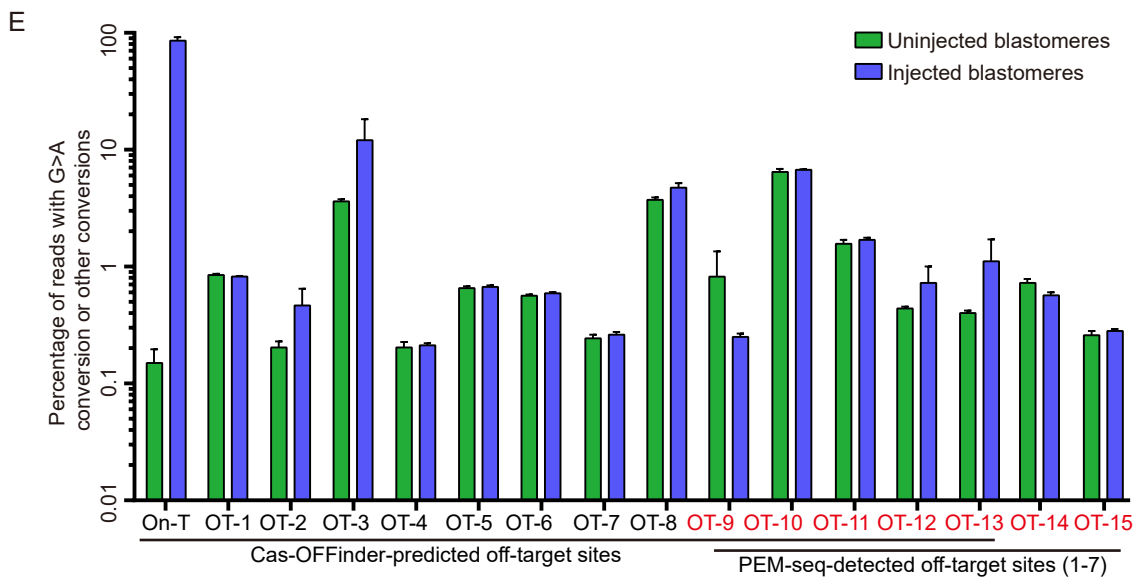


Figure S10. DNA off-target profiling of Cas9 and FNLS-YE1 targeting *WDFY4* by PEM-seq in HEK293T cells. (A and B) Editing efficiencies (A) and off-target hotspots (B) detected by PEM-seq for Cas9 and FNLS-YE1 targeting *WDFY4* in HEK293T cells. (C) List of potential off-target sites captured by PEM-seq. OnT, on-target sites; OT, off-target sites. Red letters indicate mismatched nucleotides. (D) Information of PEM-seq libraries for different samples treated with Cas9 or FNLS-YE1 targeting *WDFY4*. (E) Targeted deep sequencing analysis of the on-target and potential off-target loci predicted by Cas-OFFinder and captured by PEM-seq for *WDFY4* editing in human blastomeres injected with or without FNLS-YE1. Data are presented as the mean \pm SEM.

Table S1. Karyotype and origin of ES cells derived from FNLS-YE1 microinjected embryos

ES cell line designation	Injection stage	Karyotype of ES	Karyotype of egg donor	Karyotype of sperm donor
ES-Mutant1#	Eight-cell	46, XX	46, XX	
ES-Mutant2#	Eight-cell	46, XY	46, XX	46, XY
ES-Mutant3#	Eight-cell	46, XX	46, XX	
ES-Mutant4#	Eight-cell	46, XY	46, XX	
ES-Control1	Intact control	46, XX	46, XX	

Table S2. Preimplantation development of human oocytes and zygotes after FNLS-YE1 injection

Group	No. of MI (MII) oocytes	Fertilized	Two-cells	Eight-cells	Blastocysts	Obtained ES cell lines
Intact control	28 (20)	16	13	9	5	1
Eight-cell injection	221 (163)	130	102	70	36	4

Table S3. List of primers used in this study

List of PCR primers used for generating PCR products to serve as substrates for T7 transcription	
rev_sgRNA_T7	aaaagcaccgactcgggtgcc
fwd_OCT4	taatacgaactcaataggggtccaagccctcctggagttttagagctagaataag
fwd_PCSK9_W156X	taatacgaactcaatagggcagggtccacgggagctctgttttagagctagaataag
fwd_EMX1_site1	taatacgaactcaataggggagtcgagcagaagaagaagtttttagagctagaataag
fwd_EMX1_site2	taatacgaactcaataggggtatccactgaaagtgctgttttagagctagaataag
fwd_FANCF	taatacgaactcaatagggggaatccctctgcagcaccgttttagagctagaataag
fwd_DNMT3B_site1	taatacgaactcaataggggtctccacacggctgtgttttagagctagaataag
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fwd_DNMT3B_site3	taatacgaactcaataggggaagtcctcactactgccgttttagagctagaataag
fwd_PPP1R12C_site1	taatacgaactcaataggggactcaccagagtgctgttttagagctagaataag
fwd_PPP1R12C_site2	taatacgaactcaataggggagctcactgaacgtggcgttttagagctagaataag
fwd_HEK293	taatacgaactcaatagggggccagactgagcagctgagtttttagagctagaataag
fwd_TYK2_A928V	taatacgaactcaataggggtgctgggtgaaagccctcagtttttagagctagaataag
fwd_WDFY4_R1816Q	taatacgaactcaataggggtgctgcccacgctgggtccgttttagagctagaataag
fwd_HBB	taatacgaactcaataggggtccccacagggcagtaagtttttagagctagaataag
fwd_APOE_R158C	taatacgaactcaatagggggaagcgcctgcagctaccgttttagagctagaataag
fwd_APOE_R112C_SpRY NAG-PAM	taatacgaactcaatagggcagctgcgcgccctgtgtgttttagagctagaataag
fwd_APOE_R112C_SpRY NGT-PAM	taatacgaactcaataggggtgctgcgcgccctgtgtgttttagagctagaataag
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fwd_PCSK9_A443T	taatacgaactcaatagggcaggcggccaccagttgggttttagagctagaataag
