

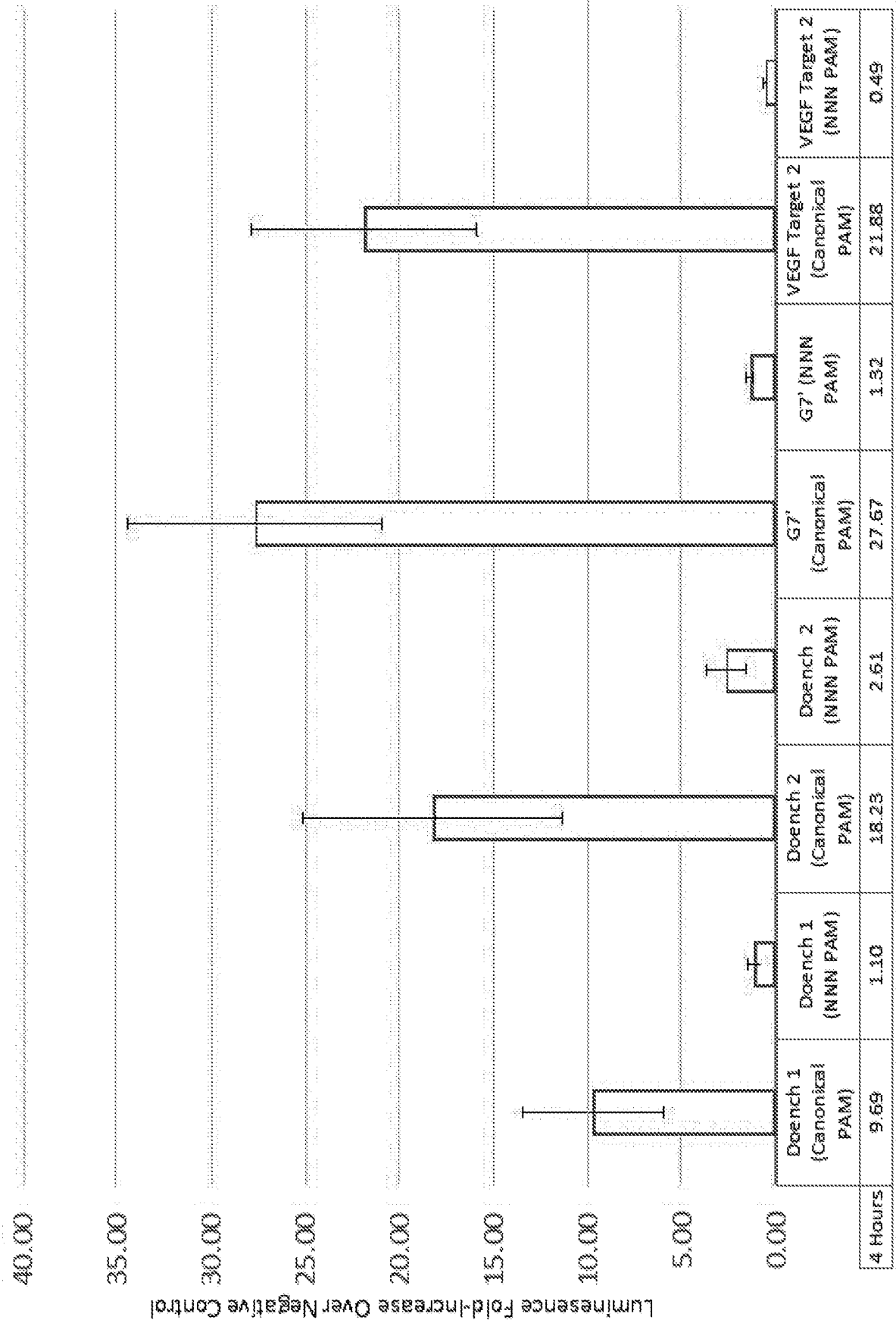


FIGURE 1

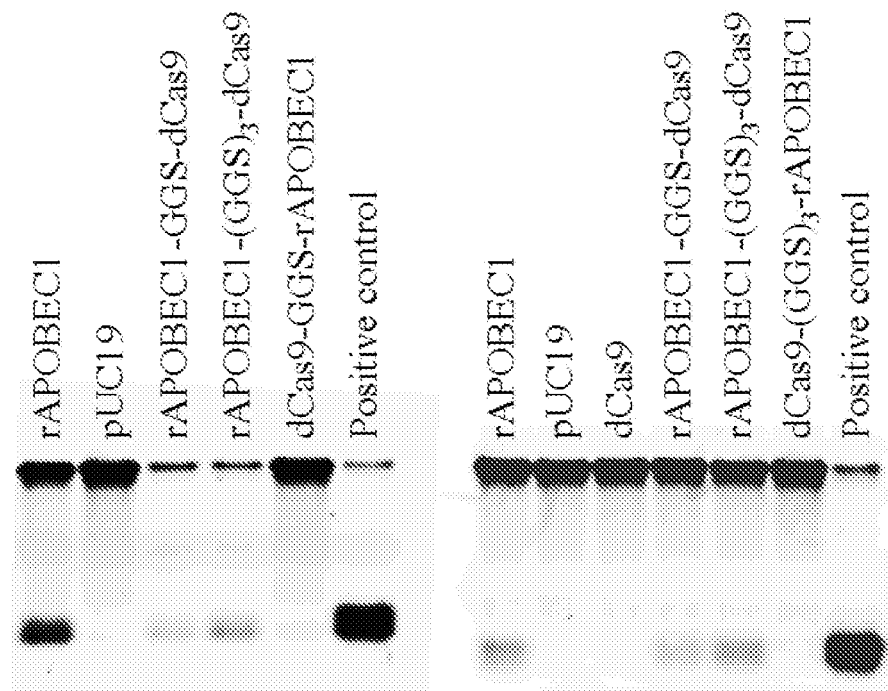


FIGURE 2

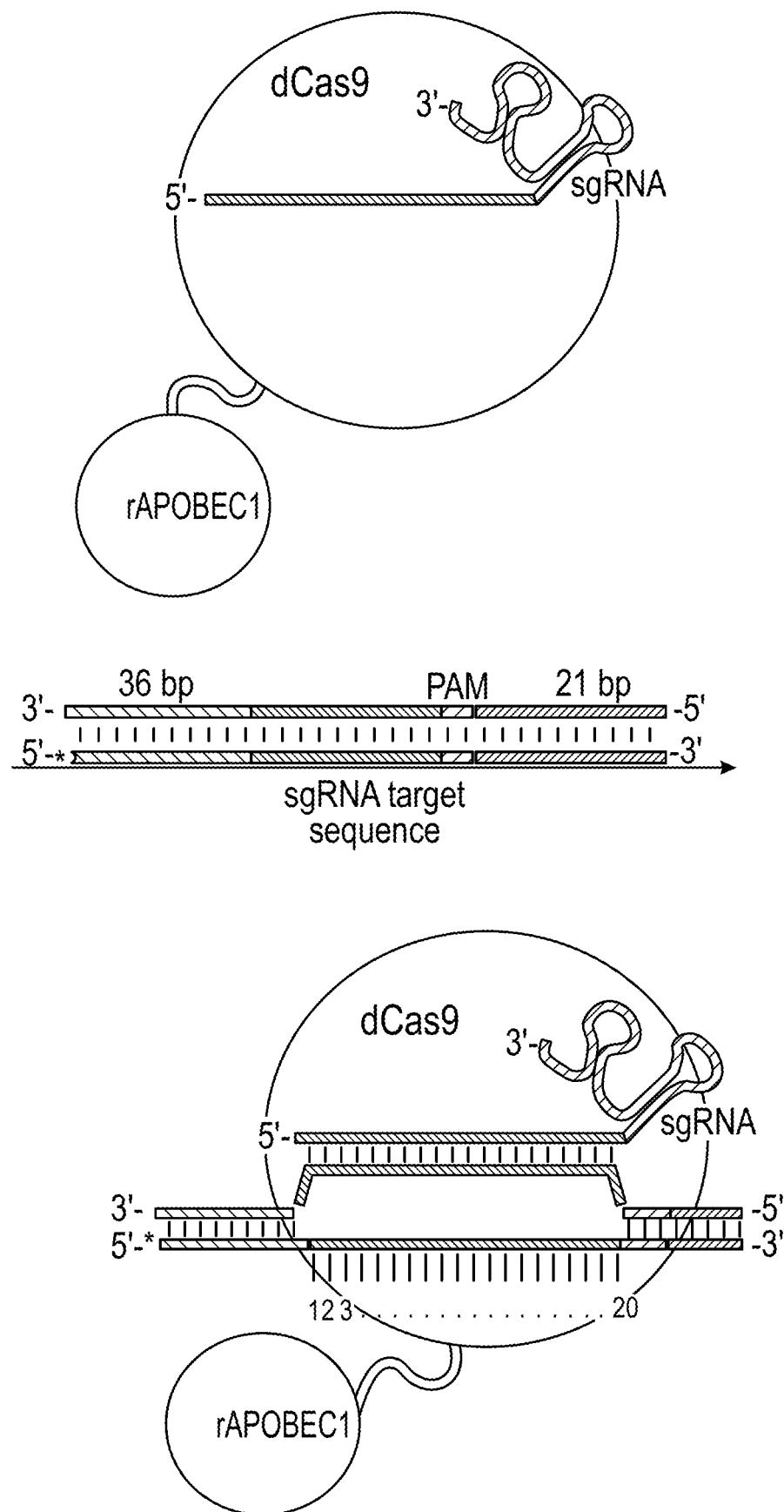


FIGURE 3

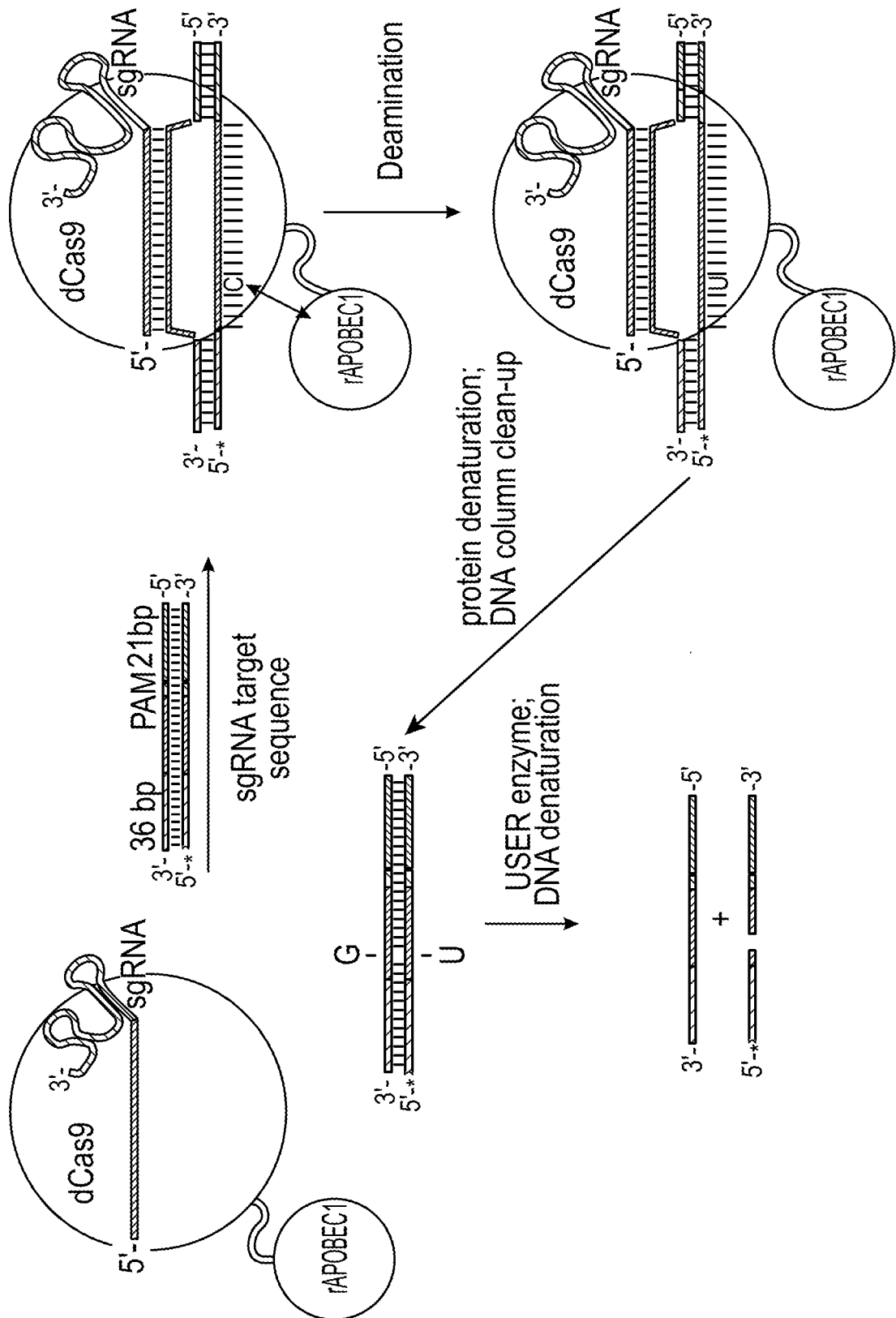


FIGURE 4

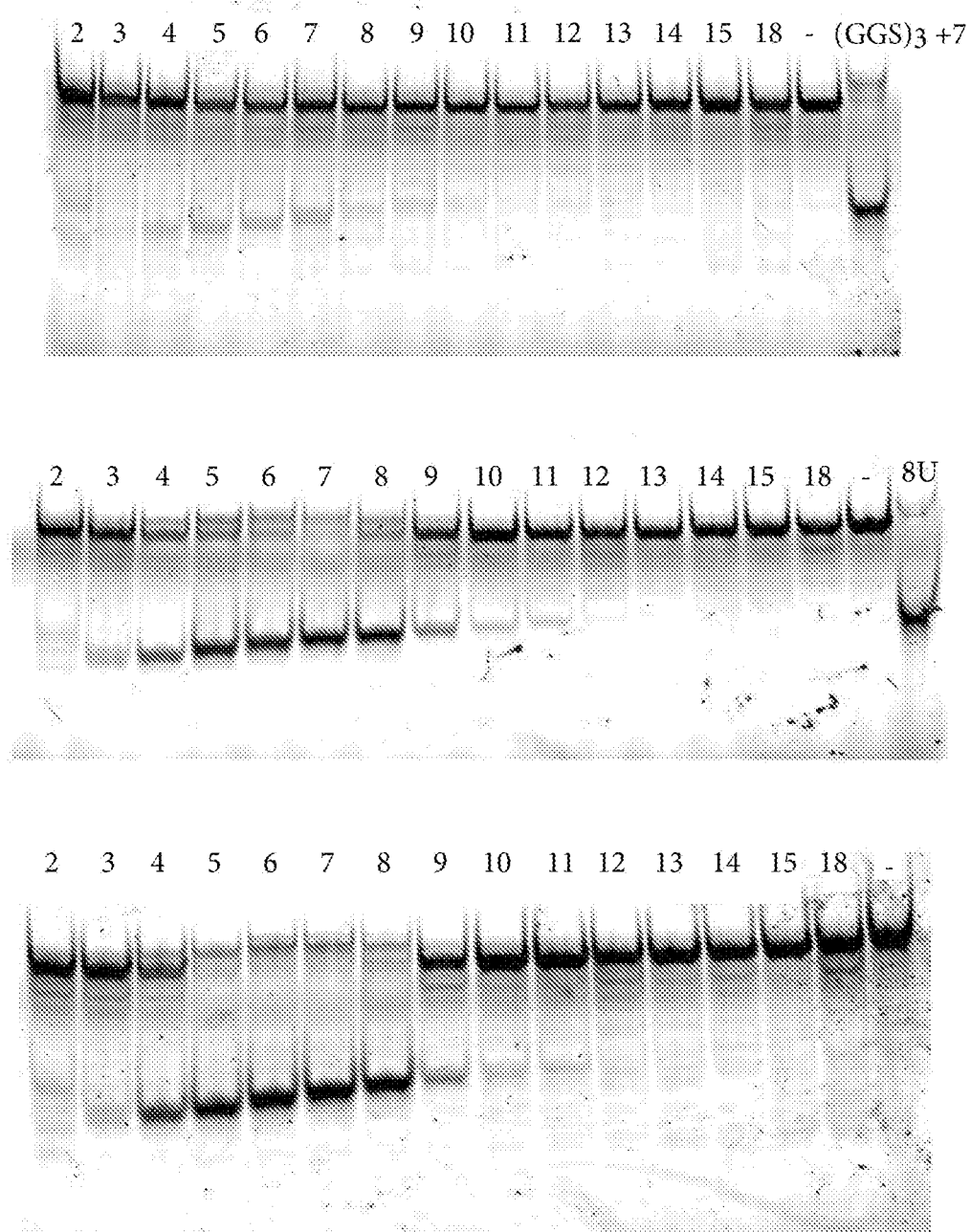


FIGURE 5

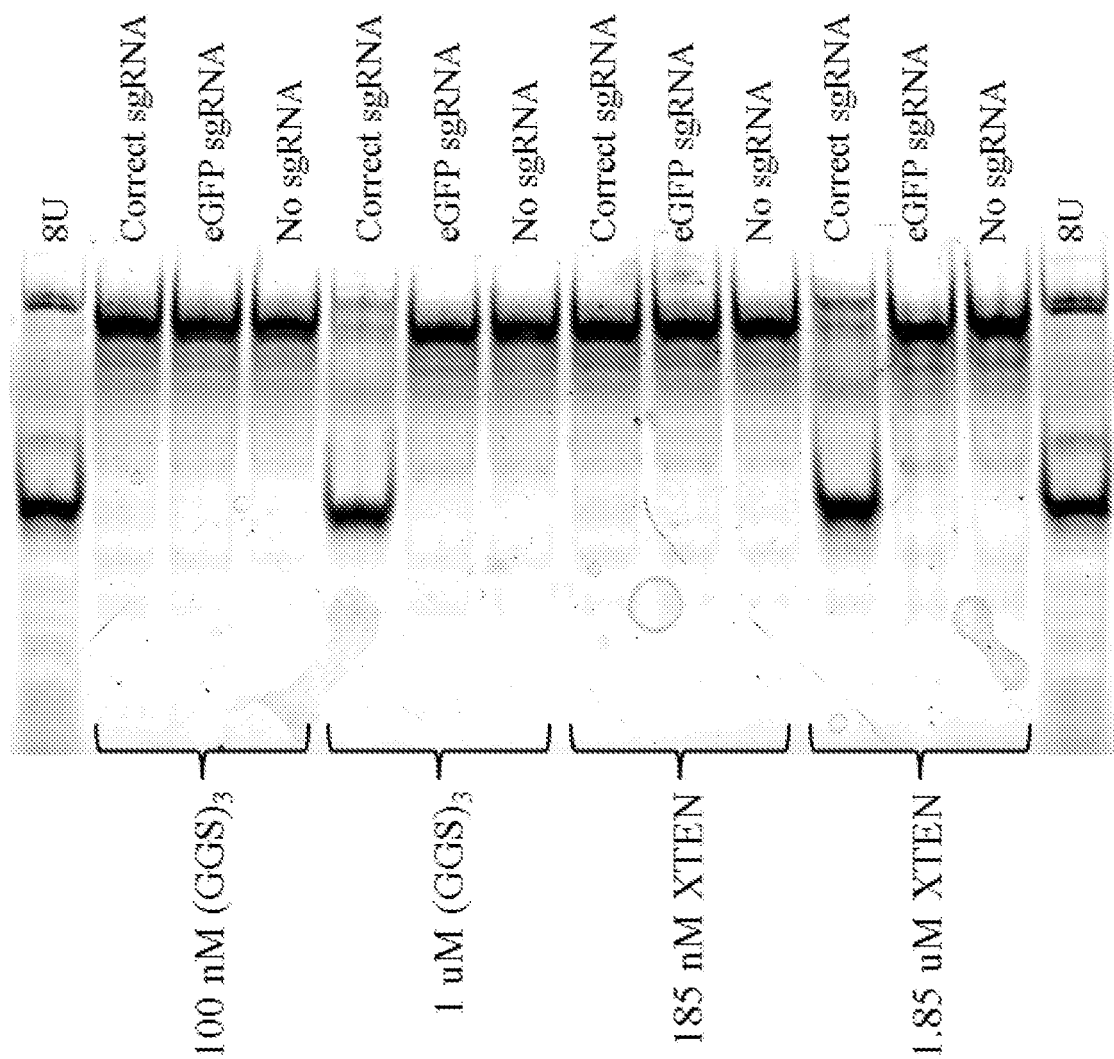


FIGURE 6

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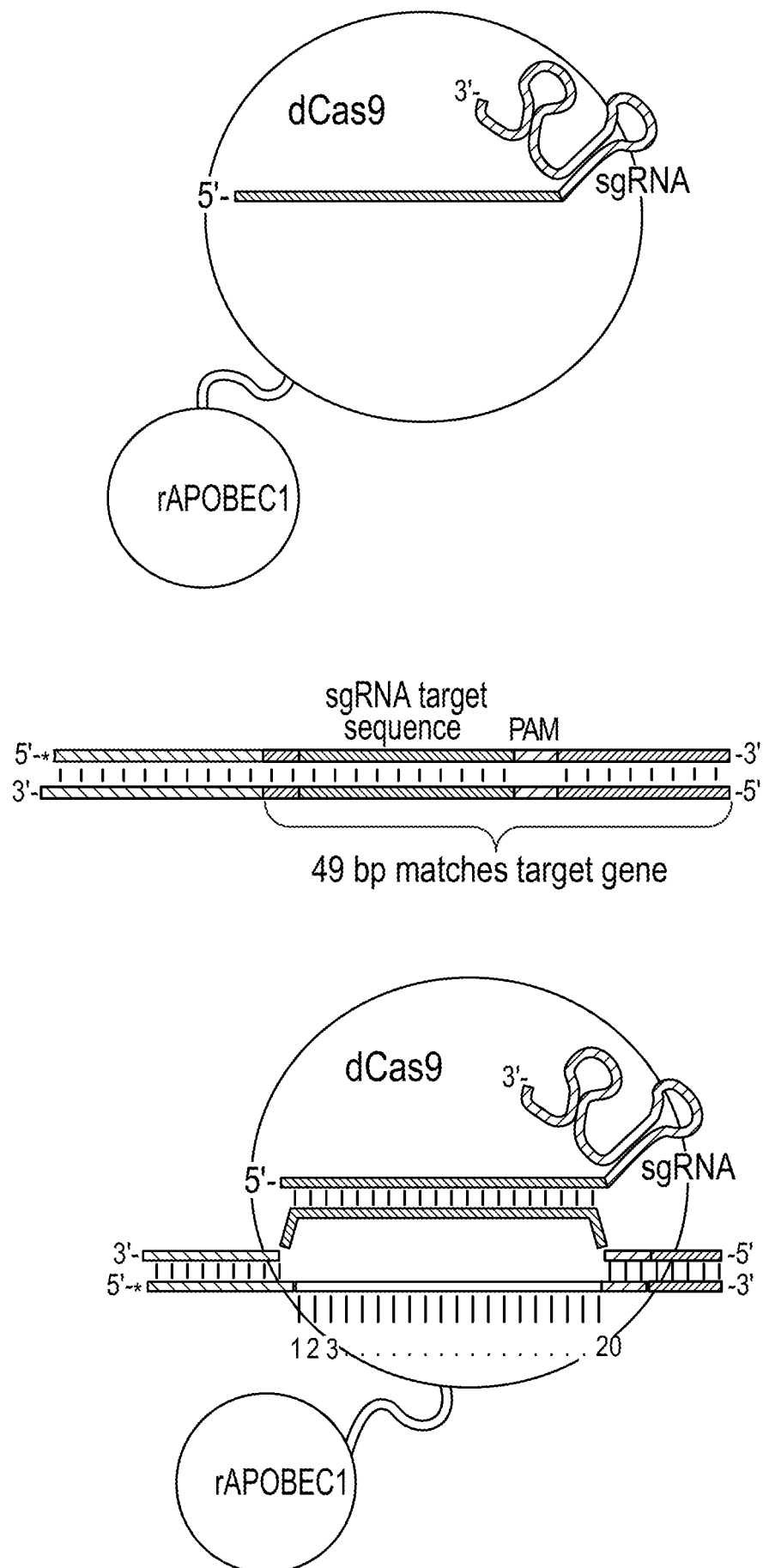


FIGURE 7

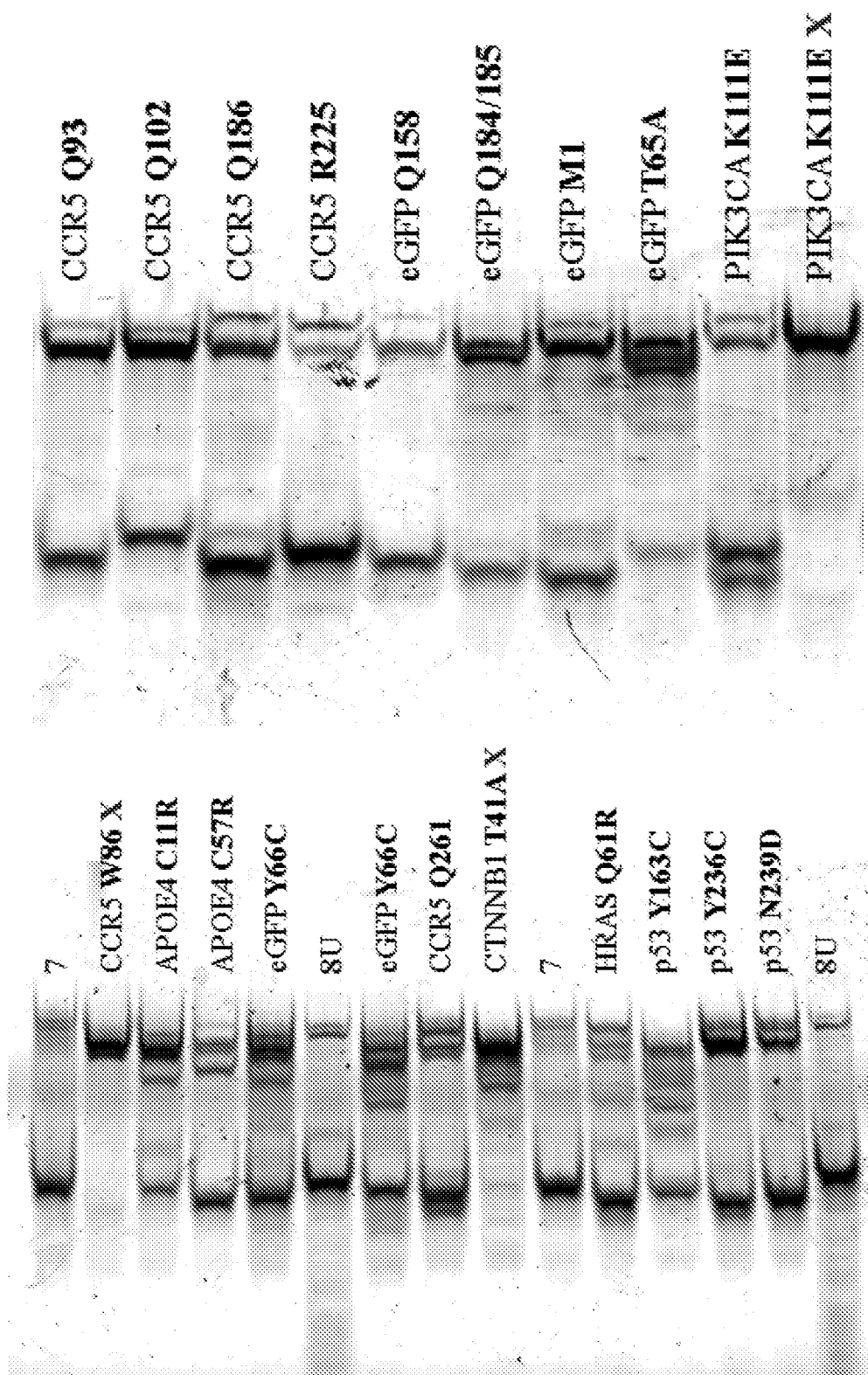


FIGURE 8

EMX1		C ₅	C ₆	C ₁₀
0 μ M XTEN	A	0.1%	0.1%	0.1%
	C	99.8%	99.8%	99.8%
	G	0.0%	0.0%	0.1%
	T	0.0%	0.1%	0.0%
1.85 μ M XTEN	A	0.1%	0.0%	0.1%
	C	60.4%	61.0%	99.1%
	G	0.0%	0.0%	0.1%
	T	39.5%	39.0%	0.7%

FANCF		C ₆	C ₇	C ₈	C ₁₁
0 μ M XTEN	A	0.1%	0.1%	0.1%	0.1%
	C	99.8%	99.8%	99.9%	99.9%
	G	0.0%	0.1%	0.0%	0.0%
	T	0.0%	0.0%	0.0%	0.0%
1.85 μ M XTEN	A	0.1%	0.1%	0.1%	0.1%
	C	63.9%	64.7%	65.0%	72.6%
	G	0.0%	0.0%	0.0%	0.0%
	T	36.0%	35.1%	34.9%	27.3%

HEK293 site 2		C ₄	C ₆	C ₁₁
0 μ M XTEN	A	0.1%	0.1%	0.1%
	C	99.9%	99.9%	99.9%
	G	0.0%	0.0%	0.0%
	T	0.0%	0.0%	0.1%
1.85 μ M XTEN	A	0.1%	0.1%	0.1%
	C	80.6%	76.9%	99.6%
	G	0.0%	0.0%	0.0%
	T	19.3%	22.9%	0.3%

HEK293 site 3		C ₃	C ₄	C ₅	C ₉
0 μ M XTEN	A	0.1%	0.1%	0.0%	0.1%
	C	99.8%	99.9%	99.9%	99.9%
	G	0.0%	0.0%	0.0%	0.0%
	T	0.1%	0.0%	0.0%	0.0%
1.85 μ M XTEN	A	0.1%	0.1%	0.0%	0.1%
	C	92.2%	74.8%	71.5%	96.6%
	G	0.0%	0.0%	0.0%	0.0%
	T	7.7%	25.1%	28.5%	3.3%

HEK293 site 4		C ₃	C ₅	C ₈	C ₁₁
0 μ M XTEN	A	0.1%	0.0%	0.1%	0.0%
	C	99.8%	99.9%	99.8%	99.9%
	G	0.0%	0.0%	0.0%	0.0%
	T	0.0%	0.0%	0.1%	0.0%
1.85 μ M XTEN	A	0.1%	0.1%	0.1%	0.1%
	C	98.8%	60.1%	97.0%	99.4%
	G	0.0%	0.0%	0.0%	0.0%
	T	1.1%	39.8%	2.9%	0.5%

RNF2		C ₃	C ₆
0 μ M XTEN	A	0.1%	0.0%
	C	99.9%	99.9%
	G	0.0%	0.0%
	T	0.0%	0.0%
1.85 μ M XTEN	A	0.1%	0.0%
	C	59.1%	57.8%
	G	0.0%	0.0%
	T	40.8%	42.1%

FIGURE 9

EMX1		C ₅	C ₆	C ₁₀
untreated	A	0.0%	0.0%	0.0%
	C	99.5%	99.7%	100.0%
	G	0.0%	0.1%	0.0%
	T	0.5%	0.2%	0.0%
XTEN	A	0.7%	0.5%	0.0%
	C	93.5%	95.8%	100.0%
	G	2.1%	0.3%	0.0%
	T	3.6%	3.3%	0.0%
XTEN-UGI	A	0.2%	0.0%	0.0%
	C	81.8%	82.5%	100.0%
	G	0.6%	0.3%	0.0%
	T	17.4%	17.1%	0.0%

FANCF		C ₆	C ₇	C ₈	C ₁₁
untreated	A	0.0%	0.0%	0.2%	0.1%
	C	99.9%	99.8%	99.8%	99.9%
	G	0.0%	0.0%	0.0%	0.0%
	T	0.1%	0.1%	0.0%	0.0%
XTEN	A	0.3%	0.1%	0.0%	0.0%
	C	98.1%	99.2%	99.0%	99.8%
	G	0.4%	0.0%	0.0%	0.0%
	T	1.2%	0.7%	1.0%	0.2%
XTEN-UGI	A	0.0%	0.0%	0.1%	0.0%
	C	93.2%	93.5%	93.4%	98.2%
	G	0.0%	0.0%	0.0%	0.0%
	T	6.7%	6.5%	6.5%	1.8%

HEK293 site 2		C ₄	C ₆	C ₁₁
untreated	A	0.3%	0.2%	0.2%
	C	99.7%	99.7%	99.7%
	G	0.0%	0.0%	0.0%
	T	0.0%	0.0%	0.0%
XTEN	A	0.3%	0.3%	0.3%
	C	99.7%	99.4%	99.7%
	G	0.0%	0.3%	0.0%
	T	0.0%	0.0%	0.0%
XTEN-UGI	A	0.3%	0.2%	0.2%
	C	98.8%	98.2%	99.8%
	G	0.0%	0.3%	0.0%
	T	0.9%	1.3%	0.0%

HEK293 site 2		C ₃	C ₄	C ₅	C ₉
untreated	A	0.0%	0.0%	0.0%	0.0%
	C	100.0%	100.0%	100.0%	99.9%
	G	0.0%	0.0%	0.0%	0.0%
	T	0.0%	0.0%	0.0%	0.1%
XTEN	A	0.0%	0.6%	0.3%	0.1%
	C	100.0%	95.8%	95.8%	99.2%
	G	0.0%	0.2%	0.7%	0.4%
	T	0.0%	3.4%	3.2%	0.3%
XTEN-UGI	A	0.0%	0.3%	0.3%	0.0%
	C	96.8%	83.0%	79.2%	98.5%
	G	0.0%	0.0%	1.1%	0.2%
	T	3.2%	16.8%	19.4%	1.3%

HEK293 site 4		C ₃	C ₅	C ₈	C ₁₁
untreated	A	0.0%	0.4%	0.0%	0.0%
	C	99.8%	97.6%	99.9%	100.0%
	G	0.0%	1.0%	0.0%	0.0%
	T	0.2%	1.0%	0.0%	0.0%
XTEN	A	0.0%	1.1%	0.0%	0.0%
	C	99.6%	92.2%	99.9%	100.0%
	G	0.0%	2.2%	0.0%	0.0%
	T	0.4%	4.5%	0.0%	0.0%
XTEN-UGI	A	0.0%	0.5%	0.0%	0.0%
	C	99.4%	86.7%	99.1%	100.0%
	G	0.0%	1.8%	0.0%	0.0%
	T	0.6%	11.0%	0.9%	0.0%

RNF2		C ₃	C ₆
untreated	A	0.0%	0.0%
	C	99.9%	99.5%
	G	0.0%	0.2%
	T	0.0%	0.3%
XTEN	A	0.0%	0.0%
	C	99.8%	99.3%
	G	0.0%	0.2%
	T	0.2%	0.5%
XTEN-UGI	A	0.0%	0.0%
	C	99.6%	99.1%
	G	0.0%	0.4%
	T	0.4%	0.5%

FIGURE 10

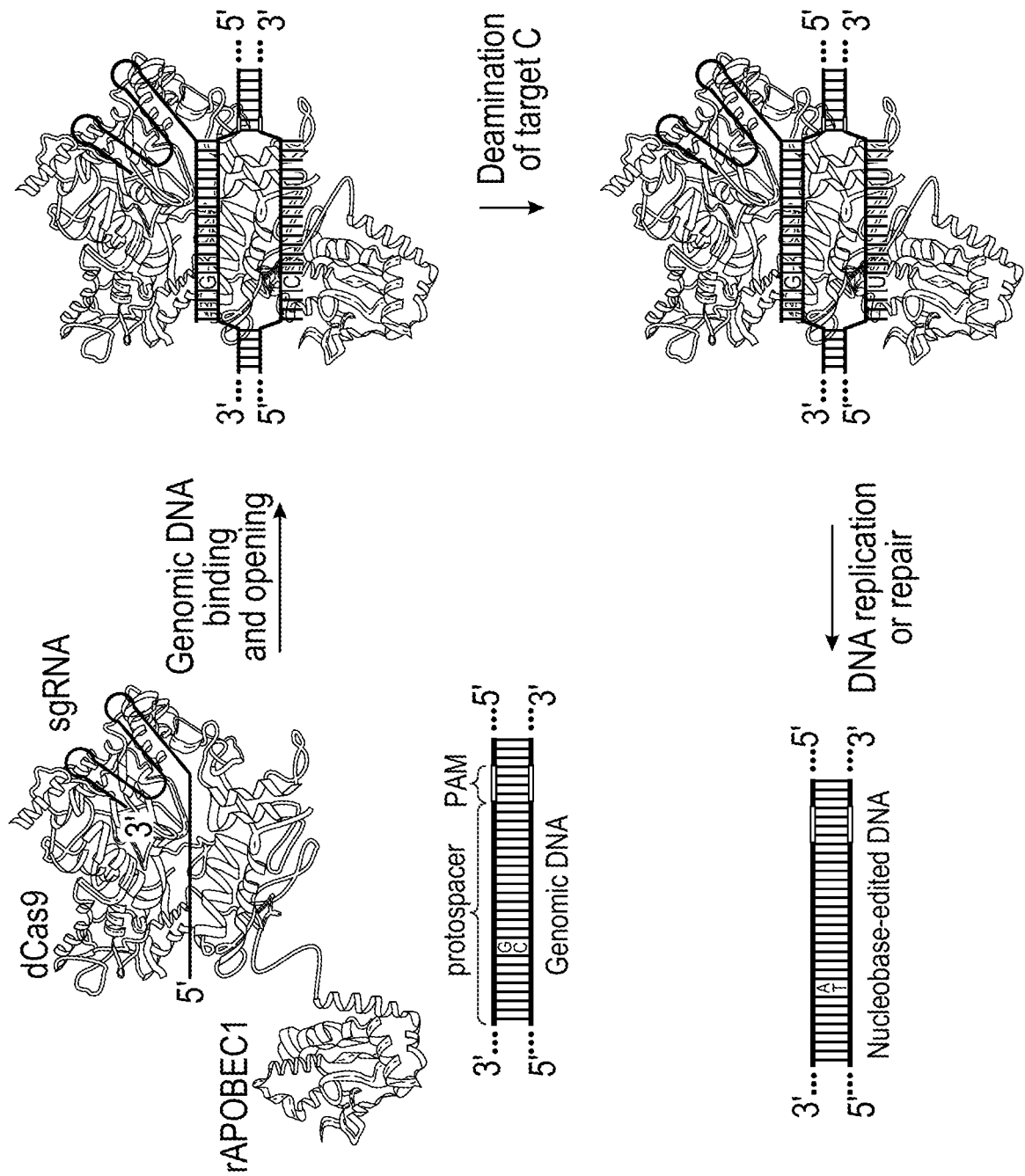


FIGURE 11A

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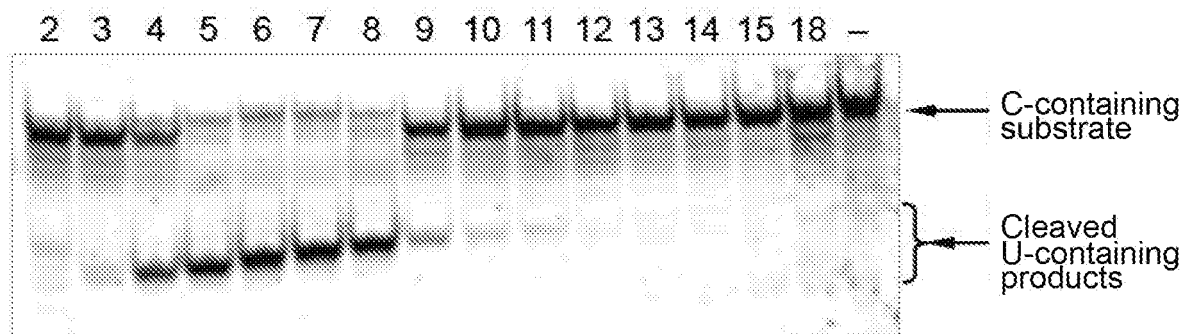


FIGURE 11B

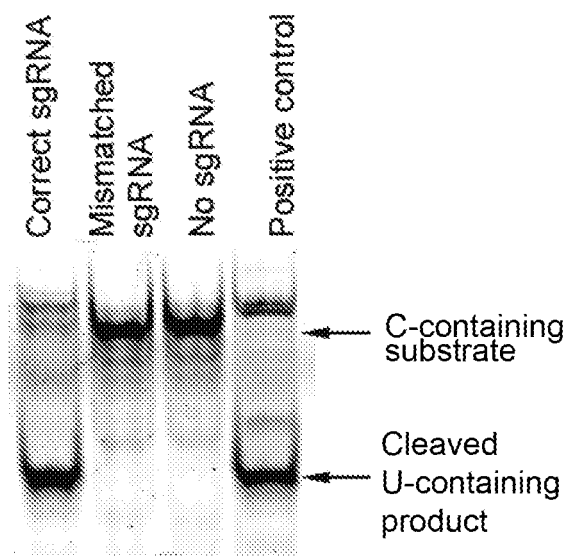


FIGURE 11C

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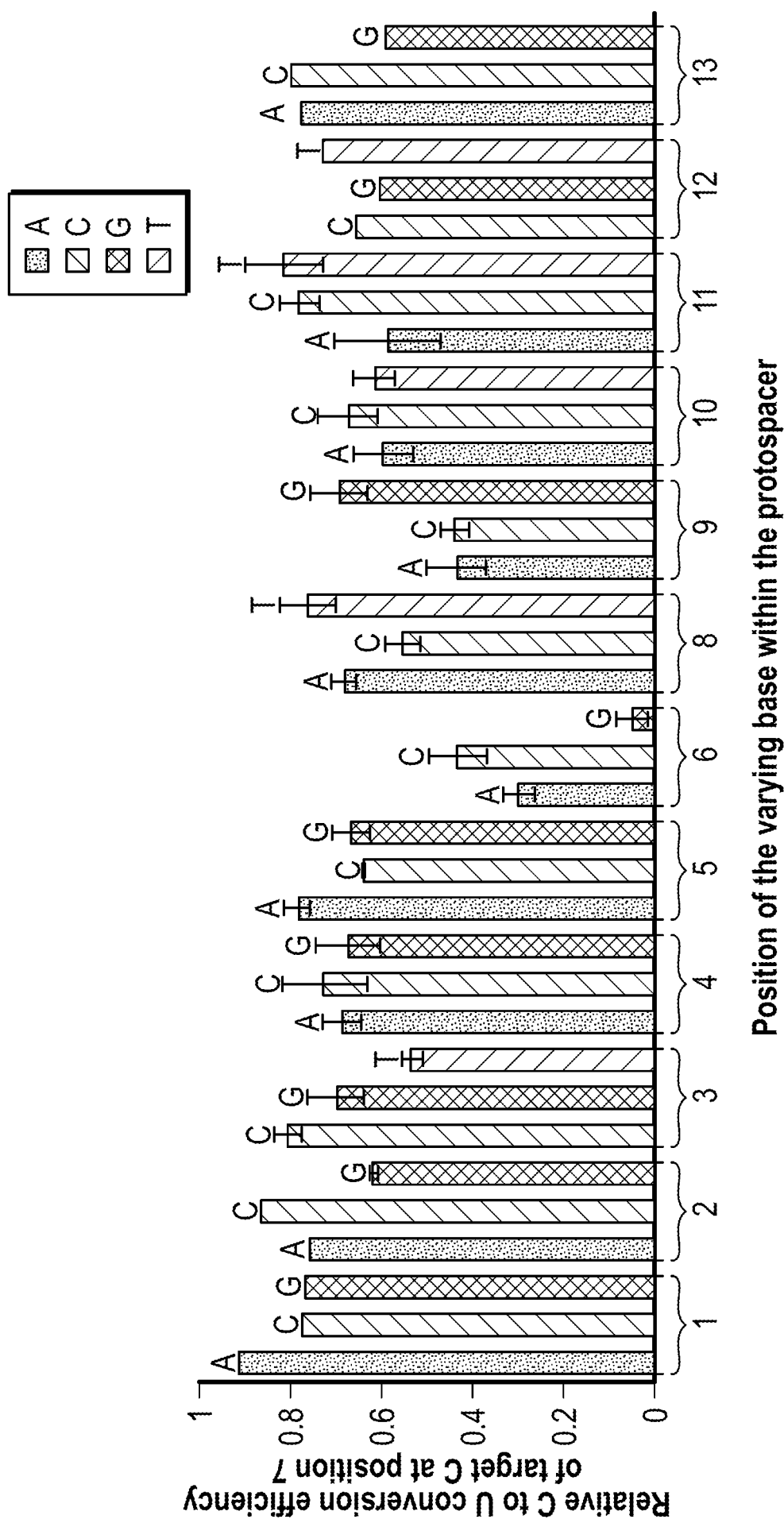


FIGURE 12A

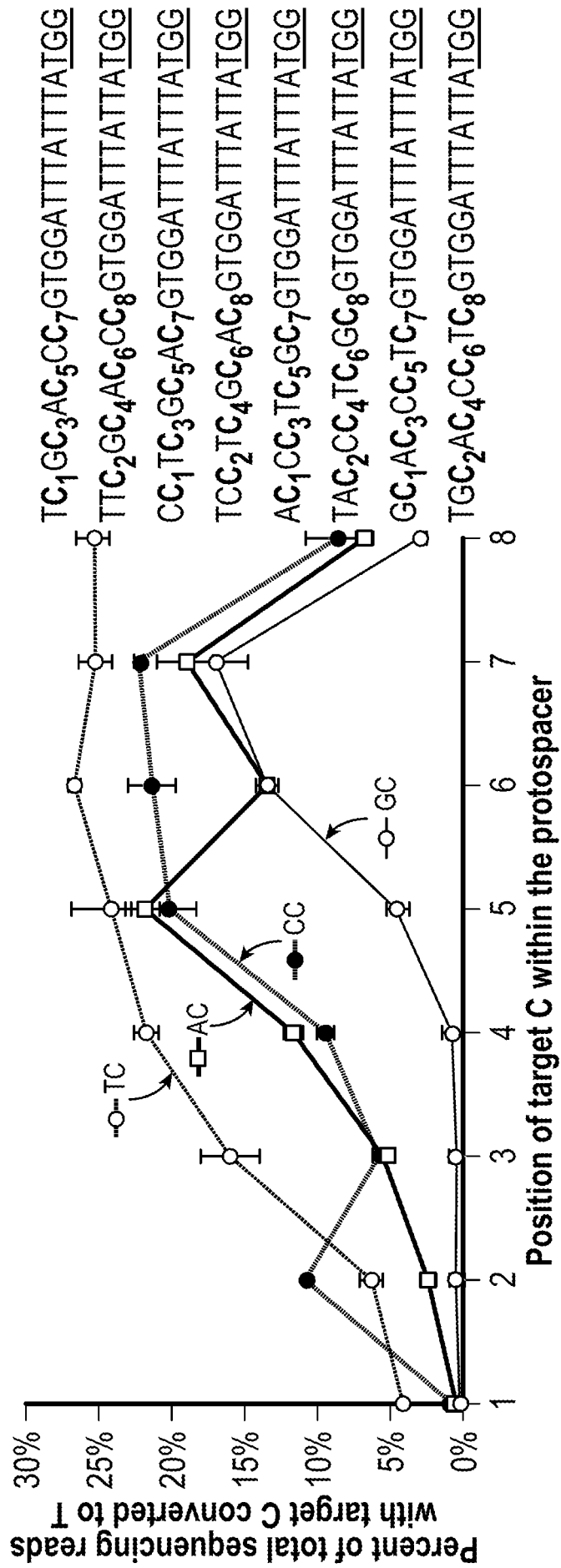


FIGURE 12B

EMX1:	GAGTC ₅ C ₆ GAGCAGAAGAAGAAGGG
FANCF:	GGAATC ₆ C ₇ C ₈ TTC ₁₁ TGCAGCACCTGG
HEK293 site 2:	GAAC ₄ AC ₆ AAAGCATAGACTGC <u>GGG</u>
HEK293 site 3:	GGCC ₄ C ₅ AGACTGAGCACGTGATGG
HEK293 site 4:	GGCAC ₅ TGCGGCTGGAGGTCC <u>GGG</u>
RNF2:	GTC ₃ ATC ₆ TTAGTC ₁₂ ATTACCTGAGG