List of PCR primers used for genotyping of targeting sites	
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OCT4 Genotyping OR	atcaggctccctgtcatga
OCT4 Genotyping IF	cacctggctcggatttcgc
OCT4 Genotyping IR	accctgctgaagctcaact
PCSK9_W156X Genotyping OF	caactgagcagacaaggtgg
PCSK9_W156X Genotyping OR	ttgcatgttggggcaacag
PCSK9_W156X Genotyping IF	tgatcaggttaagccagcct
PCSK9_W156X Genotyping OF	gaaagtggaaaccaccagcag
EMX1_site1 Genotyping OF	ccaactgtctcttctctgc
EMX1_site1 Genotyping OR	gtttgtgtgtgccacccta
EMX1_site1 Genotyping IF	ctgccatccccctctgtgaa
EMX1_site1 Genotyping IR	cccaccctagctattggagg
EMX1_site2 Genotyping OF	agacagggagccttagggag
EMX1_site2 Genotyping OR	tgagggaggacacctactg
EMX1_site2 Genotyping IF	gcatggcattgattggcct
EMX1_site2 Genotyping IR	gcgaagaaggggtggcttg
FANCF Genotyping OF	ggtaggagccctacatctgc
FANCF Genotyping OR	gttcgtaatccccgaaactg
FANCF Genotyping IF	agaggcgtatatttcggcg
FANCF Genotyping IR	ctacctgcccaccatccatc
DNMT3B_site1/site2/site3 Genotyping OF	cctcaactgcaaaagccac
DNMT3B_site1/site2/site3 Genotyping OR	acagctcaagaagcgatcc
DNMT3B_site1/site2/site3 Genotyping IF	gctgtttgtctgtggcagg
DNMT3B_site1/site2/site3 Genotyping IR	ggtaggagccctaggataca
PPP1R12C_site1 Genotyping OF	tcaaaccttccaactggg
PPP1R12C_site1 Genotyping OR	gaaccaccggaactcat
PPP1R12C_site1 Genotyping IF	ccctaccaactgggactgca
PPP1R12C_site1 Genotyping IR	acaaccaccctgaagcgg
PPP1R12C_site2 Genotyping OF	ctgctaccacaaggtgt
PPP1R12C_site2 Genotyping OR	agaaggtgtcccagatgctc
PPP1R12C_site2 Genotyping IF	gtcatcgtgacacgtgga
PPP1R12C_site2 Genotyping IR	ctgacctgccccactatt
HEK293 Genotyping OF	accactgcatatgaccacc
HEK293 Genotyping OR	taagcaaggctgatgtggg
HEK293 Genotyping IF	gcccagccaactgtcaac
HEK293 Genotyping IR	gctgcctagaagggcatgga
HBB Genotyping OF	acatttctctgacacaactgt
HBB Genotyping OR	gggtccaaaggttagaccaccag
HBB Genotyping IF	gttcatagcaacctcaaacag
HBB Genotyping IR	ccagcagcctaaggggtgga
TYK2_A928V Genotyping OF	aggagttgggggttagga
TYK2_A928V Genotyping OR	gctcaccagatgccaagaa
TYK2_A928V Genotyping IF	gctgggtgattccgaagg
TYK2_A928V Genotyping IR	caagtcttagactcgcgg

<i>WDFY4_R1816Q</i> Genotyping OF	ctcagctctctgttaggg
<i>WDFY4_R1816Q</i> Genotyping OR	caatgttccgcctcaagttgc
<i>WDFY4_R1816Q</i> Genotyping IF	tacctctaccaagtgtgcc
<i>WDFY4_R1816Q</i> Genotyping IR	ccctttgccctgaaggatga
<i>ANGPTL4_W350X</i> Genotyping OF	cgcagtggtcacaactcg
<i>ANGPTL4_W350X</i> Genotyping OR	gtcacctcttctgtggg
<i>ANGPTL4_W350X</i> Genotyping IF	gccfgggtgacagatgaag
<i>ANGPTL4_W350X</i> Genotyping IR	tgggatggagcggagta
<i>APOE_R112C/R158C</i> Genotyping OF	ggacgagaccatgaaggatt
<i>APOE_R112C/R158C</i> Genotyping OR	ggcgttcagtgttgcct
<i>APOE_R112C/R158C</i> Genotyping IF	GAATTCNNNNNNGGATCCagccctacaatcggaaactgg
<i>APOE_R112C/R158C</i> Genotyping IR	GAATTCNNNNNNGGATCCctcgaaccagctcttgagcc
<i>APP_A673T</i> Genotyping OF	tgccaacctcaaccaggat
<i>APP_A673T</i> Genotyping OR	tttagcacaagatgaaccagag
<i>APP_A673T</i> Genotyping IF	aaaggcagcagaagcctactt
<i>APP_A673T</i> Genotyping IR	taggtcattggcaacaaaca
<i>PCSK9_G106R</i> Genotyping OF	cagatgtgcccctagttc
<i>PCSK9_G106R</i> Genotyping OR	tggccaggcttaagggaat
<i>PCSK9_G106R</i> Genotyping IF	gctttttgtcgcatttgg
<i>PCSK9_G106R</i> Genotyping OF	gttactgtctgtgtaccga
<i>PCSK9_G236S/R237W/L253F</i> Genotyping OF	tctctcccacaagtctgc
<i>PCSK9_G236S/R237W/L253F</i> Genotyping OR	agatacctcggagctctcc
<i>PCSK9_G236S/R237W/L253F</i> Genotyping IF	agcctgtggaggtgtatct
<i>PCSK9_G236S/R237W/L253F</i> Genotyping OF	gagcagtggtgaaacttggga
<i>PCSK9_W428X/A443T</i> Genotyping OF	tgcacagaggaacacaggg
<i>PCSK9_W428X/A443T</i> Genotyping OR	cagctgccaacctgcacaaa
<i>PCSK9_W428X/A443T</i> Genotyping IF	gaaggcatctggagagggg
<i>PCSK9_W428X/A443T</i> Genotyping OF	ggtggcgtcatctctcttac
List of PCR primers used in targeted deep sequencing of <i>WDFY4_R1816Q</i> , <i>PCSK9_W156X</i> and <i>APOE_R158C</i> off-target sites (Cas-OFFinder-predicted or PEM-seq-detected)	
<i>WDFY4_R1816Q</i> on target primer-OF	ctcagctctctgttaggg
<i>WDFY4_R1816Q</i> on target primer-OR	caatgttccgcctcaagttgc
<i>WDFY4_R1816Q</i> on target primer-IF (Cas-OFFinder-predicted)	GAATTCAGTTCGGATCCtggcagttctgaggatggt
<i>WDFY4_R1816Q</i> on target primer-IR (Cas-OFFinder-predicted)	tgggacagcagatgtccta
<i>WDFY4_R1816Q</i> off target primer-OF site-1 (Cas-OFFinder-predicted)	acgagatgagacagcgcct
<i>WDFY4_R1816Q</i> off target primer-OR site-1 (Cas-OFFinder-predicted)	tctgaactcaggccgtt
<i>WDFY4_R1816Q</i> off target primer-IF site-1 (Cas-OFFinder-predicted)	GAATTCGATGTGGATCCcaacaagagctcccctaac
<i>WDFY4_R1816Q</i> off target primer-IR site-1 (Cas-OFFinder-predicted)	aatcacgggctggagctcgg
<i>WDFY4_R1816Q</i> off target primer-OF site-2 (Cas-OFFinder-predicted)	gcctctggagacattaccag
<i>WDFY4_R1816Q</i> off target primer-OR site-2 (Cas-OFFinder-predicted)	atgggcaatgcaagtcca
<i>WDFY4_R1816Q</i> off target primer-IF site-2 (Cas-OFFinder-predicted)	GAATTCITAGCGGATCCcctatgggctgctgcttg
<i>WDFY4_R1816Q</i> off target primer-IR site-2 (Cas-OFFinder-predicted)	atagctccaactcatgttc
<i>WDFY4_R1816Q</i> off target primer-OF site-3 (Cas-OFFinder-predicted)	gaaggtccatggtggtgagg
<i>WDFY4_R1816Q</i> off target primer-OR site-3 (Cas-OFFinder-predicted)	agaaatgccgacacaaaccg
<i>WDFY4_R1816Q</i> off target primer-IF site-3 (Cas-OFFinder-predicted)	GAATTCGACACAGGATCCagttctcagagcaggtgg
<i>WDFY4_R1816Q</i> off target primer-IR site-3 (Cas-OFFinder-predicted)	tcaagtggacaacagctca
<i>WDFY4_R1816Q</i> off target primer-OF site-4 (Cas-OFFinder-predicted)	ccacgttagcagccagatt
<i>WDFY4_R1816Q</i> off target primer-OR site-4 (Cas-OFFinder-predicted)	gttttctggaagccctgct
<i>WDFY4_R1816Q</i> off target primer-IF site-4 (Cas-OFFinder-predicted)	GAATTCACAGTGGGATCCgacattctgtgagacacc
<i>WDFY4_R1816Q</i> off target primer-OR site-4 (Cas-OFFinder-predicted)	ggttctcagtggaagca
<i>WDFY4_R1816Q</i> off target primer-OF site-5 (Cas-OFFinder-predicted)	gagaatgaaatggaggaatg
<i>WDFY4_R1816Q</i> off target primer-OR site-5 (Cas-OFFinder-predicted)	gagaatcgttgaactgg
<i>WDFY4_R1816Q</i> off target primer-IF site-5 (Cas-OFFinder-predicted)	GAATTCGCCAATGGATCCtctctgagagatgttt