FIGURE 13A

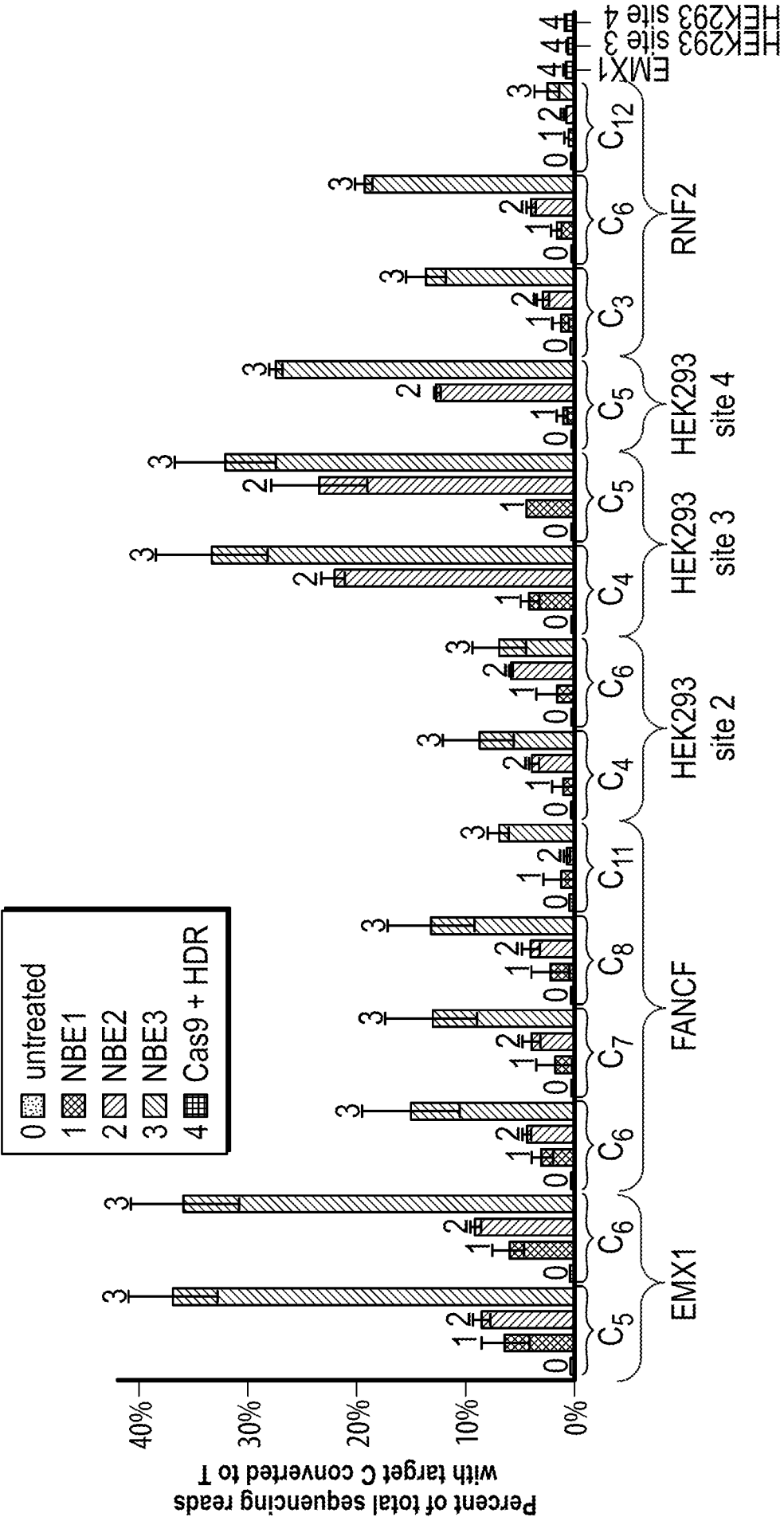


FIGURE 13B

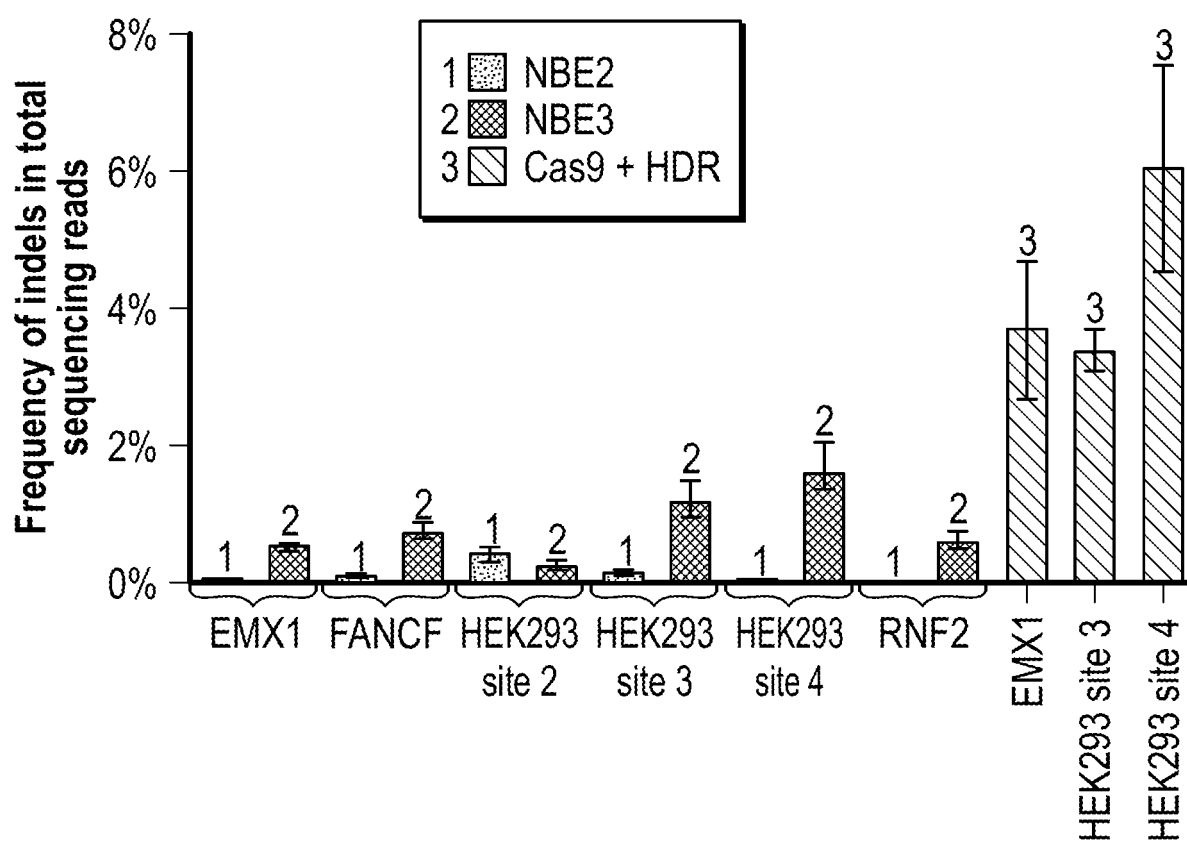


FIGURE 13C

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	Lys			Arg → Cys			Leu → Leu			Ala			Val			Tyr			Gln		
	G	A	G	C ₅	G	C	C	T	G	G	C	A	G	T	G	T	A	C	C	A	G
APOE4C158R																					
A	0.0	100.0	100.0	0.0	0.2	0.0	0.1	0.3	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0
C	0.0	0.0	0.0	0.0	88.7	0.0	91.3	91.1	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0	0.0
G	100.0	0.0	0.0	100.0	0.2	100.0	0.4	0.1	0.0	100.0	100.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	100.0	100.0
T	0.0	0.0	0.0	0.0	10.9	0.0	8.2	8.4	100.0	0.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0

FIGURE 14A

	His			Tyr			Asn			Tyr			Met			Cys			Asp → Asn			
	C	C	A	C	C	T	A	C	A	C	T	A	C	A	T	G	T	G	A	C	A	
TP53N239D																						
A	0.0	0.0	100.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	55.7	100.0	0.0	100.0
C	100.0	100.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0
G	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	44.3	0.0	0.0	0.0
T	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0

FIGURE 14B

	Arg			Ala			Met			Ala			Ile			Cys → Tyr			Lys		
	C	C	A	G	C	G	A	T	G	C	C	A	T	C	T	C	A	A	G	C	
TP53Y183C																					
A	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.1	0.0	0.0	100.0	0.0	0.0	7.6	0.0	100.0	100.0	0.0	
C	100.0	100.0	0.0	100.0	0.0	100.0	100.0	0.0	0.0	0.0	99.9	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	
G	0.0	0.0	100.0	0.0	99.9	0.0	0.0	0.0	99.9	99.9	0.0	0.0	0.0	0.0	0.0	91.8	0.0	0.0	100.0	0.0	
T	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.1	0.0	0.1	0.0	0.0	100.0	0.0	100.0	0.1	0.0	0.0	0.0	

FIGURE 14C

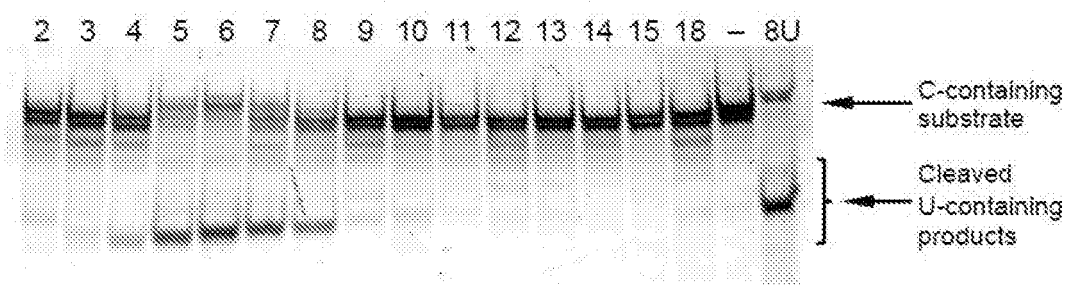


FIGURE 15A

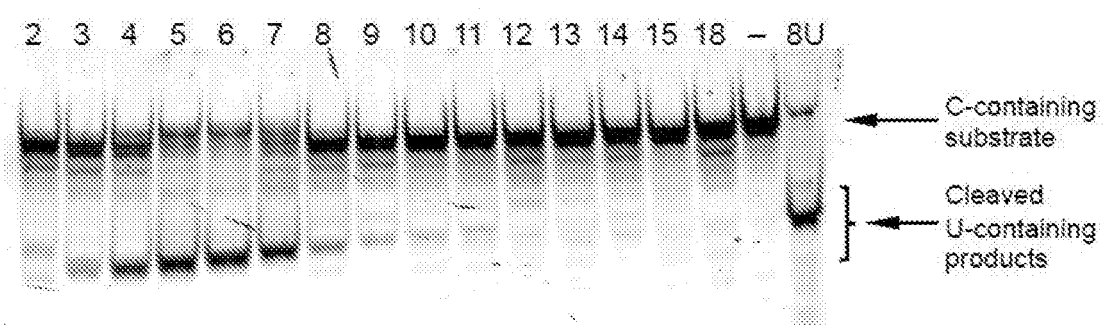


FIGURE 15B

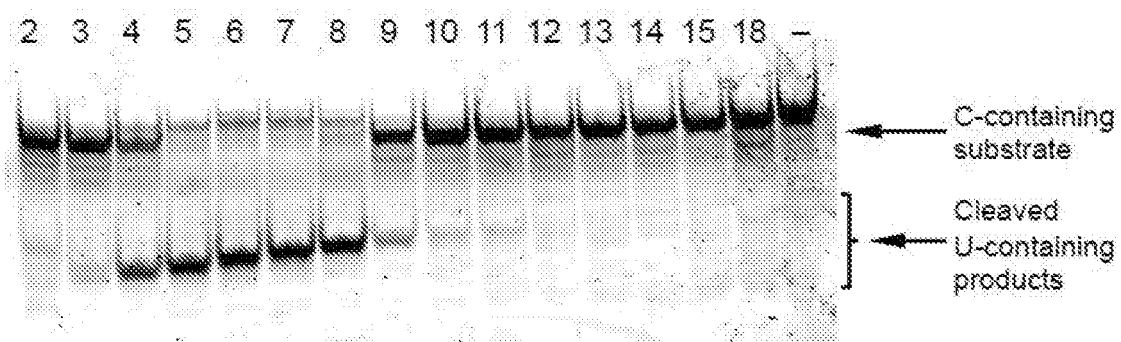


FIGURE 15C

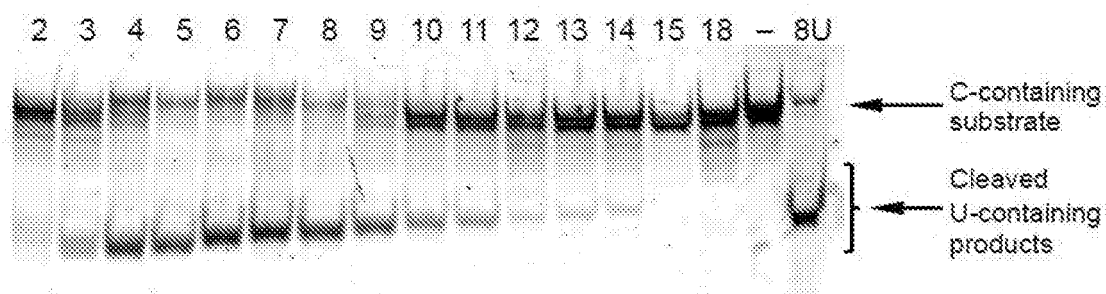


FIGURE 15D

APOE4 Cys112Arg: 5'-GGAGGACGTGC₁₁GCGGCCGCCTGG
 APOE4 Cys158Arg: 5'-GAAGC₅GCCTGGCAGTGTACCAGG
 CTNNB1 Thr41Ala: 5'-CTGTGGC₇AGTGGCACCAGAATGG
 HRAS Gln61Arg: 5'-CCTCCC₅GGCCGGCGGTATCCAGG
 p53 Tyr163Cys: 5'-GCTTGC₈AGATGGCCATGGCGCGG
 p53 Tyr236Cys: 5'-ACACATGC₈AGTTGTAGTGGATGG
 p53 Asn239Asp: 5'-TGTC₄ACACATGTAGTTGTAGTGG

FIGURE 16A

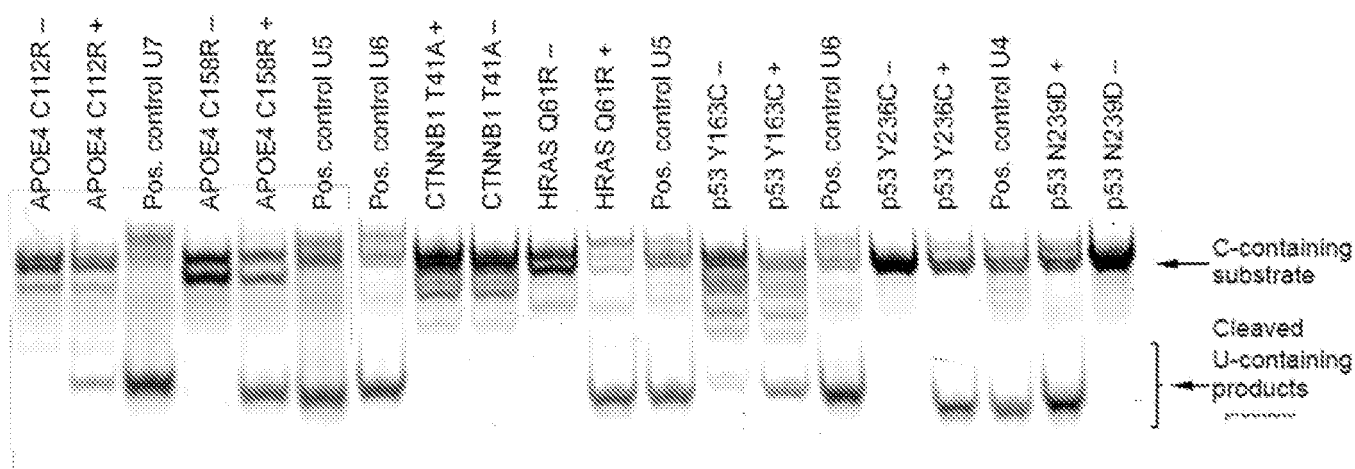


FIGURE 16B

Protospacer and PAM sequence: 5'-TTCCCCCCCCGATTTATTTATGG-3'

Sequence	% of total reads
CCCCCCCC	62.4
TTTTTTCC	18.2
TTTTTTTC	13.4
TTTTTTTT	3.3
TCCCCCCC	0.8
CCCCTTCC	0.3
CCCTTTCC	0.3
TTTTTCCC	0.3
CCCCTCCC	0.3

FIGURE 17

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EMX1: GAGTC₅C₈GAGCAGAAGAAGAAGGG
 FANCF: GGAATC₆C₇C₈TTC₁₁TGCAGCACCTGG
 HEK293 site 2: GAAC₄AC₆AAAGCATAGACTGCGGG
 HEK293 site 3: GGCC₄C₅AGACTGAGCACGTGATGG
 HEK293 site 4: GGCAC₅TGCGGCTGGAGGTCCGGG
 RNF2: GTC₃ATC₆TTAGTCATTACCTGAGG

FIGURE 18A

EMX1	C ₅	C ₆
NBE1	6.2%	6.5%
NBE1 + UGI	9.7%	10.1%
NBE2	8.0%	8.7%

FIGURE 18B

FANCF	C ₆	C ₇	C ₈	C ₁₀
NBE1	3.7%	3.2%	3.4%	2.4%
NBE1 + UGI	7.5%	7.6%	7.5%	1.6%
NBE2	4.7%	4.6%	4.6%	0.8%

FIGURE 18C

HEK293 site 2	C ₄	C ₆
NBE1	0.4%	0.4%
NBE1 + UGI	1.6%	2.6%
NBE2	3.4%	5.9%

FIGURE 18D

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HEK293 site 3	C ₄	C ₅
NBE1	2.0%	1.9%
NBE1 + UGI	6.5%	6.7%
NBE2	10.0%	12.5%

FIGURE 18E

HEK293 site 4	C ₅
NBE1	1.4%
NBE1 + UGI	5.4%
NBE2	8.2%

FIGURE 18F

RNF2	C ₃	C ₆
NBE1	0.7%	1.4%
NBE1 + UGI	3.4%	3.9%
NBE2	2.5%	3.7%

FIGURE 18G

Non-protospacer Cs	C	T
untreated	99.93%	0.03%
NBE1	99.95%	0.03%
NBE1 + UGI	99.91%	0.06%
NBE2	99.92%	0.04%

FIGURE 18H

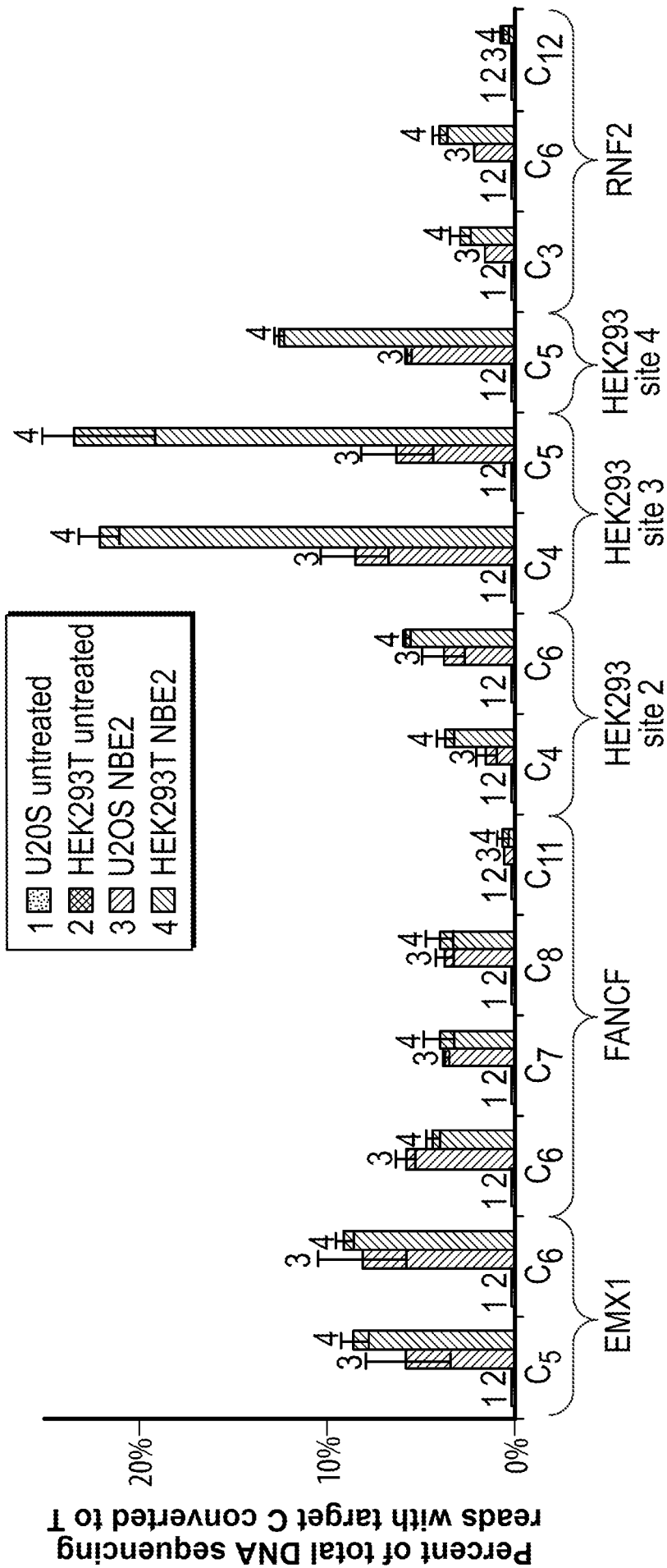


FIGURE 19

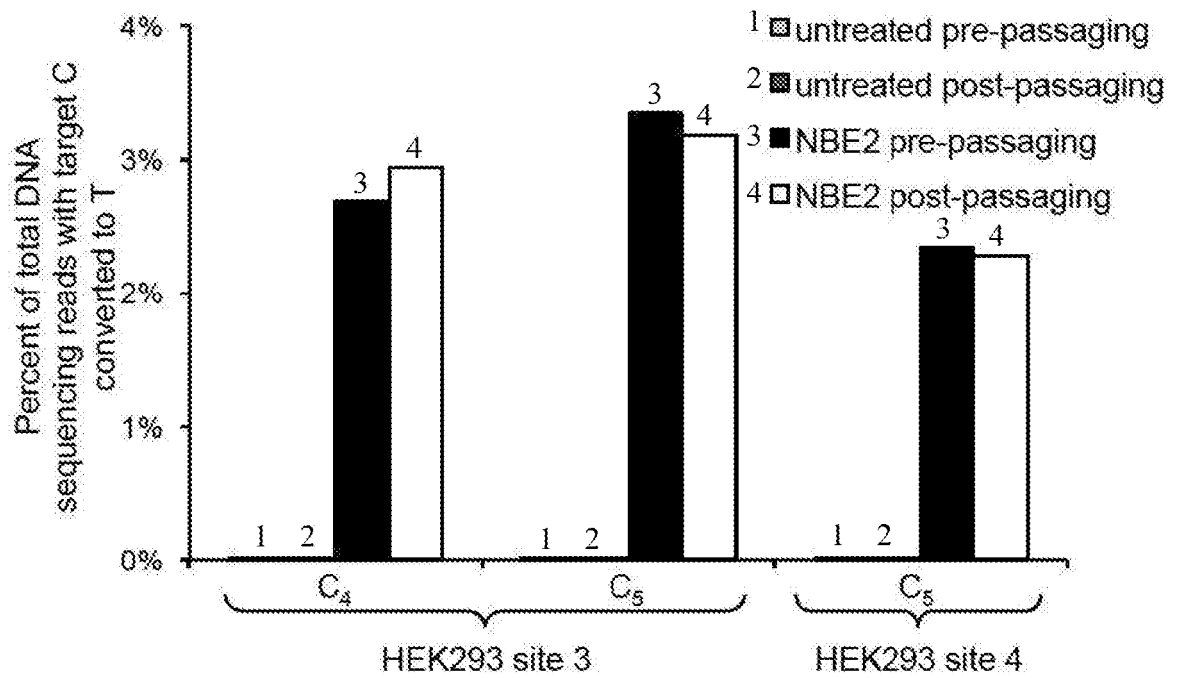


FIGURE 20

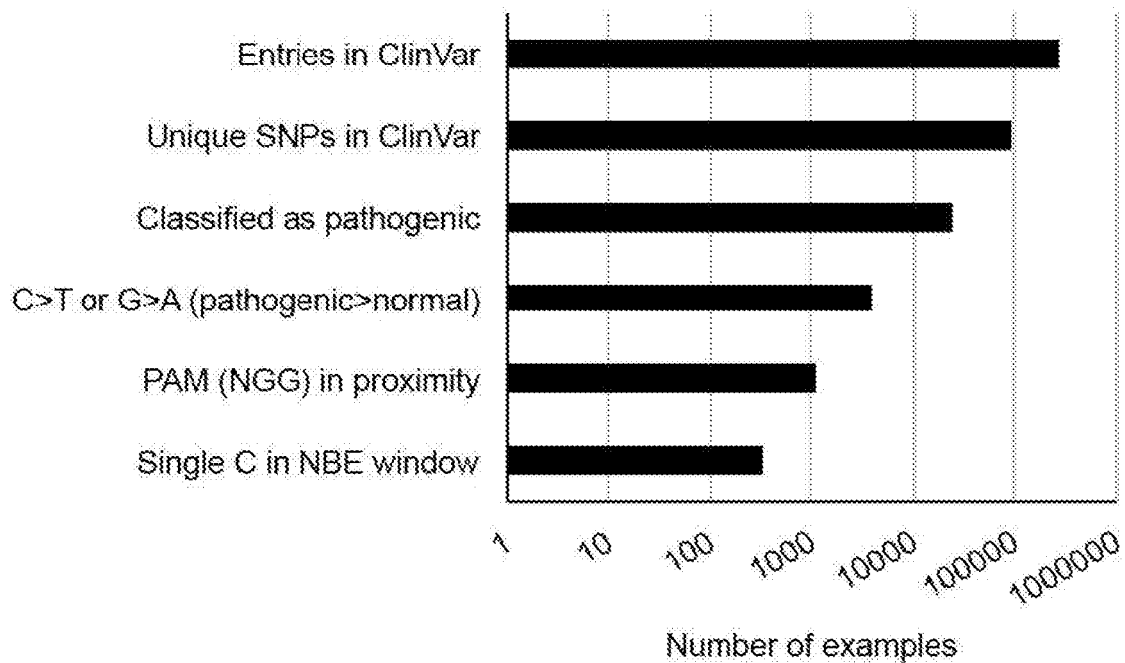


FIGURE 21

EMX1	185 uM NBE1															
	G	A	G	T	C5	C6	G	A	G	C	A	G	A	A	G	A
A	0.2	99.9	0.1	0.1	0.1	0.0	0.3	100.0	0.1	0.1	99.9	0.2	99.9	99.7	0.3	100.0
C	0.0	0.0	0.0	0.0	60.4	61.0	0.0	0.0	0.0	99.1	0.0	0.0	0.2	0.0	0.0	0.0
G	99.7	0.0	99.9	0.0	0.0	0.0	99.7	0.0	99.9	0.1	0.0	99.7	0.0	0.0	99.8	99.8
T	0.1	0.0	0.0	99.9	39.5	39.0	0.0	0.0	0.0	0.7	0.0	0.0	0.0	0.1	0.0	0.0

FANCF	185 uM NBE1															
	G	G	A	A	T	C6	C7	C8	T	T	C11	T	G	C	A	G
A	0.1	0.2	99.8	99.9	0.0	0.1	0.1	0.1	0.0	0.1	0.1	0.1	0.1	0.1	99.9	0.2
C	0.0	0.0	0.1	0.1	0.0	63.9	64.7	65.0	0.0	0.0	72.6	0.0	0.0	99.4	0.1	0.0
G	99.8	99.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.8	0.2	0.0	99.7
T	0.1	0.1	0.0	0.0	99.9	36.0	35.1	34.9	99.9	99.9	27.3	99.8	0.1	0.3	0.0	0.1

HEK293 site 2	185 uM NBE1															
	G	A	A	A	C4	A	A	A	A	A	G	C	A	T	A	G
A	0.1	100.0	99.8	0.1	100.0	0.1	99.9	100.0	99.9	0.1	0.1	100.0	0.0	99.9	0.2	100.0
C	0.0	0.0	0.1	80.6	0.0	78.9	0.0	0.0	0.0	0.0	99.6	0.0	0.0	0.1	0.0	0.0
G	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.8	0.0	0.0	0.1	0.0	99.8	0.0
T	0.1	0.0	0.0	19.3	0.0	22.9	0.0	0.0	0.0	0.1	0.3	0.0	99.9	0.0	0.1	0.0

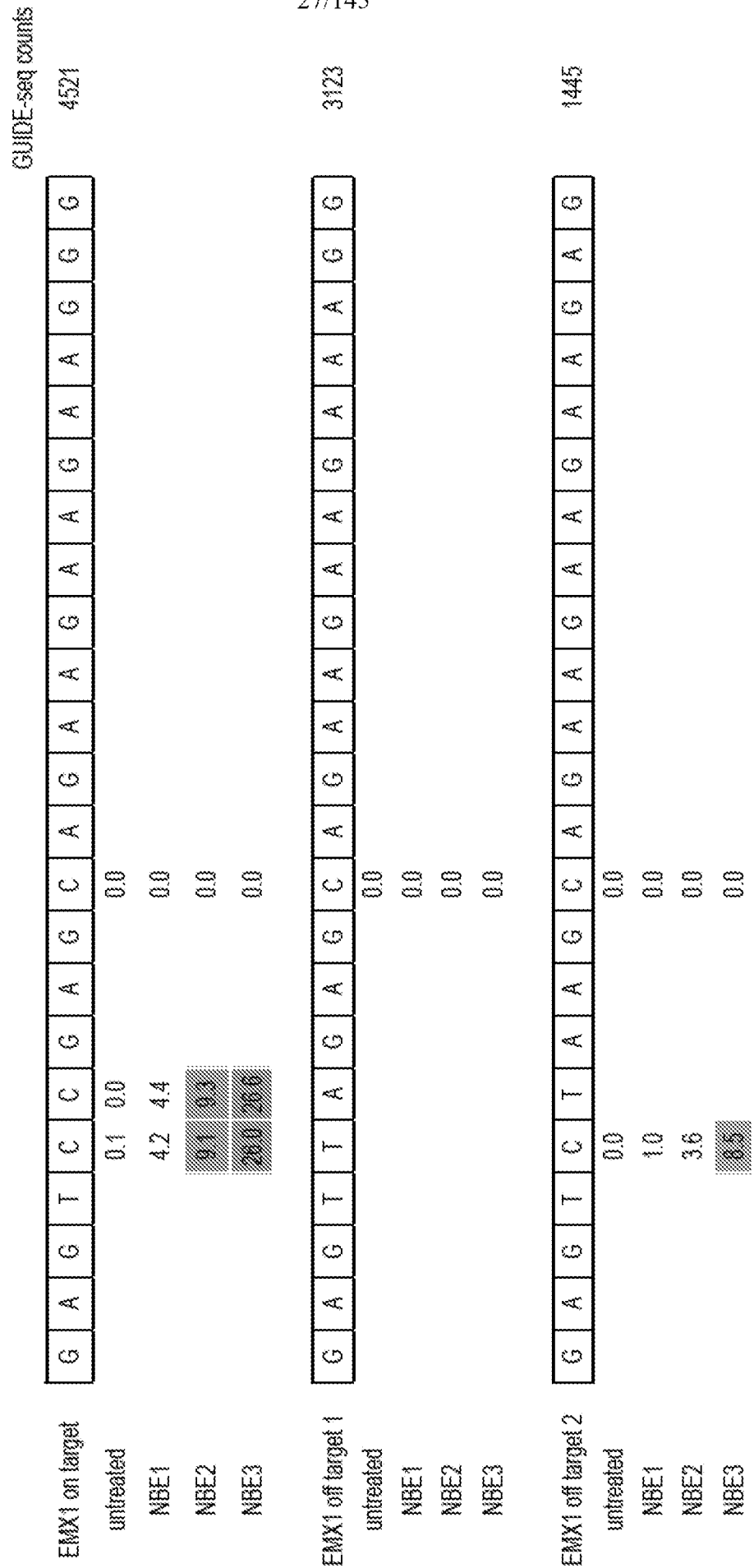
HEK293 site 3	185 uM NBE1															
	G	G	C	C	C4	C5	A	G	A	C	T	G	A	G	C	A
A	0.2	0.1	0.1	0.1	0.1	0.0	99.9	0.2	99.9	0.1	0.0	0.2	99.9	0.1	0.1	100.0
C	0.0	0.0	92.2	74.8	71.5	0.0	0.0	0.0	96.6	0.0	0.0	0.0	0.0	99.8	0.0	99.7
G	99.7	99.8	0.0	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	99.8	0.0	99.8	0.0	99.8
T	0.1	0.1	7.7	25.1	28.5	0.0	0.0	0.0	3.3	99.9	0.1	0.0	0.0	0.1	0.0	0.0

FIGURE 22

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HEK293 site 3															
	G	G	C	C4	C5	A	G	A	C	T	G	A	G	C	A
1.85 uM NBE1	A	0.2	0.1	0.1	0.1	0.0	99.9	0.2	99.9	0.1	0.0	0.2	99.9	0.1	0.1
	C	0.0	0.0	92.2	74.8	71.5	0.0	0.0	0.0	96.6	0.0	0.0	0.0	99.7	0.0
	G	99.7	99.8	0.0	0.0	0.0	99.8	0.0	0.0	0.0	99.8	0.0	99.8	0.0	99.8
	T	0.1	0.1	7.7	25.1	28.5	0.0	0.0	3.3	99.9	0.1	0.0	0.0	0.2	0.0
HEK293 site 4															
	G	G	C	A	C5	T	G	C	G	G	C	T	G	G	A
1.85 uM NBE1	A	0.3	0.2	0.1	100.0	0.1	0.0	0.2	0.1	0.2	0.2	0.1	0.0	0.3	0.5
	C	0.0	0.0	95.8	0.0	60.1	0.0	0.0	97.0	0.0	0.0	99.4	0.0	0.0	0.0
	G	99.7	99.7	0.0	0.0	0.0	99.8	0.0	99.8	99.8	0.0	0.0	99.7	99.4	0.0
	T	0.0	0.1	1.1	0.0	39.8	100.0	0.1	2.9	0.0	0.1	0.5	100.0	0.0	0.1
RNF2															
	G	T	C3	A	T	C6	T	T	A	G	T	C12	A	T	T
1.85 uM NBE1	A	0.1	0.0	0.1	99.9	0.0	0.0	0.0	99.9	0.1	0.0	0.1	99.9	0.0	0.0
	C	0.0	0.0	59.1	0.0	0.0	57.8	0.0	0.0	0.1	0.0	0.0	86.4	0.0	0.0
	G	99.8	0.1	0.0	0.0	0.0	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.0
	T	0.0	99.9	40.8	0.0	100.0	42.1	100.0	100.0	0.0	0.1	99.9	13.4	0.0	99.9

FIGURE 22 (CONTINUED)



GUIDE-seq counts

EMX1 off target 3	G	A	G	G	C	C	G	A	G	A	G	A	A	G	A	C	G	G	700
	untreated																		0.0
	NBE1																		0.0
	NBE2																		0.0
	NBE3																		0.0

EMX1 off target 4	G	A	G	T	C	C	T	A	G	C	A	G	A	G	A	A	G	A	300
	untreated																		0.0
	NBE1																		0.0
	NBE2																		0.0
	NBE3																		0.0

EMX1 off target 6	G	A	G	T	C	C	G	G	G	A	A	G	A	G	A	A	A	G	216
	untreated																		0.0
	NBE1																		0.1
	NBE2																		0.2
	NBE3																		1.0

FIGURE 23 (CONTINUED)

		GUIDE-seq counts																143	
EMX1 off target 7		G	A	G	C	C	G	G	A	G	A	G	A	A	G	G	A	G	G
	untreated				0.0	0.0									0.0				
	NBE1				0.0	0.0									0.0				
	NBE2				0.1	0.0									0.0				
NBE3				0.1	0.1									0.0					
		A	A	G	T	C	C	C	G	A	G	A	G	A	G	A	A	G	G
EMX1 off target 8						0.0	0.0												
	untreated																		
	NBE1					0.0	0.0												
	NBE2					0.0	0.0												
NBE3					0.1	0.1													
		A	A	G	T	C	C	C	G	A	G	A	G	A	G	A	A	G	G
EMX1 off target 9		G	A	A	T	C	C	C	A	A	A	G	A	G	A	A	A	G	A
	untreated					0.0	0.1								0.0				
	NBE1					0.0	0.1								0.0				
	NBE2					0.0	0.1								0.0				
NBE3					0.3	0.3								0.0					
		G	A	A	T	C	C	C	A	A	A	G	A	G	A	A	A	G	A
EMX1 off target 10		A	C	G	T	C	T	C	T	G	A	G	A	A	G	A	A	T	G
	untreated		0.0			0.1									0.0				
	NBE1		0.0			0.3									0.0				
	NBE2		0.0			0.5									0.0				
NBE3		0.0			2.1									0.0					

FIGURE 23 (CONTINUED)

		GUIDE-seq counts																								
		G	G	A	A	T	C	C	C	C	T	T	C	T	G	C	A	G	C	A	C	C	T	G	G	
FANCF on target																										4816
untreated		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
NBE1		37	32	34									24													
NBE2		41	35	35									0.4													
NBE3		191	160	167									0.8													
FANCF off target 1																										2099
untreated		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
NBE1		0.0	0.4	0.0	0.1								0.0													
NBE2		0.2	0.2	0.3	0.3								0.0													
NBE3		19	21	15	13								13													
FANCF off target 2																										524
untreated		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
NBE1		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
NBE2		0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	
NBE3		0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	
FANCF off target 3																										150
untreated		0.0	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
NBE1		0.0	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
NBE2		0.0	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
NBE3		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
FANCF off target 4																										125
untreated		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
NBE1		0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	
NBE2		0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
NBE3		0.0	0.0	0.7	0.4	0.3	0.1	0.0	0.1	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

FIGURE 24

squnob bes-30176

FANCF off target 5	unreated	G	G	A	T	T	G	C	C	C	A	T	C	C	G	C	A	C	C	T	G	G	100
	NBE1						0.1	0.0				0.0	0.0			0.0		0.0	0.0				
	NBE2						0.1	0.0				0.0	0.1			0.0		0.0	0.0				
							0.1	0.0				0.0	0.0			0.0		0.0	0.0				
	NBE3						0.1	0.0				0.0	0.0			0.0		0.0	0.0				
FANCF off target 6	unreated	T	G	A	A	T	C	C	C	C	A	T	C	T	C	C	A	C	C	A	G	G	78
	NBE1						0.0	0.0	0.0				0.0		0.1	0.1		0.0	0.0	0.0			
	NBE2						0.0	0.0	0.0				0.0		0.0	0.0		0.0	0.0	0.0			
							0.2	0.2	0.2				0.2		0.1	0.0		0.0	0.0	0.0			
	NBE3						0.3	0.3	0.3				0.3		0.1	0.0		0.0	0.0	0.0			
FANCF off target 7	unreated	G	G	A	G	T	C	C	C	C	T	C	C	T	A	C	A	C	C	A	G	G	77
	NBE1						0.0	0.0	0.0				0.0	0.0		0.0		0.0	0.0				
	NBE2						0.0	0.0	0.0				0.0	0.0		0.0		0.0	0.0				
							0.0	0.0	0.0				0.0	0.0		0.0		0.0	0.0				
	NBE3						0.5	0.5	0.5				0.3	0.1		0.0		0.0	0.0				
FANCF off target 8	unreated	G	G	A	G	T	C	C	C	C	T	C	C	T	G	C	A	C	C	T	G	A	4
	NBE1						0.0	0.0	0.0				0.0	0.0		0.0		0.0	0.0				
	NBE2						0.0	0.0	0.0				0.0	0.0		0.0		0.0	0.0				
							1.4	0.5	0.5				0.4	0.5		0.0		0.0	0.0				
	NBE3						0.1	0.1	0.0				0.0	0.0		0.0		0.0	0.0				

FIGURE 24 (CONTINUED)

																GUIDE-seq counts	
																1670	
HEK site 2 on target																	
G	A	C	A	C	A	C	A	C	A	C	A	C	A	C	A		
untreated																	
0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0		
NBE1																	
1.8	0.0	2.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0		
NBE2																	
8.5	0.0	10.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0		
NBE3																	
17.6	0.0	14.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0		
HEK site 2 off target 1																99	
G	A	C	A	C	A	C	A	C	A	C	A	C	A	C	A		
untreated																	
0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0		
NBE1																	
0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2		
NBE2																	
0.0	0.0	0.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0		
NBE3																	
0.2	0.0	0.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0		
HEK site 2 off target 2																4	
A	A	C	A	C	A	C	A	C	A	C	A	C	A	C	A		
untreated																	
0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0		
NBE1																	
0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0		
NBE2																	
0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0		
NBE3																	
0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0		

FIGURE 25

GUIDE-seq counts

2074

HEK site 3 on target												
G	G	C	C	C	A	A	G	A	C	T	G	G
untreated												
	0.1	0.1	0.1	0.1					0.0			
NBE1	0.1	4.6	4.3						0.0			
NBE2	5.6	20.3	20.4						0.0			
NBE3	0.5	35.4	33		0.5				0.0		0.2	

HEK site 3 off target 1												
C	A	C	C	C	A	A	G	A	C	T	G	G
untreated												
	0.0	0.0	0.0	0.0					0.0			0.0
NBE1	0.0	0.0	0.0	0.0					0.0			0.0
NBE2	0.0	0.0	0.0	0.0					0.0			0.0
NBE3	0.0	0.0	0.0	0.0					0.0			0.0

HEK site 3 off target 2												
G	A	C	C	A	C	A	G	A	C	T	G	G
untreated												
	0.0			0.0					0.0			
NBE1	0.0			0.0					0.0			
NBE2	0.0			0.0					0.0			
NBE3	0.0			0.0					0.0			

HEK site 3 off target 3												
A	G	C	T	C	A	A	G	A	C	T	G	G
untreated												
	0.0			0.0					0.0			
NBE1	0.0			0.0					0.0			
NBE2	0.0			0.0					0.0			
NBE3	0.0			0.9					0.0			

HEK site 3 off target 4												
A	G	A	C	C	A	A	G	A	C	T	G	G
untreated												
			0.0	0.0					0.0			
NBE1			0.0	0.0					0.1			
NBE2			0.0	0.0					0.0			
NBE3			0.0	0.0					0.0			

HEK site 3 off target 5												
G	A	G	C	C	A	A	G	A	C	T	G	G
untreated												
			0.0	0.0					0.0			
NBE1			0.0	0.0					0.0			
NBE2			0.0	0.0					0.0			
NBE3			0.0	0.0					0.0			

FIGURE 26

FIGURE 27

GUIDE-seq counts

1002

HEK site 4 off target 5	G	G	C	G	C	G	C	T	G	C	G	G	C	G	G	G	G	G	T	G	G	A	G	G
	untreated	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NBE1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NBE2	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NBE3	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

982

HEK site 4 off target 6	G	G	C	A	C	T	G	A	G	A	G	G	C	T	G	G	G	G	T	G	G	G	G	G
	untreated	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NBE1	0.0	0.0	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NBE2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NBE3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

981

HEK site 4 off target 7	A	G	C	A	G	T	G	C	T	A	G	A	C	T	G	G	G	G	T	G	G	T	G	G
	untreated	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NBE1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NBE2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NBE3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

789

HEK site 4 off target 8	G	G	C	A	C	T	G	C	T	A	G	G	C	T	G	G	G	G	T	G	G	T	G	G
	untreated	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NBE1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NBE2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NBE3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

712

HEK site 4 off target 9	G	G	C	A	C	T	G	G	G	G	C	T	G	G	G	G	G	G	A	G	G	G	G	G
	untreated	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NBE1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NBE2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NBE3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

664

HEK site 4 off target 10	G	G	C	A	C	T	G	G	G	G	T	T	G	G	A	G	G	G	T	G	G	G	G	G
	untreated	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NBE1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NBE2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NBE3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

FIGURE 27 (CONTINUED)

Non-protospacer Cs	C (%)	T (%)
untreated	99.94	0.04
NBE1	99.92	0.05
NBE2	99.92	0.05
NBE3	99.94	0.03