<i>WDFY4_R1816Q</i> off target primer-IR site-5 (Cas-OFFinder-predicted)	aaagagactgccctcactc
<i>WDFY4_R1816Q</i> off target primer-OF site-6 (Cas-OFFinder-predicted)	tacaccctccagagaccaa
<i>WDFY4_R1816Q</i> off target primer-OR site-6 (Cas-OFFinder-predicted)	gagctcgcagcacaagaacc
<i>WDFY4_R1816Q</i> off target primer-IF site-6 (Cas-OFFinder-predicted)	GAATTCACITGAGGATCCcggccattatccccggga
<i>WDFY4_R1816Q</i> off target primer-IR site-6 (Cas-OFFinder-predicted)	aggaggtatccatgtggga
<i>WDFY4_R1816Q</i> off target primer-OF site-7 (Cas-OFFinder-predicted)	atccggatgcttctgctt
<i>WDFY4_R1816Q</i> off target primer-OR site-7 (Cas-OFFinder-predicted)	ttgctggcattctggcctt
<i>WDFY4_R1816Q</i> off target primer-IF site-7 (Cas-OFFinder-predicted)	GAATTCITAGCTGGATCCgattgagcctccaagtga
<i>WDFY4_R1816Q</i> off target primer-IR site-7 (Cas-OFFinder-predicted)	cttattccaagcctcctgc
<i>WDFY4_R1816Q</i> off target primer-OF site-8 (Cas-OFFinder-predicted)	aaataggaccacagctgcc
<i>WDFY4_R1816Q</i> off target primer-OR site-8 (Cas-OFFinder-predicted)	tggaaagactctctctggg
<i>WDFY4_R1816Q</i> off target primer-IF site-8 (Cas-OFFinder-predicted)	GAATTCCTTGTAGGATCCtatttaccctcaagacc
<i>WDFY4_R1816Q</i> off target primer-IR site-8 (Cas-OFFinder-predicted)	tcaatgtccagcgttgccc
<i>WDFY4_R1816Q</i> off target primer-OF site-9 (Cas-OFFinder-predicted and PEM-seq-detected)	ctttagcgttccctcctc
<i>WDFY4_R1816Q</i> off target primer-OR site-9 (Cas-OFFinder-predicted and PEM-seq-detected)	tggggttctgttggcattg
<i>WDFY4_R1816Q</i> off target primer-IF site-9 (Cas-OFFinder-predicted and PEM-seq-detected)	GAATTCGGTACTCGGATCCaccacccttggagctgga
<i>WDFY4_R1816Q</i> off target primer-IR site-9 (Cas-OFFinder-predicted and PEM-seq-detected)	ggggtcaccacctctgcta
<i>WDFY4_R1816Q</i> off target primer-OF site-10 (Cas-OFFinder-predicted and PEM-seq-detected)	gagccagatgtgccacatt
<i>WDFY4_R1816Q</i> off target primer-OR site-10 (Cas-OFFinder-predicted and PEM-seq-detected)	ccagaccggaaaactacg
<i>WDFY4_R1816Q</i> off target primer-IF site-10 (Cas-OFFinder-predicted and PEM-seq-detected)	GAATTCGATCAGGATCCctctcctcgggaaagaaca
<i>WDFY4_R1816Q</i> off target primer-IR site-10 (Cas-OFFinder-predicted and PEM-seq-detected)	gcacctggcctcagattgt
<i>WDFY4_R1816Q</i> off target primer-OF site-11 (Cas-OFFinder-predicted and PEM-seq-detected)	atcgtcagtttcagccag
<i>WDFY4_R1816Q</i> off target primer-OR site-11 (Cas-OFFinder-predicted and PEM-seq-detected)	tgcttccacacctctgac
<i>WDFY4_R1816Q</i> off target primer-IF site-11 (Cas-OFFinder-predicted and PEM-seq-detected)	GAATTCATCACGGATCCcagattgaggtctgcttg

WDFY4 R1816Q off target primer-IR site-11 (Cas-OFFinder-predicted and PEM-seq-detected)	aacgggaacaagtaaggcta
WDFY4 R1816Q off target primer-OF site-12 (Cas-OFFinder-predicted and PEM-seq-detected)	tggggagagctctatc
WDFY4 R1816Q off target primer-OR site-12 (Cas-OFFinder-predicted and PEM-seq-detected)	gagcctttaccatgttgc
WDFY4 R1816Q off target primer-IF site-12 (Cas-OFFinder-predicted and PEM-seq-detected)	GAATTCAGTCAAGGATCCttataacatgtagaagt