FIGURE 28

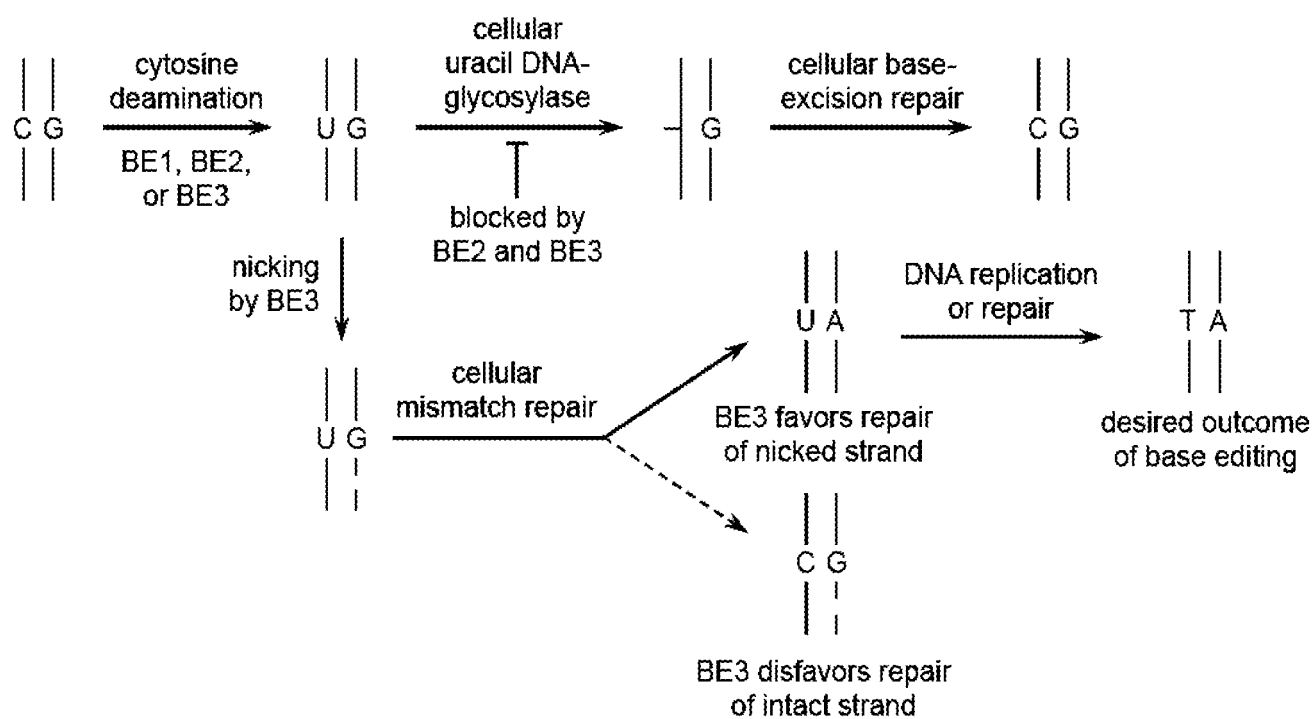


FIGURE 29A

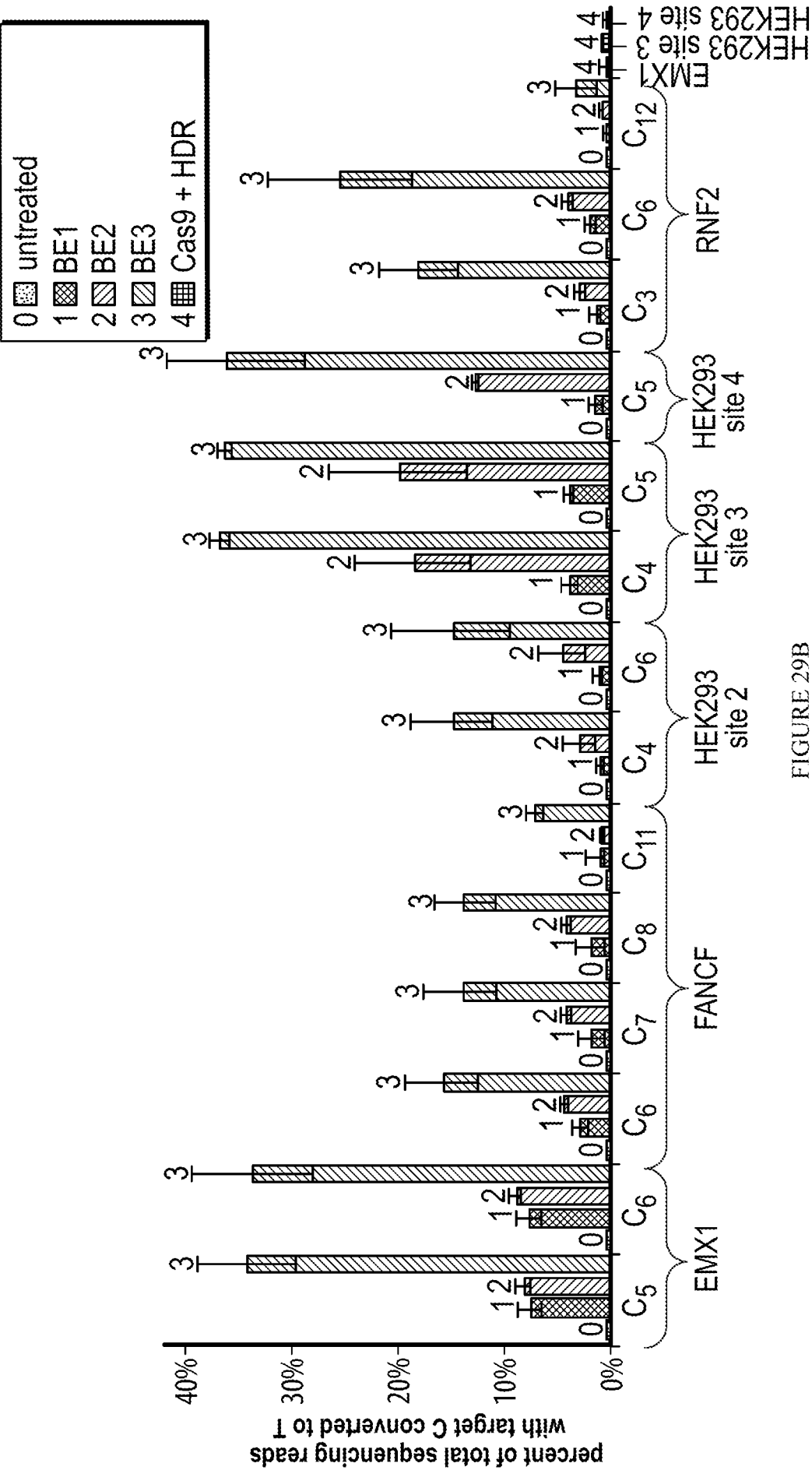


FIGURE 29B

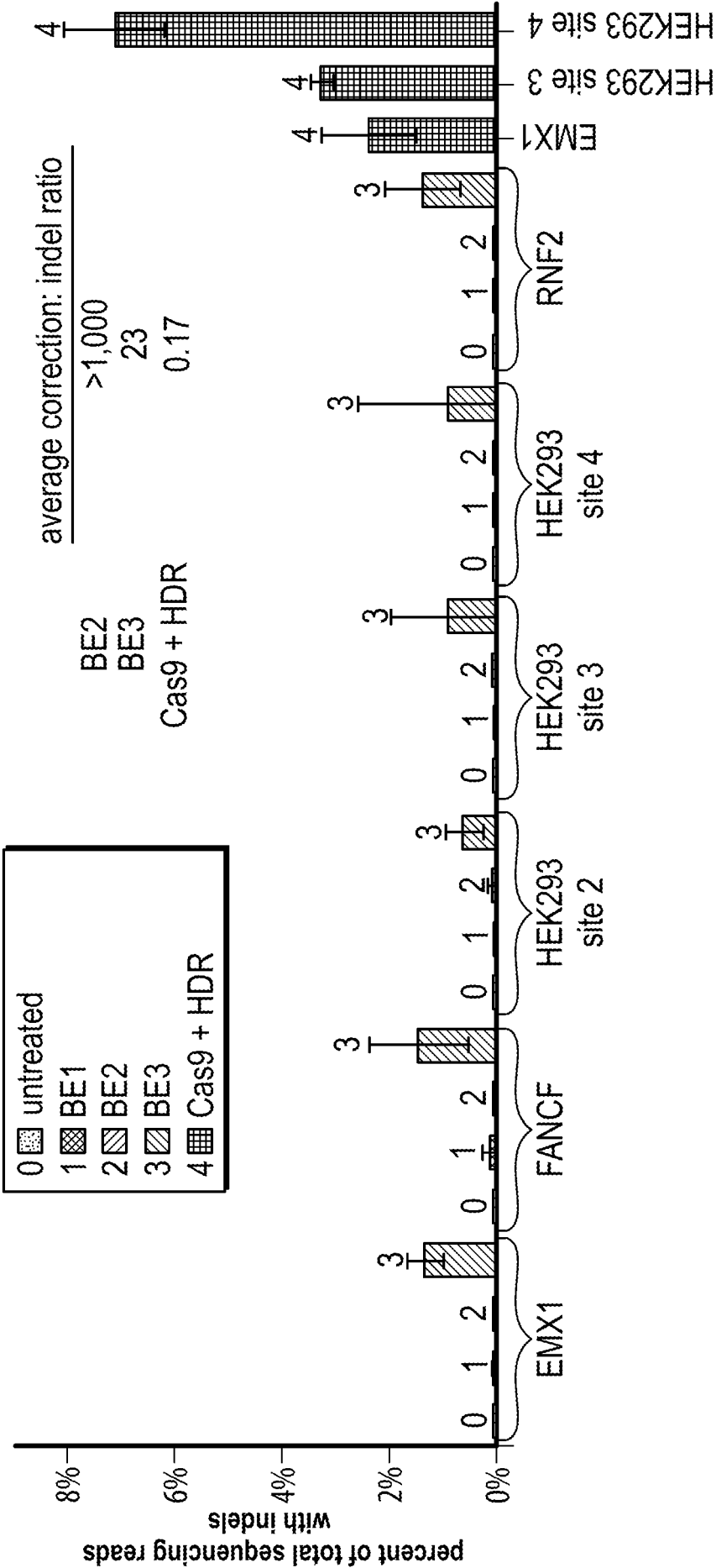


FIGURE 29C

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untreated	Lys			Arg			Leu			Ala			Val			Tyr			Gln			indel %
	G			C			T			C			A			G			A			
	A	A	G	C _s	G	C	T	G	C	A	C	G	T	G	A	T	A	C	A	G		
APOE4C158R	0.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
A	0.0	0.0	0.0	100.0	0.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
C	0.0	0.0	0.0	0.0	100.0	0.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
G	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	100.0	
T	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
BE3 treated	Lys			Arg → Cys			Leu → Leu			Ala			Val			Tyr			Gln			indel %
APOE4C158R	G			C			C			A			T			A			C			
	A			C _s			T			C			G			T			C			
	A			G			G			A			T			A			C			
	G			C _s			T			A			G			T			C			
	A			G			G			A			T			A			C			
A	0.1	100.0	100.0	0.0	0.5	0.0	1.3	0.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	
C	0.0	0.0	0.0	0.0	23.7	0.0	47.4	43.5	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
G	99.9	0.0	0.0	100.0	0.9	99.9	1.1	0.7	0.0	100.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	99.9	
T	0.0	0.0	0.0	0.0	74.9	0.1	50.2	55.0	100.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
Cas9 + HDR	Lys			Arg → Cys			Leu			Ala			Val			Tyr			Gln			indel %
APOE4C158R	G			C			C			A			T			A			C			
	A			C _s			T			C			G			T			C			
	A			G			G			A			T			A			C			
	G			C _s			T			A			G			T			C			
	A			G			G			A			T			A			C			
A	0.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
C	0.0	0.0	0.0	0.0	99.7	0.0	99.9	99.9	0.0	0.0	0.0	100.0	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
G	100.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	99.6	0.6	99.9	0.2	0.0	0.0	0.0	100.0	
T	0.0	0.0	0.0	0.0	0.3	0.0	0.1	0.1	100.0	0.0	0.0	0.0	0.1	0.4	99.3	0.1	99.8	0.0	0.0	0.0	0.0	

FIGURE 30A

untreated			Arg		Ala		Met		Ala		Ile		Cys		Lys		indel %				
	C	C	G	C	G	C	A	T	G	G	C	A	T	C	T	G		A	G	C	
TP53Y163C	C	C	G	C	G	C	C	A	T	G	G	C	C	A	T	C	C	A	G	C	0.0
A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.1	0.0	0.0	100.0	0.0	0.0	0.0	99.9	0.0	0.0
C	100.0	100.0	0.0	100.0	0.0	100.0	100.0	0.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0
G	0.0	0.0	100.0	0.0	99.9	0.0	0.0	0.0	0.0	100.0	99.9	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	100.0	0.0
T	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0
BE3 treated			Arg		Ala		Met		Ala		Ile		Cys → Tyr		Lys		indel %				
	C	C	G	C	G	C	C	A	T	G	G	C	C	A	T	C		C	A	G	C
TP53Y163C	C	C	G	C	G	C	C	A	T	G	G	C	C	A	T	C	C	A	G	C	0.7
A	0.0	0.0	0.0	0.0	0.1	0.0	0.0	100.0	0.0	0.0	0.0	0.1	0.0	0.0	100.0	0.0	0.0	7.6	0.0	100.0	0.0
C	100.0	100.0	0.0	100.0	0.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	99.9	100.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0
G	0.0	0.0	100.0	0.0	99.9	0.0	0.0	0.0	0.0	99.9	99.9	0.0	0.0	0.0	0.0	0.0	0.0	91.8	0.0	100.0	0.0
T	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.1	0.0	0.0	0.1	0.0	0.0	100.0	0.0	100.0	0.1	0.0	0.0
Cas9+HDR			Arg		Ala		Met		Ala		Ile		Cys → Tyr		Lys		indel %				
	C	C	G	C	G	C	C	A	T	G	G	C	C	A	T	C		C	A	G	C
TP53Y163C	C	C	G	C	G	C	C	C	A	T	G	G	C	C	A	T	C	C	A	G	6.1
A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	99.9	100.0	0.0
C	100.0	100.0	0.0	100.0	0.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0
G	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0
T	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0

FIGURE 30B

GUIDE-seq
counts/ ChIP-seq
intensity

HEK site 2 on target															1670/ 117
G	A	A	C	A	C	A	C	A	C	A	T	A	G	A	
untreated															99
BE1															
BE2															
BE3															
HEK site 2 GUIDE-seq															99
off target 1															
untreated															
BE1															
BE2															
BE3															
HEK site 2 GUIDE-seq															4
off target 2															
untreated															
BE1															
BE2															
BE3															
HEK site 2 ChIP-seq															31
off target 1															
untreated															
BE1															
BE2															
BE3															

FIGURE 31

		GUIDE-seq counts/ ChIP-seq intensity 1670/ 117																							28	
HEK site 2 ChIP-seq off target 2		G	A	A	T	C	G	G	G	A	G	A	G	A	C	T	G	C	G	G	G					
untreated		0.0																			0.0					
BE1		0.0																			0.1					
BE2		0.0																			0.1					
BE3		0.0																			0.1					
HEK site 2 ChIP-seq off target 3		T	G	A	A	G	T	G	T	T	G	C	A	T	A	G	A	C	T	G	C	A	G	G		
untreated		0.0																			0.0					
BE1		0.0																			0.1					
BE2		0.0																			0.0					
BE3		0.0																			0.0					
HEK site 2 ChIP-seq off target 4		G	G	A	G	A	G	A	G	A	G	A	G	C	A	T	A	G	A	C	T	G	C	T	G	G
untreated		0.0																			0.0					
BE1		0.0																			0.0					
BE2		0.0																			0.0					
BE3		0.0																			0.0					
HEK site 2 ChIP-seq off target 5		C	C	A	A	A	C	A	C	A	A	A	A	C	A	T	A	G	A	C	T	G	C	T	G	G
untreated		0.0	0.0	0.0												0.0	0.0	0.0								
BE1		0.0	0.0	0.0												0.0	0.0	0.0								
BE2		0.0	0.0	0.0												0.0	0.0	0.0								
BE3		0.0	0.0	0.0												0.0	0.0	0.2								

FIGURE 31 (CONTINUED)

GUIDE-seq
counts/ ChIP-seq
intensity
2074/ 163

HEK site 3 on target	G	G	C	C	C	C	A	A	G	A	G	C	A	C	G	T	G	A	T	G	G
untreated	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

BE1	0.1	4.8	4.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE2	3.6	21.3	20.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE3	0.5	33.4	33.1	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

HEK site 3 GUIDE-seq off target 1	C	A	C	C	C	A	G	A	C	T	G	A	G	C	A	C	G	T	G	C	T	G	G
untreated	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

BE1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

HEK site 3 GUIDE-seq off target 2	G	A	C	C	A	C	A	G	A	C	A	G	G	T	G	G	C	C	A	C	G	T	G	A	G	C	G
untreated	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

HEK site 3 GUIDE-seq off target 3	A	G	C	C	T	C	A	G	A	C	T	G	A	G	C	A	G	T	G	A	G	C	T	G	G
	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

BE1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

HEK site 3 GUIDE-seq off target 4	A	G	A	C	C	C	A	G	A	C	T	G	A	G	C	C	A	A	G	A	G	G	G
untreated				0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
BE1				0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
BE2				0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
BE3				0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

BE1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

FIGURE 32

GUIDE-seq
counts/ChIP-seq
intensity

2074/153
2

G	A	G	C	C	A	G	A	A	A	T	G	A	G	C	A	C	G	T	G	A	G	G	G
---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---

HEK site 3 GUIDE-seq
off target 5
untreated
BE1
BE2
BE3

C	A	G	G	A	A	G	C	T	G	G	A	G	C	A	C	G	T	G	A	G	G	G
---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---

HEK site 3 ChIP-seq
off target 1
untreated
BE1
BE2
BE3

A	A	G	G	C	T	G	A	G	G	G	A	G	C	A	C	G	T	G	A	A	G	G
---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---

HEK site 3 ChIP-seq
off target 2
untreated
BE1
BE2
BE3

G	T	C	A	G	G	G	G	A	A	G	A	G	C	A	C	G	T	G	A	C	G	G
---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---

HEK site 3 ChIP-seq
off target 3
untreated
BE1
BE2
BE3

G	T	T	G	T	G	A	A	C	T	G	A	G	C	A	C	G	T	G	A	G	G	G
---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---

HEK site 3 ChIP-seq
off target 4
untreated
BE1
BE2
BE3

A	T	A	T	T	T	G	C	T	G	G	A	G	C	A	C	G	T	G	A	A	G	G
---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---

HEK site 3 ChIP-seq
off target 5
untreated
BE1
BE2
BE3

FIGURE 32 (CONTINUED)

[illegible]

FIGURE 33

GUIDE-seq
counts/ Chip-seq
intensity
1054/ 49

HEK site 4 GUIDE-seq off target 5	G	G	C	G	C	T	G	C	G	G	C	G	G	A	G	G	T	G	G	A	G	G	G
untreated	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE2	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE3	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

1002

HEK site 4 GUIDE-seq off target 6	G	G	C	A	A	C	T	G	A	A	G	A	G	G	G	G	T	G	G	G	G	G	G
untreated	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE1	0.0	0.0	0.5	0.5	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE2	0.8	0.8	3.6	3.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE3	0.0	0.0	6.8	6.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

982

HEK site 4 GUIDE-seq off target 7	A	G	C	A	A	G	T	G	C	G	G	C	T	A	G	A	G	G	T	G	G	T	G
untreated	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE1	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE2	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE3	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

981

HEK site 4 GUIDE-seq off target 8	G	G	C	A	A	C	T	G	C	T	A	C	T	G	G	G	G	T	G	G	T	G	G
untreated	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE1	0.0	0.0	2.1	2.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE2	0.2	0.2	5.1	5.1	0.5	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE3	0.2	0.2	8.2	8.2	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

789

HEK site 4 GUIDE-seq off target 9	G	G	C	A	A	C	T	G	G	G	G	C	T	G	G	G	G	A	G	G	G	G	G
untreated	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE1	0.0	0.0	0.3	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE2	0.0	0.0	0.4	0.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BE3	0.0	0.0	0.9	0.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

712

FIGURE 33 (CONTINUED)

														GUIDE-seq counts/ ChIP-seq intensity 1054/ 49
HEK site 4 GUIDE-seq off target 10														664
untreated	G	G	C	A	C	T	G	G	G	G	T	T	G	G
BE1														
BE2														
BE3														
HEK site 4 ChIP-seq off target 1														110
untreated	G	T	G	G	C	C	T	G	G	A	G	G	T	G
BE1														
BE2														
BE3														
HEK site 4 ChIP-seq off target 3														89
untreated	G	A	G	G	G	A	A	A	G	G	C	T	G	G
BE1														
BE2														
BE3														

FIGURE 33 (CONTINUED)

APOE4	C30	A49	C48	C47	T46	G45	C44	G43	C42	A41	A40	G39	C38	T37	G36	C35	G34	T33	A32	A31	G30	C29	G28	G27	C26
Untreated																									
A	0.140.1	100±0.1	0±0	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	100±0.1	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	100±0.1	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1
C	100±0.1	0.140.1	100±0.1	100±0.1	0.140.1	0.140.1	100±0.1	0.140.1	100±0.1	0±0	0.140.1	0±0	100±0.1	0.140.1	0.140.1	0±0	100±0.1	0.140.1	0.140.1	0±0	0.140.1	0±0	100±0.1	0.140.1	100±0.1
G	0.140.1	0.140.1	0±0	0±0	0.140.1	100±0.1	0±0	99.9±0.1	0.140.1	0.140.1	0.140.1	100±0.1	0±0	0±0	100±0.1	0.140.1	100±0.1	0.140.1	0.140.1	0±0	0.140.1	0.140.1	100±0.1	100±0.1	0±0
T	0.140.1	0.140.1	0.140.1	0.140.1	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	100±0.1	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1
BE3 + on-target sgRNA																									
A	0±0	100±0.1	0±0	0.140.1	0.140.1	0.140.1	0±0	0.140.1	0.140.1	100±0.1	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1	0±0	0.140.1	0±0	100±0.1	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1
C	100±0.1	0.140.1	100±0.1	100±0.1	0.140.1	0.140.1	100±0.1	0.140.1	100±0.1	0.140.1	0.140.1	0±0	100±0.1	0.140.1	0±0	100±0.1	0.140.1	0.140.1	0±0	0.140.1	0±0	100±0.1	0.140.1	0±0	100±0.1
G	0.140.1	0.140.1	0±0	0.140.1	0.140.1	100±0.1	0±0	99.9±0.1	0.140.1	0.140.1	0.140.1	100±0.1	0±0	0.140.1	100±0.1	0.140.1	100±0.1	0.140.1	0.140.1	0±0	0.140.1	0.140.1	100±0.1	100±0.1	0.140.1
T	0.140.1	0.140.1	0.140.1	0.140.1	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	100±0.1	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1	0±0	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1
BE3 + off-target sgRNA																									
A	0±0	100±0.1	0±0	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	100±0.1	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1	0±0	0.140.1	0.140.1	0.140.1	100±0.1	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1
C	100±0.1	0.140.1	100±0.1	100±0.1	0.140.1	0.140.1	100±0.1	0.140.1	100±0.1	0.140.1	0.140.1	0±0	100±0.1	0.140.1	0±0	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1
G	0.140.1	0.140.1	0±0	0.140.1	0.140.1	100±0.1	0±0	99.9±0.1	0.140.1	0.140.1	0.140.1	100±0.1	0±0	0.140.1	100±0.1	0.140.1	100±0.1	0.140.1	0.140.1	0±0	0.140.1	0.140.1	100±0.1	100±0.1	0.140.1
T	0.140.1	0.140.1	0.140.1	0.140.1	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	100±0.1	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1	0±0	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1
APOE4	T25	C24	C23	T22	C21	C20	G19	C18	G17	A16	T15	G14	C13	C12	G11	A10	T9	G8	A7	C6	C5	T4	G3	C2	A1
Untreated																									
A	0.140.1	0±0	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	100±0.1	0±0	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	100±0.1	0.140.1	0.140.1	100±0.1	0±0	0.140.1	0.140.1	0.140.1	0.140.1
C	0.140.1	100±0	100±0.1	0.140.1	100±0.1	100±0.1	0±0	100±0.1	0.140.1	0±0	0.140.1	0±0	100±0.1	100±0.1	0±0	0±0	100±0.1	100±0.1	0.140.1	0.140.1	0±0	100±0.1	100±0.1	0.140.1	0.140.1
G	0±0	0±0	0.140.1	0.140.1	0.140.1	0.140.1	100±0.1	0.140.1	100±0.1	0±0	0.140.1	0.140.1	100±0.1	0.140.1	0.140.1	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1	0±0	100±0.1	0.140.1	0.140.1	0.140.1
T	100±0.1	0±0	0.140.1	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	100±0.1	0.140.1	0.140.1	0.140.1
BE3 + on-target sgRNA																									
A	0±0	0±0	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	100±0.1	0±0	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1
C	0.140.1	99.9±0.1	100±0.1	0.140.1	99.9±0.1	100±0.1	0.140.1	0.140.1	0.140.1	100±0.1	0±0	0.140.1	0.140.1	100±0.1	0.140.1	0.140.1	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1
G	0±0	0±0	0.140.1	0.140.1	0.140.1	0.140.1	100±0.1	0.140.1	100±0.1	0.140.1	0.140.1	0.140.1	100±0.1	0.140.1	0.140.1	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1
T	100±0.1	0.140.1	0.140.1	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1
BE3 + off-target sgRNA																									
A	0.140.1	0±0	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	100±0.1	0±0	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1
C	0.140.1	100±0.1	100±0.1	0.140.1	100±0.1	100±0.1	0±0	100±0.1	0.140.1	0.140.1	0.140.1	0±0	100±0.1	100±0.1	0±0	0.140.1	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1
G	0±0	0±0	0.140.1	0.140.1	0.140.1	0.140.1	100±0.1	0.140.1	100±0.1	0.140.1	0.140.1	0.140.1	100±0.1	0.140.1	0.140.1	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1
T	100±0.1	0.140.1	0.140.1	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	100±0.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1	0.140.1

FIGURE 34

APOE4	A-1	G-2	G-3	C-4	C-5	G-6	G-7	G-8	C-9	C-10	C-11	C-12	G-13	C-14	G-15	A-16	G-17	G-18	G-19	C-20	G-21	C-22	C-23	G-24	A-25	
Untreated																										
A	100±0.1	0.1±0.1	0.1±0.1	0±0	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.2±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0±0	0.2±0.1	0.1±0.1	0±0	0.1±0.1	100±0.1
C	0.1±0.1	0.1±0.1	0±0	100±0.1	100±0.1	0.1±0.1	0±0	0.1±0.1	0.1±0.1	100±0.1	100±0.1	100±0.1	0.1±0.1	99.9±0.1	0.1±0.1	0.1±0.1	0±0	0±0	0±0	0±0	100±0.1	0.1±0.1	100±0.1	100±0.1	0±0	0.1±0.1
G	0.1±0.1	100±0.1	100±0.1	0.1±0.1	0±0	99.9±0.1	100±0.1	100±0.1	100±0.1	0.1±0.1	0±0	0.1±0.1	99.9±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	100±0.1	100±0.1	100±0.1	0.1±0.1	99.9±0.1	0.1±0.1	100±0.1	0.1±0.1	
T	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0±0	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	
BE3 + on-target sgRNA																										
A	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0±0	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.2±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.2±0.1	0.2±0.1	0.2±0.1	0.1±0.1	0.1±0.1	0.1±0.1	99.9±0.1	
C	0.1±0.1	0±0	0.1±0.1	100±0.1	100±0.1	0.1±0.1	0±0	0.1±0.1	0±0	100±0.1	100±0.1	100±0.1	0.1±0.1	100±0.1	0±0	0±0	0±0	0±0	0±0	99.8±0.2	0±0	99.9±0.1	100±0.1	0±0	0±0	
G	0.1±0.1	100±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	100±0.1	100±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	99.9±0.1	0±0	100±0.1	0.1±0.1	100±0.1	100±0.1	99.9±0.1	0.2±0.1	99.8±0.2	0±0	99.9±0.1	0.1±0.1	0.1±0.1	
T	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.2±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.2±0.1	
BE3 + off-target sgRNA																										
A	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0±0	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.2±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	
C	0.1±0.1	0±0	0.1±0.1	100±0.1	100±0.1	0.1±0.1	0±0	0±0	0±0	100±0.1	100±0.1	100±0.1	0.1±0.1	100±0.1	0±0	0±0	0±0	0±0	0±0	100±0.1	0.1±0.1	100±0.1	100±0.1	0±0	0±0	
G	0.1±0.1	100±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	100±0.1	100±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	99.9±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	100±0.1	100±0.1	100±0.1	0.1±0.1	99.8±0.2	0±0	99.9±0.1	0.1±0.1	
T	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.2±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.2±0.1	
APOE4	G-26	C-27	G-28	C-29	G-30	G-31	C-32	C-33	T-34	C-35	A-36	G-37	C-38	G-39	C-40	C-41	A-42	T-43	C-44	C-45	G-46	C-47	G-48	A-49	G-50	
Untreated																										
A	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0±0	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.2±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	
C	0±0	100±0.1	0.1±0.1	99.9±0.1	0±0	0.1±0.1	100±0.1	100±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	99.9±0.1	0.1±0.1	100±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	
G	100±0.1	0.1±0.1	99.9±0.1	0.1±0.1	100±0.1	100±0.1	0±0	0±0	0.1±0.1	100±0.1	0.1±0.1	100±0.1	0.1±0.1	99.9±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	99.9±0.1	0.1±0.1	0.1±0.1	100±0.1	
T	0.1±0.1	0.1±0.1	0.2±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.3±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	99.6±0.1	0.1±0.1	0.1±0.1	0.2±0.1	0.1±0.1	0.3±0.1	0±0	0.1±0.1	
BE3 + on-target sgRNA																										
A	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.2±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	
C	0±0	100±0.1	0.1±0.1	100±0.1	0±0	0.1±0.1	100±0.1	100±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	99.9±0.1	0.1±0.1	100±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.2±0.1	
G	100±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	100±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	99.9±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	99.9±0.1	0.1±0.1	0.1±0.1	99.9±0.1	
T	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	99.6±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.4±0.1	0±0	0±0	
BE3 + off-target sgRNA																										
A	0.1±0.1	0±0	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0±0	0.1±0.1	0±0	0±0	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	
C	0.1±0.1	100±0.1	0±0	100±0.1	0.1±0.1	0.1±0.1	0±0	100±0.1	100±0.1	0.1±0.1	100±0.1	0.1±0.1	99.9±0.1	0.1±0.1	100±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	
G	100±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	100±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	99.9±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	99.9±0.1	0.1±0.1	0.1±0.1	100±0.1	
T	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.2±0.1	0.1±0.1	0.1±0.1	0.1±0.1	99.7±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.4±0.1	0±0	0.1±0.1	

FIGURE 34 (CONTINUED)

[illegible]

FIGURE 35

TP53	A1	G2	T3	C4	A5	C6	A7	G8	C9	A10	C11	A12	T13	G14	A15	C16	G17	C18	A19	G20	C21	I22	I23	G24	T25
Untreated																									
A	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1
C	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1
G	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	100±0.1	0.1±0.1	100±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1
T	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	100±0.1	0.1±0.1	100±0.1
BEC2 + on-target sgRNA																									
A	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1
C	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1
G	0.1±0.1	99.9±0.3	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	99.8±0.4	0.1±0.1	100±0.1	99.9±0.7	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1
T	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	100±0.1	0.1±0.1	100±0.1
BEC2 + off-target sgRNA																									
A	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1
C	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1
G	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	100±0.1	0.1±0.1	100±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1
T	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	100±0.1	0.1±0.1	100±0.1
TP53	G26	A27	G28	G29	C30	G31	C32	T33	G34	C35	C36	C37	C38	C39	A40	C41	C42	A43	T44	G45	A46	G47	C48	G49	C50

FIGURE 35 (CONTINUED)

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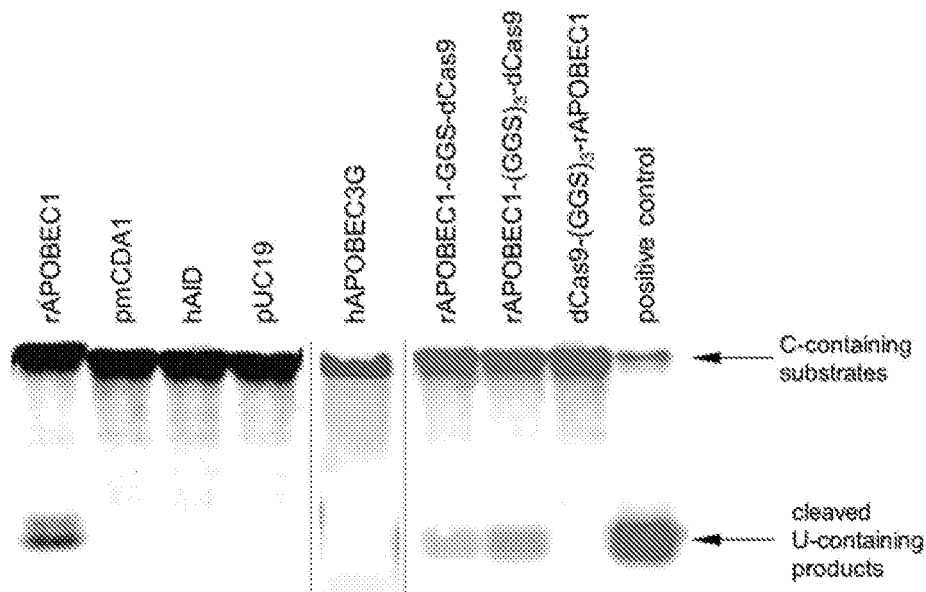


FIGURE 36A

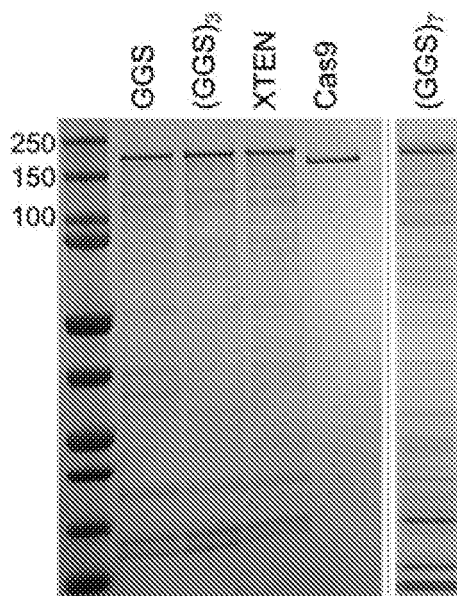


FIGURE 36B

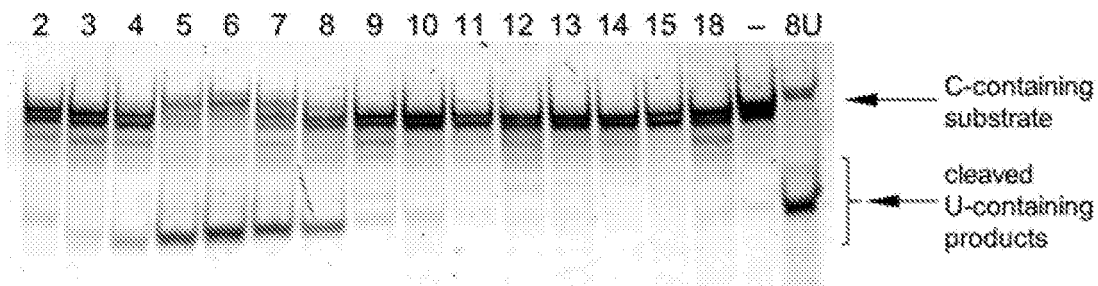


FIGURE 36C

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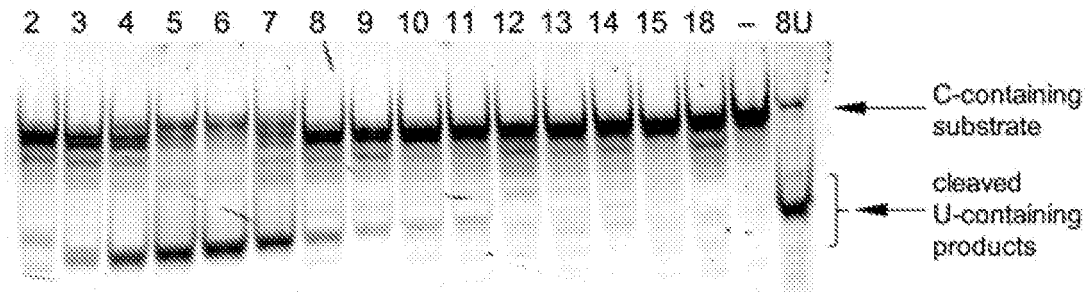


FIGURE 36D

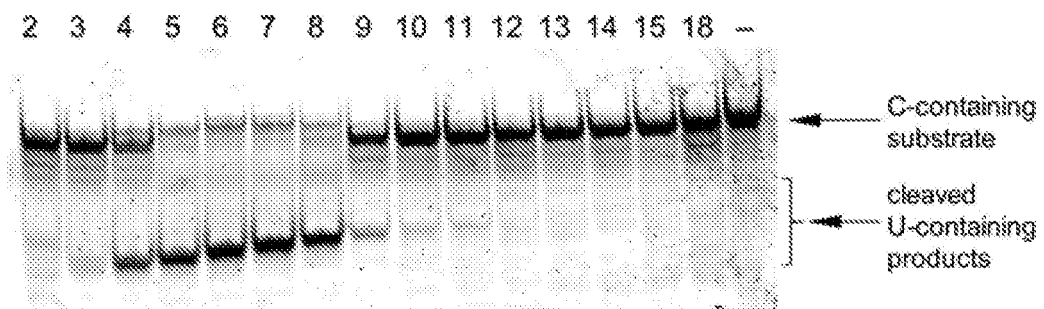


FIGURE 36E

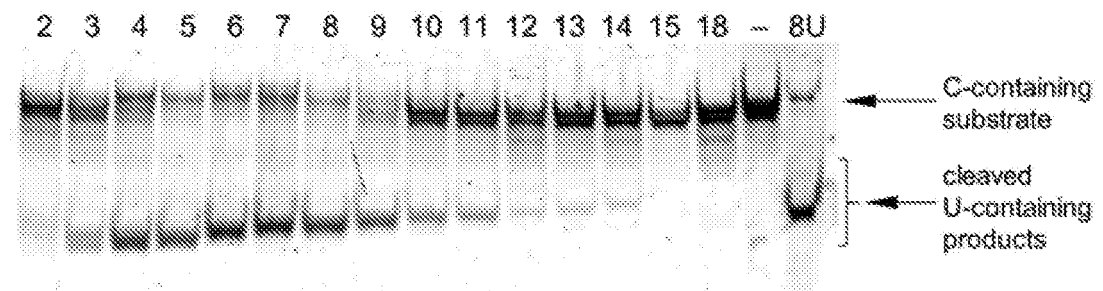


FIGURE 36F

EMX1: GAGTC₅C₆GAGCAGAAGAAGAAGGGG
FANCF: GGAATC₆C₇C₈TTC₁₁TGCAGCACCTTGG
HEK293 site 2: GAAC₄AC₆AAAGCATAGACTGCGGGG
HEK293 site 3: GGCC₄C₅AGACTGAGCACGTGATTGG
HEK293 site 4: GGCAC₅TGCGGCTGGAGGTCCGGG
RNF2: GTC₃ATC₆TTAGTC₁₂ATTACCTGAGG

FIGURE 37A

EMX1		G	A	G	T	C ₁	C ₂	C ₃	C ₄	G	A	G	C	A	G	C	A	G	A	G	A	G	A	G	G	G
1.85 uM BE1		A	0.2	99.9	0.1	0.1	0.1	0.0	0.3	100.0	0.1	0.1	99.9	0.2	99.9	99.7	0.3	100.0	99.9	0.2	99.9	97.9	0.1	0.1	0.2	0.2
		C	0.0	0.0	0.0	0.0	60.4	61.0	0.0	0.0	0.0	99.1	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.0	0.0	2.0	0.0	0.0	0.0	
		G	99.7	0.0	99.9	0.0	0.0	0.0	99.7	0.0	99.9	0.1	0.0	99.7	0.0	0.0	99.7	0.0	0.0	99.8	0.0	0.0	99.8	99.8	99.8	
		T	0.1	0.0	0.0	99.9	99.5	99.0	0.0	0.0	0.0	0.7	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
FANCF		G	G	A	A	T	C ₁	C ₂	C ₃	T	T	C ₁	T	G	C	A	G	A	G	C	A	C	T	G	G	G
1.85 uM BE1		A	0.1	0.2	99.8	99.9	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	99.9	0.2	0.2	95.0	0.1	0.1	0.1	0.1	0.1	0.3	0.4	
		C	0.0	0.0	0.1	0.1	0.0	63.9	64.7	65.0	0.0	0.0	72.6	0.0	0.0	99.4	0.1	0.0	99.7	4.9	99.8	99.9	0.0	0.0	0.0	
		G	99.8	99.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.8	0.2	0.0	99.7	0.2	0.0	0.1	0.0	0.0	99.8	99.8	99.5	
		T	0.1	0.1	0.0	0.0	99.9	96.0	95.1	99.9	99.9	27.3	99.8	0.1	0.3	0.0	0.1	0.0	0.0	0.0	0.0	99.9	0.1	0.1	0.1	
HEK293 site 2		G	A	A	C ₁	A	C ₂	A	C ₃	A	A	G	C	A	T	A	G	A	C	T	G	C	G	G	G	G
1.85 uM BE1		A	0.1	100.0	99.8	0.1	100.0	0.1	99.9	100.0	99.9	0.1	0.1	100.0	0.0	99.9	0.2	100.0	0.1	0.0	0.1	0.1	0.1	0.2	0.2	
		C	0.0	0.0	0.1	80.6	0.0	76.9	0.0	0.0	0.0	0.0	99.6	0.0	0.0	0.1	0.0	99.9	0.0	0.0	99.9	0.0	0.0	0.0	0.0	
		G	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.8	0.0	0.0	0.1	0.0	99.8	0.0	0.0	99.8	0.0	99.8	0.0	99.8	99.8	
		T	0.1	0.0	0.0	19.3	0.0	22.9	0.0	0.0	0.0	0.1	0.3	0.0	99.9	0.0	0.1	0.0	0.0	99.9	0.0	0.1	0.0	0.1	0.0	
HEK293 site 3		G	G	C	C ₁	C ₂	A	G	A	C	T	G	C	A	G	C	A	C	G	T	G	A	T	G	G	G
1.85 uM BE1		A	0.2	0.1	0.1	0.1	0.0	99.9	0.2	99.9	0.1	0.0	0.2	99.9	0.1	0.1	100.0	0.1	0.1	0.0	0.2	98.6	0.0	0.1	0.1	
		C	0.0	0.0	92.2	74.8	71.5	0.0	0.0	0.0	96.6	0.0	0.0	99.8	0.0	0.0	99.7	0.0	0.0	0.0	0.0	1.3	0.0	0.0	0.0	
		G	99.7	99.8	0.0	0.0	0.0	0.0	99.8	0.0	0.0	0.0	99.8	0.0	99.8	0.0	0.0	99.8	0.0	99.8	0.0	99.8	0.0	99.9	99.8	
		T	0.1	0.1	7.7	25.1	28.5	0.0	0.0	0.0	3.3	99.9	0.1	0.0	0.0	0.1	0.0	0.2	0.0	99.9	0.0	0.0	100.0	0.0	0.0	
HEK293 site 4		G	G	C	A	C ₁	T	G	C	G	C	G	C	T	G	G	A	G	G	T	G	G	G	G	G	G
1.85 uM BE1		A	0.3	0.2	0.1	100.0	0.1	0.0	0.2	0.1	0.2	0.1	0.0	0.3	0.5	100.0	0.1	0.1	0.0	0.1	0.1	0.1	0.1	0.2	0.2	
		C	0.0	0.0	98.8	0.0	60.1	0.0	0.0	97.0	0.0	0.0	99.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
		G	99.7	99.7	0.0	0.0	0.0	0.0	99.8	0.0	99.8	99.8	0.0	0.0	99.7	99.4	0.0	99.8	99.8	0.1	99.8	99.8	99.8	99.8	99.7	
		T	0.0	0.1	1.1	0.0	39.8	100.0	0.1	2.9	0.0	0.1	0.5	100.0	0.0	0.1	0.0	0.0	0.0	99.9	0.0	0.1	0.1	0.0	0.0	
RNF2		G	T	C ₁	A	T	C ₂	T	T	A	G	T	C ₁	A	T	A	C	T	A	C	T	G	A	G	G	G
1.85 uM BE1		A	0.1	0.0	0.1	99.9	0.0	0.0	0.0	99.9	0.1	0.0	0.1	99.9	0.0	0.0	99.9	0.1	0.0	0.0	0.1	98.6	0.0	0.0	0.0	
		C	0.0	0.0	59.1	0.0	0.0	57.8	0.0	0.0	0.1	0.0	0.0	86.4	0.0	0.0	0.1	99.9	99.9	0.0	0.0	1.4	0.0	0.0	0.0	
		G	99.9	0.1	0.0	0.0	0.0	0.0	0.0	99.8	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.8	0.0	99.9	99.9	
		T	0.0	99.9	40.8	0.0	100.0	42.1	100.0	100.0	0.0	0.1	99.9	13.4	0.0	100.0	99.9	0.0	0.0	0.0	99.9	0.1	0.0	0.1	0.0	