WDFY4 R1816Q off target primer-IR site-12 (Cas-OFFinder-predicted and PEM-seq-detected)	cttcattctctctcctc
WDFY4 R1816Q off target primer-OF site-13 (Cas-OFFinder-predicted and PEM-seq-detected)	gagcctccaccagtaacc
WDFY4 R1816Q off target primer-OR site-13 (Cas-OFFinder-predicted and PEM-seq-detected)	gctcatcagaccagagcc
WDFY4 R1816Q off target primer-IF site-13 (Cas-OFFinder-predicted and PEM-seq-detected)	GAATTCAGATCCGGATCCttctgtgccactcctgcc
WDFY4 R1816Q off target primer-IR site-13 (Cas-OFFinder-predicted and PEM-seq-detected)	ggcgatgatgtgatgac
PCSK9 W156X on target primer-OF	cactagcaggacaaggtgg
PCSK9 W156X on target primer-OR	ttgcatttggggcaacag
PCSK9 W156X on target primer-IF	GAATTCAGTCCGGATCCaatggcttaagcagagtc
PCSK9 W156X on target primer-IR	aatggattcagctcagatgg
PCSK9 W156X off target primer-OF site-1 (Cas-OFFinder-predicted)	accagtagccagcctgtaa
PCSK9 W156X off target primer-OR site-1 (Cas-OFFinder-predicted)	gttccctgaaacgcaacat
PCSK9 W156X off target primer-IF site-1 (Cas-OFFinder-predicted)	GAATTCGATGTGGATCCggcgcgcctcctggctgggt
PCSK9 W156X off target primer-IR site-1 (Cas-OFFinder-predicted)	agtccgagtgtagcaagcc
PCSK9 W156X off target primer-OF site-2 (Cas-OFFinder-predicted)	ctggcaaatctagacataggg
PCSK9 W156X off target primer-OR site-2 (Cas-OFFinder-predicted)	cttcattgttcttctggcac
PCSK9 W156X off target primer-IF site-2 (Cas-OFFinder-predicted)	GAATTCCTTAGCCGGATCCtagacataggggttcca
PCSK9 W156X off target primer-IR site-2 (Cas-OFFinder-predicted)	ccctacacagtttttctc
PCSK9 W156X off target primer-OF site-3 (Cas-OFFinder-predicted)	gtggctccttctccaggg
PCSK9 W156X off target primer-OR site-3 (Cas-OFFinder-predicted)	gagcacagagactccatgg
PCSK9 W156X off target primer-IF site-3 (Cas-OFFinder-predicted)	GAATTCACAGTGGATCCgagcctgttctctaggatg
PCSK9 W156X off target primer-IR site-3 (Cas-OFFinder-predicted)	ctgaaaaccgccttacct
PCSK9 W156X off target primer-OF site-4 (Cas-OFFinder-predicted)	gcccagggtagaacaattgc
PCSK9 W156X off target primer-OR site-4 (Cas-OFFinder-predicted)	gacctcctgagttcaacc
PCSK9 W156X off target primer-IF site-4 (Cas-OFFinder-predicted)	GAATTCGCAATGGATCCgcttggcacaatagatgaga
PCSK9 W156X off target primer-IR site-4 (Cas-OFFinder-predicted)	atgttggggaccagttacgc
PCSK9 W156X off target primer-OF site-5 (Cas-OFFinder-predicted)	ttgtaagatcagttgtcccac
PCSK9 W156X off target primer-OR site-5 (Cas-OFFinder-predicted)	ggacaagcctccagaatcag
PCSK9 W156X off target primer-IF site-5 (Cas-OFFinder-predicted)	GAATTCAGATCCGGATCCctctccagcagttcgggt
PCSK9 W156X off target primer-IR site-5 (Cas-OFFinder-predicted)	accctcctgtggagcccat
PCSK9 W156X off target primer-OF site-6 (Cas-OFFinder-predicted)	cctgaactcccactcacc
PCSK9 W156X off target primer-OR site-6 (Cas-OFFinder-predicted)	agtgtgagatgctgtgagcc
PCSK9 W156X off target primer-IF site-6 (Cas-OFFinder-predicted)	GAATTCAGTGGATCCcctcctagtgtgagctcat
PCSK9 W156X off target primer-IR site-6 (Cas-OFFinder-predicted)	tcttgggtgaagctaggag
PCSK9 W156X off target primer-OF site-7 (Cas-OFFinder-predicted)	gcactgccaaacacatctc