FIGURE 37B

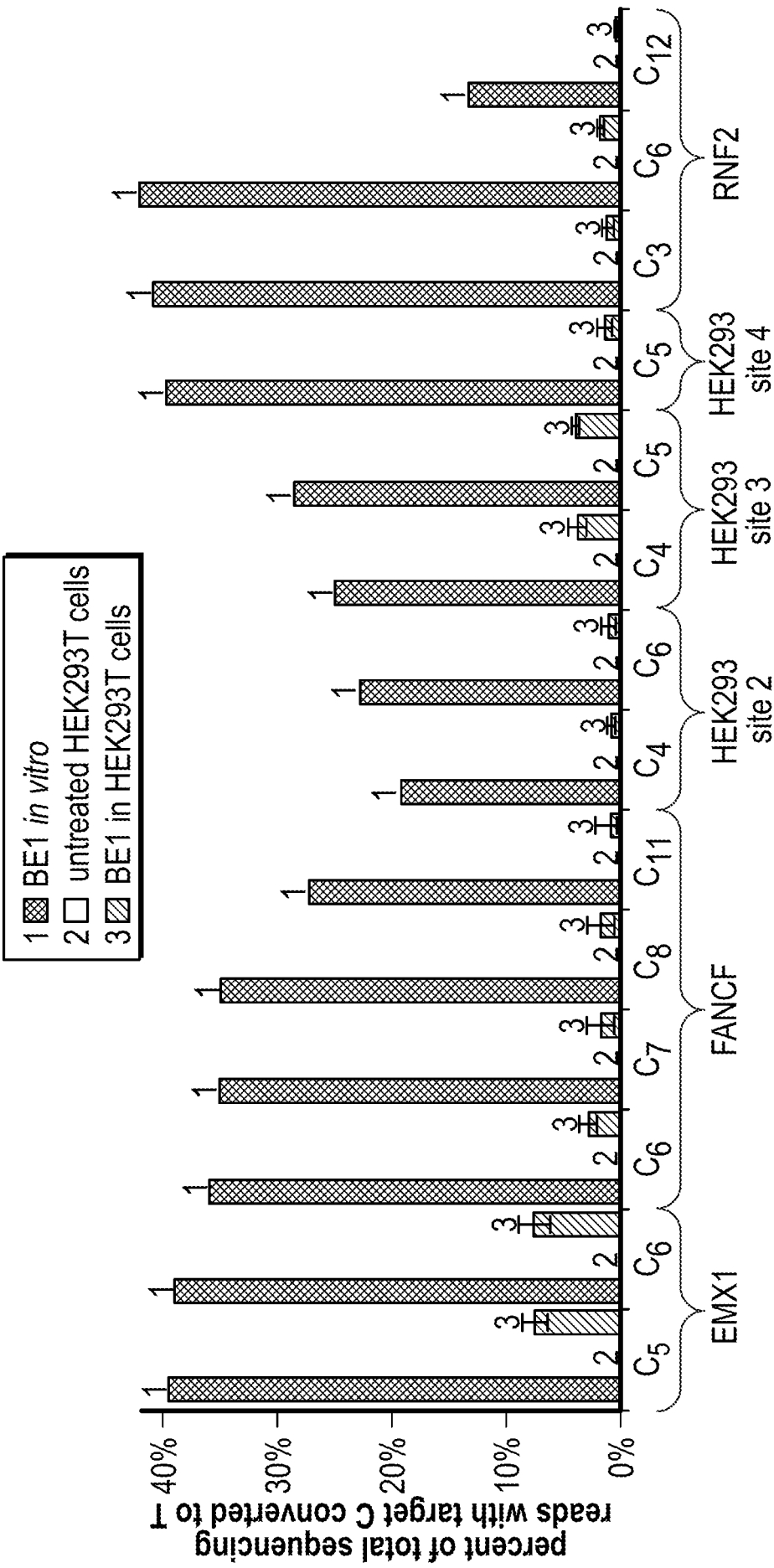


FIGURE 37C

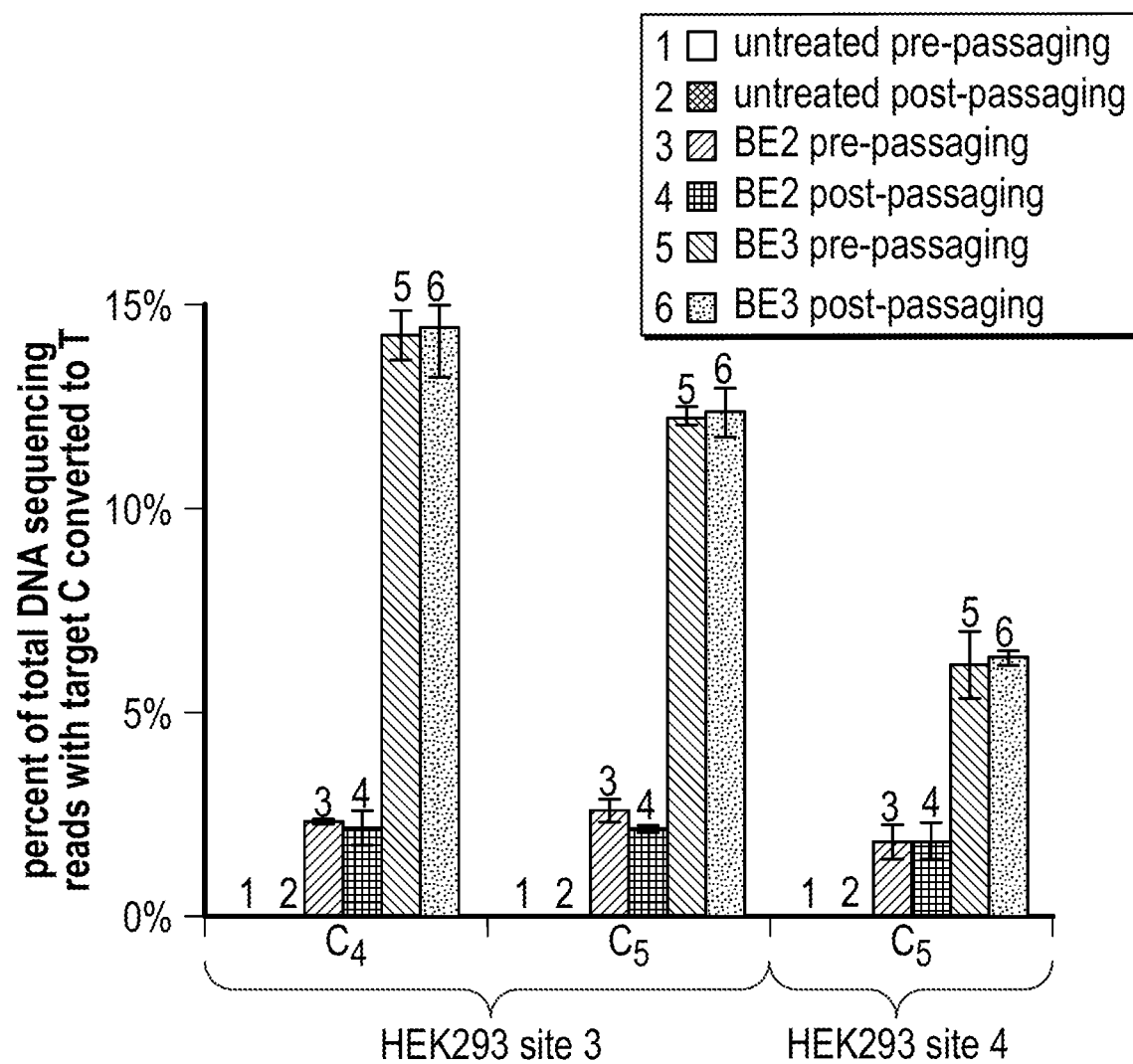


FIGURE 38

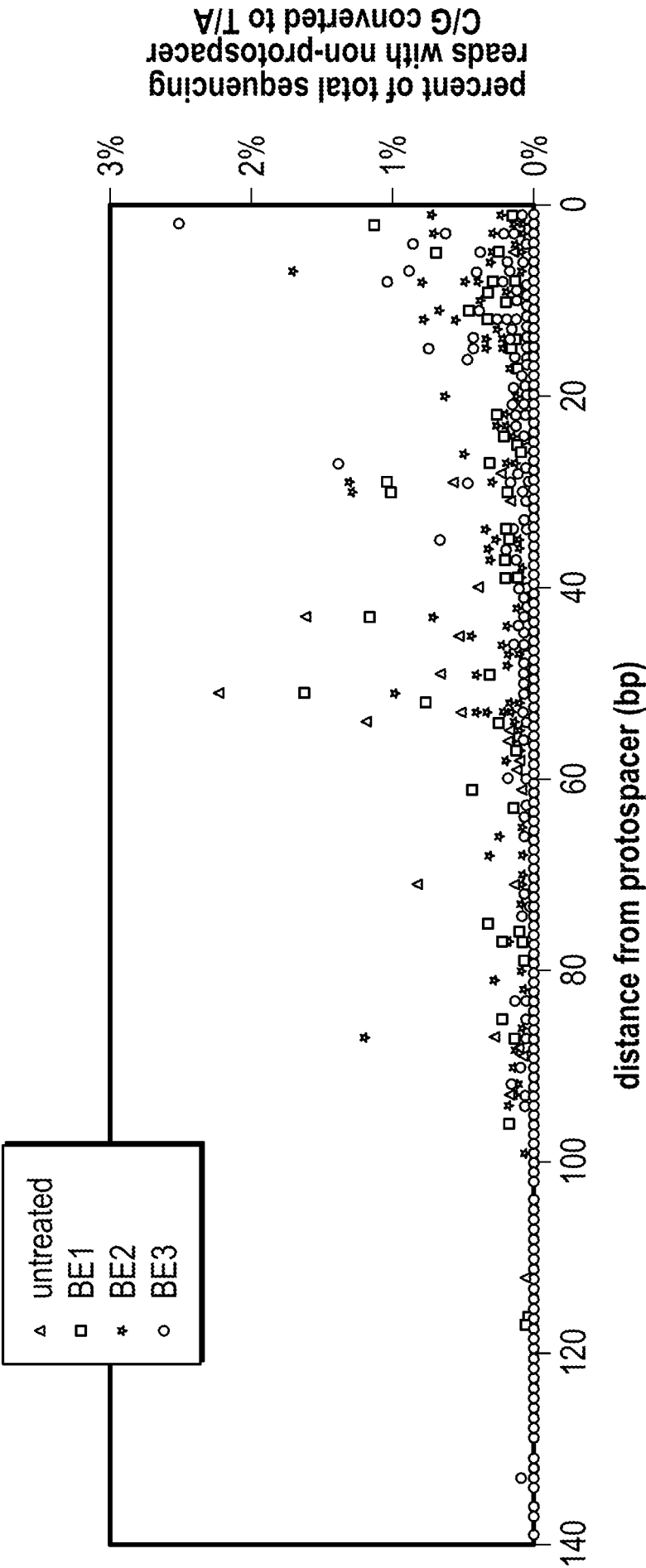


FIGURE 39A

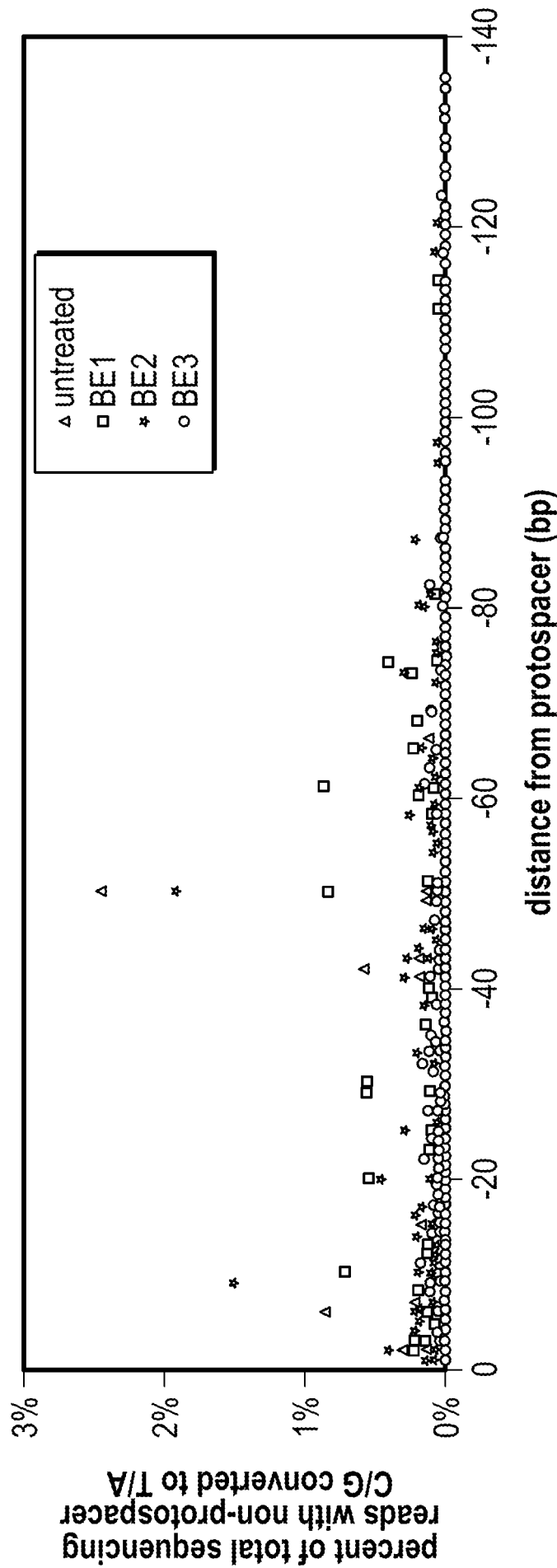


FIGURE 39B

non-protospacer C/Gs	average C/G (%)	average T/A (%)	lowest T/A (%)	highest T/A (%)
untreated	99.95 ± 0.14	0.02 ± 0.02	0.00	2.44
BE1	99.95 ± 0.24	0.03 ± 0.03	0.00	1.64
BE2	99.95 ± 0.13	0.03 ± 0.03	0.00	1.92
BE3	99.97 ± 0.09	0.02 ± 0.02	0.00	2.52

FIGURE 39C

untreated APOE4C158R	Lys				Arg				Leu				Ala				Val				Tyr				Gln				indel %
	A		G		C		G		C		T		G		C		G		T		A		C		A		G		
	G	A	A	G	C	G	C	G	C	T	G	C	A	G	C	A	G	T	G	A	T	A	C	C	A	G	G	0.0	
A	0.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	
C	0.0	0.0	0.0	0.0	100.0	0.0	100.0	100.0	0.0	0.0	0.1	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0	0.0	0.0	
G	100.0	0.0	0.0	99.9	0.0	100.0	0.0	0.0	100.0	99.9	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	100.0	0.0	
T	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	

BE3 + on-target sgRNA APOE4C158R	Lys				Arg → Cys				Leu → Leu				Ala				Val				Tyr				Gln				indel %
	A		G		C		G		C		T		G		C		G		T		A		C		A		G		
	G	A	A	G	C	G	C	G	C	T	G	C	A	G	C	A	G	T	G	A	T	A	C	C	A	G	G	6.1	
A	0.1	100.0	100.0	0.0	1.0	0.0	1.6	0.6	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.1	0.1	
C	0.0	0.0	0.0	0.0	39.1	0.0	62.9	61.3	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0	0.0	0.0	
G	99.9	0.0	0.0	100.0	1.5	99.9	0.7	0.5	0.0	100.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	99.9	0.0	
T	0.0	0.0	0.0	0.0	59.3	0.1	35.7	37.5	100.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

BE3 + off-target sgRNA APOE4C158R	Lys				Arg				Leu				Ala				Val				Tyr				Gln				indel %
	A		G		C		G		C		T		G		C		G		T		A		C		A		G		
	G	A	A	G	C	G	C	G	C	T	G	C	A	G	C	A	G	T	G	A	T	A	C	C	A	G	G	0.0	
A	0.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	
C	0.0	0.0	0.0	0.0	99.9	0.0	100.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0	0.0	0.0	
G	100.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0	0.0	
T	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

Cas9 + HDR APOE4C158R	Lys				Arg → Cys				Leu				Ala				Val				Tyr				Gln				indel %
	A		G		C		G		C		T		G		C		G		T		A		C		A		G		
	G	A	A	G	C	G	C	G	C	T	G	C	A	G	C	A	G	T	G	A	T	A	C	C	A	G	G	40.1	
A	0.0	99.7	99.7	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	98.0	0.0	0.0	0.0	0.0	0.0	99.1	0.1	0.5	98.8	0.0	0.0	0.0	0.0	0.0	0.0	
C	0.0	0.3	0.2	0.0	99.8	0.0	99.8	99.9	0.1	0.1	0.2	99.9	1.8	0.4	0.2	0.3	0.2	0.2	0.5	99.7	99.6	0.7	0.0	0.0	0.0	0.0	0.0	0.0	
G	99.7	0.0	0.0	99.9	0.0	99.7	0.1	0.0	0.1	99.8	99.7	0.0	0.1	98.6	1.4	99.4	0.2	0.3	0.1	99.4	0.2	0.3	0.1	0.0	0.0	99.4	100.0	0.0	
T	0.2	0.0	0.1	0.1	0.1	0.3	0.1	0.1	99.8	0.2	0.1	0.1	0.1	1.1	98.4	0.4	99.7	0.2	0.2	0.0	0.5	0.6	0.0	0.0	0.0	0.0	0.0	0.0	

FIGURE 40A

untreated TP53Y163C	Arg				Ala				Met				Ala				Ile				Cys				Lys				indel %
	C		G		C		G		A		T		C		G		A		T		C		G		A		T		
	C	G	C	G	C	G	C	G	A	T	A	T	C	G	C	G	A	T	C	T	C	G	A	A	A	G	C	C	
A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	99.9	0.0	0.0	0.0	
C	100.0	100.0	0.0	100.0	0.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0	100.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	
G	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	100.0	0.0	
T	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

BE3 + on-target sgRNA TP53Y163C	Arg				Ala				Met				Ala				Ile				Cys → Tyr				Lys				indel %
	C		G		C		G		A		T		C		G		A		T		C		G		A		T		
	C	G	C	G	C	G	C	G	A	T	A	T	C	G	C	G	A	T	C	T	C	G	A	A	A	G	C	C	
A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	100.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.3	0.5	99.9	99.9	0.0	0.0	
C	100.0	100.0	0.0	100.0	0.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0	100.0	100.0	0.0	0.0	100.0	0.0	0.0	99.5	0.0	0.0	0.0	100.0	
G	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.2	0.0	0.0	0.0	100.0	0.0	
T	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.5	0.0	0.0	0.0	0.0	0.0	

BE3 + off-target sgRNA TP53Y163C	Arg				Ala				Met				Ala				Ile				Cys				Lys				indel %
	C		G		C		G		A		T		C		G		A		T		C		G		A		T		
	C	G	C	G	C	G	C	G	A	T	A	T	C	G	C	G	A	T	C	T	C	G	A	A	A	G	C	C	
A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	100.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	99.9	0.0	0.0	0.0		
C	100.0	100.0	0.0	99.9	0.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0	100.0	99.9	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	
G	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	
T	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

Cas9 + HDR TP53Y163C	Arg				Ala				Met				Ala				Ile				Cys → Tyr				Lys				indel %
	C		G		C		G		A		T		C		G		A		T		C		G		A		T		
	C	G	C	G	C	G	C	G	A	T	A	T	C	G	C	G	A	T	C	T	C	G	A	A	A	G	C	C	
A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	100.0	0.0	0.4	0.0		
C	100.0	100.0	0.0	100.0	0.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0	100.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	99.6	
G	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	
T	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

FIGURE 40B

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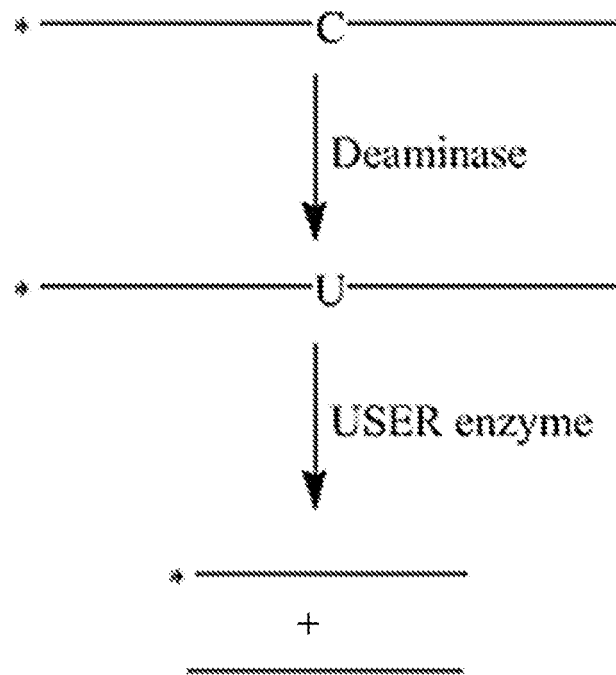


FIGURE 41

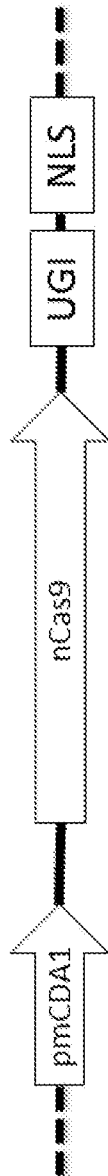
[illegible]

FIGURE 42



Hek-2 site, shown: coding strand ($G \rightarrow A$), target: template strand ($C \rightarrow T$)

	P	A	M	C	C	G	C	C	A	G	T	C	T	A	T	G	C	T	9	8	7	6	5	4	3	2	1	-1	-2	-3
	C	G	C	C	C	G	C	C	A	G	T	C	T	A	T	G	C	T	9	8	7	6	5	4	3	2	1	-1	-2	-3
CDA																														
A	0.0%	0.0%	0.2%	0.0%	0.5%	0.2%	0.0%	99.9%	0.0%	0.0%	0.0%	0.0%	0.0%	99.9%	0.0%	19.2%	0.0%	0.0%	0.0%	0.0%	0.0%	32.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	99.9%	0.8%
C	99.9%	0.0%	99.7%	99.9%	99.5%	0.0%	99.9%	0.0%	0.0%	0.0%	0.0%	99.9%	0.0%	0.0%	0.0%	0.5%	100.0%	0.0%	0.0%	0.0%	4.5%	0.0%	0.0%	0.1%	0.0%	0.0%	99.8%	99.6%	0.0%	0.3%
G	0.0%	0.0%	0.0%	0.0%	0.0%	99.7%	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	80.0%	0.0%	0.0%	0.0%	0.0%	60.4%	0.0%	0.0%	58.3%	0.0%	0.0%	0.0%	0.0%	0.0%	98.8%
T	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%	100.0%	0.0%	100.0%	100.0%	0.3%	0.0%	100.0%	100.0%	100.0%	2.4%	100.0%	100.0%	8.0%	100.0%	100.0%	0.2%	0.4%	0.0%	0.1%
TAPOBEC1																														
A	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.0%	99.9%	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	18.4%	0.0%	0.0%	20.9%	0.0%	0.0%	0.0%	0.0%	99.9%	0.0%
C	99.9%	0.0%	100.0%	99.9%	99.9%	0.0%	100.0%	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	38.6%	0.0%	0.0%	0.4%	0.0%	0.0%	99.9%	99.9%	0.0%	0.0%	0.0%
G	0.0%	99.9%	0.0%	0.0%	0.0%	99.9%	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	99.3%	0.0%	0.0%	0.0%	42.3%	0.0%	0.0%	77.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	99.7%
T	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%	100.0%	0.0%	100.0%	100.0%	0.0%	0.0%	100.0%	100.0%	100.0%	0.7%	100.0%	100.0%	1.1%	100.0%	100.0%	0.0%	0.0%	0.0%	0.3%
untreated																														
A	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.0%	99.9%	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	99.9%	0.0%
C	99.9%	0.0%	100.0%	99.9%	99.9%	0.0%	100.0%	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	99.9%	99.9%	0.0%	0.0%
G	0.0%	0.0%	0.0%	0.0%	0.0%	99.9%	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%	0.0%	99.9%	0.0%	99.9%	99.9%	0.0%	0.0%	0.0%	0.0%	0.0%	99.9%
T	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%	100.0%	0.0%	100.0%	100.0%	0.0%	0.0%	100.0%	100.0%	100.0%	0.0%	100.0%	100.0%	0.1%	100.0%	100.0%	0.0%	0.0%	0.0%	0.0%

FIGURE 43

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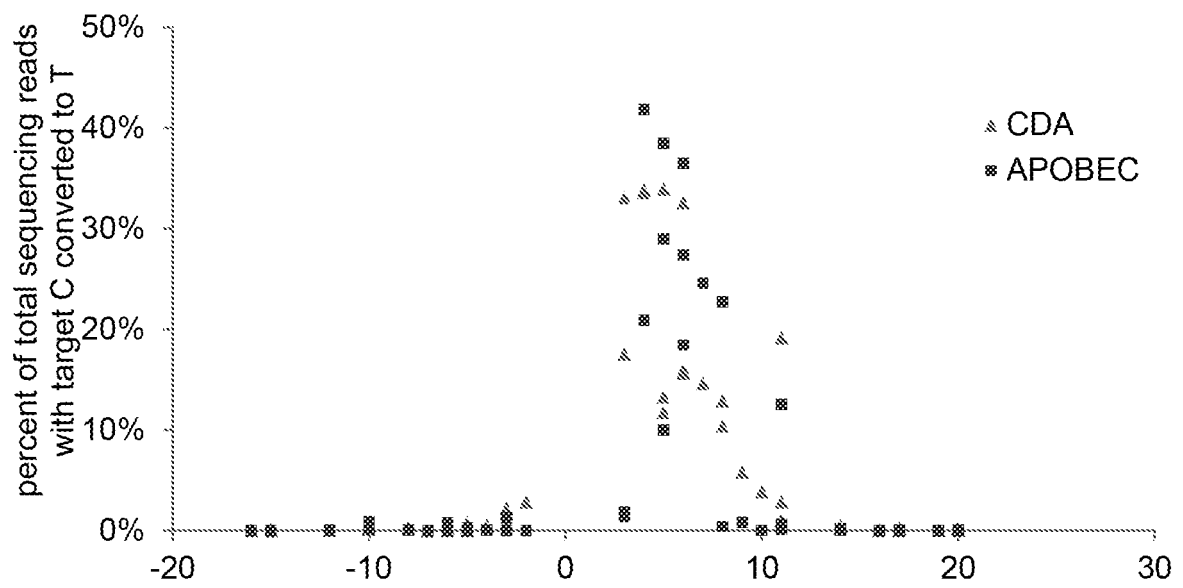


FIGURE 44

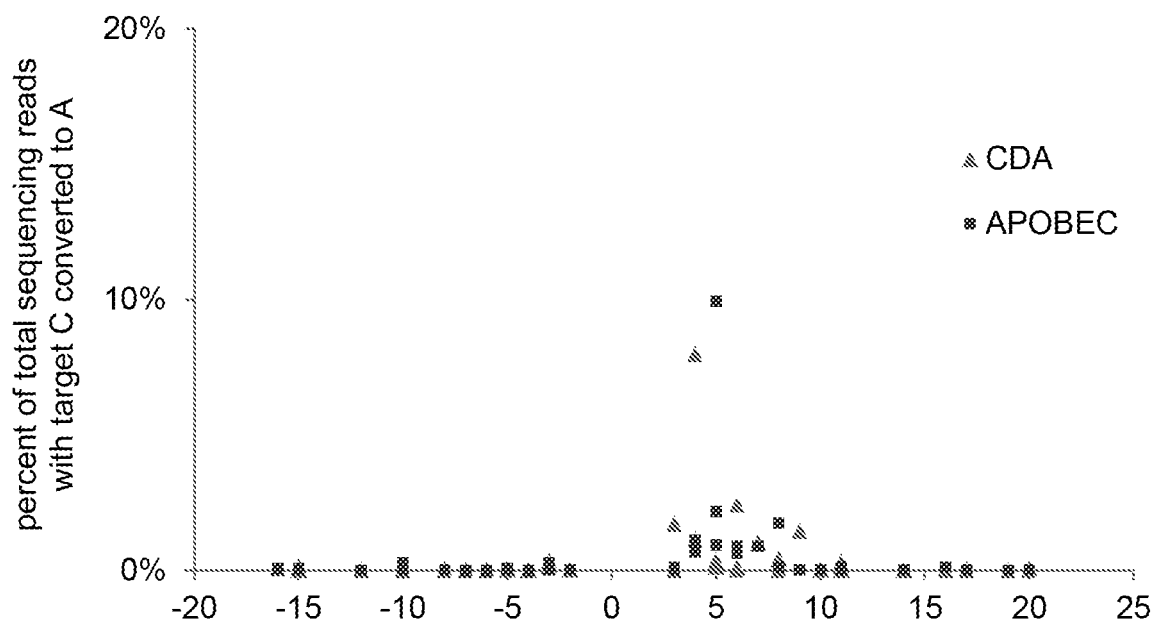


FIGURE 45

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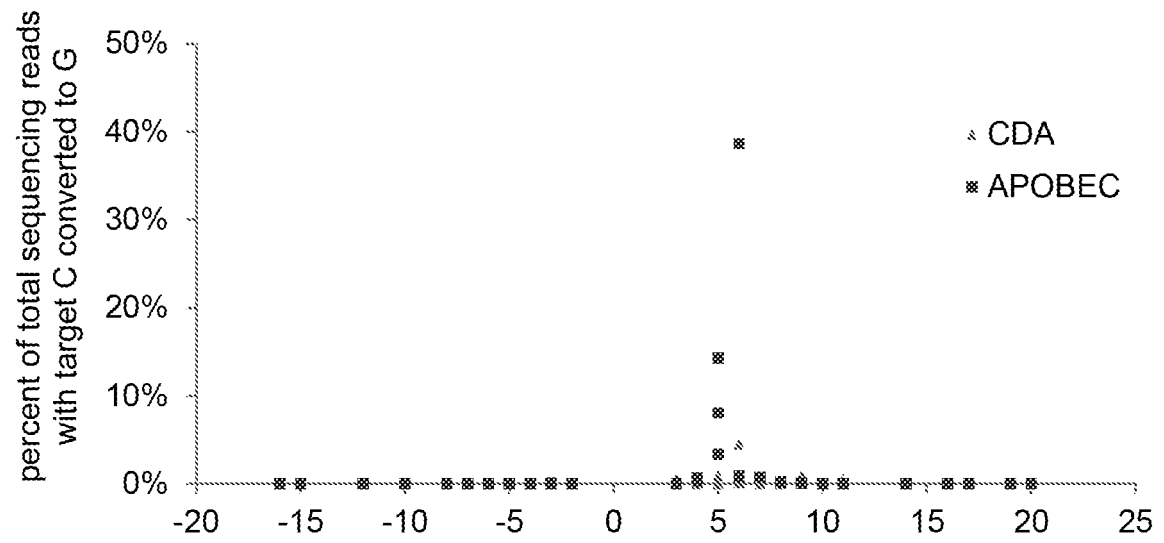
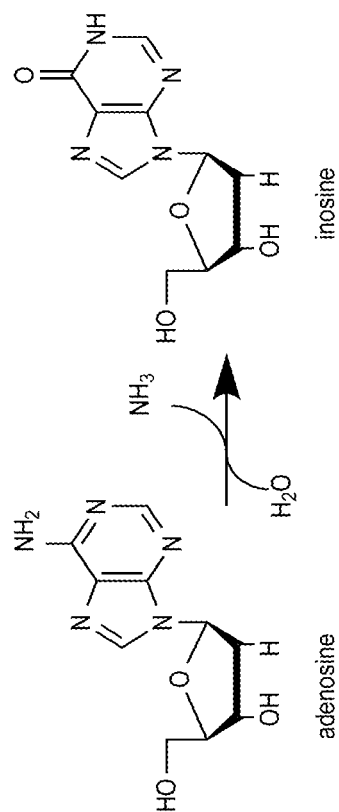
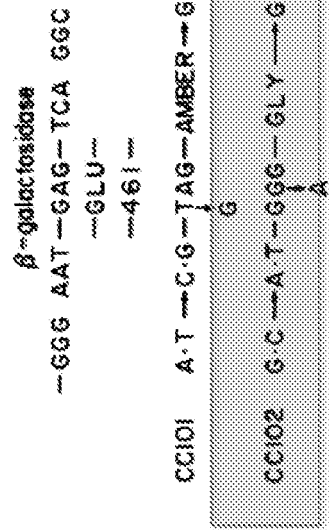


FIGURE 46

FIGURE 47



Utilizing a bacterial strain with lacZ encoded on the F plasmid
Critical glutamic acid residue is mutated. Reversion restores lacZ activity.



Strain used to develop selection assay
Constructs used: APOBEC1 and CDA

FIGURE 48

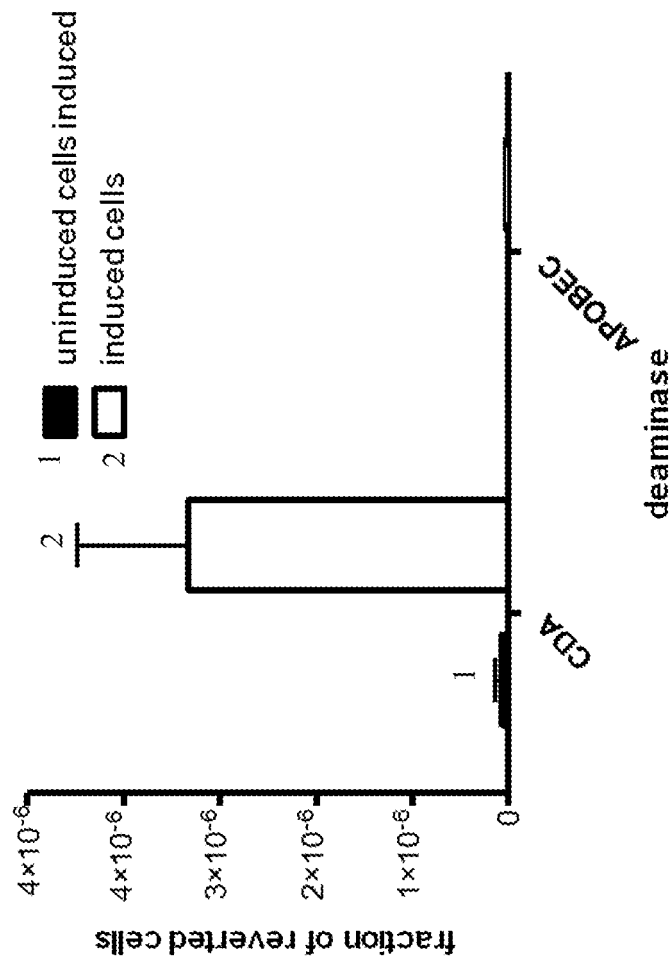
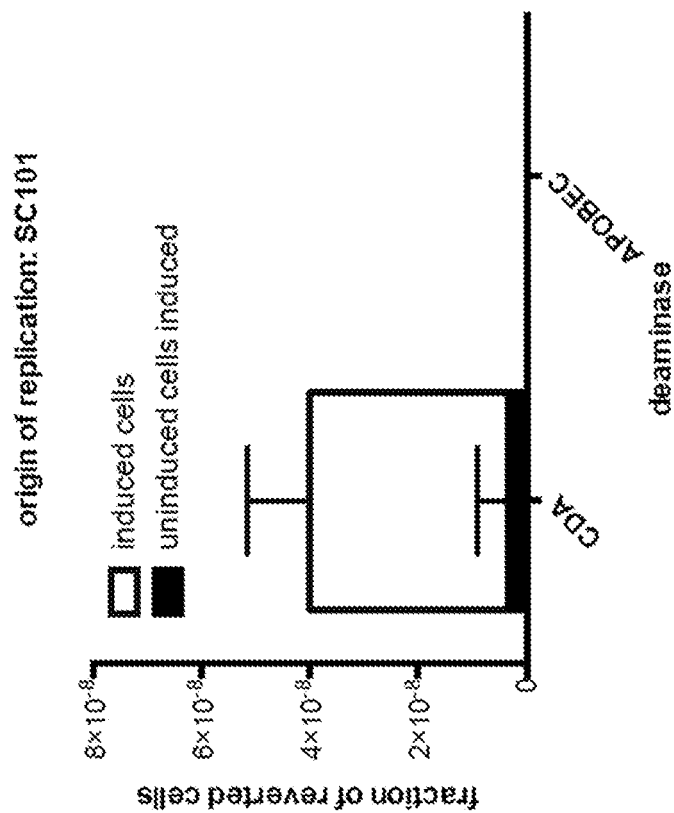


FIGURE 49



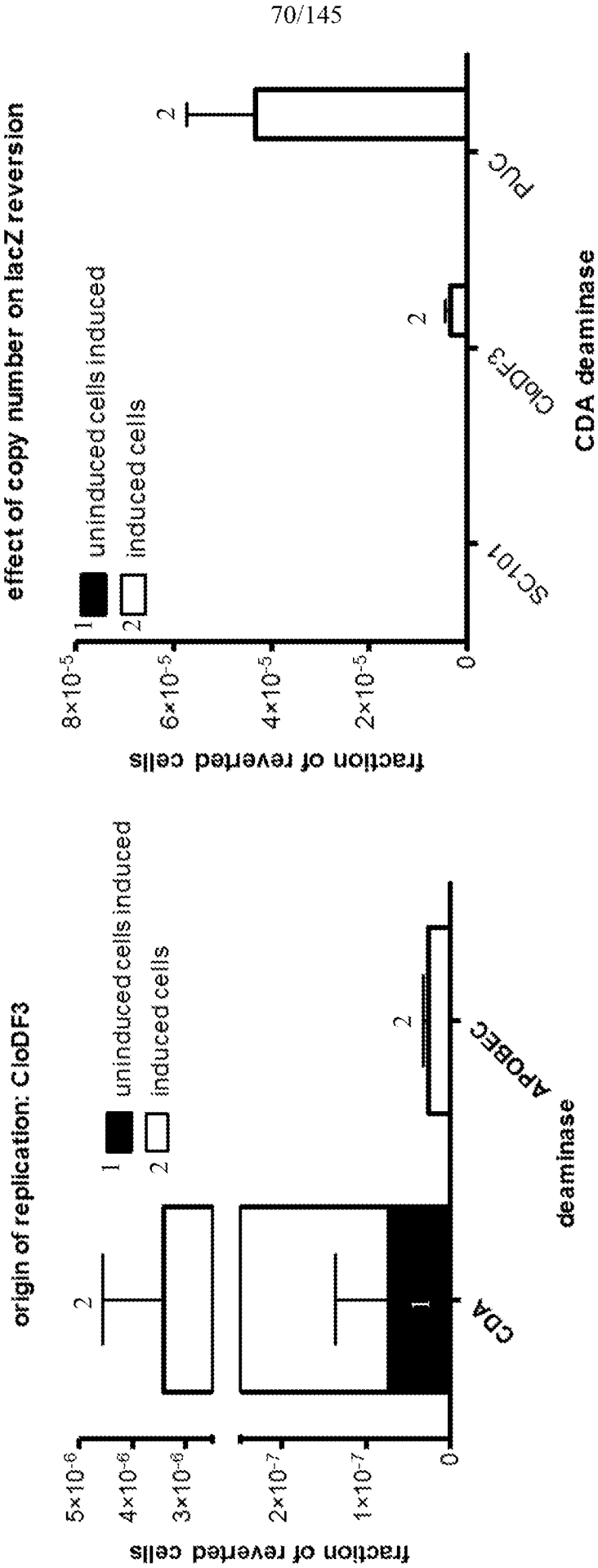
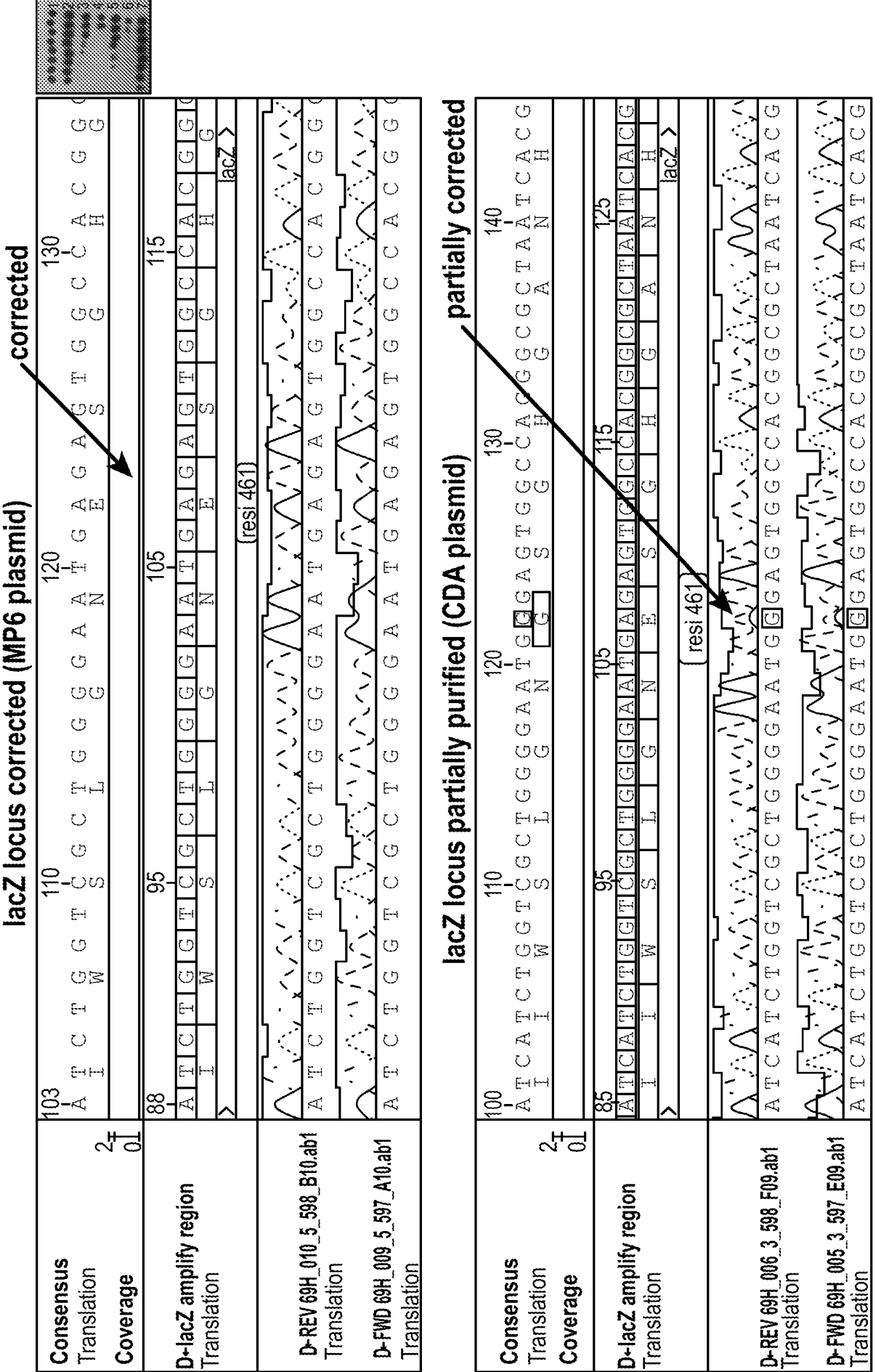


FIGURE 49 (CONTINUED)



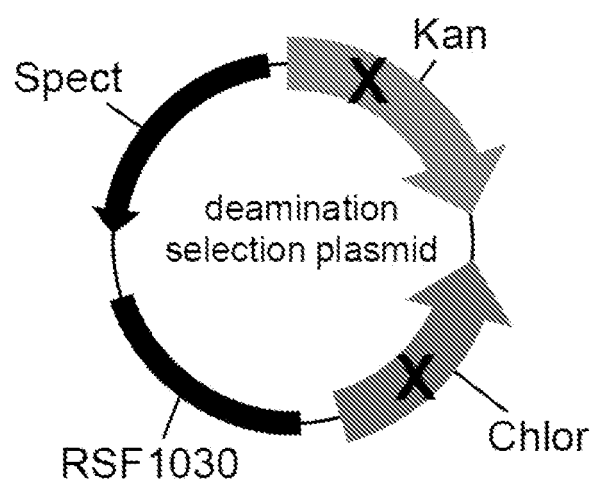
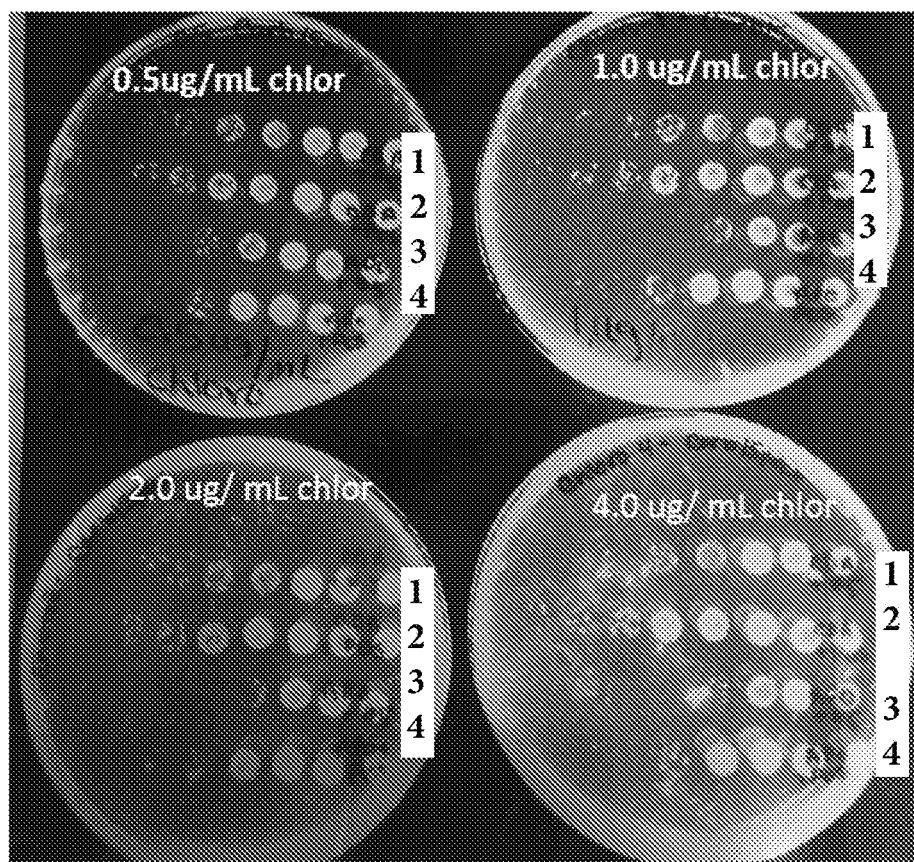
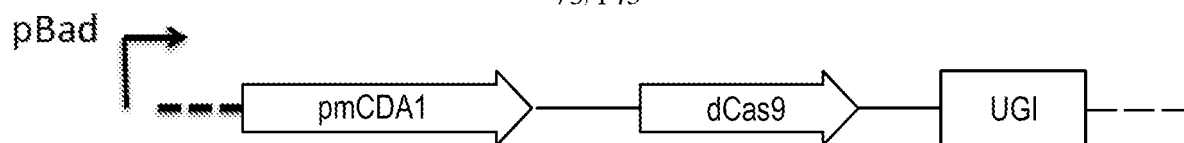


FIGURE 51

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Row 1: CDA-dCas9 + selection plasmid (chlor^S)

Row 2: CDA-dCas9 + pos. control selection (chlor^R)

Row 3: rAPOBEC-dCas9 + selection plasmid (chlor^S)

Row 4: rAPOBEC-dCas9 + pos. control selection (chlor^R)

FIGURE 52

rAPOBEC-XTEN-dCas9-UGI on 8 ug/mL chlor

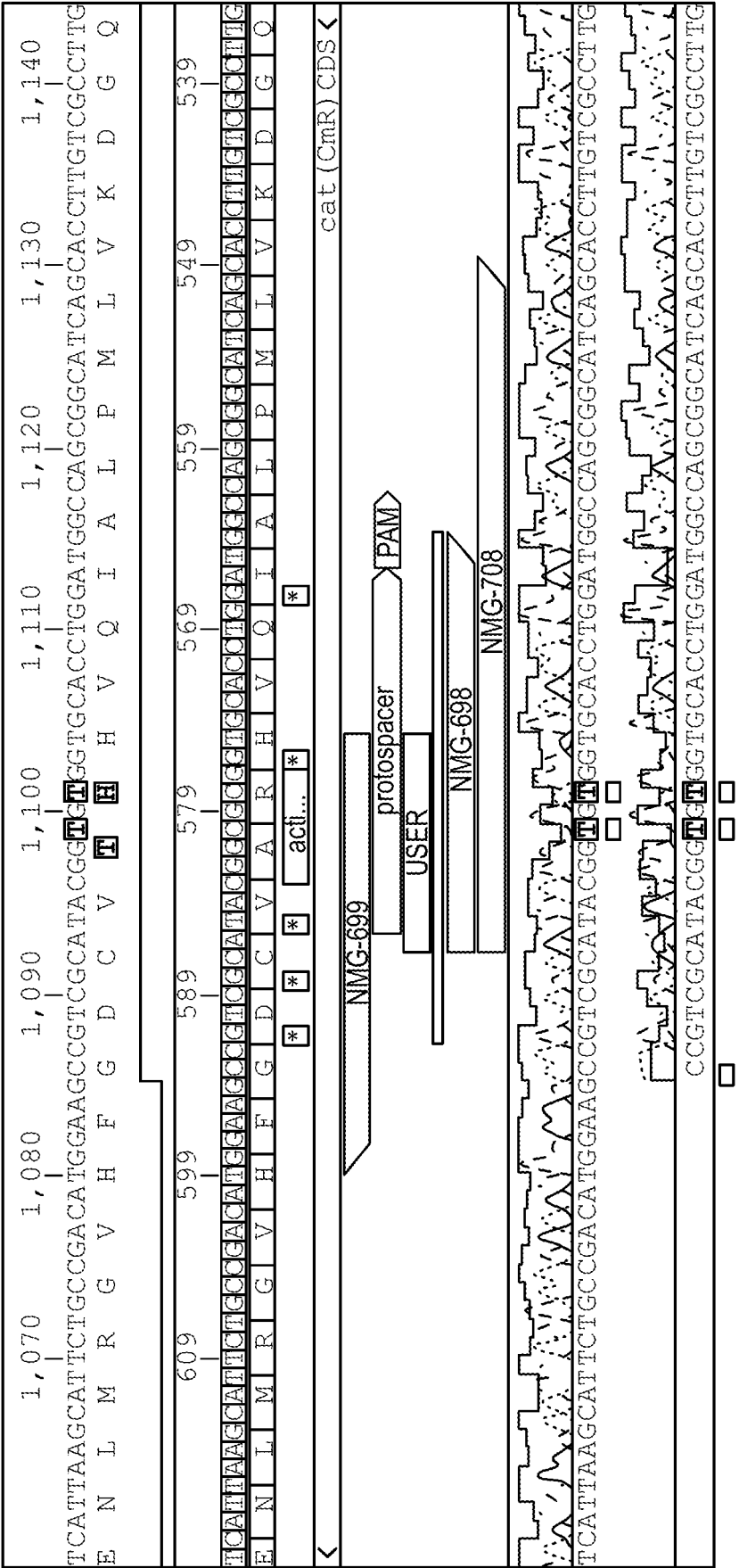


FIGURE 53A

FIGURE 53B

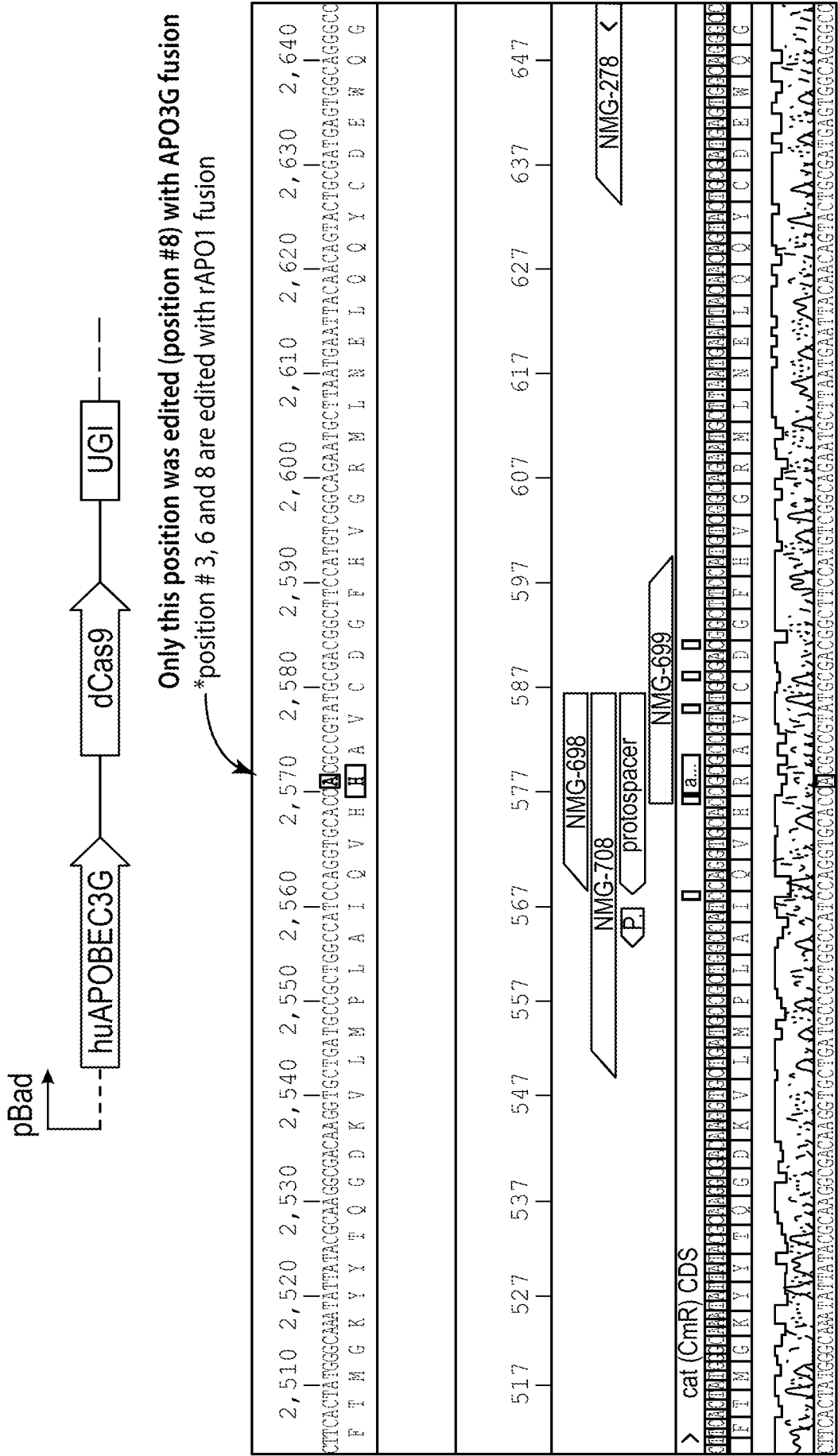


FIGURE 54

EMX1 on target	G	A	G	T	C	C	G	A	G	A	G	A	A	G	A	A	G	G	G
untreated					0±0	0±0													
BE3					42.8±1.3	41.9±5.5													
HF-BE3					40.3±5.5	40.7±5.6													
EMX1 off target 1	G	A	G	T	T	A	G	A	G	A	G	A	A	G	A	A	A	G	G
untreated																			
BE3																			
HF-BE3																			
EMX1 off target 2	G	A	G	T	C	T	A	A	G	A	G	A	A	G	A	A	G	A	G
untreated					0±0														
BE3					12.1±0.9														
HF-BE3					1.7±0.3														
EMX1 off target 3	G	A	G	G	C	C	G	A	G	A	G	A	A	G	A	A	C	G	G
untreated					0±0	0±0													
BE3					6.8±2	8.1±2.5													
HF-BE3					0±0	0±0													
EMX1 off target 4	G	A	G	T	C	C	T	A	G	A	G	A	A	G	A	A	G	A	G
untreated					0±0	0±0													
BE3					1.3±0.1	1.3±0.1													
HF-BE3					0.1±0	0.2±0													

FIGURE 55

EMX1 off target 6	G	A	G	T	C	C	G	G	G	A	A	A	G	A	A	G	A	A	G	G
	untreated																			
	BE3																			
HF-BE3	0±0																			
	0.4±0																			
	0±0																			
EMX1 off target 7	G	A	G	C	C	G	G	A	G	C	A	A	G	A	A	G	A	G	G	G
	untreated																			
	BE3																			
HF-BE3	0±0																			
	0±0																			
	0±0																			
EMX1 off target 8	A	A	G	T	C	C	G	A	G	G	A	G	A	G	A	A	G	A	A	G
	untreated																			
	BE3																			
HF-BE3	0±0																			
	0±0																			
	0±0																			
EMX1 off target 9	G	A	A	T	C	C	A	A	G	C	A	G	A	G	A	A	G	A	G	A
	untreated																			
	BE3																			
HF-BE3	0±0																			
	0.1±0																			
	0±0																			
EMX1 off target 10	A	C	G	T	C	T	G	A	G	C	A	G	A	A	G	A	A	T	G	G
	untreated																			
	BE3																			
HF-BE3	0±0																			
	1.5±0.1																			
	1.1±0.2																			

FIGURE S5 (CONTINUED)

EMX1		C ₃	C ₈	C ₁₂	indel %
untreated	A	0±0	0±0	0±0	0±0
	C	99.9±0	99.9±0	99.9±0	
	G	0±0	0±0	0±0	
	T	0±0	0±0	0±0	
BE3	A	1.3±0.1	0.7±0.2	0±0	2.6±0.3
	C	51.7±1	55.2±0.1	99.9±0	
	G	4±0.7	1.9±0.4	0±0	
	T	42.8±0.2	41.9±0.4	0±0	
HF BE3	A	1.5±0.7	0.5±0.1	0±0	1±0.1
	C	44.8±8.5	49.9±6.6	99.9±0	
	G	4.2±1.2	0.6±0.2	0±0	
	T	49.3±6.5	48.7±6.3	0±0	

RNF2		C ₃	C ₈	C ₁₂	indel %
untreated	A	0±0	0±0	0±0	0±0
	C	99.9±0	99.9±0	99.9±0	
	G	0±0	0±0	0±0	
	T	0±0	0±0	0±0	
BE3	A	0.4±0	1.5±0.2	0.1±0	2.3±0.3
	C	70.9±2.7	45±0	95±0.2	
	G	0±0	12.6±2.4	0.1±0	
	T	28.5±2.7	40.7±2.7	4.6±0.2	
HF BE3	A	0±0	0.2±0	0±0	0.5±0.1
	C	76.8±1.8	64.5±3.3	95.4±0.1	
	G	0±0	2.4±0.5	0±0	
	T	23±1.8	32.7±2.6	4.5±0.1	

FANCF		C ₅	C ₇	C ₈	C ₁₁	indel %
untreated	A	0±0	0±0	0±0	0±0	0±0
	C	99.9±0	99.9±0	99.9±0	99.9±0	
	G	0±0	0±0	0±0	0±0	
	T	0±0	0±0	0±0	0±0	
BE3	A	0.8±0.1	1.2±0.3	1.2±0.1	0.2±0.1	5.8±0.9
	C	64.7±5.9	67.9±5.1	68.9±5.2	85.4±2.7	
	G	0.6±0	0.7±0	0.7±0.1	0.1±0	
	T	33.8±5.7	29.9±4.8	29±5	14.1±2.6	
HF BE3	A	0.9±0.2	2±0.4	0.9±0.2	0.4±0	5.9±0.7
	C	52.5±8.4	57.7±7.6	61.9±6.8	84.7±2.4	
	G	1.4±0.2	0.6±0	0.5±0.1	0.3±0	
	T	45±8	39.5±7.2	36.5±6.5	14.4±2.2	

HEK3		C ₅	C ₇	C ₈	C ₁₁	indel %
untreated	A	0±0	0±0	0±0	0±0	0±0
	C	99.9±0	99.9±0	99.9±0	99.9±0	
	G	0±0	0±0	0±0	0±0	
	T	0±0	0±0	0±0	0±0	
BE3	A	0±0	1.6±0.2	1.5±0.3	0.2±0	2.7±0.4
	C	98.7±0.2	48.6±5.4	40.8±6.7	96.6±0.1	
	G	0±0	1.4±0.2	10.5±1.2	0.3±0	
	T	1.1±0.2	48.2±4.9	47±5.2	0.7±0.1	
HF BE3	A	0±0	0.8±0.2	1.1±0.3	0.4±0	4.1±0.7
	C	97.8±0.4	65±3.8	40.4±6.3	95.9±0.5	
	G	0±0	0.9±0.2	6.1±1.1	0.7±0.2	
	T	2±0.4	33±3.4	52.2±5.2	2.7±0.2	

HEK4		C ₅	C ₇	C ₈	C ₁₁	indel %
untreated	A	0±0	0±0	0±0	0±0	0±0
	C	99.9±0	99.9±0	99.9±0	99.9±0	
	G	0±0	0±0	0±0	0±0	
	T	0±0	0±0	0±0	0±0	
BE3	A	0±0	5.4±1.3	0±0	0±0	3±0.7
	C	98.7±0	44.5±8.2	98.9±0	99.8±0	
	G	0±0	18.1±2.3	0±0	0±0	
	T	1.1±0.1	31.9±4.8	0.9±0.1	0.1±0	
HF BE3	A	0±0	5.2±0.8	0±0	0±0	1.3±0
	C	99.6±0	38.6±9	98.5±0.1	99.9±0	
	G	0±0	16±2.8	0±0	0±0	
	T	0.2±0	42.1±5.3	1.3±0.1	0±0	

FIGURE 56

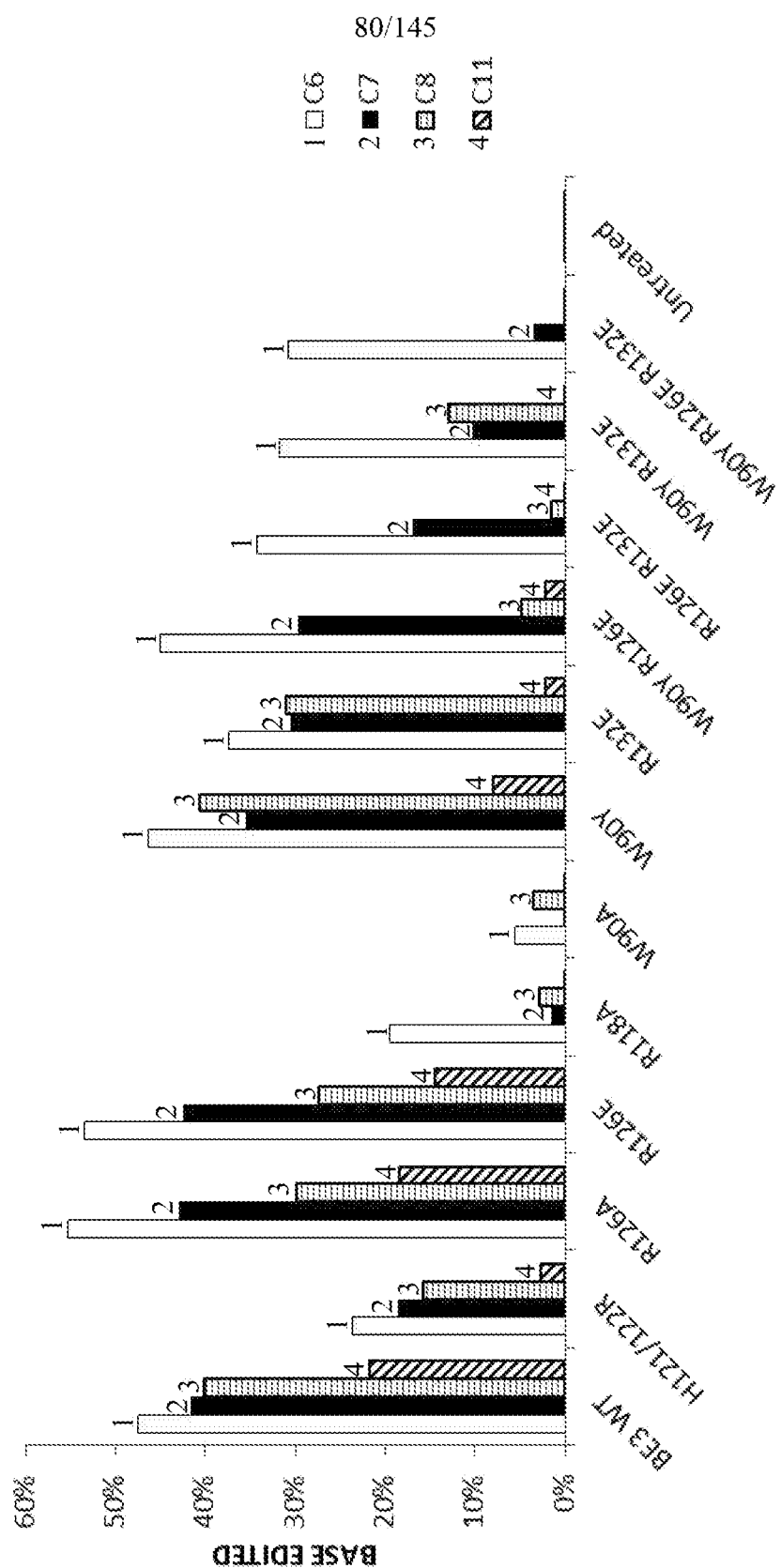


FIGURE 57

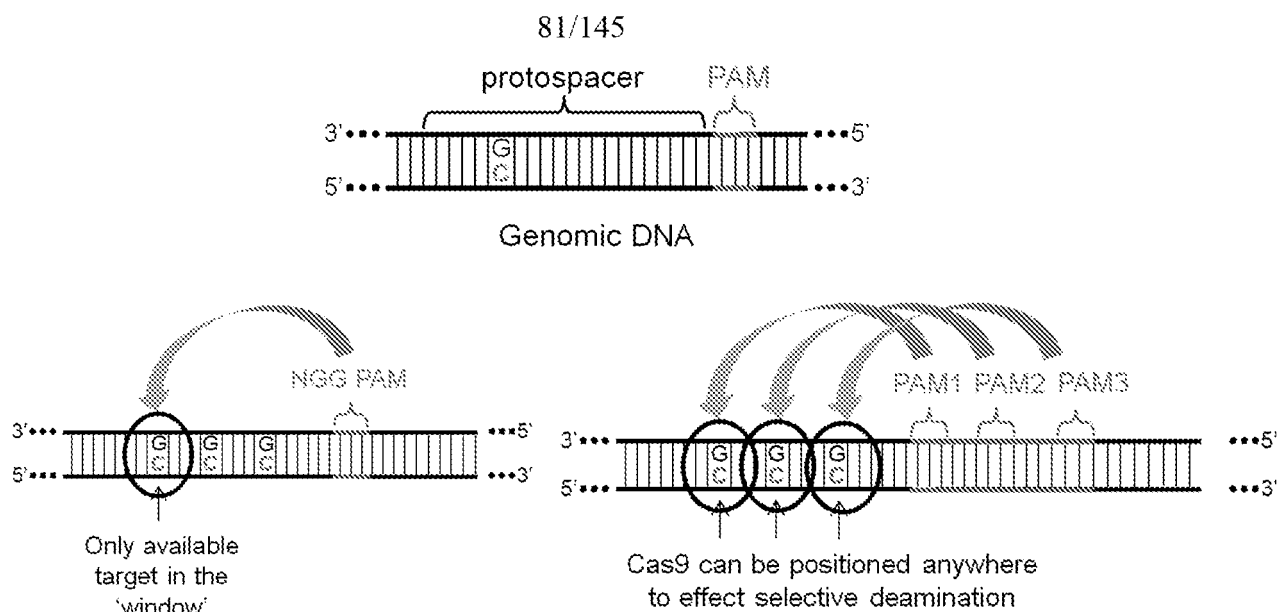


FIGURE 58

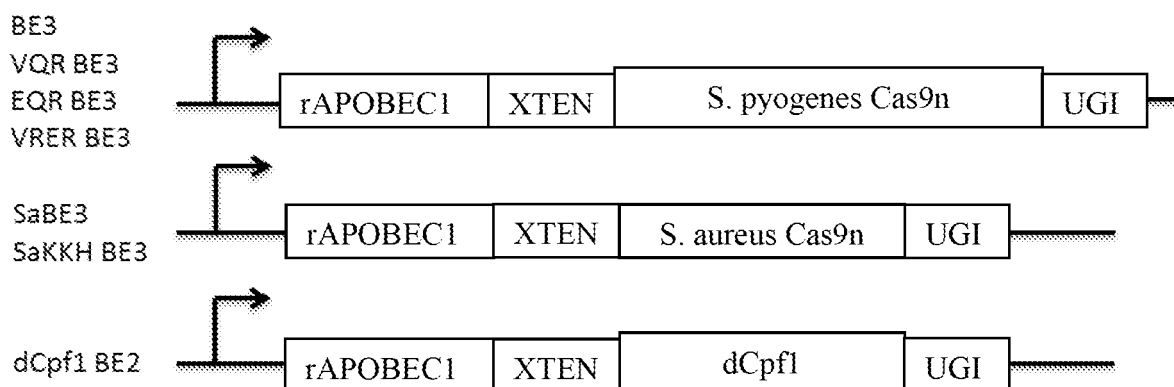


FIGURE 59

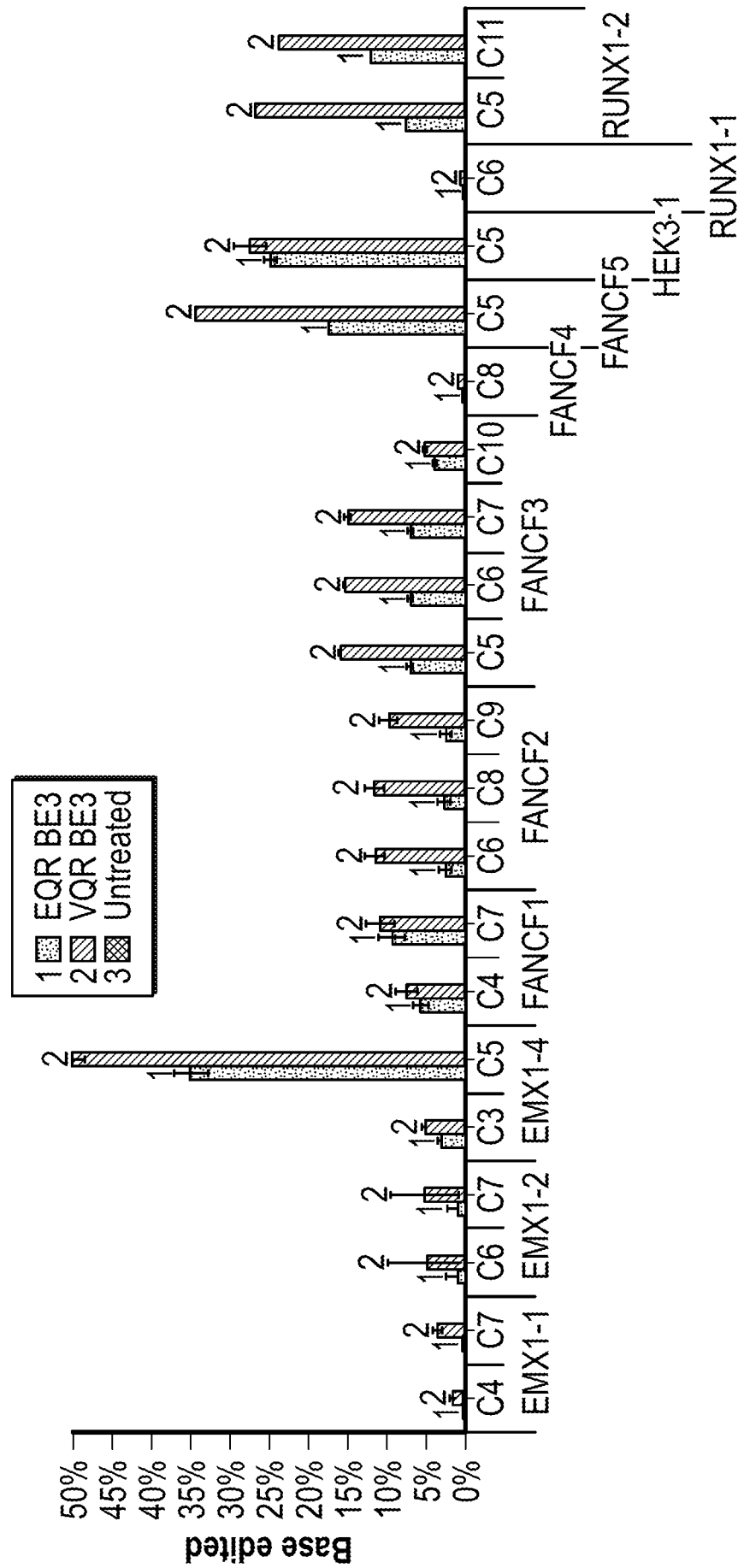


FIGURE 60

NGCG PAM EMX (VRER BE3)

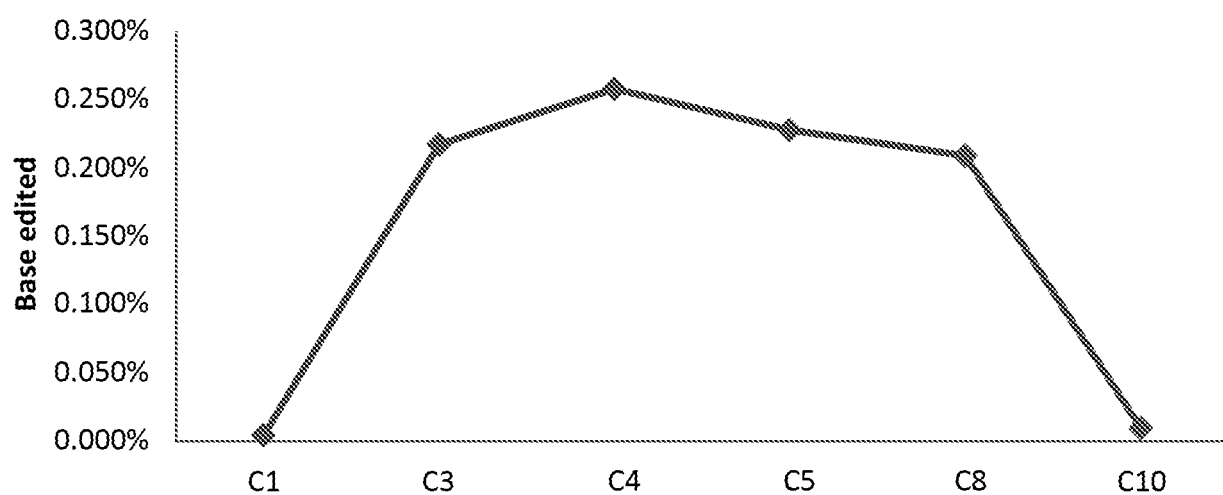


FIGURE 61

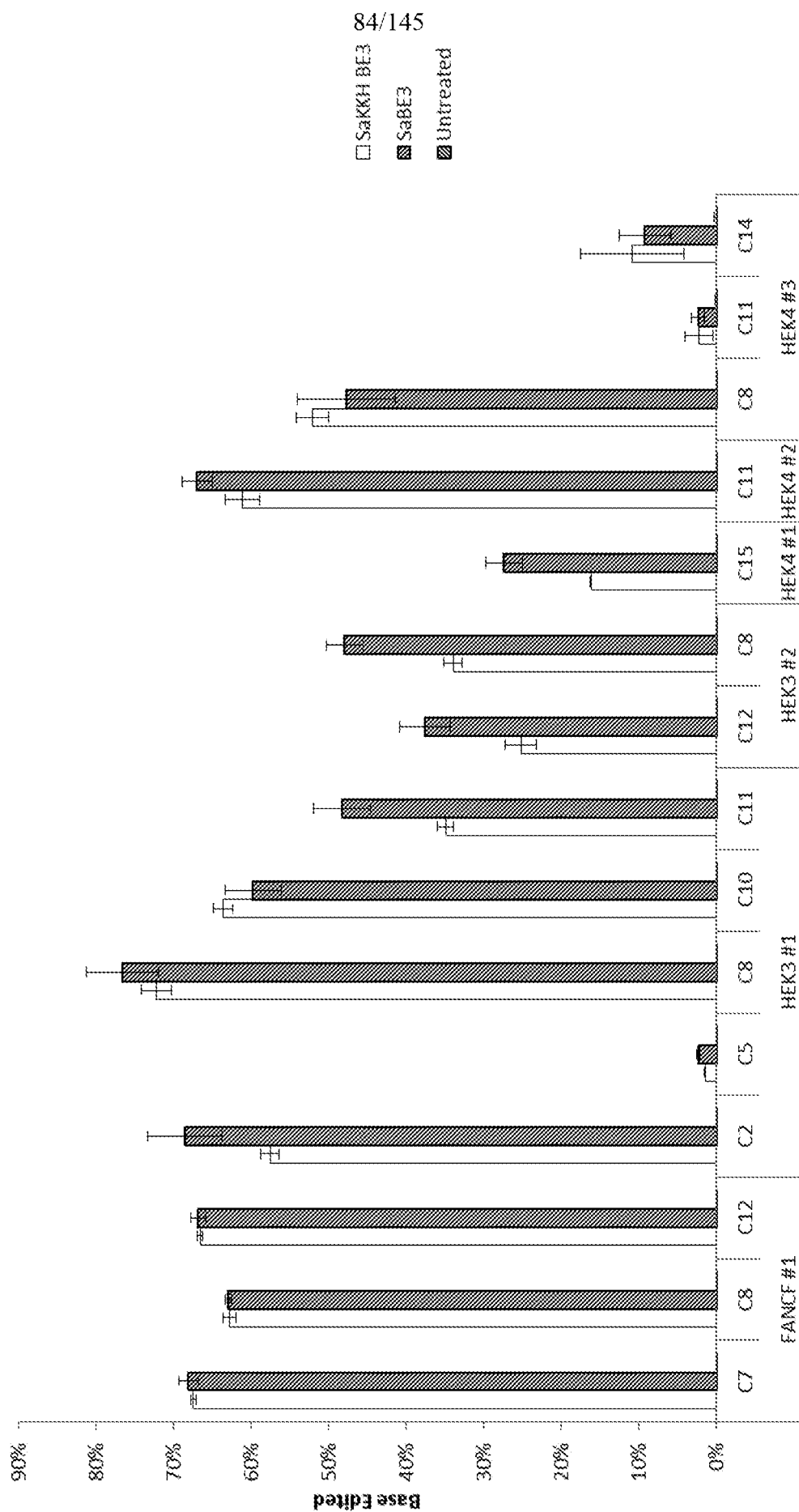


FIGURE 62

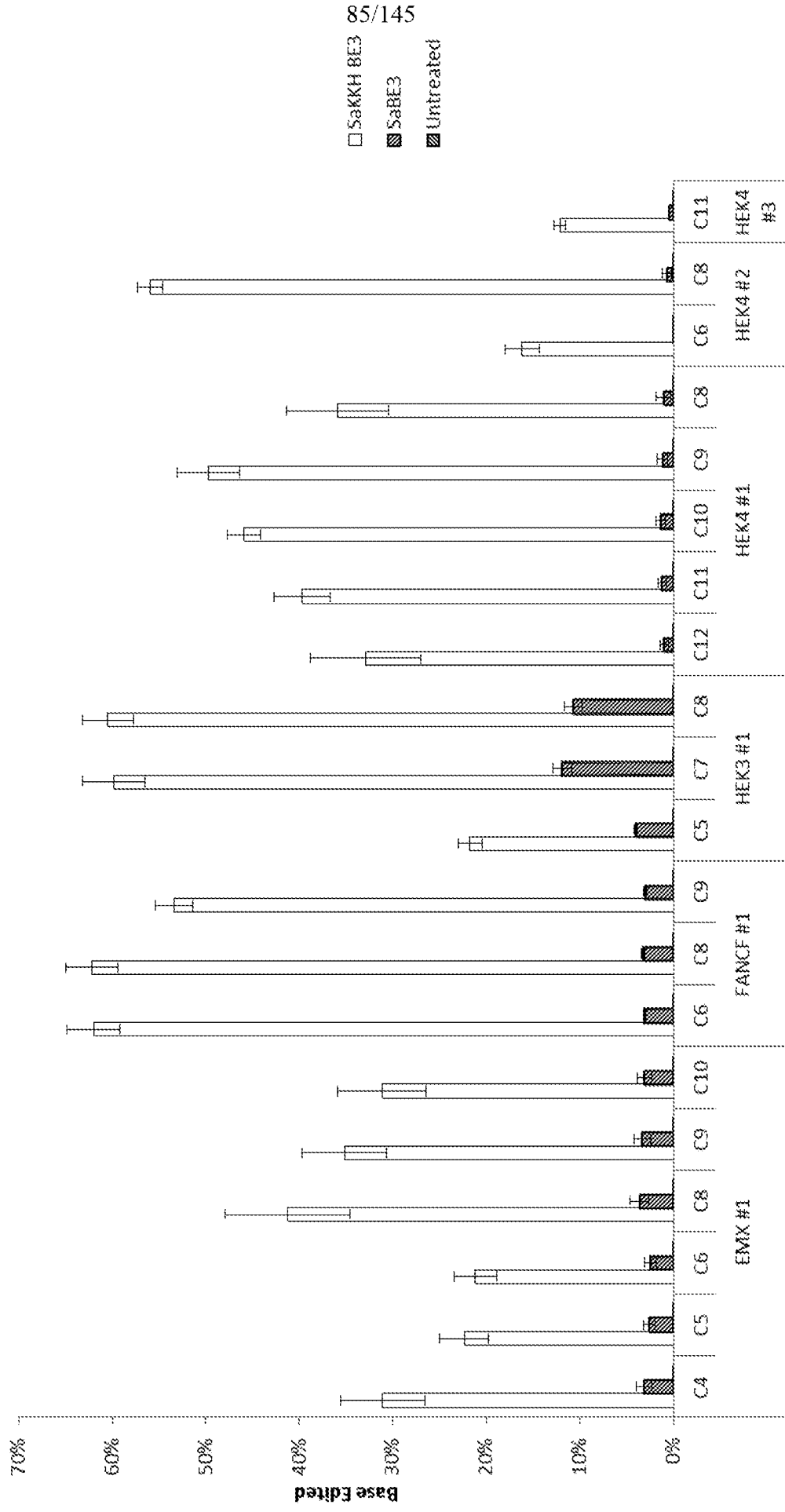


FIGURE 63

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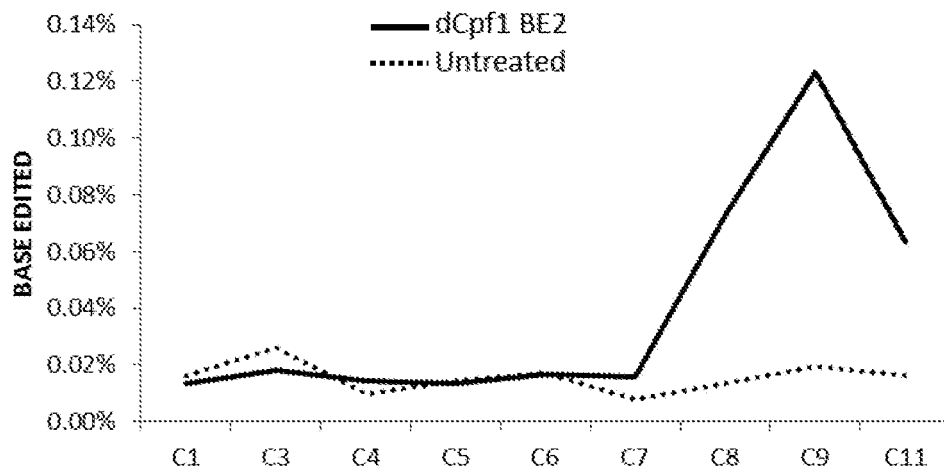