PCSK9 W156X off target primer-OR site-7 (Cas-OFFinder-predicted)	ggggcactcctctctctcfa
PCSK9 W156X off target primer-IF site-7 (Cas-OFFinder-predicted)	GAATTCGATCAGGGATCCgaatcagttggccttggga
PCSK9 W156X off target primer-IR site-7 (Cas-OFFinder-predicted)	ttggcttccatggcatg
PCSK9 W156X off target primer-OF site-8 (Cas-OFFinder-predicted)	agaggtctgctctcaacca
PCSK9 W156X off target primer-OR site-8 (Cas-OFFinder-predicted)	atggattgcagatgcctct
PCSK9 W156X off target primer-IF site-8 (Cas-OFFinder-predicted)	GAATTCAGTGGATCCctacagagatcattgtgac
PCSK9 W156X off target primer-IR site-8 (Cas-OFFinder-predicted)	ttcatttagccatttccca
PCSK9 W156X off target primer-OF site-9 (Cas-OFFinder-predicted)	gctcctcctgggaagatt
PCSK9 W156X off target primer-OR site-9 (Cas-OFFinder-predicted)	aagcctctgaagccctcaac
PCSK9 W156X off target primer-IF site-9 (Cas-OFFinder-predicted)	GAATTCGGCTACGGATCCctactaacagctcccctt
PCSK9 W156X off target primer-IR site-9 (Cas-OFFinder-predicted)	tggtgttccagctagaga
PCSK9 W156X off target primer-OF site-10 (Cas-OFFinder-predicted)	ggcactggacaactctct
PCSK9 W156X off target primer-OR site-10 (Cas-OFFinder-predicted)	gtcctctctcctctcag
PCSK9 W156X off target primer-IF site-10 (Cas-OFFinder-predicted)	GAATTCAGTCAAGGATCCcaacacagccatgtctccag
PCSK9 W156X off target primer-IR site-10 (Cas-OFFinder-predicted)	tcagccttggtttagcgc
PCSK9 W156X off target primer-OF site-11 (Cas-OFFinder-predicted and PEM-seq-detected)	ggacaagatgcccagc
PCSK9 W156X off target primer-OR site-11 (Cas-OFFinder-predicted and PEM-seq-detected)	cttgattgtccctgcggttg
PCSK9 W156X off target primer-IF site-11 (Cas-OFFinder-predicted and PEM-seq-detected)	GAATTCCTTGTAGGATCCctcgccttaagcagttca
PCSK9 W156X off target primer-IR site-11 (Cas-OFFinder-predicted and PEM-seq-detected)	tgtgtttccagctacgga
PCSK9 W156X off target primer-OF site-12 (Cas-OFFinder-predicted and PEM-seq-detected)	ggccatgatgagccatagtc
PCSK9 W156X off target primer-OR site-12 (Cas-OFFinder-predicted and PEM-seq-detected)	agacattgtcagattgaccca
PCSK9 W156X off target primer-IF site-12 (Cas-OFFinder-predicted and PEM-seq-detected)	GAATTCATCACGGGATCCttgctcagctccagcaca
PCSK9 W156X off target primer-IR site-12 (Cas-OFFinder-predicted and PEM-seq-detected)	acaagacgagagaatagga
PCSK9 W156X off target primer-OF site-13 (Cas-OFFinder-predicted and PEM-seq-detected)	tgggtgttcagaggtaaaag
PCSK9 W156X off target primer-OR site-13 (Cas-OFFinder-predicted and PEM-seq-detected)	aatgcaacttaggaacc
PCSK9 W156X off target primer-IF site-13 (Cas-OFFinder-predicted and PEM-seq-detected)	GAATTCGTAGAGGGATCCtggcttgggagctcttg
PCSK9 W156X off target primer-IR site-13 (Cas-OFFinder-predicted and PEM-seq-detected)	atggctcaggagccagttg
PCSK9 W156X off target primer-OF site-14 (PEM-seq-detected)	ggtgttccctccaccctcfa
PCSK9 W156X off target primer-OR site-14 (PEM-seq-detected)	agaggtctctctgggtcag
PCSK9 W156X off target primer-IF site-14 (PEM-seq-detected)	GAATTCATGTCAGGATCCctgattctgactctgac
PCSK9 W156X off target primer-IR site-14 (PEM-seq-detected)	tgggtctctcagctccac
PCSK9 W156X off target primer-OF site-15 (PEM-seq-detected)	cgtggagatccggtcagtg
PCSK9 W156X off target primer-OR site-15 (PEM-seq-detected)	ccgcctctagaggaattgg
PCSK9 W156X off target primer-IF site-15 (PEM-seq-detected)	GAATTCCTCCGGATCCtagccaagcccaatgctc
PCSK9 W156X off target primer-IR site-15 (PEM-seq-detected)	cagtcctcaclatacaag
PCSK9 W156X off target primer-OF site-16 (PEM-seq-detected)	acacctcaagagcagcctc
PCSK9 W156X off target primer-OR site-16 (PEM-seq-detected)	ctgttgcagtttgcaccc
PCSK9 W156X off target primer-IF site-16 (PEM-seq-detected)	GAATTCGTCGGGATCCgagctctccttcccctt
PCSK9 W156X off target primer-IR site-16 (PEM-seq-detected)	ccactgtgacagcccttg
PCSK9 W156X off target primer-OF site-17 (PEM-seq-detected)	attccagctctgccccttgc

<i>PCSK9 W156X</i> off target primer-OR site-17 (PEM-seq-detected)	ctgggtgctctcagtggaac
<i>PCSK9 W156X</i> off target primer-IF site-17 (PEM-seq-detected)	GAATTCGTGAAAGGATCCgccctgctcaagcctgt
<i>PCSK9 W156X</i> off target primer-IR site-17 (PEM-seq-detected)	tcctagggacagcggctat
<i>APOE R158C</i> on target primer-OF	aggcctacaatcggaactgg
<i>APOE R158C</i> on target primer-OR	ctcgaaccagctctgagcc
<i>APOE R158C</i> on target primer-IF	GAATTCATATAATGGATCCatgctggccagagaccga
<i>APOE R158C</i> on target primer-IR	acgcggccctgttccaccag
<i>APOE R158C</i> off target primer-OF site-1 (Cas-OFFinder-predicted)	accagcttttagtgacggctg
<i>APOE R158C</i> off target primer-OR site-1 (Cas-OFFinder-predicted)	cagagccttgctcctgaat
<i>APOE R158C</i> off target primer-IF site-1 (Cas-OFFinder-predicted)	GAATTCACAGATGGATCCggctgtctgttgcactctg
<i>APOE R158C</i> off target primer-IR site-1 (Cas-OFFinder-predicted)	gctactggttccctgaacaa
<i>APOE R158C</i> off target primer-OF site-2 (Cas-OFFinder-predicted)	cgccaaaatcaaccctgaa
<i>APOE R158C</i> off target primer-OR site-2 (Cas-OFFinder-predicted)	ctgcctctggtctgactgg
<i>APOE R158C</i> off target primer-IF site-2 (Cas-OFFinder-predicted)	GAATTCACATCAGGATCCgcagacagaaccaagg
<i>APOE R158C</i> off target primer-IR site-2 (Cas-OFFinder-predicted)	aggctgaagtgaatggcgtc
<i>APOE R158C</i> off target primer-OF site-3 (Cas-OFFinder-predicted)	ctgggacactgggatgaac
<i>APOE R158C</i> off target primer-OR site-3 (Cas-OFFinder-predicted)	ggacacagactctgatgggc
<i>APOE R158C</i> off target primer-IF site-3 (Cas-OFFinder-predicted)	GAATTCAGCGGGATCCtaaatgctgctctgcctcc
<i>APOE R158C</i> off target primer-IR site-3 (Cas-OFFinder-predicted)	agctgcttaaccctctgtg
<i>APOE R158C</i> off target primer-OF site-4 (Cas-OFFinder-predicted)	cattctgggtgctgaggt
<i>APOE R158C</i> off target primer-OR site-4 (Cas-OFFinder-predicted)	tgtgctcctgctaatcaaa
<i>APOE R158C</i> off target primer-IF site-4 (Cas-OFFinder-predicted)	GAATTCATGGCGGATCCgtggaaataactaagcc
<i>APOE R158C</i> off target primer-IR site-4 (Cas-OFFinder-predicted)	tctgagcctcagttctca
<i>APOE R158C</i> off target primer-OF site-5 (Cas-OFFinder-predicted)	tgaacttaccacagcactg
<i>APOE R158C</i> off target primer-OR site-5 (Cas-OFFinder-predicted)	cactgggtctctgtgtgag