FIGURE 64A

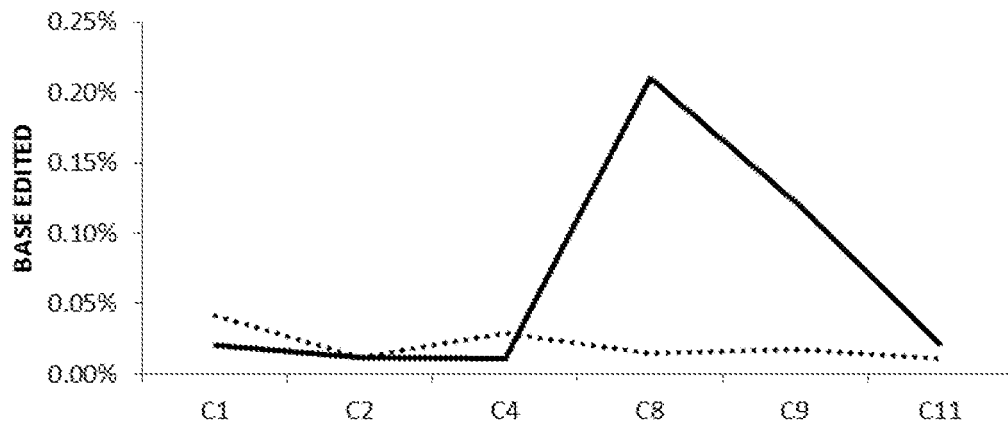


FIGURE 64B

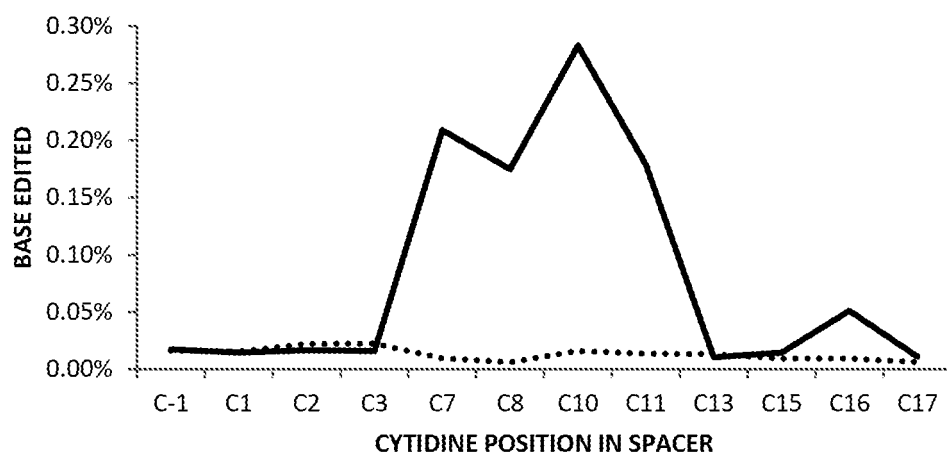


FIGURE 64C

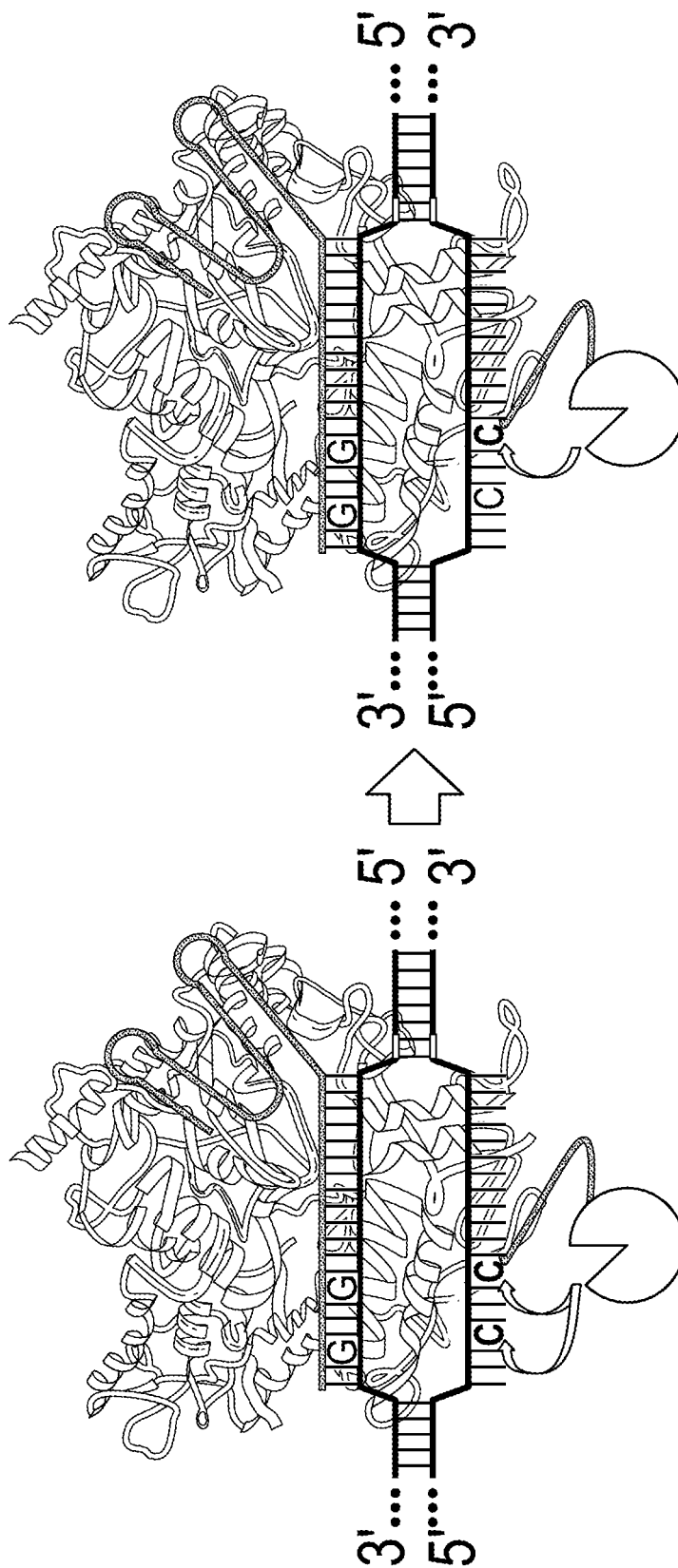


FIGURE 65

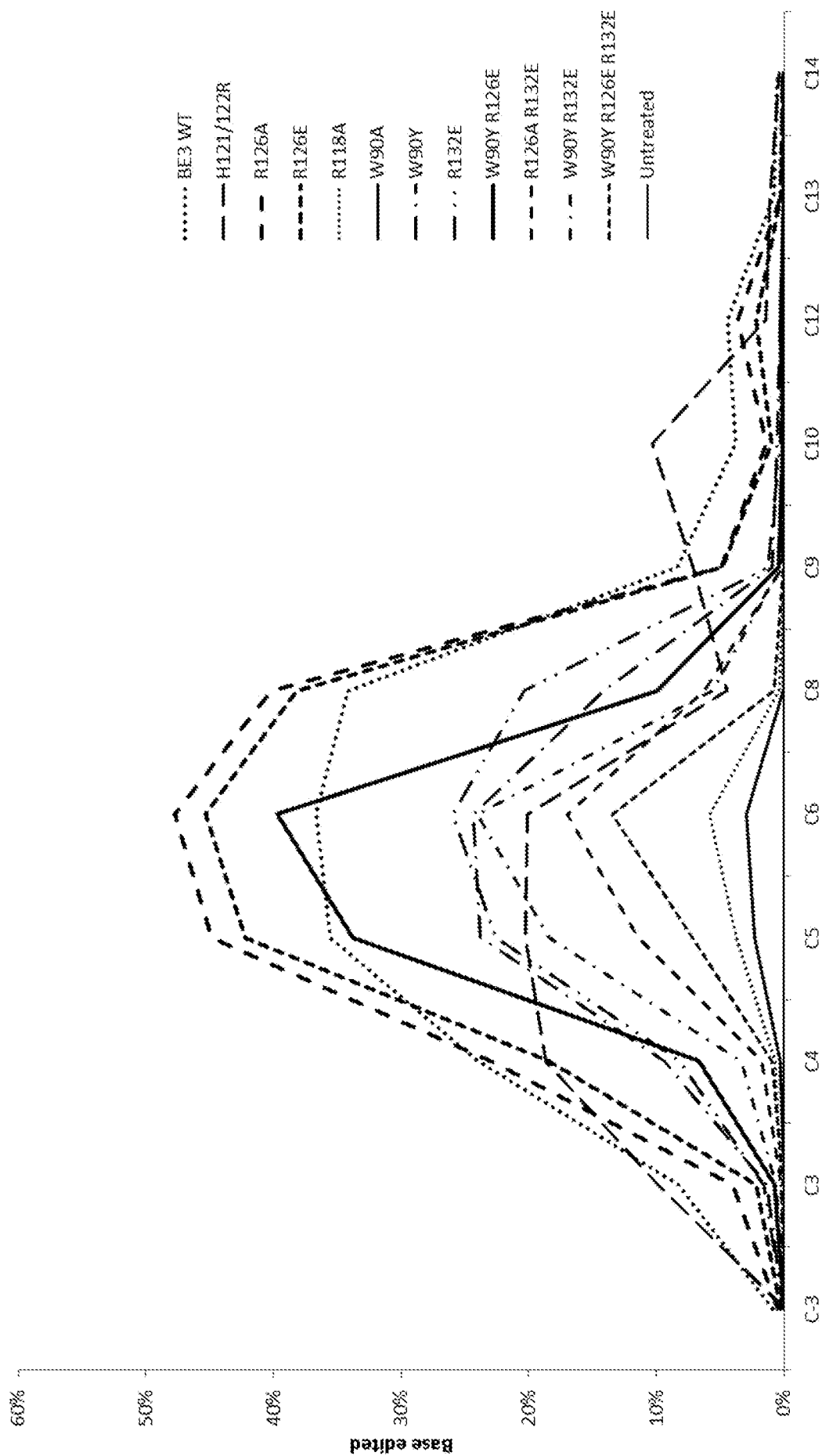


FIGURE 66

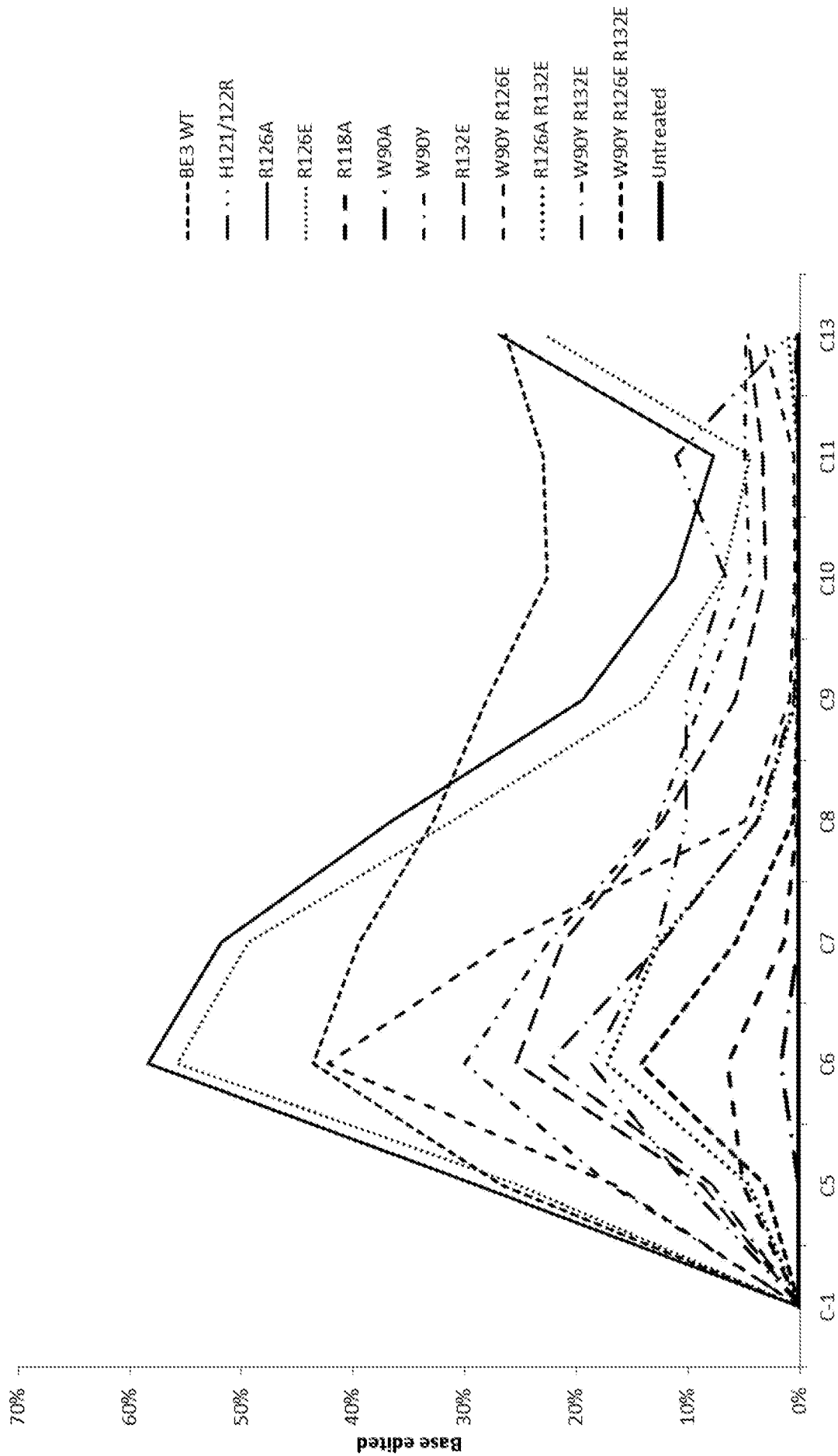


FIGURE 67

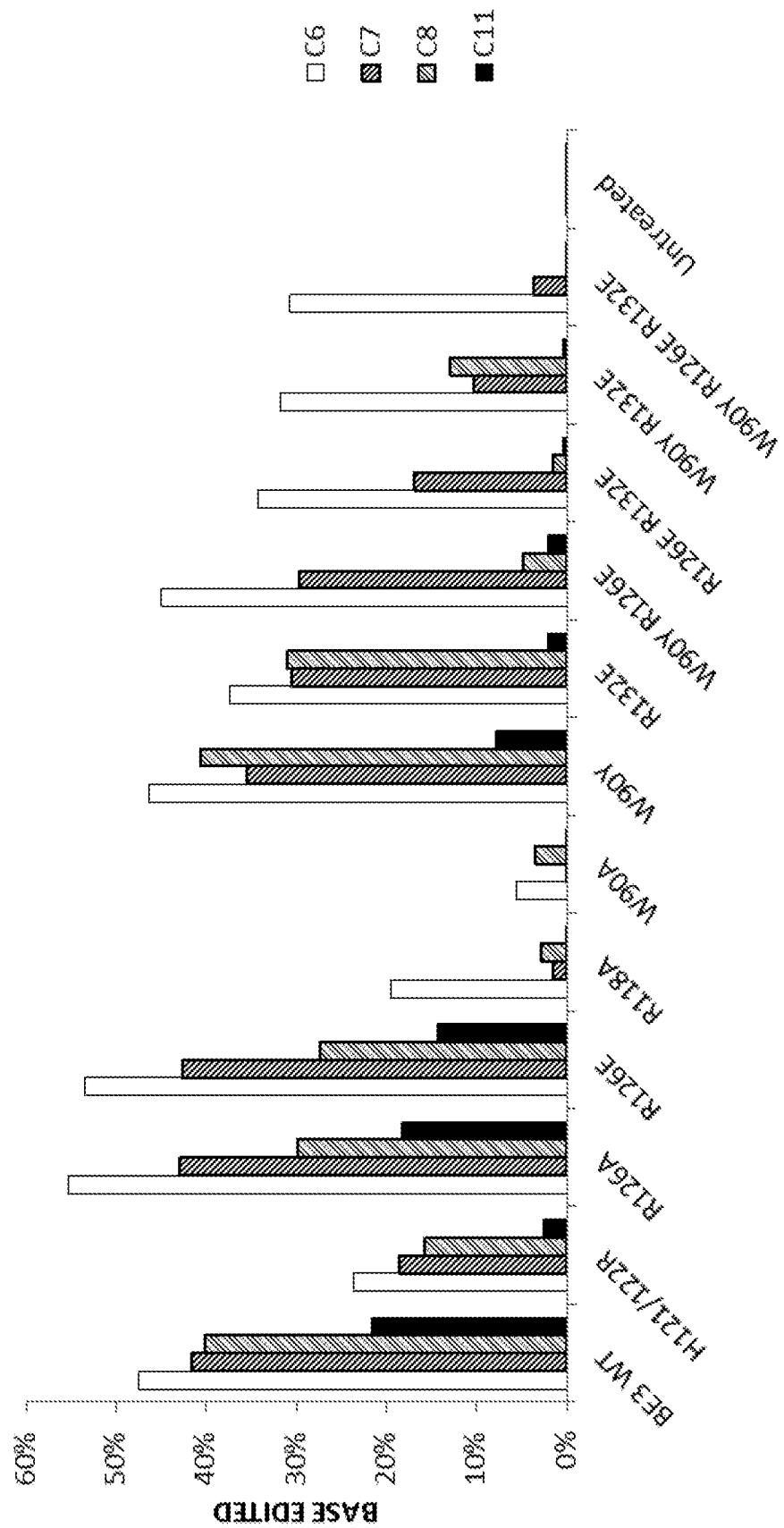


FIGURE 68

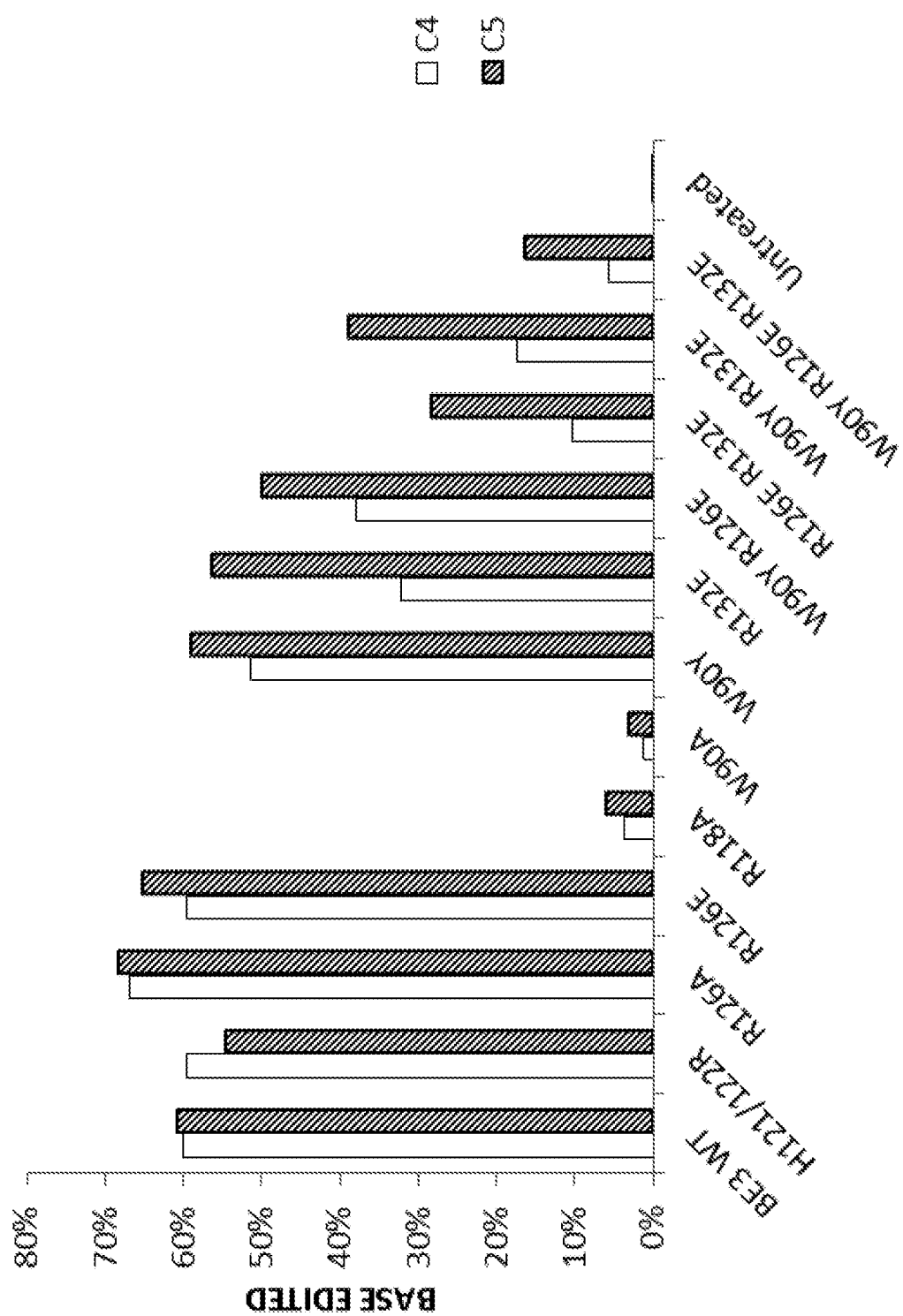


FIGURE 69

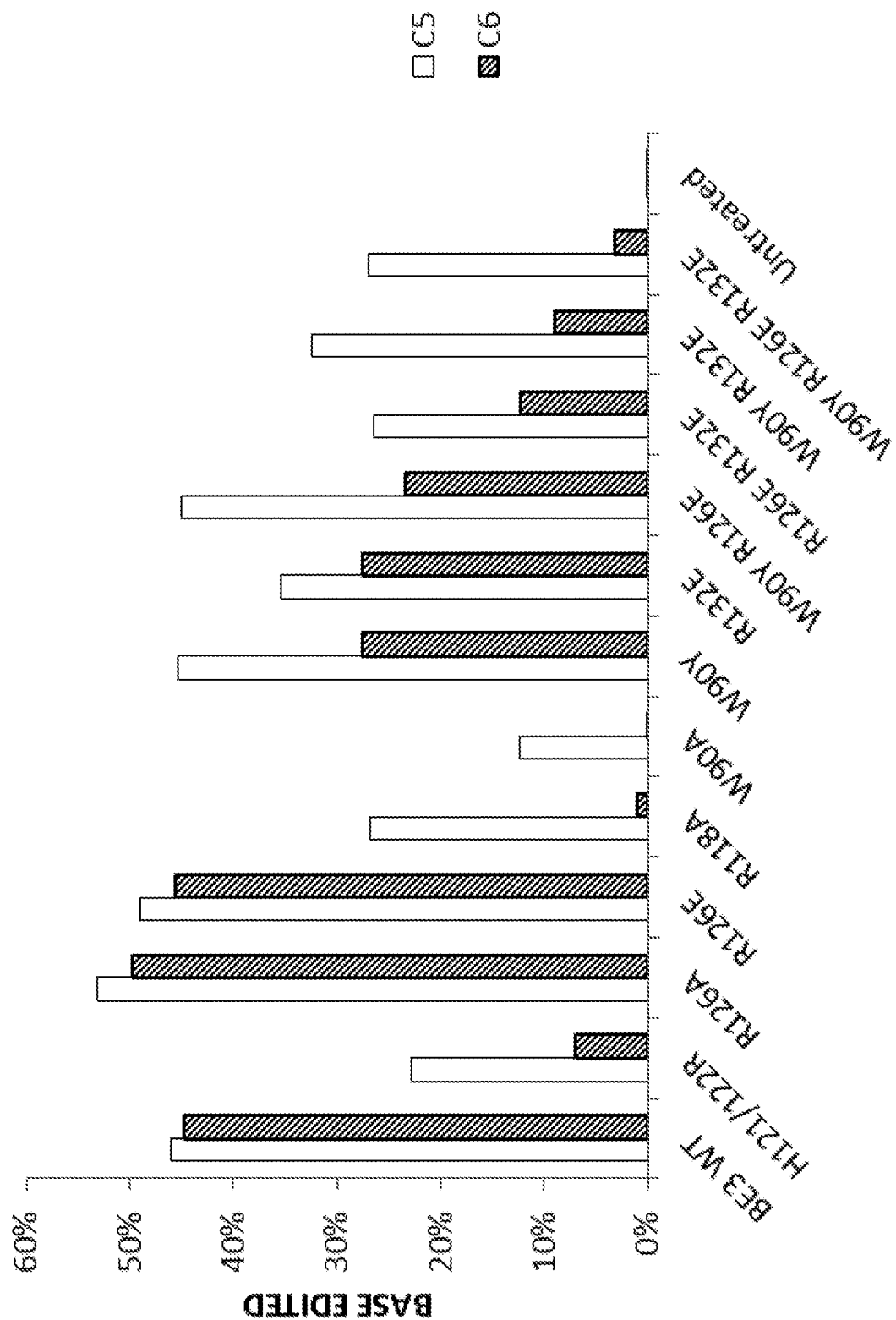


FIGURE 70

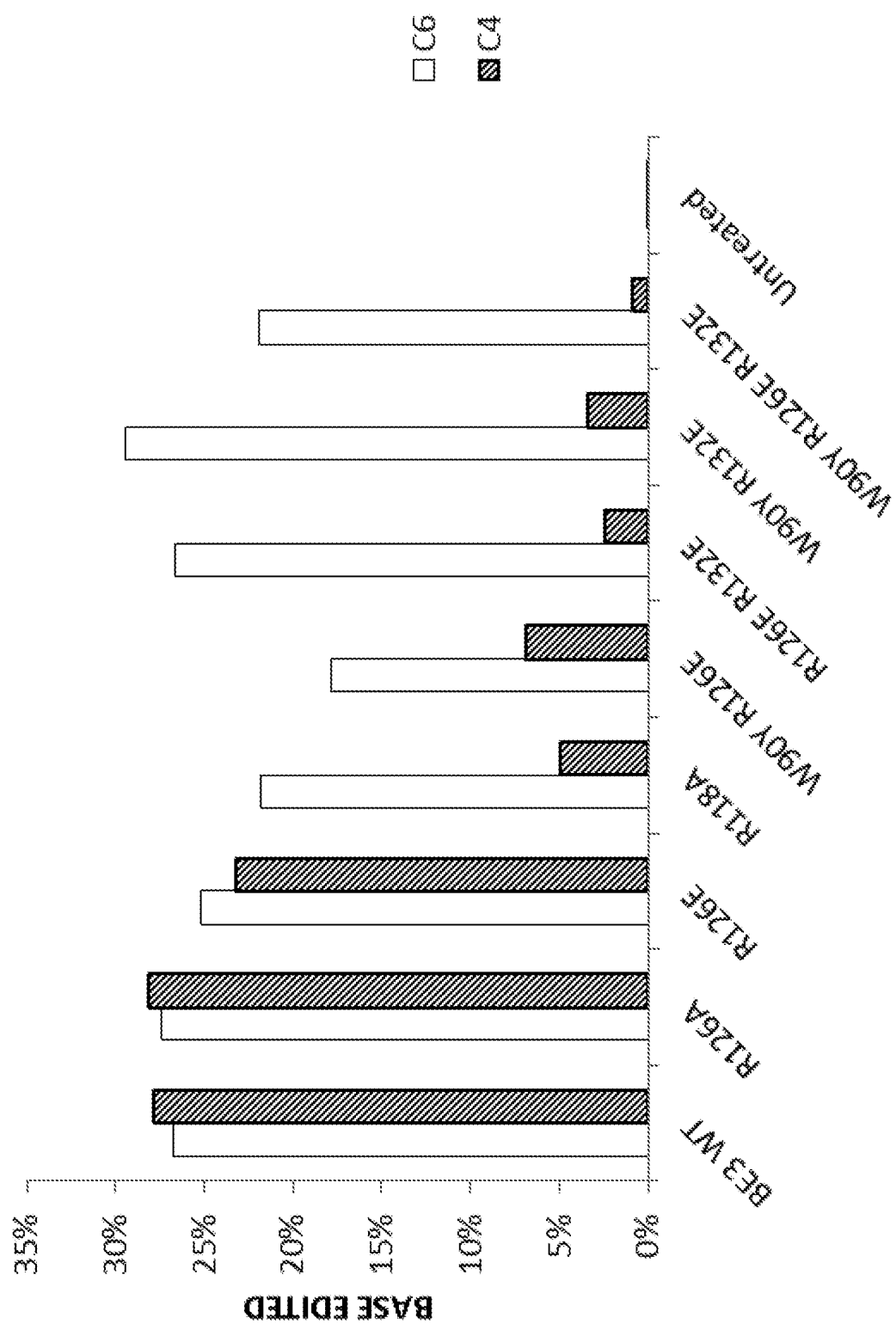


FIGURE 71

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BE3

Base	Lys			Arg → Cys			Leu → Leu			Ala			Tyr			Gln		
	G	A	A	G	C	G	C	T	G	G	C	A	G	T	G	T	A	C
A	0.2	99.9	99.8	0.0	1.0	0.1	1.8	1.2	0.0	0.0	0.1	0.1	99.8	0.0	0.0	0.1	99.9	0.1
C	0.0	0.0	0.1	0.0	38.1	0.0	49.8	52.3	0.0	0.0	0.0	99.7	0.1	0.0	0.1	0.0	0.0	99.9
G	99.8	0.0	0.0	99.9	1.8	99.8	1.3	0.7	0.1	99.9	99.8	0.0	0.1	99.9	0.1	99.9	0.1	0.0
T	0.0	0.0	0.1	0.1	59.2	0.1	47.0	45.8	99.9	0.1	0.1	0.2	0.0	0.0	99.8	0.0	99.8	0.1

BE3 W90Y R132E

Base	Lys			Arg → Cys			Leu → Leu			Ala			Tyr			Gln		
	G	A	A	G	C	G	C	T	G	G	C	A	G	T	G	T	A	C
A	0.0	99.9	99.9	0.0	0.5	0.1	0.3	0.1	0.0	0.0	0.1	99.8	0.0	0.0	0.0	0.1	99.9	0.1
C	0.0	0.0	0.0	0.1	78.0	0.0	94.8	98.9	0.0	0.0	0.0	99.8	0.1	0.0	0.0	0.0	0.0	99.9
G	100.0	0.0	0.0	99.9	0.5	99.9	0.1	0.1	0.0	99.9	99.9	0.0	0.1	100.0	0.1	99.9	0.0	0.0
T	0.0	0.0	0.0	0.0	21.0	0.0	4.8	0.9	99.9	0.0	0.0	0.1	0.0	0.0	99.8	0.0	99.9	0.0

FIGURE 72

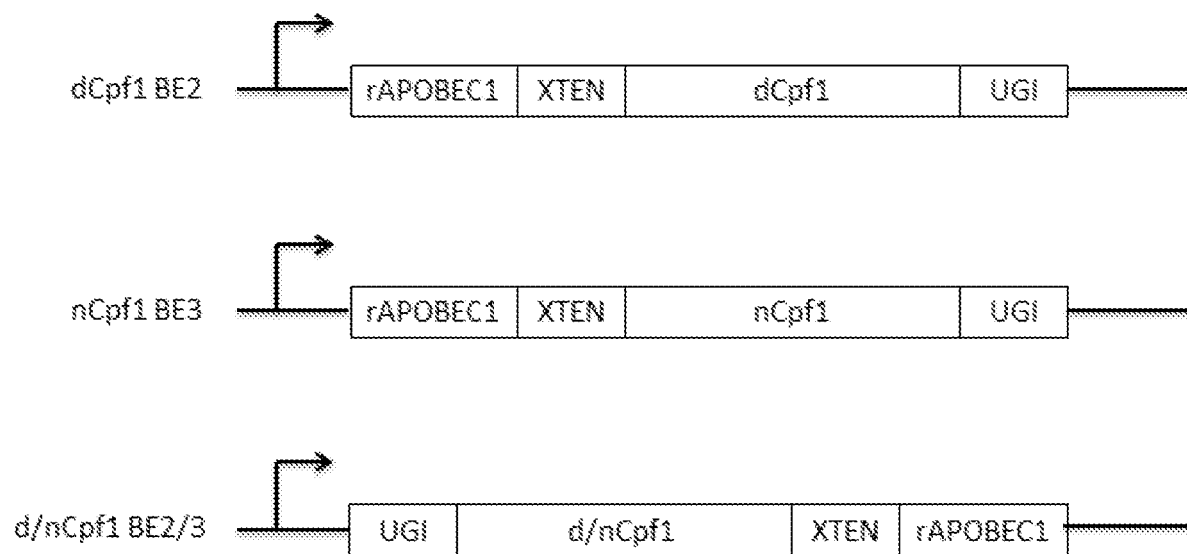


FIGURE 73

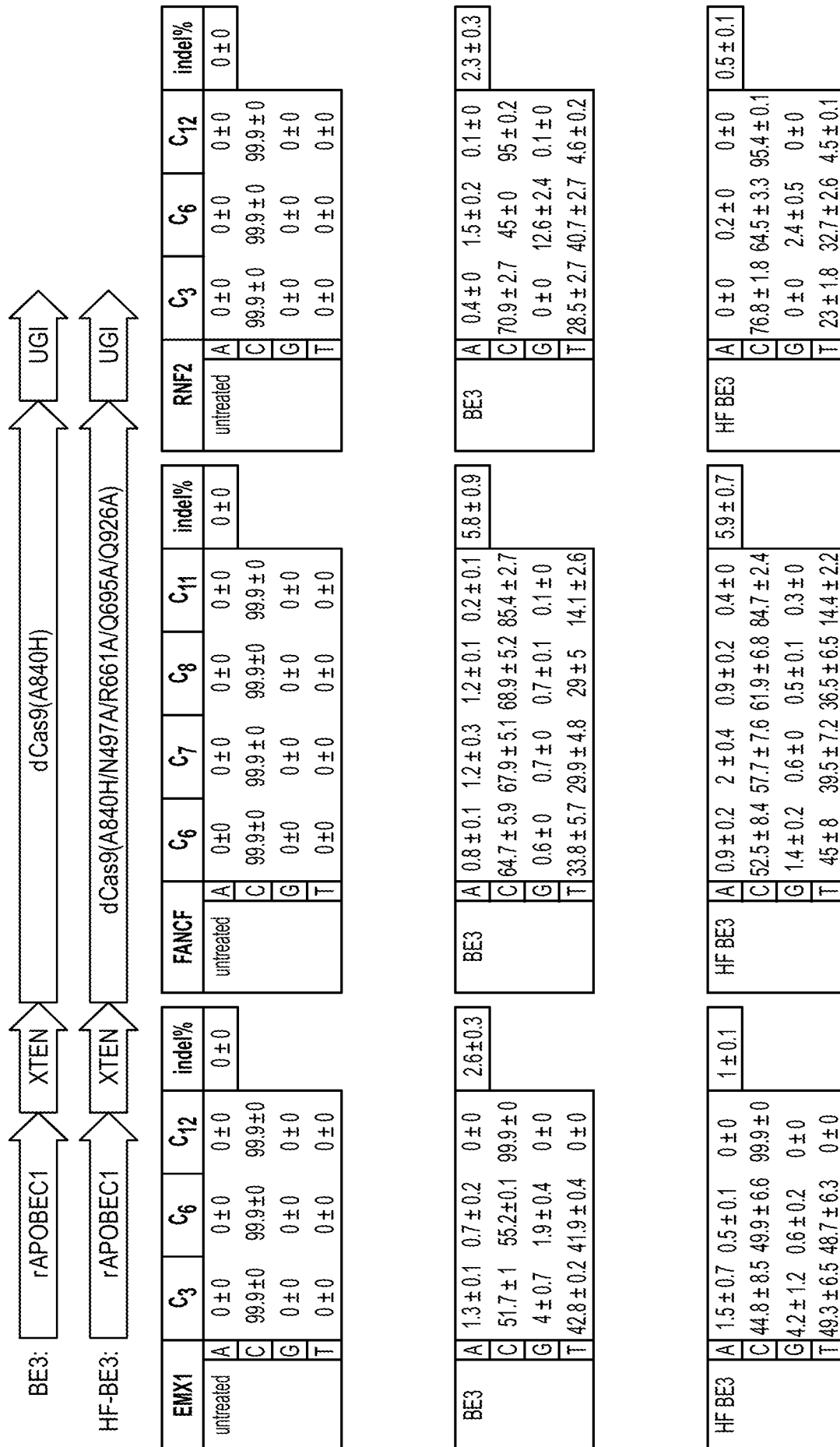
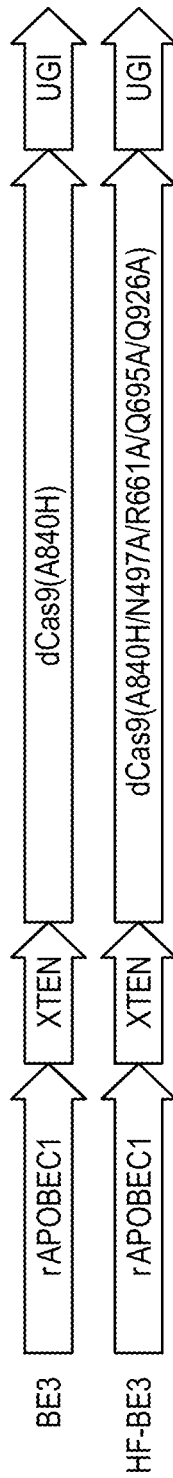


FIGURE 74



HEK3	C ₆	C ₇	C ₈	C ₁₁	indel %
untreated	A	0 ± 0	0 ± 0	0 ± 0	0 ± 0
	C	99.9 ± 0	99.9 ± 0	99.9 ± 0	99.9 ± 0
	G	0 ± 0	0 ± 0	0 ± 0	0 ± 0
	T	0 ± 0	0 ± 0	0 ± 0	0 ± 0

HEK4	C ₆	C ₇	C ₈	C ₁₁	indel %
untreated	A	0 ± 0	0 ± 0	0 ± 0	0 ± 0
	C	99.9 ± 0	99.9 ± 0	99.9 ± 0	99.9 ± 0
	G	0 ± 0	0 ± 0	0 ± 0	0 ± 0
	T	0 ± 0	0 ± 0	0 ± 0	0 ± 0

BE3	A	0 ± 0	5.4 ± 1.3	0 ± 0	0 ± 0	3 ± 0.7
	C	98.7 ± 0	44.5 ± 8.2	98.9 ± 0	99.8 ± 0	
	G	0 ± 0	18.1 ± 2.3	0 ± 0	0 ± 0	
	T	1.1 ± 0.1	31.9 ± 4.8	0.9 ± 0.1	0.1 ± 0	

HF BE3	A	0 ± 0	5.2 ± 0.8	0 ± 0	0 ± 0	1.3 ± 0
	C	99.6 ± 0	36.6 ± 9	98.5 ± 0.1	99.9 ± 0	
	G	0 ± 0	16 ± 2.8	0 ± 0	0 ± 0	
	T	0.2 ± 0	42.1 ± 5.3	1.3 ± 0.1	0 ± 0	

numbers are $\mu \pm \sigma$ from three independent replicates

FIGURE 75

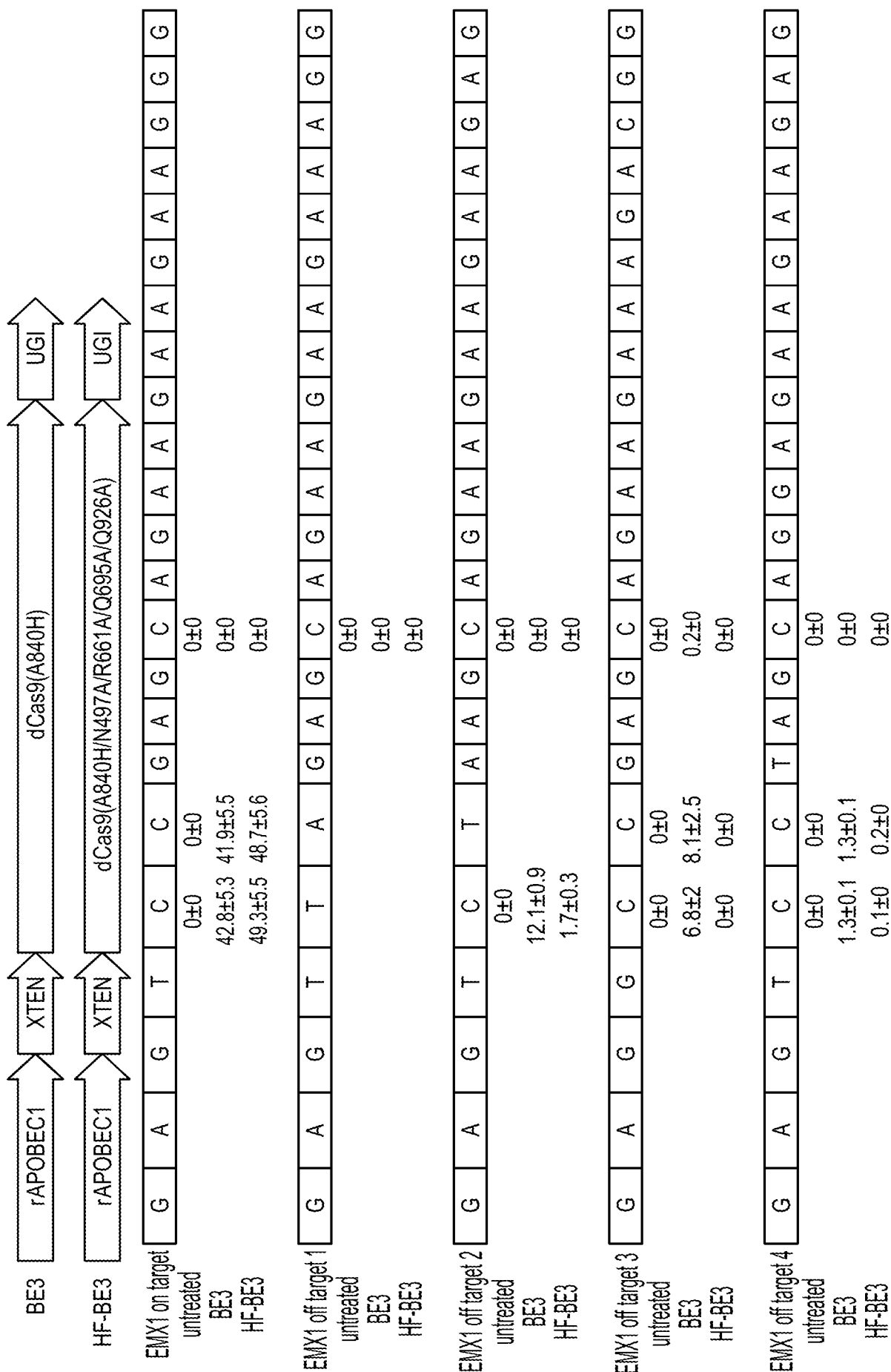


FIGURE 76

EMX1 off target 6 untreated BE3 HF-BE3	G	A	G	T	C	C	C	G	G	G	A	A	G	A	G	A	A	A	G	G
					0±0	0±0														
					0.4±0	0.4±0														
					0±0	0±0														
EMX1 off target 7 untreated BE3 HF-BE3	G	A	G	C	C	C	G	G	A	G	A	A	G	A	G	A	G	G	G	G
				0±0	0±0															
				0±0	0±0															
				0±0	0±0															
EMX1 off target 8 untreated BE3 HF-BE3	A	A	G	T	C	C	C	G	A	G	G	A	G	A	G	A	A	A	G	G
					0±0	0±0														
					0±0	0±0														
					0±0	0±0														
EMX1 off target 9 untreated BE3 HF-BE3	G	A	A	T	C	C	C	A	A	G	C	A	G	A	G	A	A	G	G	A
					0±0	0±0														
					0.1±0	0.1±0														
					0±0	0±0														
EMX1 off target 10 untreated BE3 HF-BE3	A	C	G	T	C	T	T	G	A	G	C	A	G	A	A	G	A	A	T	G
		0±0			0±0															
		0±0			1.5±0.1															
		0±0			1.1±0.2															

numbers are $\mu \pm \sigma$ from three independent replicates

FIGURE 76 (CONTINUED)

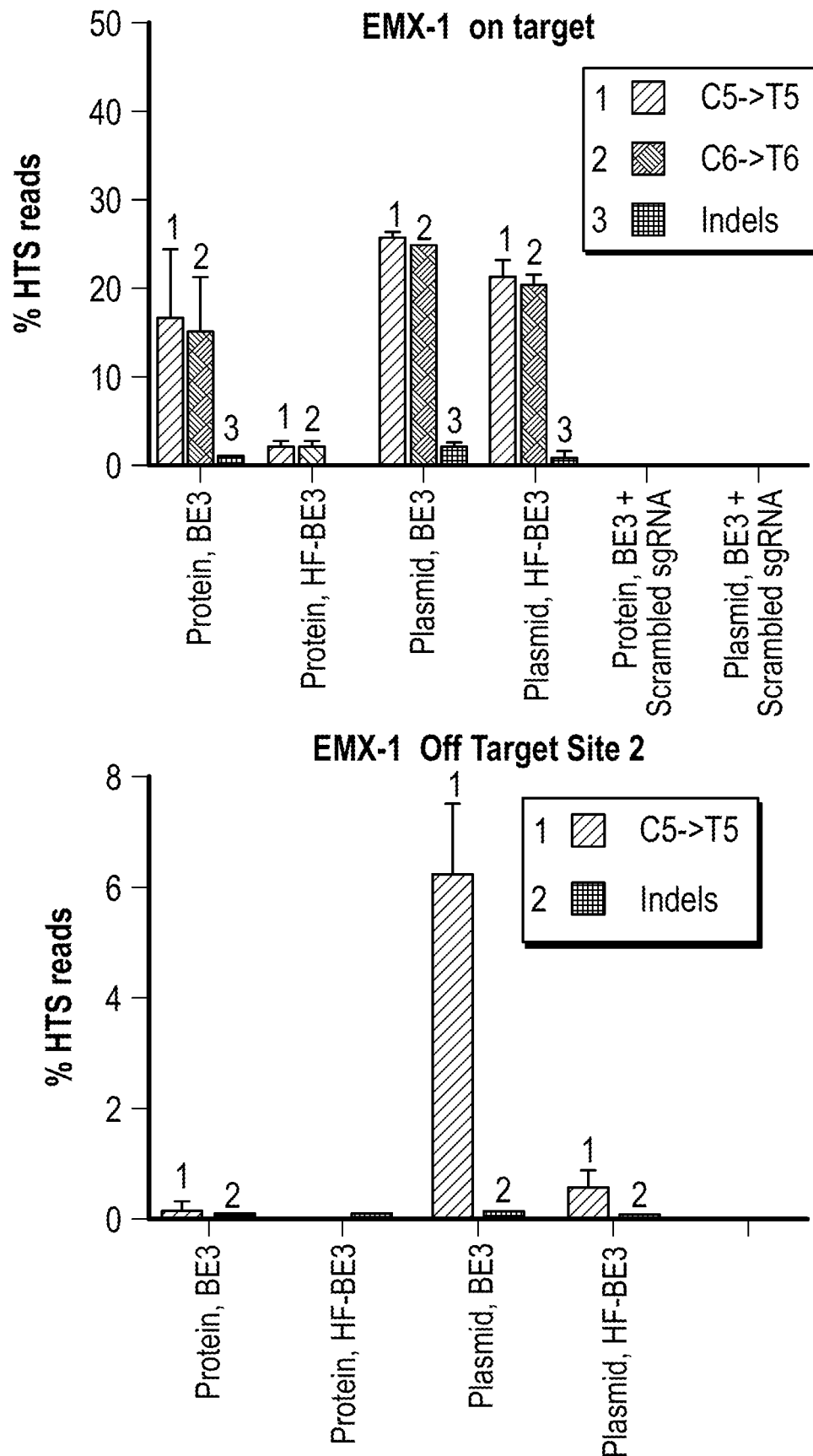


FIGURE 77

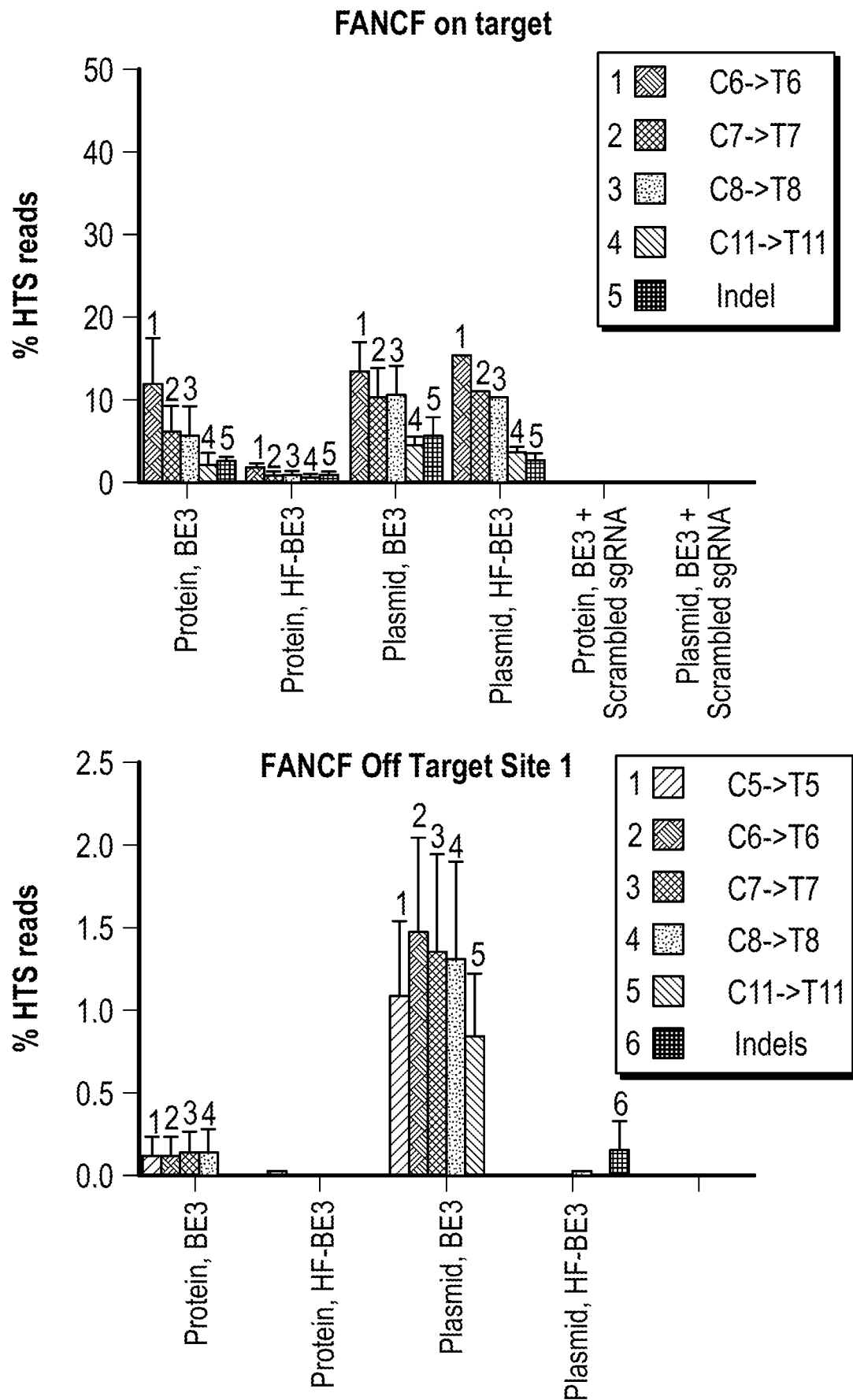


FIGURE 78

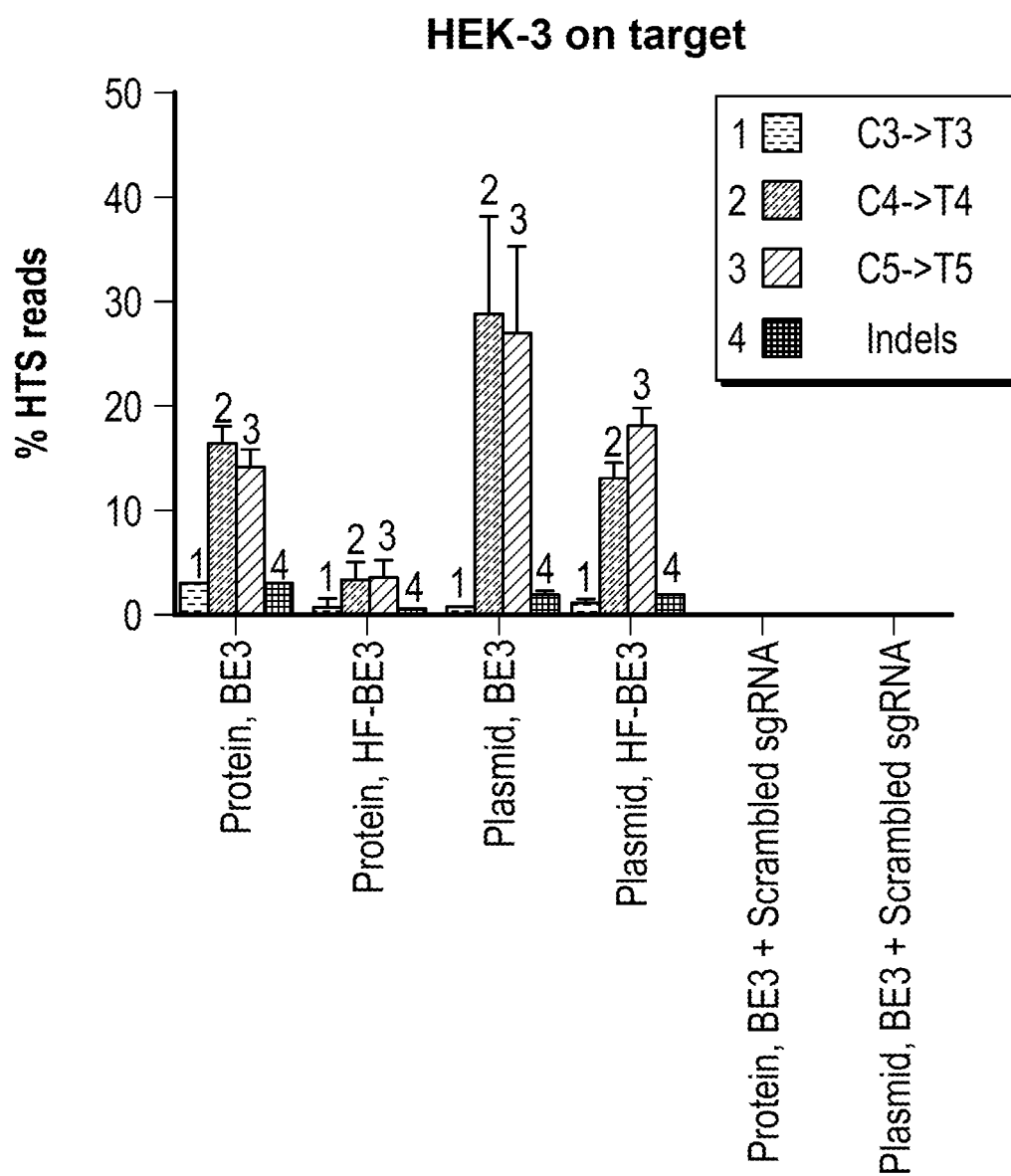


FIGURE 79

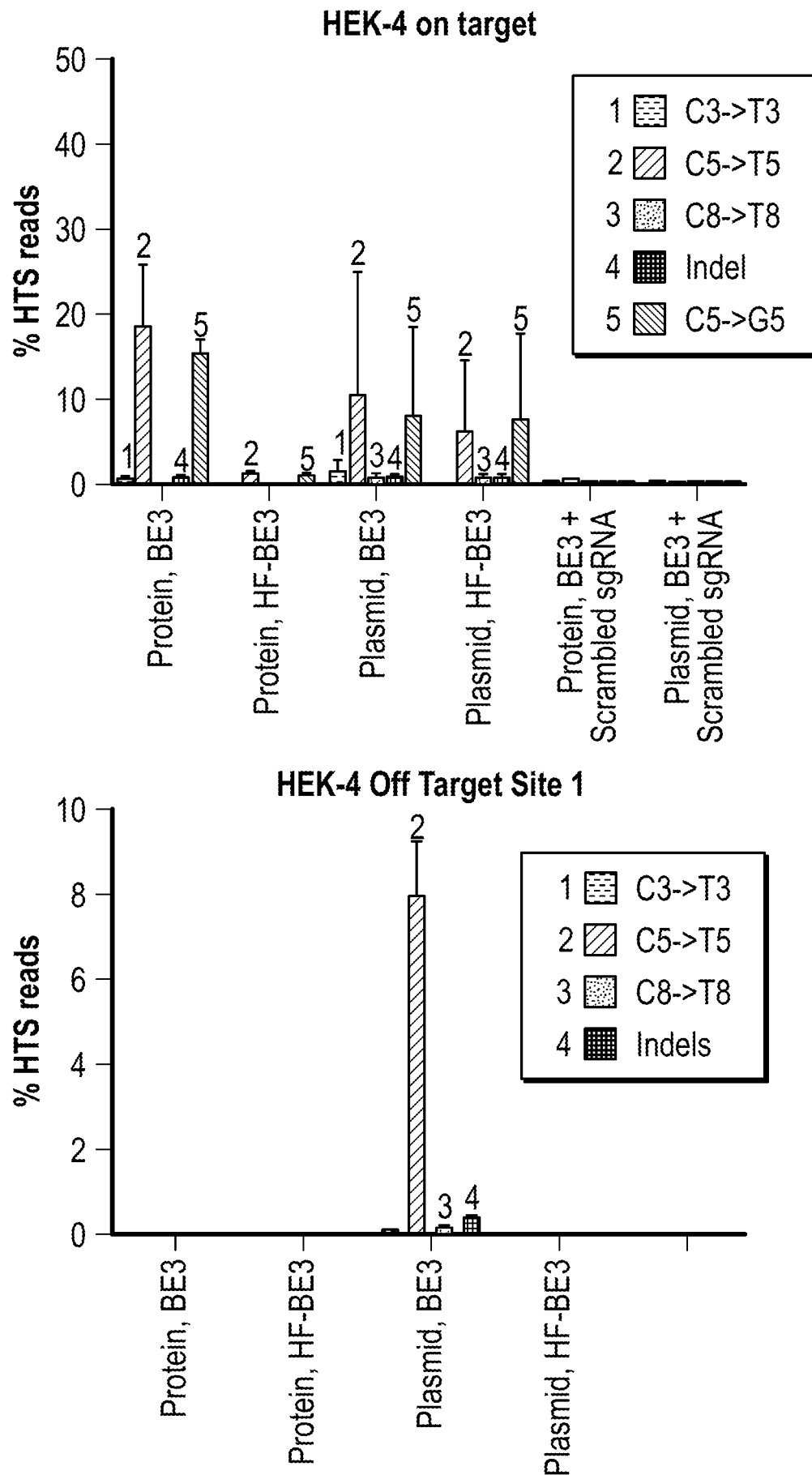


FIGURE 80

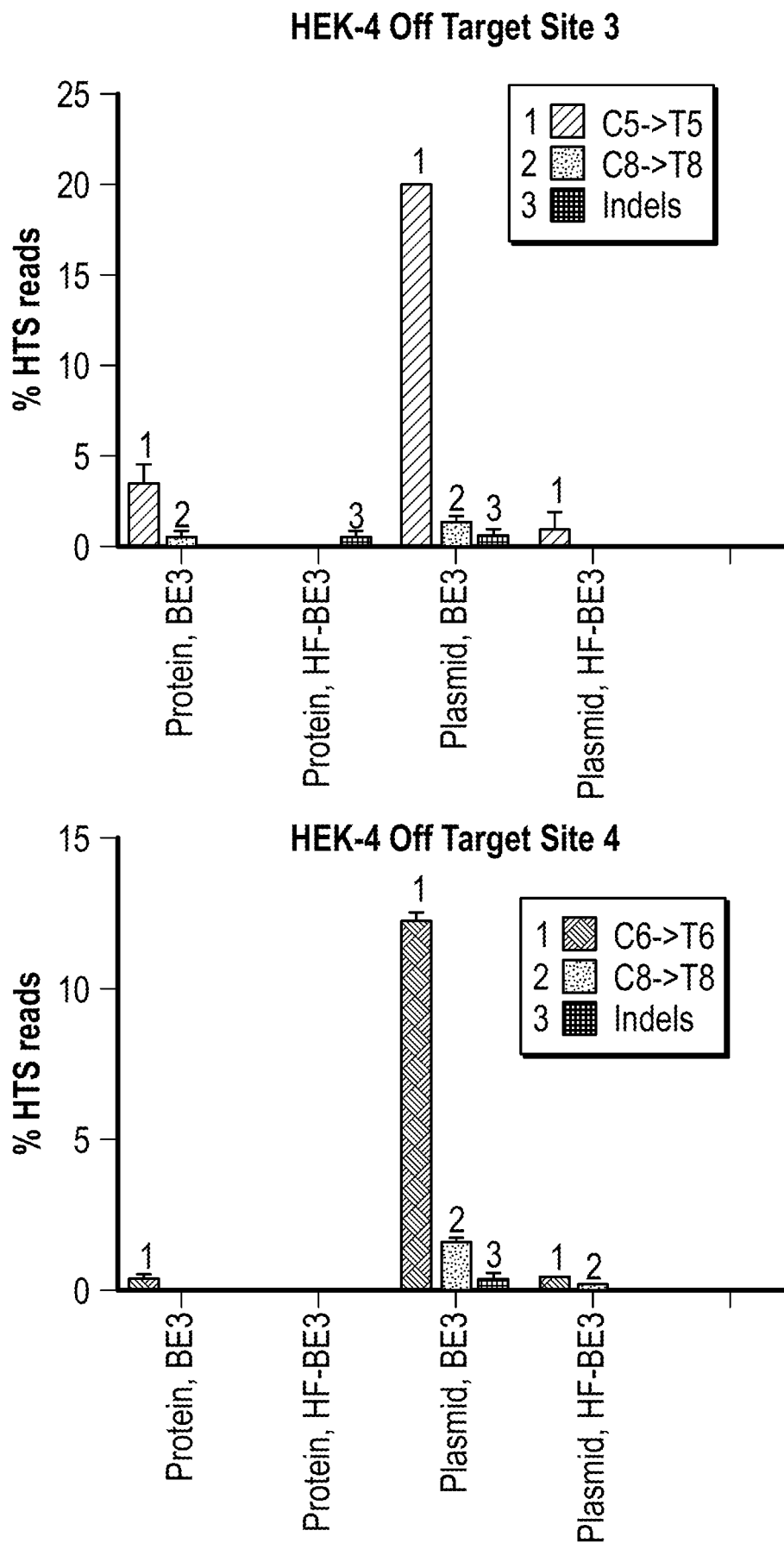


FIGURE 80 (CONTINUED)