<i>APOE R158C</i> off target primer-IF site-5 (Cas-OFFinder-predicted)	GAATTCATTTGGATCCctgctgattaccagatt
<i>APOE R158C</i> off target primer-IR site-5 (Cas-OFFinder-predicted)	tcttgctccctggcagaca
<i>APOE R158C</i> off target primer-OF site-6 (Cas-OFFinder-predicted)	agccaggggaatagatgc
<i>APOE R158C</i> off target primer-OR site-6 (Cas-OFFinder-predicted)	cctgagctcggaaaccactgt
<i>APOE R158C</i> off target primer-IF site-6 (Cas-OFFinder-predicted)	GAATTCACAACAGGATCCactgtgagccactctct
<i>APOE R158C</i> off target primer-IR site-6 (Cas-OFFinder-predicted)	cagctggccattttacagg
<i>APOE R158C</i> off target primer-OF site-7 (Cas-OFFinder-predicted)	ctccaagctgaacagacc
<i>APOE R158C</i> off target primer-OR site-7 (Cas-OFFinder-predicted)	gagacacagagaagcgggac
<i>APOE R158C</i> off target primer-IF site-7 (Cas-OFFinder-predicted)	GAATTCGGAAATGGATCCaagaagctaatgggtggc
<i>APOE R158C</i> off target primer-IR site-7 (Cas-OFFinder-predicted)	ctctctctgtaggccactg
<i>APOE R158C</i> off target primer-OF site-8 (Cas-OFFinder-predicted)	gccggaatagagcactggt
<i>APOE R158C</i> off target primer-OR site-8 (Cas-OFFinder-predicted)	ctctccgaagctgttacc
<i>APOE R158C</i> off target primer-IF site-8 (Cas-OFFinder-predicted)	GAATTCCTAGCTGGATCCgtgattatgagcaactcaga
<i>APOE R158C</i> off target primer-IR site-8 (Cas-OFFinder-predicted)	ctgtccactagaatcaage
<i>APOE R158C</i> off target primer-OF site-9 (Cas-OFFinder-predicted)	tcttccatggcaggcaatc
<i>APOE R158C</i> off target primer-OR site-9 (Cas-OFFinder-predicted)	ctctcccttctcctgctc
<i>APOE R158C</i> off target primer-IF site-9 (Cas-OFFinder-predicted)	GAATTCCTATACGGATCCcaactccctgctgctgct
<i>APOE R158C</i> off target primer-IR site-9 (Cas-OFFinder-predicted)	atagtgtgaaccccaccgc
<i>APOE R158C</i> off target primer-OF site-10 (Cas-OFFinder-predicted)	gctgccactcactcctag
<i>APOE R158C</i> off target primer-OR site-10 (Cas-OFFinder-predicted)	agcagctgtgtttcccat
<i>APOE R158C</i> off target primer-IF site-10 (Cas-OFFinder-predicted)	GAATTCCTCAGAGGATCCgcagcaacacactcct
<i>APOE R158C</i> off target primer-IR site-10 (Cas-OFFinder-predicted)	atgcttgcaggggtttgg
<i>APOE R158C</i> off target primer-OF site-11 (Cas-OFFinder-predicted and PEM-seq-detected)	aaagagttaactcagcttctca
<i>APOE R158C</i> off target primer-OR site-11 (Cas-OFFinder-predicted and PEM-seq-detected)	taattgaaagctgctcagaga
<i>APOE R158C</i> off target primer-IF site-11 (Cas-OFFinder-predicted and PEM-seq-detected)	GAATTCGACGACGGATCCctctgactgtgctcatatg
<i>APOE R158C</i> off target primer-IR site-11 (Cas-OFFinder-predicted and PEM-seq-detected)	aagcactgaactctggccc
<i>APOE R158C</i> off target primer-OF site-12 (Cas-OFFinder-predicted and PEM-seq-detected)	tagaaagcagcatacaag
<i>APOE R158C</i> off target primer-OR site-12 (Cas-OFFinder-predicted and PEM-seq-detected)	gagaagggcagatgaaa
<i>APOE R158C</i> off target primer-IF site-12 (Cas-OFFinder-predicted and PEM-seq-detected)	GAATTCATACGGGATCCaaagcagcatacaagacc
<i>APOE R158C</i> off target primer-IR site-12 (Cas-OFFinder-predicted and PEM-seq-detected)	caagtgagactgtggaag