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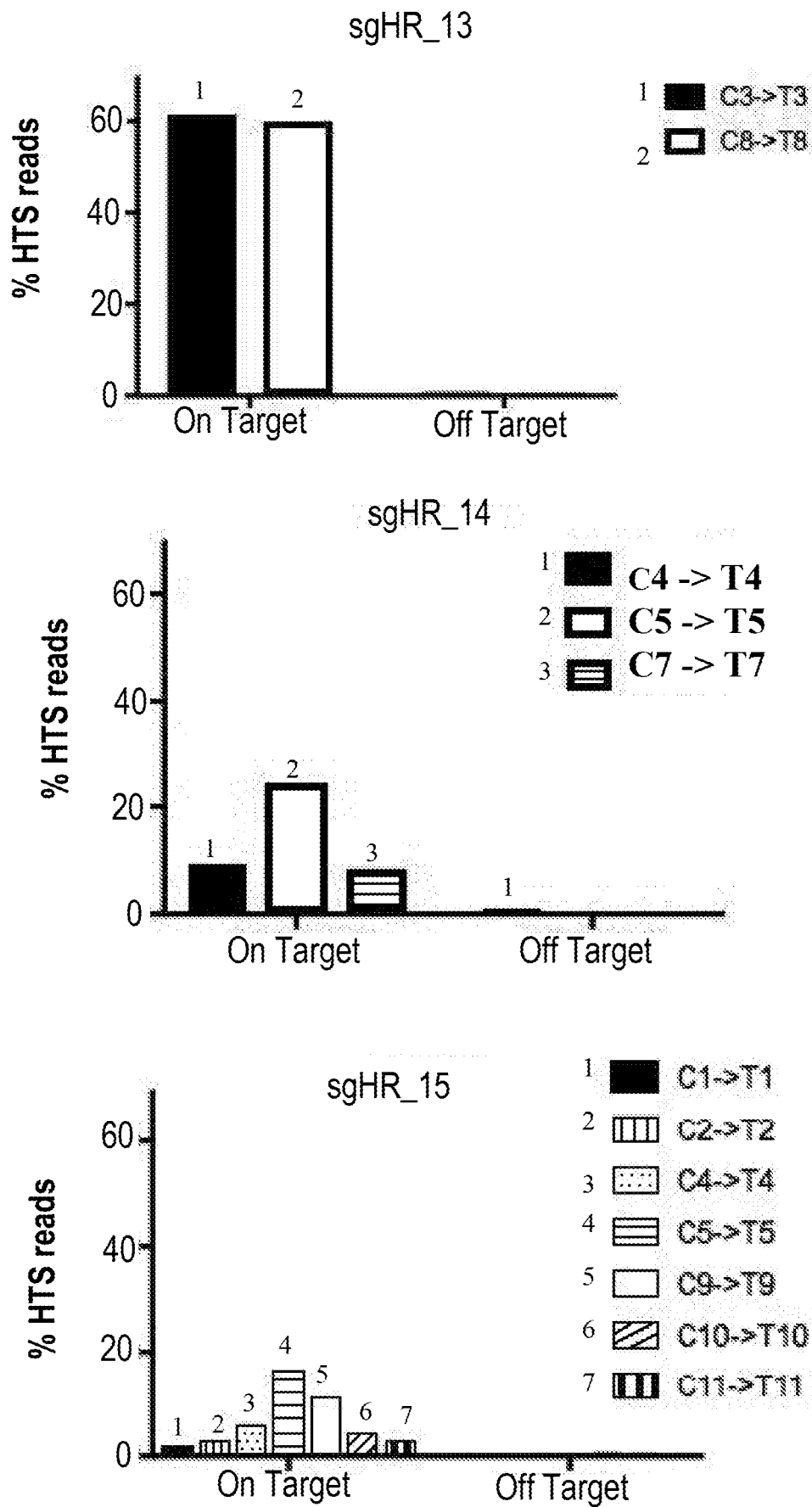


FIGURE 81

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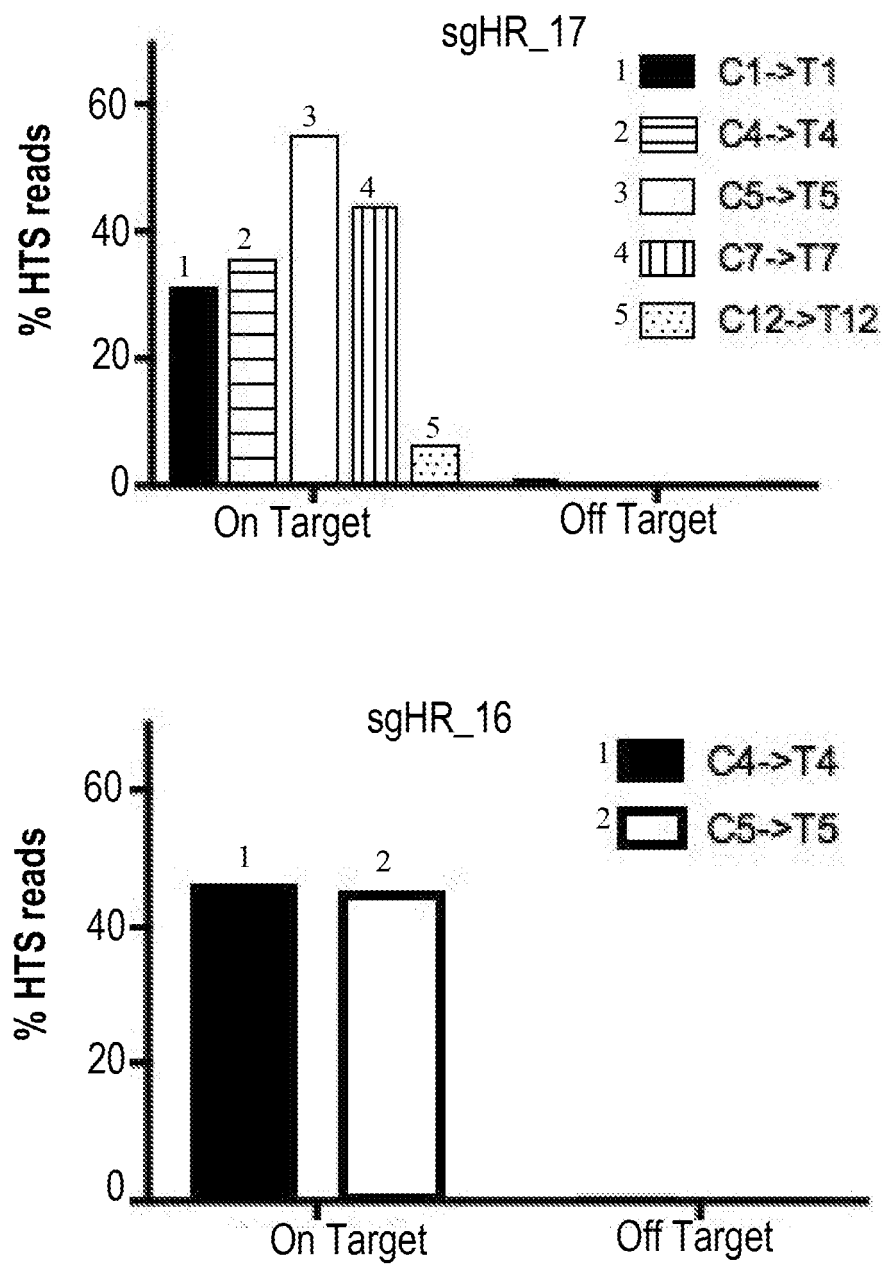


FIGURE 82

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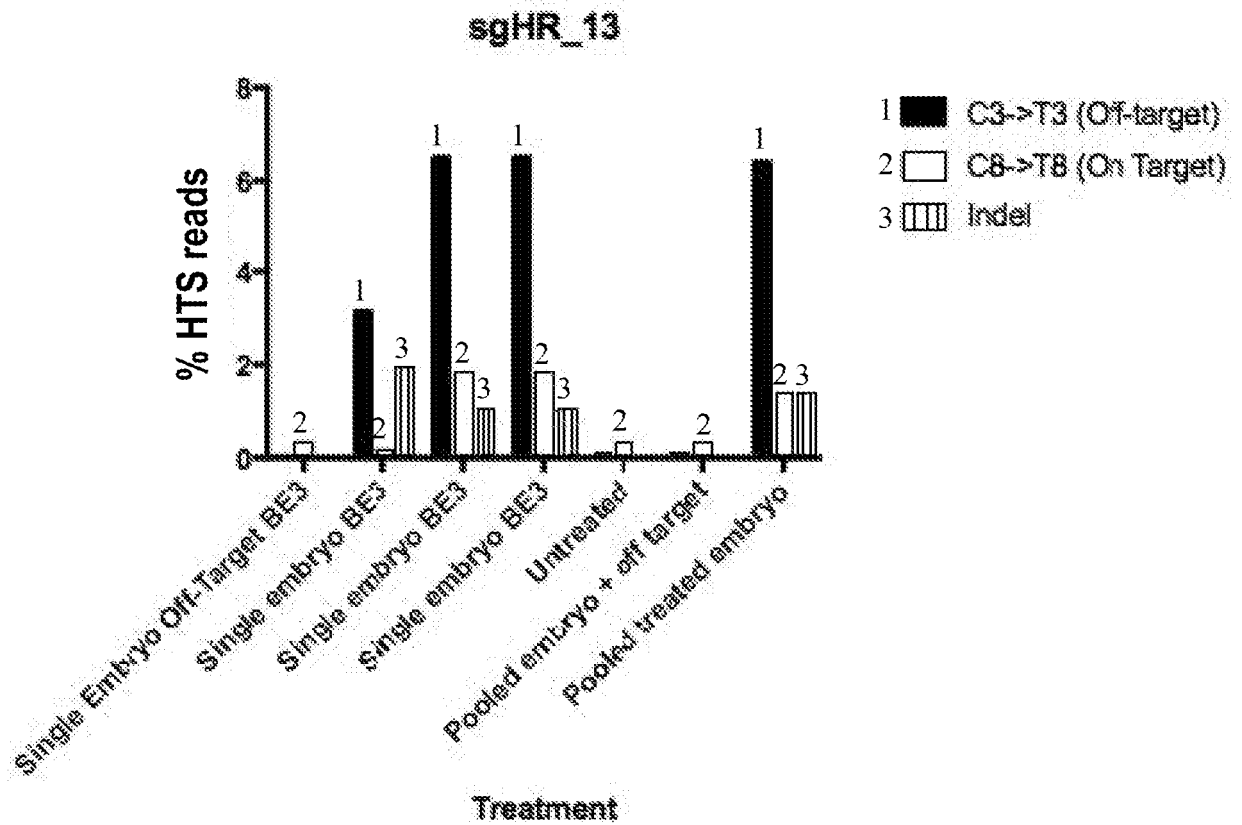


FIGURE 83

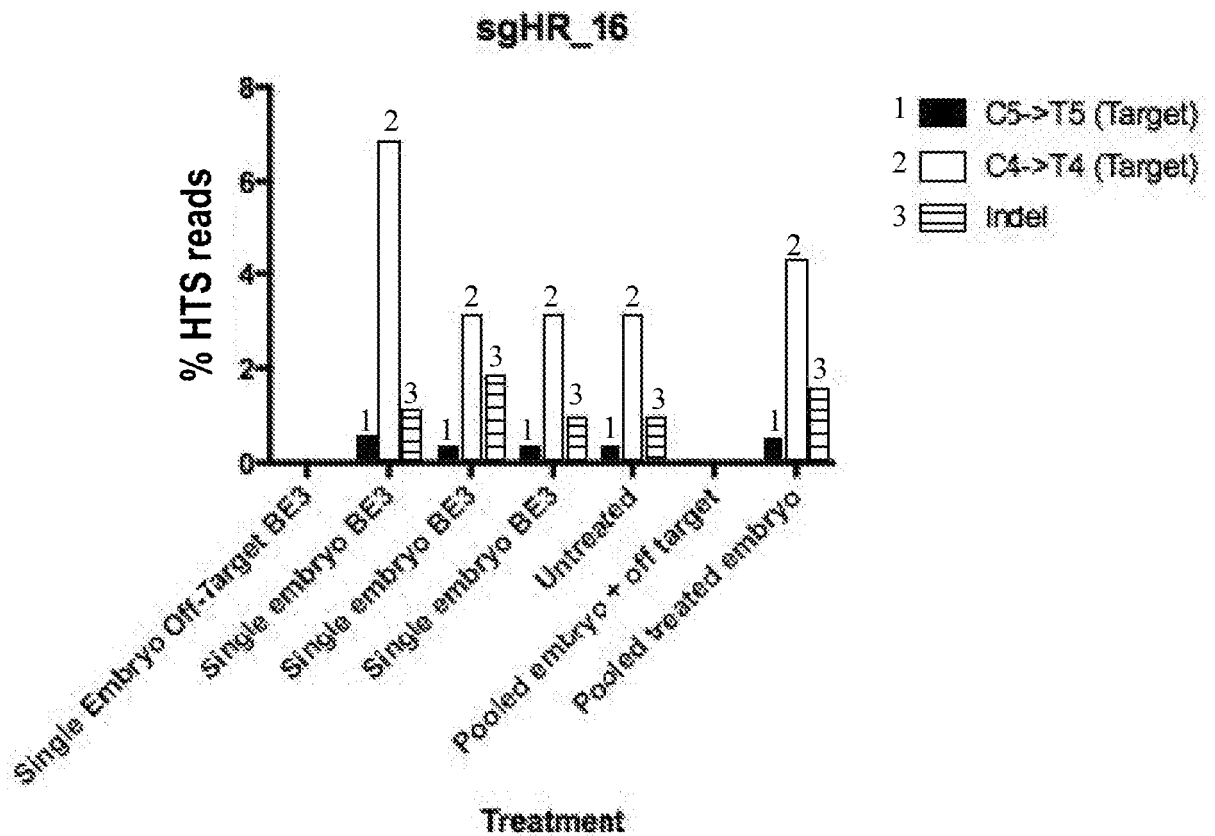


FIGURE 84

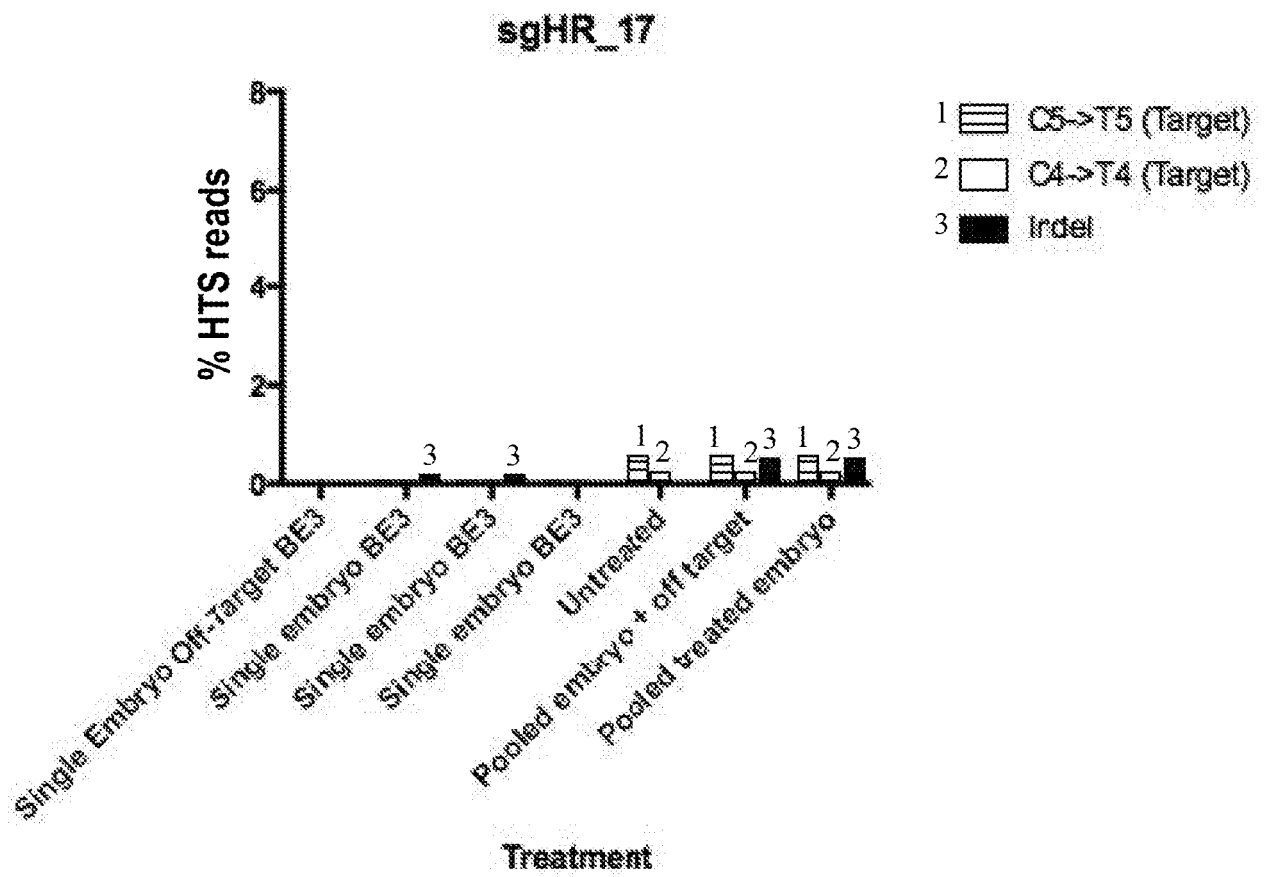


FIGURE 85

Possible Changes Using C→T Base Editors

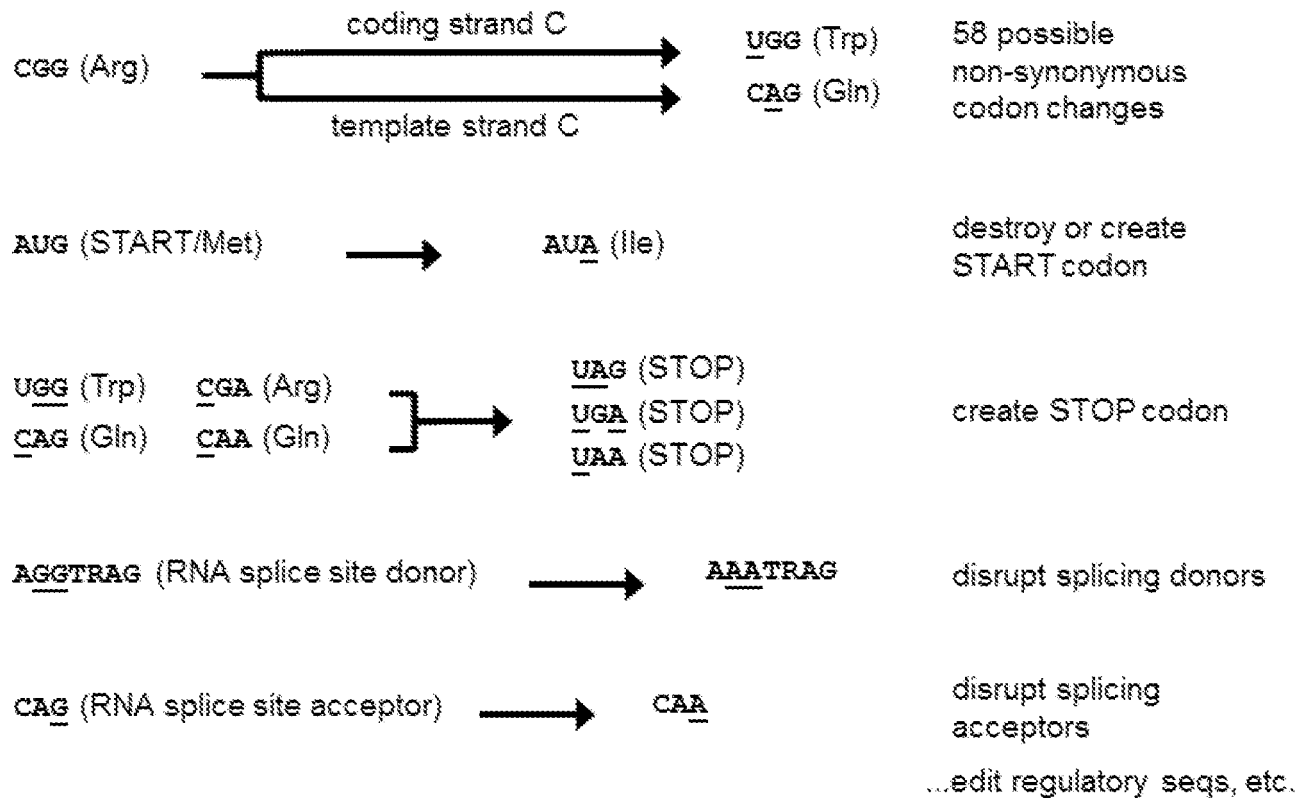
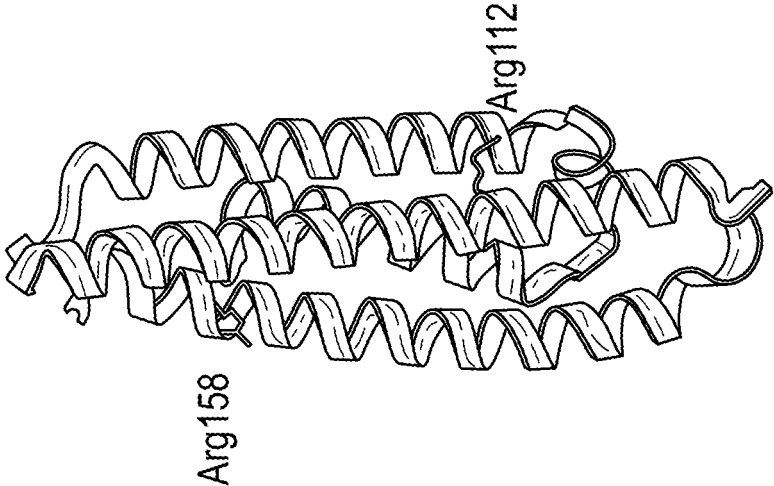


FIGURE 86

Base Editing APOE4 to APOE3r



- Apolipoprotein E has four isoforms that differ at amino acids 112 and 158
- APOE4 is the largest and most common genetic risk factor for late-onset Alzheimer's disease

allele	residue 112	residue 158	AD risk (known or presumed)
APOE2	Cys TGC	Cys TGC	low
APOE3	Cys TGC	Arg CGC	neutral
APOE3r	Arg CGC	Cys TGC	neutral
APOE4	Arg CGC	Arg BE3 CGC	high

FIGURE 87

untreated	Lys			Arg 158			Leu			Ala			Val			Tyr			Gln			indel %
	G	A		G	C ₆	G	C	T	G	G	C	A	G	T	G	T	A	C	A	G		
		A	G																			
APOE4C158R	G	A	A	G	C ₆	G	C	C	T	G	G	C	A	G	T	G	T	A	C	C	G	0.0
A	0.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0
C	0.0	0.0	0.0	0.0	100.0	0.0	100.0	100.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0
G	100.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	100.0	100.0	0.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	99.9	100.0
T	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0

Cas9 + HDR	Lys			Arg 158 → Cys			Leu			Ala			Val			Tyr			Gln			indel%
	G	A		G	C ₆	G	C	T	G	G	C	A	G	T	G	T	A	C	A	G		
		A	G																			
APOE4C158R	G	A	A	G	C ₆	G	C	C	T	G	G	C	A	G	T	G	T	A	C	C	G	26.1
A	0.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.4	0.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0
C	0.0	0.0	0.0	0.0	99.7	0.0	99.9	99.9	0.0	0.0	0.0	100.0	0.5	0.0	0.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0
G	100.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	100.0	99.9	0.0	0.0	99.6	0.6	99.9	0.2	0.0	0.0	0.0	0.0	100.0	100.0
T	0.0	0.0	0.0	0.0	0.3	0.0	0.1	100.0	0.0	0.0	0.0	0.1	0.4	99.3	0.1	99.8	0.0	0.0	0.0	0.0	0.0	0.0

BE3-treated	Lys			Arg 158 → Cys			Leu → Leu			Ala			Val			Tyr			Gln			indel%
	G	A		G	C ₆	G	C ₇	C ₈	T	G	G	C	A	G	T	G	T	A	C	A	G	
		A	G																			
APOE4C158R	G	A	A	G	C ₆	G	C ₇	C ₈	T	G	G	C	A	G	T	G	T	A	C	C	G	4.6
A	0.1	100.0	100.0	0.0	0.5	0.0	1.3	0.9	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.1
C	0.0	0.0	0.0	0.0	23.7	0.0	47.4	43.5	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0
G	99.9	0.0	0.0	100.0	0.9	99.9	1.1	0.7	0.0	100.0	100.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	99.9
T	0.0	0.0	0.0	0.0	74.9	0.1	50.2	55.0	100.0	0.0	0.0	0.1	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0

FIGURE 88

BE3-treated PRNPR37X	Gly			Ser → Ser			Arg 27 → Stop			Tyr			Pro			Gly			Glu		
	G	G	C	A	G	C ₇	C ₈	G	A	T	A	C	C	C	G	G	G	C	A	G	G
A	0.0	0.0	0.1	100.0	0.0	1.1	0.3	0.1	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0
C	0.0	0.0	98.9	0.0	0.0	54.9	57.8	0.0	0.0	0.0	0.0	99.8	99.8	100.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0
G	100.0	100.0	0.0	0.0	100.0	2.1	0.6	99.9	0.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0	100.0	0.0	0.0	100.0	100.0
T	0.0	0.0	1.1	0.0	0.0	41.9	41.2	0.0	0.0	100.0	0.0	0.2	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

FIGURE 89

BE1:									
BE2:									
BE3:									

EMX1-parental		C5	C6	C10	indel %	EMX1-UDG KO		C5	C6	C10	indel %
untreated	A	0.0%	0.0%	0.0%	0.01%	untreated	A	0.0%	0.0%	0.0%	0.01%
	C	100.0%	100.0%	100.0%	C		99.9%	99.9%	100.0%		
	G	0.0%	0.0%	0.0%	G		0.0%	0.0%	0.0%		
	T	0.0%	0.0%	0.0%	T		0.1%	0.1%	0.0%		

BE1	A	0.4%	0.1%	0.0%	BE1	A	0.0%	0.0%	0.04%
	C	95.8%	97.4%	100.0%		C	76.5%	76.6%	100.0%
	G	0.9%	0.2%	0.0%		G	0.0%	0.0%	0.0%
	T	2.9%	2.3%	0.0%		T	23.5%	23.4%	0.0%

BE2	A	0.3%	0.1%	0.0%	BE2	A	0.0%	0.0%	0.02%
	C	94.9%	95.7%	100.0%		C	96.3%	96.3%	100.0%
	G	1.0%	0.1%	0.0%		G	0.0%	0.0%	0.0%
	T	3.8%	4.0%	0.0%		T	3.7%	3.7%	0.0%

BE3	A	1.4%	0.8%	0.0%	BE3	A	0.0%	0.0%	0.04%
	C	78.5%	84.7%	100.0%		C	84.5%	86.8%	100.0%
	G	3.0%	1.4%	0.0%		G	0.0%	0.0%	0.0%
	T	17.1%	13.0%	0.0%		T	15.5%	13.2%	0.0%

FIGURE 90

FANCF-parental				C ₆	C ₇	C ₈	C ₁₁	indel %
untreated	A			0.0%	0.0%	0.0%	0.0%	0.03%
	C			99.9%	99.9%	99.9%	99.9%	
	G			0.0%	0.0%	0.0%	0.0%	
	T			0.1%	0.1%	0.1%	0.0%	

BE1	A			0.5%	0.5%	0.3%	0.0%	0.13%
	C			94.2%	97.8%	97.9%	99.8%	
	G			0.7%	0.0%	0.0%	0.0%	
	T			4.7%	1.6%	1.8%	0.2%	

BE2	A			0.3%	0.4%	0.2%	0.0%	0.25%
	C			95.3%	97.3%	97.6%	99.8%	
	G			0.4%	0.1%	0.0%	0.0%	
	T			4.0%	2.3%	2.1%	0.1%	

BE3	A			2.4%	3.2%	2.2%	0.9%	18.88%
	C			60.3%	72.6%	73.8%	86.6%	
	G			1.2%	0.6%	0.4%	0.3%	
	T			36.2%	23.6%	23.5%	12.3%	

FANCF-UDG KO				C ₆	C ₇	C ₈	C ₁₁	indel %
untreated	A			0.0%	0.0%	0.0%	0.0%	0.02%
	C			99.9%	99.9%	100.0%	100.0%	
	G			0.0%	0.0%	0.0%	0.0%	
	T			0.1%	0.0%	0.0%	0.0%	

BE1	A			0.0%	0.1%	0.0%	0.0%	0.09%
	C			60.9%	61.1%	61.3%	94.7%	
	G			0.1%	0.1%	0.1%	0.0%	
	T			39.0%	38.8%	38.6%	5.2%	

BE2	A			0.0%	0.0%	0.0%	0.0%	0.02%
	C			88.6%	88.6%	88.7%	98.9%	
	G			0.0%	0.0%	0.0%	0.0%	
	T			11.4%	11.4%	11.3%	1.1%	

BE3	A			0.0%	0.1%	0.1%	0.0%	0.35%
	C			47.9%	48.5%	48.8%	55.8%	
	G			0.0%	0.1%	0.3%	0.2%	
	T			52.1%	51.3%	50.8%	44.0%	

FIGURE 90 (CONTINUED)

HEK3-parental		C ₃	C ₄	C ₅	C ₉	indel %
untreated	A	0.0%	0.0%	0.0%	0.0%	0.00%
	C	100.0%	99.9%	99.9%	100.0%	
	G	0.0%	0.0%	0.0%	0.0%	
	T	0.0%	0.0%	0.0%	0.0%	

HEK3-UDG KO		C ₃	C ₄	C ₅	C ₉	indel %
untreated	A	0.0%	0.0%	0.0%	0.0%	0.00%
	C	100.0%	100.0%	100.0%	100.0%	
	G	0.0%	0.0%	0.0%	0.0%	
	T	0.0%	0.0%	0.0%	0.0%	

BE1		C ₃	C ₄	C ₅	C ₉	indel %
BE1	A	0.0%	0.0%	0.0%	0.0%	0.03%
	C	96.0%	50.3%	41.1%	96.3%	
	G	0.0%	0.0%	0.1%	0.1%	
	T	4.0%	49.6%	58.8%	3.6%	

BE2		C ₃	C ₄	C ₅	C ₉	indel %
BE2	A	0.0%	0.0%	0.0%	0.0%	0.00%
	C	99.0%	80.2%	73.2%	98.8%	
	G	0.0%	0.0%	0.0%	0.0%	
	T	1.0%	19.7%	26.8%	1.1%	

BE3		C ₃	C ₄	C ₅	C ₉	indel %
BE3	A	0.0%	0.0%	0.0%	0.0%	0.09%
	C	98.5%	55.6%	40.3%	99.4%	
	G	0.0%	0.0%	0.0%	0.0%	
	T	1.4%	44.3%	59.7%	0.6%	

BE1		C ₃	C ₄	C ₅	C ₉	indel %
BE1	A	0.0%	0.4%	0.3%	0.1%	0.07%
	C	99.9%	96.3%	94.4%	99.8%	
	G	0.0%	0.1%	1.9%	0.1%	
	T	0.1%	3.2%	3.4%	0.1%	

BE2		C ₃	C ₄	C ₅	C ₉	indel %
BE2	A	0.0%	0.2%	0.3%	0.1%	0.05%
	C	100.0%	97.7%	96.1%	99.8%	
	G	0.0%	0.0%	1.2%	0.1%	
	T	0.0%	2.1%	2.4%	0.1%	

BE3		C ₃	C ₄	C ₅	C ₉	indel %
BE3	A	0.1%	2.9%	2.4%	0.3%	3.27%
	C	99.4%	62.6%	55.9%	98.8%	
	G	0.0%	1.5%	10.4%	0.3%	
	T	0.6%	33.0%	31.3%	0.6%	

FIGURE 90 (CONTINUED)

HEK4-parental		C ₃	C ₅	C ₈	C ₁₁	indel %
untreated	A	0.0%	0.0%	0.0%	0.0%	0.00%
	C	100.0%	100.0%	99.9%	100.0%	
	G	0.0%	0.0%	0.0%	0.0%	
	T	0.0%	0.0%	0.1%	0.0%	

HEK4-UDG KO		C ₃	C ₅	C ₈	C ₁₁	indel %
untreated	A	0.0%	0.0%	0.0%	0.0%	0.00%
	C	100.0%	100.0%	99.9%	100.0%	
	G	0.0%	0.0%	0.0%	0.0%	
	T	0.0%	0.0%	0.1%	0.0%	

BE1		C ₃	C ₅	C ₈	C ₁₁	indel %
BE1	A	0.0%	0.0%	0.0%	0.0%	0.00%
	C	99.9%	67.5%	99.0%	100.0%	
	G	0.0%	0.0%	0.1%	0.0%	
	T	0.1%	32.5%	1.0%	0.0%	

BE2		C ₃	C ₅	C ₈	C ₁₁	indel %
BE2	A	0.0%	0.0%	0.0%	0.0%	0.00%
	C	100.0%	91.9%	99.7%	100.0%	
	G	0.0%	0.0%	0.0%	0.0%	
	T	0.0%	8.1%	0.2%	0.0%	

BE3		C ₃	C ₅	C ₈	C ₁₁	indel %
BE3	A	0.0%	0.0%	0.0%	0.0%	0.03%
	C	99.9%	65.9%	99.7%	100.0%	
	G	0.0%	0.3%	0.0%	0.0%	
	T	0.1%	33.8%	0.3%	0.0%	

HEK4-parental		C ₃	C ₅	C ₈	C ₁₁	indel %
untreated	A	0.0%	0.0%	0.0%	0.0%	0.00%
	C	100.0%	100.0%	99.9%	100.0%	
	G	0.0%	0.0%	0.0%	0.0%	
	T	0.0%	0.0%	0.1%	0.0%	

BE1		C ₃	C ₅	C ₈	C ₁₁	indel %
BE1	A	0.0%	1.4%	0.0%	0.0%	0.08%
	C	100.0%	95.5%	99.9%	100.0%	
	G	0.0%	2.2%	0.0%	0.0%	
	T	0.0%	0.9%	0.1%	0.0%	

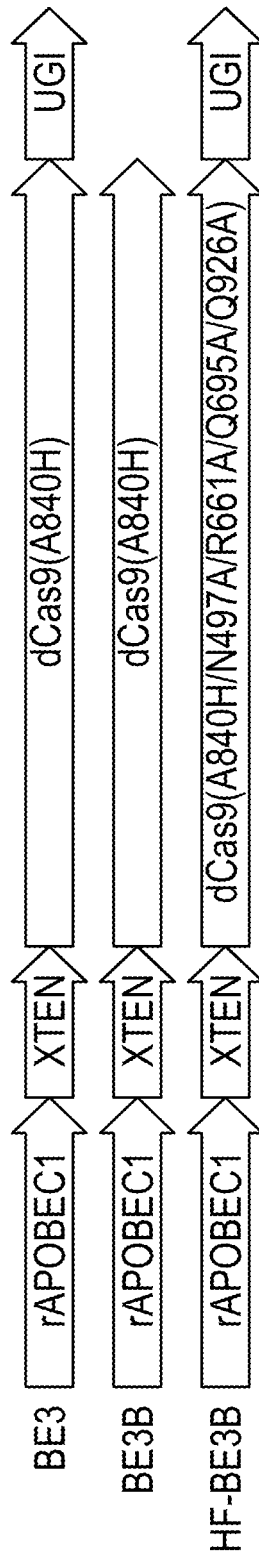
BE2		C ₃	C ₅	C ₈	C ₁₁	indel %
BE2	A	0.0%	0.4%	0.0%	0.0%	0.07%
	C	100.0%	97.7%	99.9%	100.0%	
	G	0.0%	1.1%	0.0%	0.0%	
	T	0.0%	0.7%	0.1%	0.0%	

BE3		C ₃	C ₅	C ₈	C ₁₁	indel %
BE3	A	0.0%	7.1%	0.0%	0.0%	6.05%
	C	99.9%	58.5%	99.7%	100.0%	
	G	0.0%	17.4%	0.0%	0.0%	
	T	0.1%	17.0%	0.2%	0.0%	

FIGURE 90 (CONTINUED)

BE3: $\xrightarrow{\text{rAPOBEC1}}$ $\xrightarrow{\text{XTEN}}$ $\xrightarrow{\text{dCas9(A840H)}}$ $\xrightarrow{\text{UGI}}$ BE3B: $\xrightarrow{\text{rAPOBEC1}}$ $\xrightarrow{\text{XTEN}}$ $\xrightarrow{\text{dCas9(A840H)}}$											
EMX1	C3	C6	C12	indel %	FANCF	C6	C7	C8	C11	indel %	
untreated	A	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	untreated	A	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	
	C	99.9 $\pm$ 0	99.9 $\pm$ 0	99.9 $\pm$ 0		C	99.9 $\pm$ 0	99.9 $\pm$ 0	99.9 $\pm$ 0	99.9 $\pm$ 0	
	G	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0		G	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	
	T	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0		T	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	
BE3	A	1.3 $\pm$ 0.1	0.7 $\pm$ 0.2	0 $\pm$ 0	BE3	A	0.8 $\pm$ 0.1	1.2 $\pm$ 0.3	1.2 $\pm$ 0.1	0.2 $\pm$ 0.1	5.8 $\pm$ 0.9
	C	51.7 $\pm$ 1	55.2 $\pm$ 0.1	99.9 $\pm$ 0		C	64.7 $\pm$ 5.9	67.9 $\pm$ 5.1	68.9 $\pm$ 5.2	85.4 $\pm$ 2.7	
	G	4 $\pm$ 0.7	1.9 $\pm$ 0.4	0 $\pm$ 0		G	0.6 $\pm$ 0	0.7 $\pm$ 0	0.7 $\pm$ 0.1	0.1 $\pm$ 0	
	T	42.8 $\pm$ 0.2	41.9 $\pm$ 0.4	0 $\pm$ 0		T	33.8 $\pm$ 5.7	29.9 $\pm$ 4.8	29 $\pm$ 5	14.1 $\pm$ 2.6	
BE3B	A	4.9 $\pm$ 1.4	3.9 $\pm$ 1.1	0 $\pm$ 0	BE3B	A	2.9 $\pm$ 0.9	4.1 $\pm$ 1.4	2.8 $\pm$ 0.9	1.1 $\pm$ 0	20.5 $\pm$ 3.8
	C	52.6 $\pm$ 12.1	61.9 $\pm$ 10.5	99.9 $\pm$ 0		C	67.3 $\pm$ 8.8	79.3 $\pm$ 5.8	79.5 $\pm$ 5.2	92 $\pm$ 1.9	
	G	12.3 $\pm$ 3.3	11.3 $\pm$ 3.1	0 $\pm$ 0		G	2 $\pm$ 0.5	0.7 $\pm$ 0.3	0.9 $\pm$ 0.2	0.5 $\pm$ 0.1	
	T	30.1 $\pm$ 7.3	22.7 $\pm$ 6.1	0 $\pm$ 0		T	27.7 $\pm$ 7.3	15.6 $\pm$ 4	16.5 $\pm$ 4	6.1 $\pm$ 1.3	

FIGURE 91



HEK3	C6	C7	C8	C11	indel %
untreated	A	0 ± 0	0 ± 0	0 ± 0	0 ± 0
	C	99.9 ± 0	99.9 ± 0	99.9 ± 0	99.9 ± 0
	G	0 ± 0	0 ± 0	0 ± 0	0 ± 0
	T	0 ± 0	0 ± 0	0 ± 0	0 ± 0
BE3	A	0 ± 0	1.6 ± 0.2	1.5 ± 0.3	0.2 ± 0
	C	98.7 ± 0.2	48.6 ± 5.4	40.8 ± 6.7	98.6 ± 0.1
	G	0 ± 0	1.4 ± 0.2	10.5 ± 1.2	0.3 ± 0
	T	1.1 ± 0.2	48.2 ± 4.9	47 ± 5.2	0.7 ± 0.1
BE3B	A	0.1 ± 0	4.9 ± 0.8	3.8 ± 0.8	0.8 ± 0.1
	C	99.4 ± 0.1	57.6 ± 6.3	44.4 ± 8.4	97.7 ± 0.3
	G	0 ± 0	3.3 ± 0.7	21.2 ± 2.8	0.7 ± 0.1
	T	0.4 ± 0.1	33.9 ± 4.7	30.4 ± 4.7	0.6 ± 0

HEK4	C6	C7	C8	C11	indel %
untreated	A	0 ± 0	0 ± 0	0 ± 0	0 ± 0
	C	99.9 ± 0	99.9 ± 0	99.9 ± 0	99.9 ± 0
	G	0 ± 0	0 ± 0	0 ± 0	0 ± 0
	T	0 ± 0	0 ± 0	0 ± 0	0 ± 0
BE3	A	0 ± 0	5.4 ± 1.3	0 ± 0	0 ± 0
	C	98.7 ± 0	44.5 ± 8.2	98.9 ± 0	99.8 ± 0
	G	0 ± 0	18.1 ± 2.3	0 ± 0	0 ± 0
	T	1.1 ± 0.1	31.9 ± 4.8	0.9 ± 0.1	0.1 ± 0
BE3B	A	0 ± 0	10.6 ± 2.6	0.3 ± 0	0 ± 0
	C	99.6 ± 0	45 ± 9.9	99.2 ± 0.1	99.9 ± 0
	G	0 ± 0	32.8 ± 5.8	0 ± 0	0 ± 0
	T	0.2 ± 0	11.4 ± 1.6	0.4 ± 0.2	0 ± 0

HEK4	C6	C7	C8	C11	indel %
untreated	A	0 ± 0	0 ± 0	0 ± 0	0 ± 0
	C	99.9 ± 0	99.9 ± 0	99.9 ± 0	99.9 ± 0
	G	0 ± 0	0 ± 0	0 ± 0	0 ± 0
	T	0 ± 0	0 ± 0	0 ± 0	0 ± 0
BE3	A	0 ± 0	5.4 ± 1.3	0 ± 0	0 ± 0
	C	98.7 ± 0	44.5 ± 8.2	98.9 ± 0	99.8 ± 0
	G	0 ± 0	18.1 ± 2.3	0 ± 0	0 ± 0
	T	1.1 ± 0.1	31.9 ± 4.8	0.9 ± 0.1	0.1 ± 0
BE3B	A	0 ± 0	10.6 ± 2.6	0.3 ± 0	0 ± 0
	C	99.6 ± 0	45 ± 9.9	99.2 ± 0.1	99.9 ± 0
	G	0 ± 0	32.8 ± 5.8	0 ± 0	0 ± 0
	T	0.2 ± 0	11.4 ± 1.6	0.4 ± 0.2	0 ± 0

FIGURE 91 (CONTINUED)

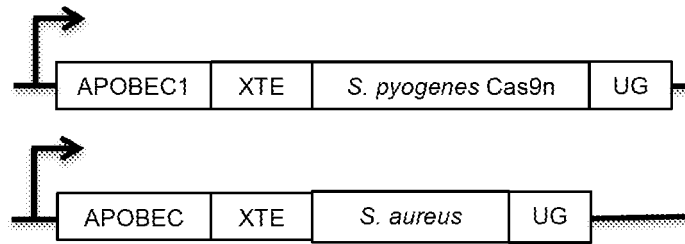


FIGURE 92A

Species	PAM	Base editor	Reference
<i>S. pyogenes</i>	NGG	BE3	Wild-type
	NGA	VQR, EQR BE3	Ref #7
	NGCG	VRER BE3	Ref #7
<i>S. aureus</i>	NNGRRT	SaBE3	Wild-type
	NNNRRT	SaKKHBE3	Ref #8

FIGURE 92B

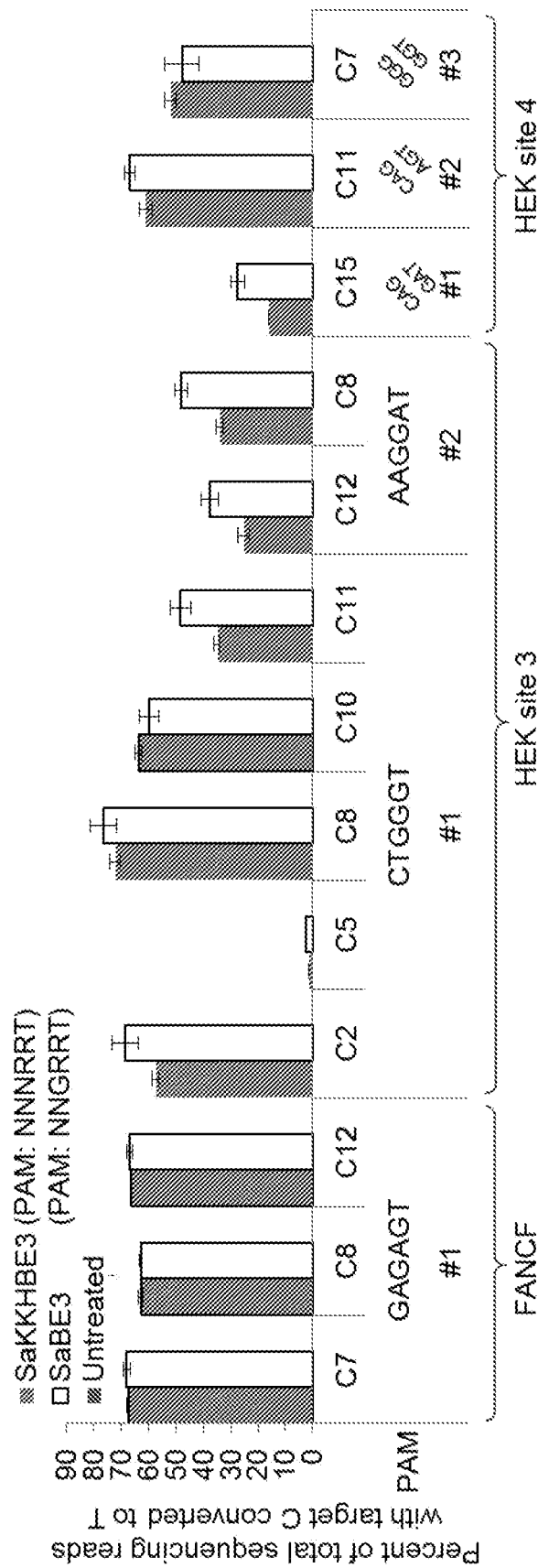


FIGURE 92C

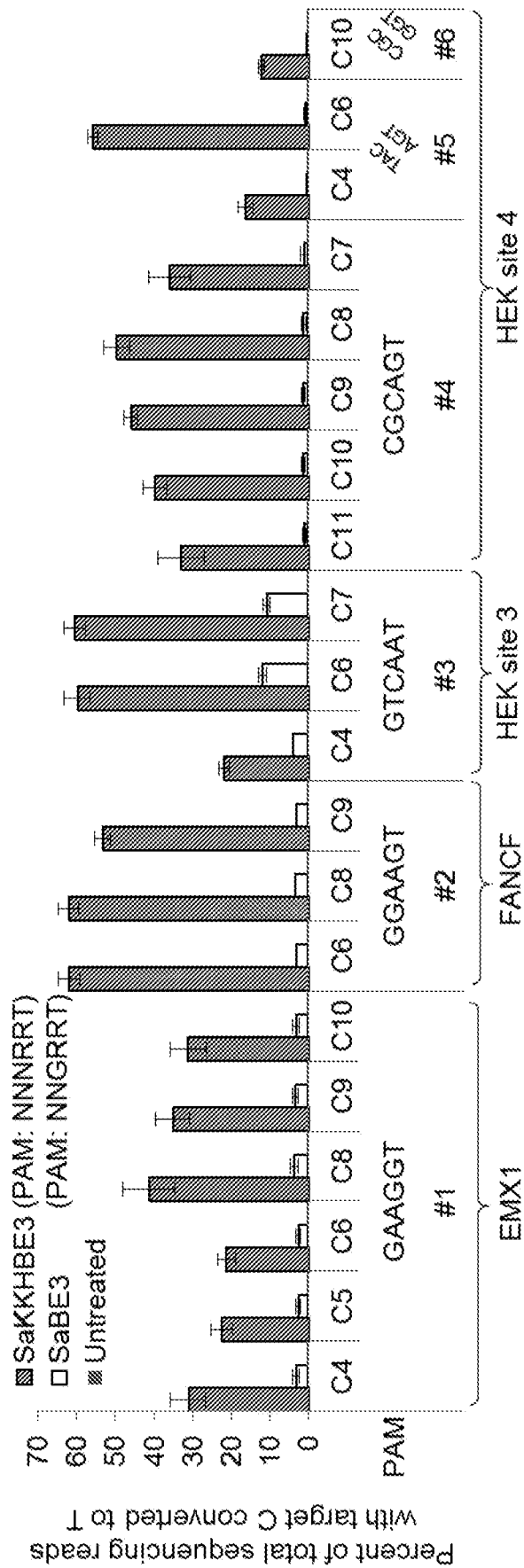


FIGURE 92D

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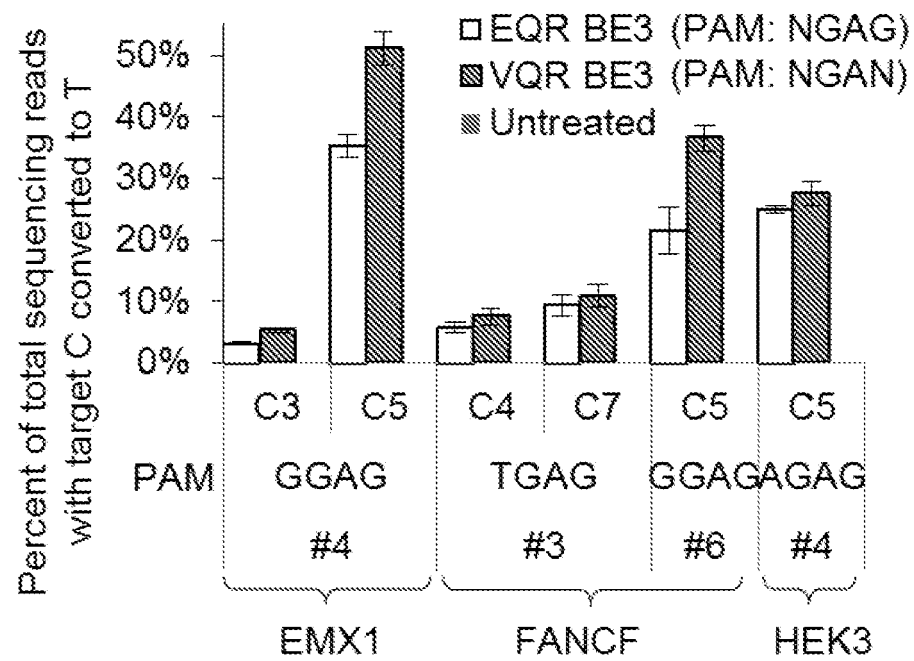


FIGURE 92E

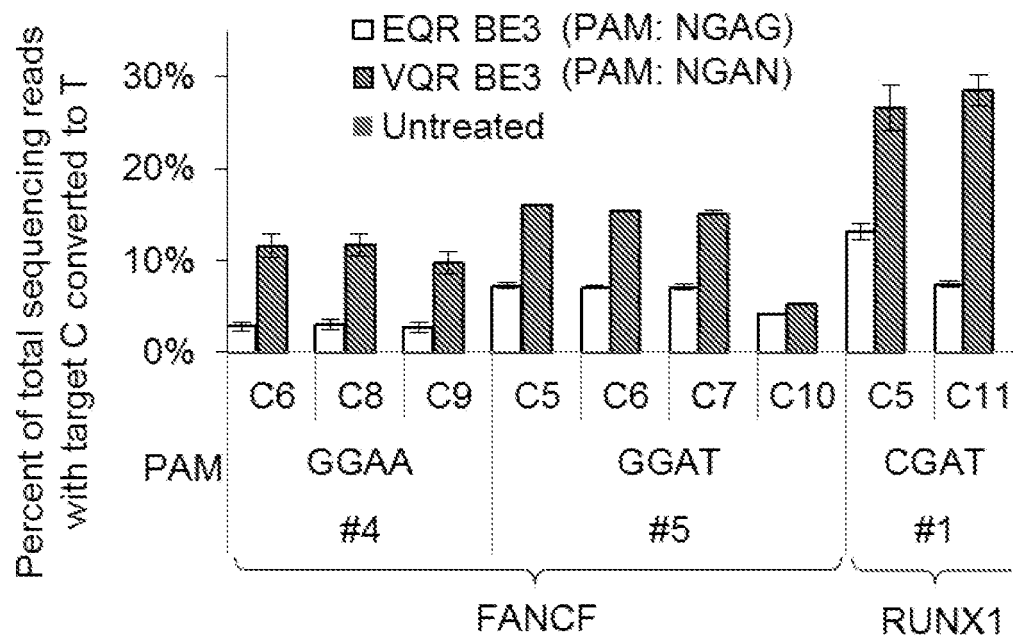


FIGURE 92F

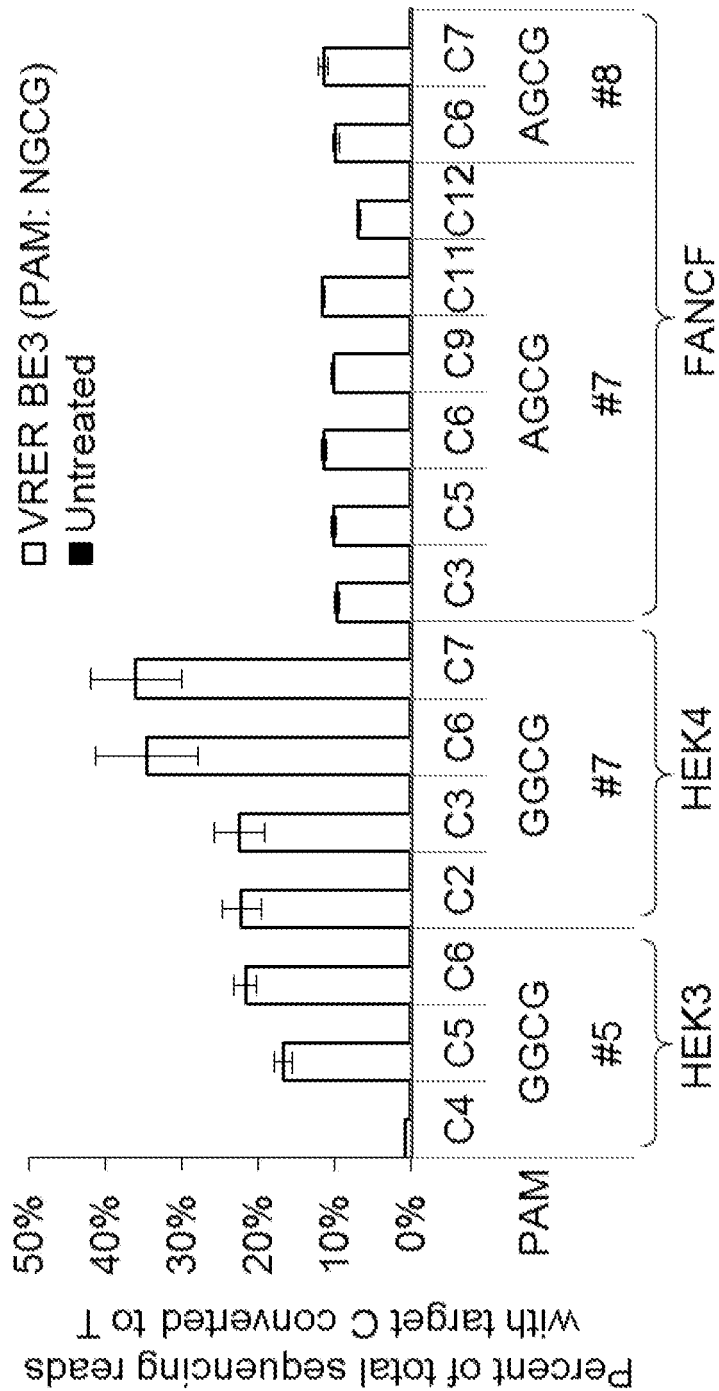


FIGURE 92G

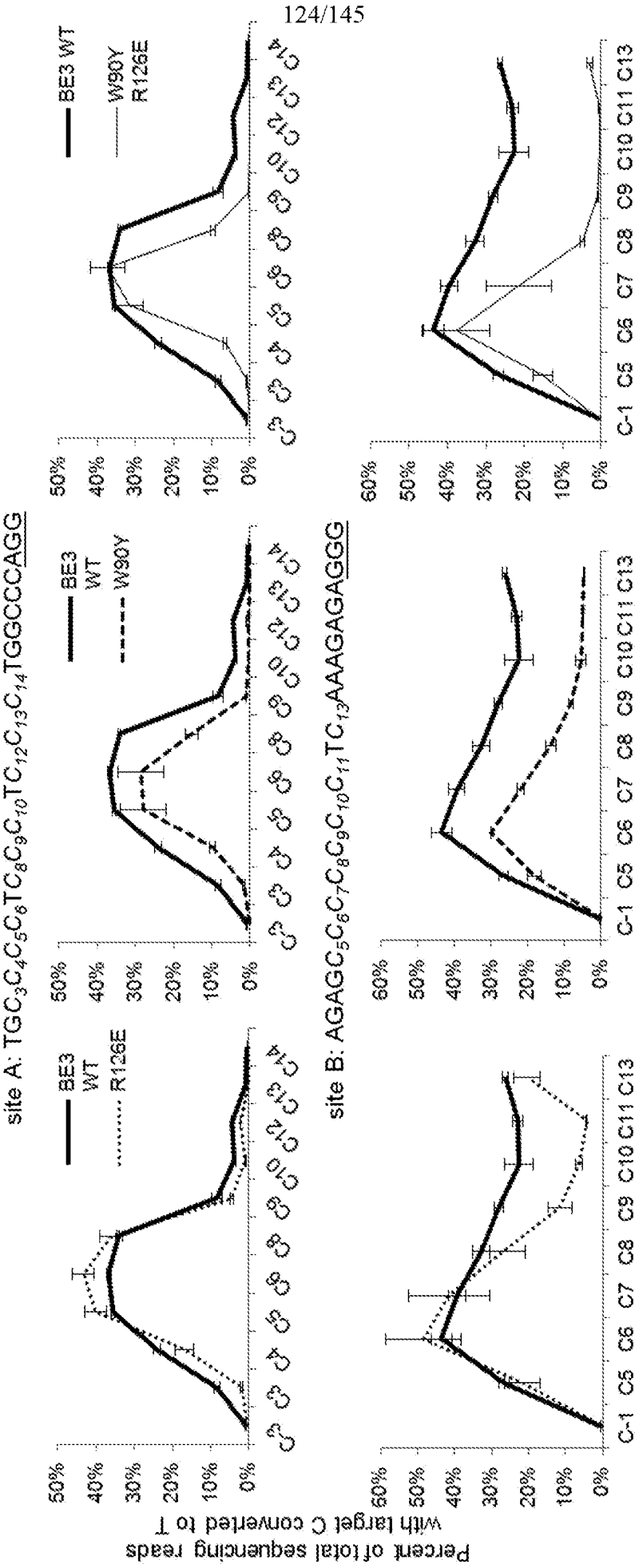


FIGURE 93A

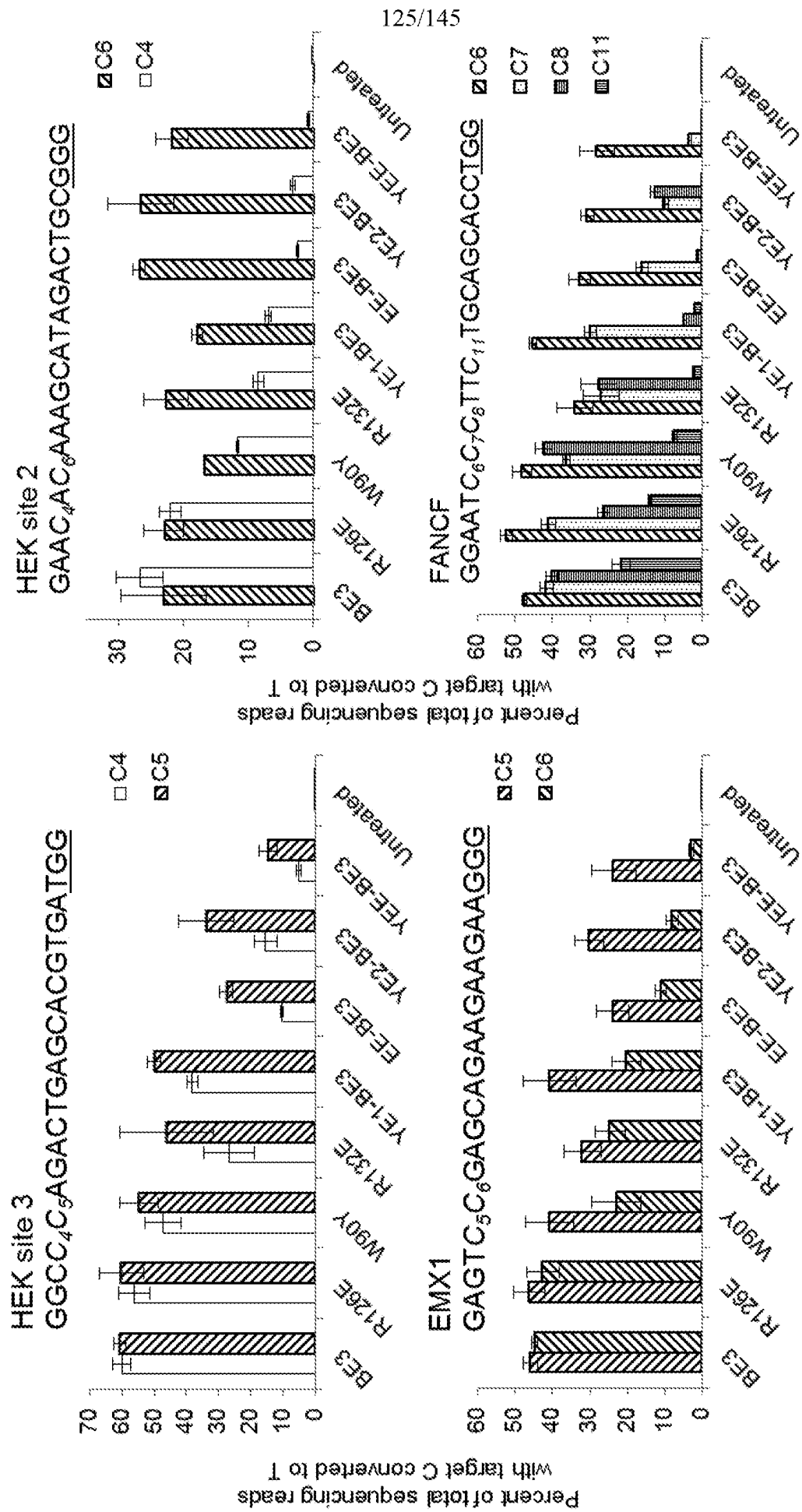


FIGURE 93B

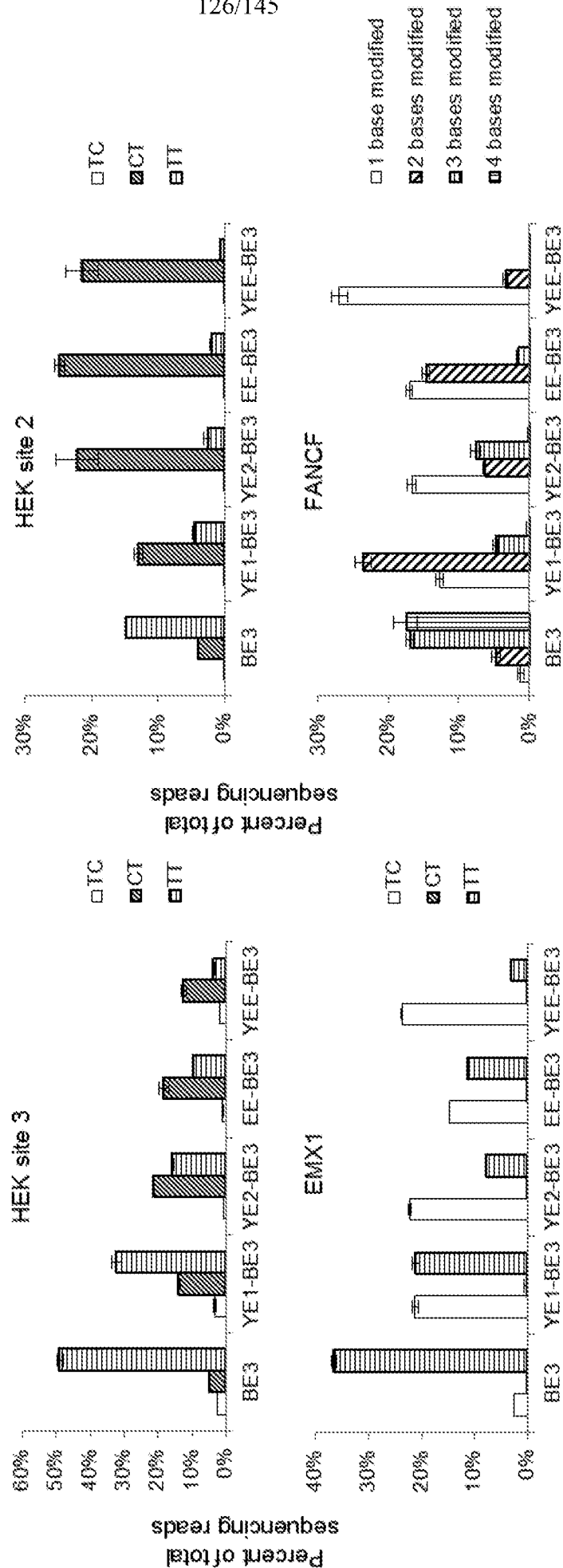


FIGURE 93C

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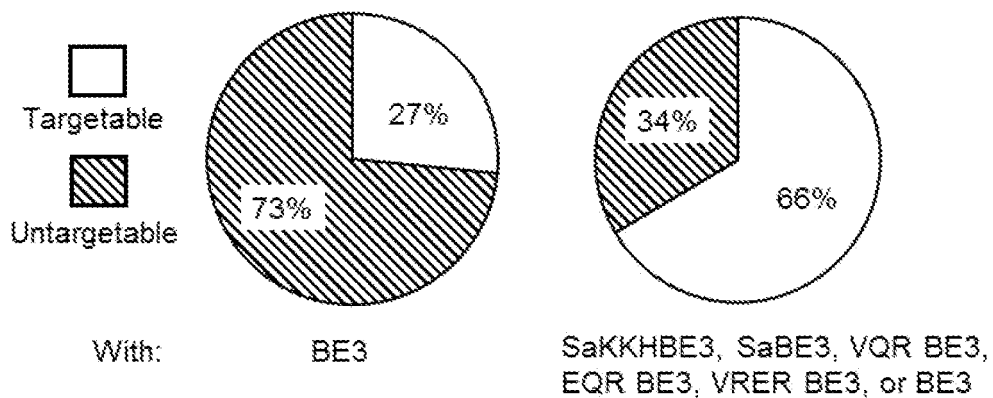


FIGURE 94A

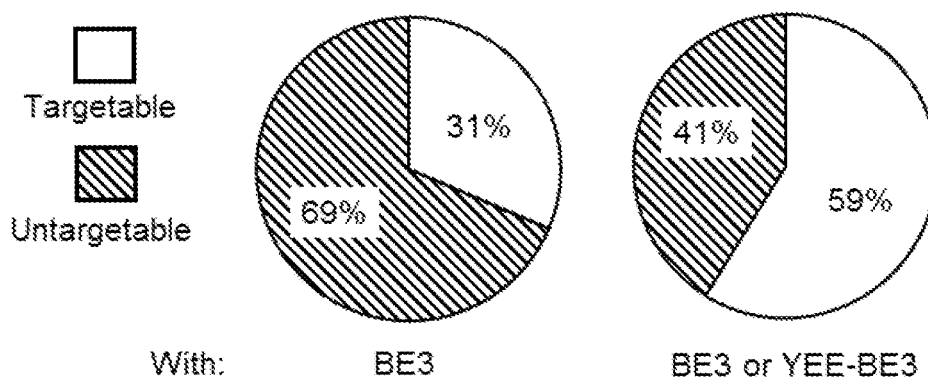


FIGURE 94B

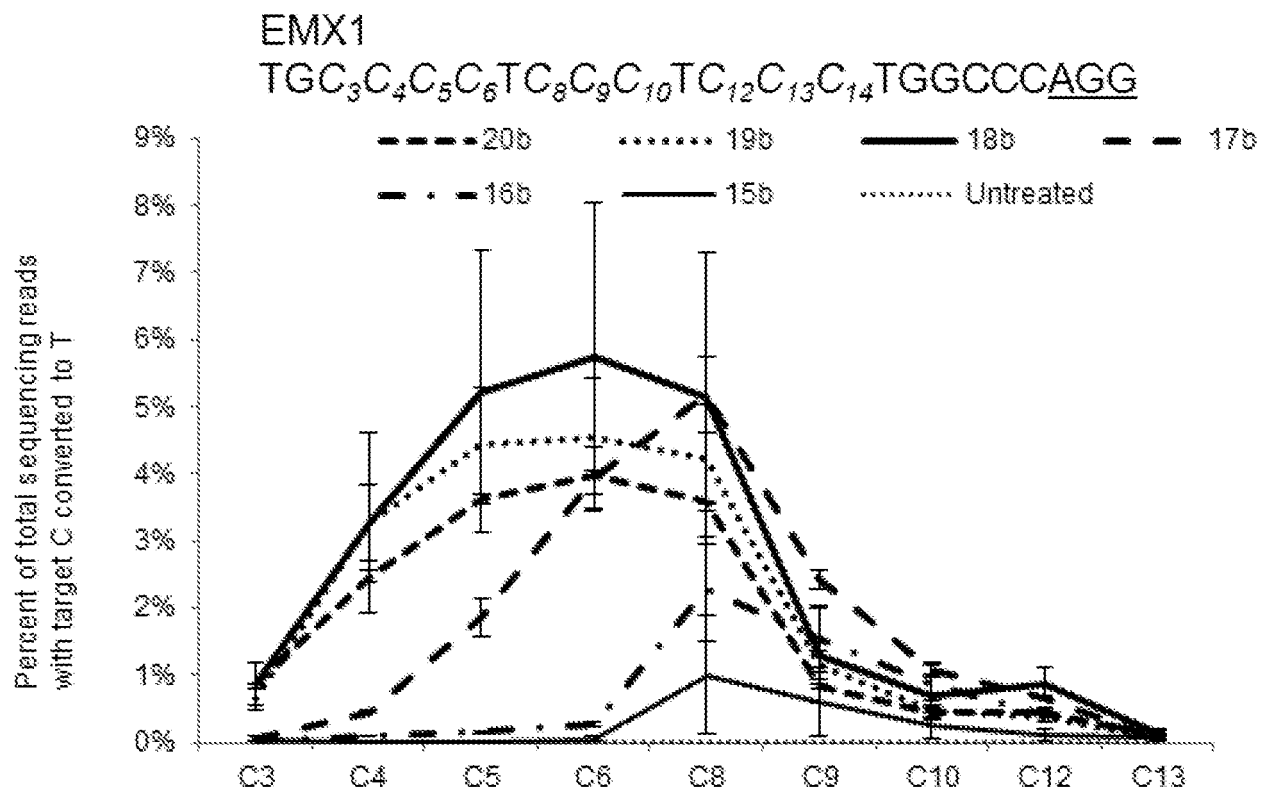


FIGURE 95A

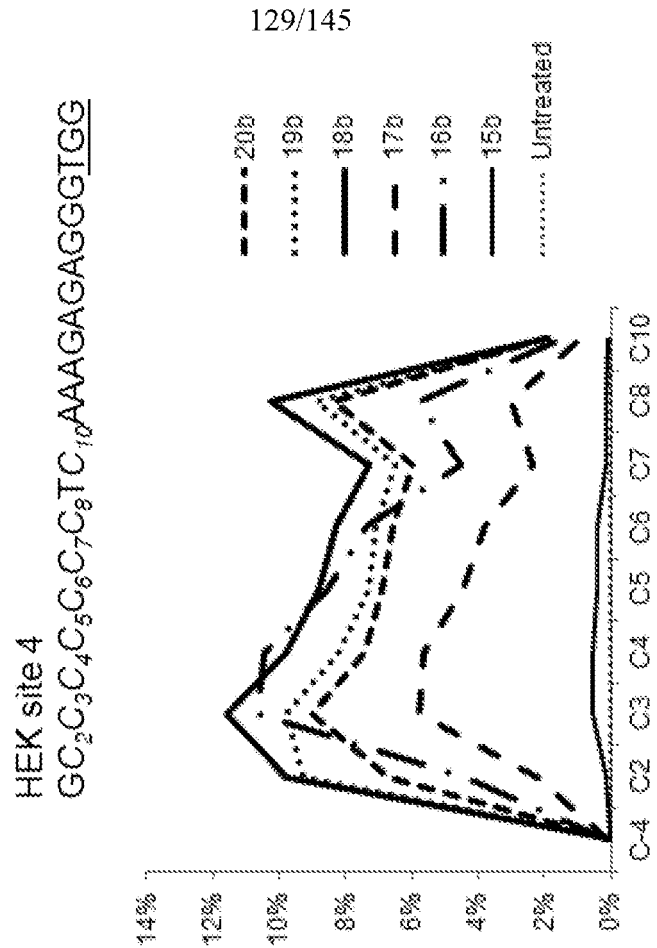
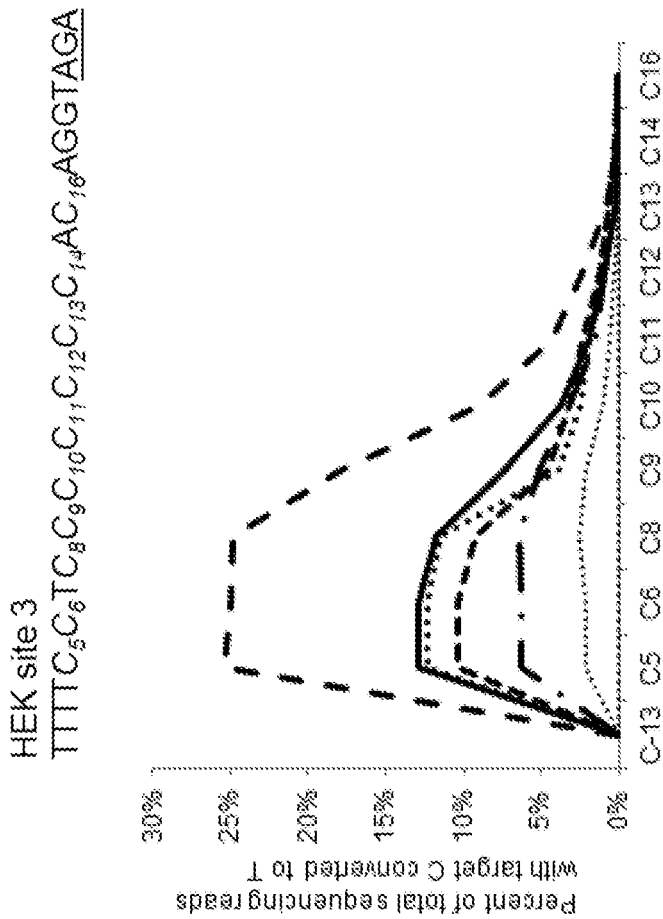


FIGURE 95B

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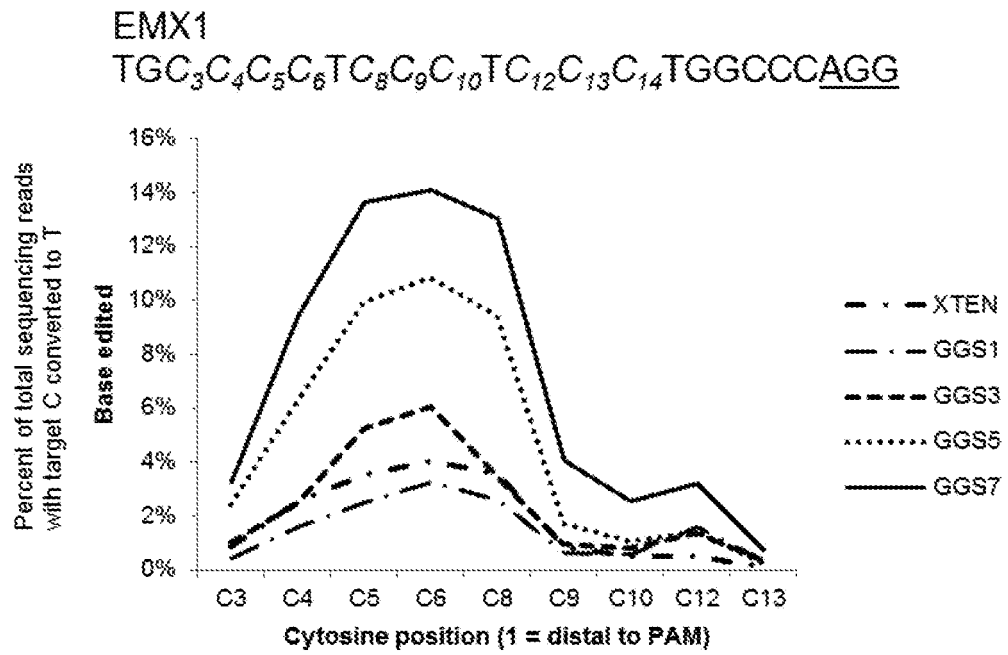


FIGURE 96

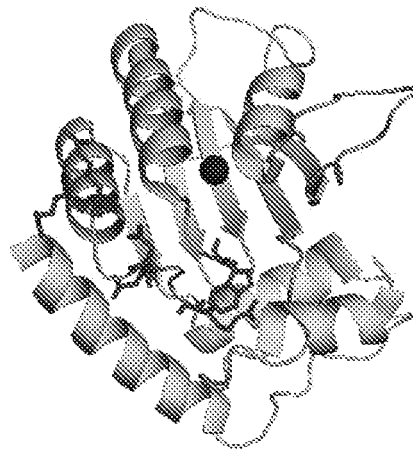


FIGURE 97A

APOBEC1 mutation	APOBEC3G mutation	Reference
R126A	R320A	#9,10
R126E	R320E	#9,10
W90A	W285A	#9,10
W90Y	W285Y	This work
R132E	R326E	This work

FIGURE 97B

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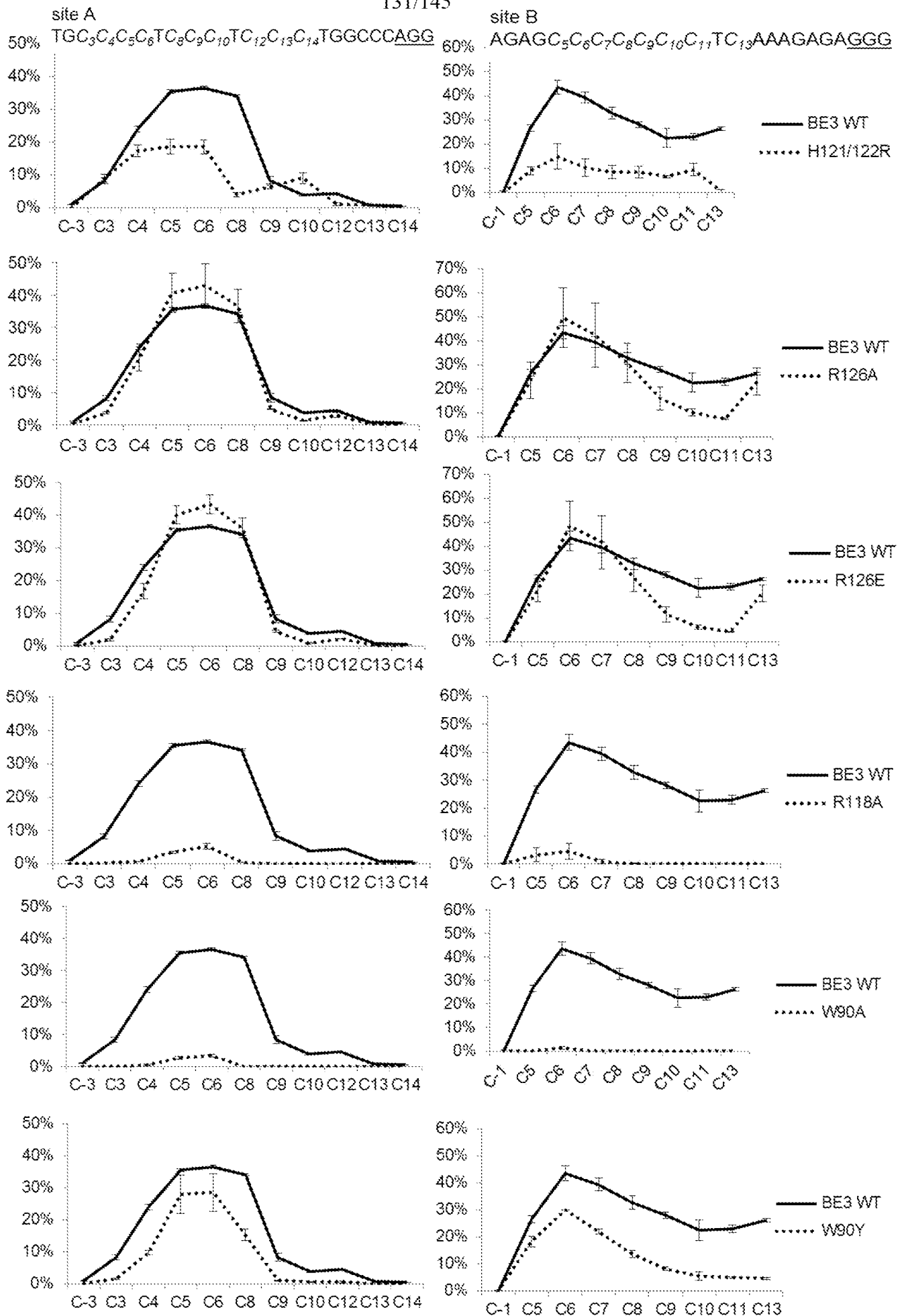
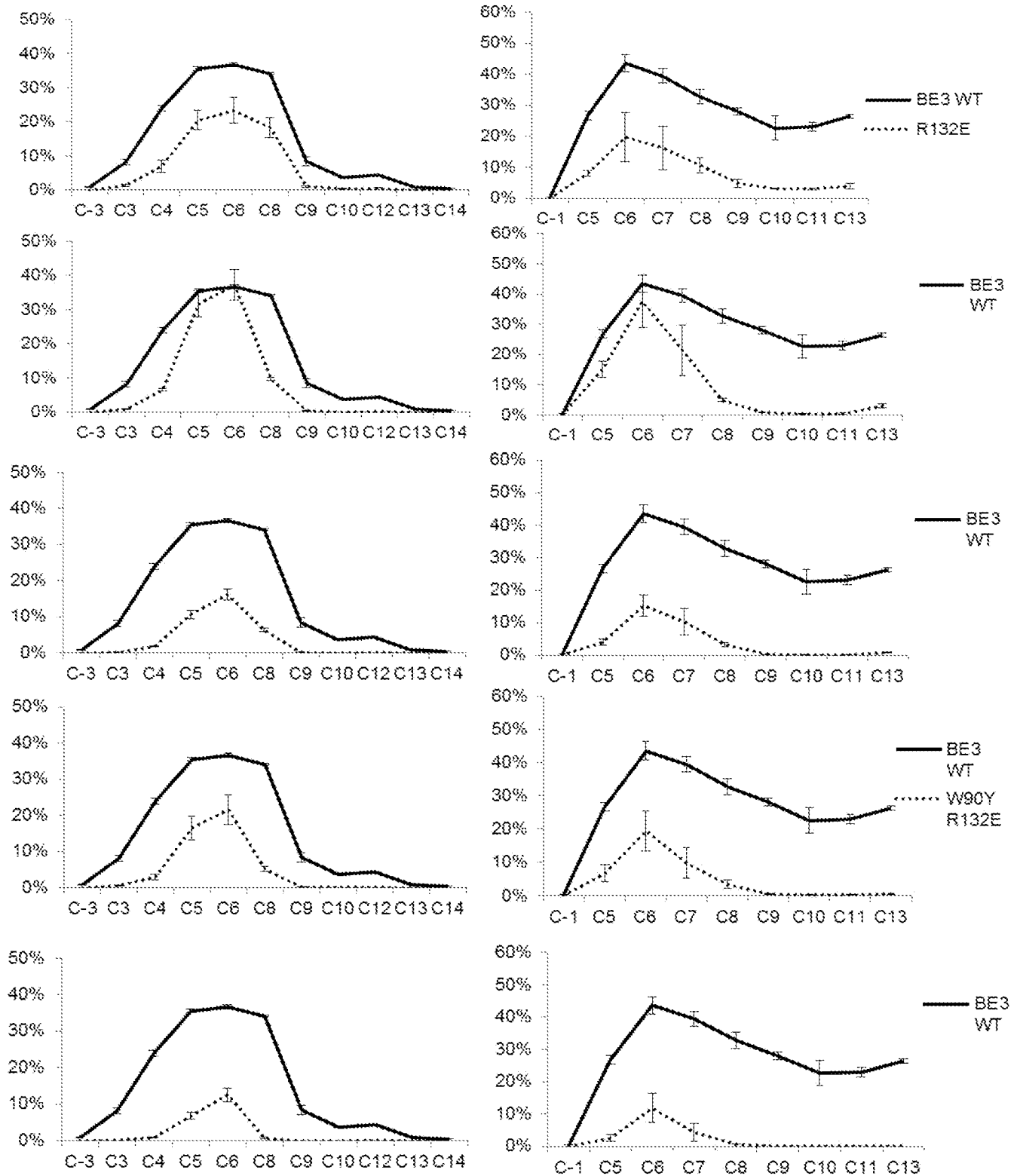


FIGURE 97C
SUBSTITUTE SHEET (RULE 26)

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Editing window width

	Site A	Site B		Site A	Site B
BE3 WT	5.0	6.1	W90Y	3.8	4.9
H121/122R	4.2	7.4	R132E	4.0	3.0
R126A	4.4	3.4	W90Y R126E	2.9	3.0
R126E	4.2	3.1	R126E R132E	2.9	3.0
R118A	2.4	3.6	W90Y R132E	2.7	2.8
W90A	2.5	1.1	W90Y R126E R132E	2.1	1.4

FIGURE 97C (CONTINUED)
SUBSTITUTE SHEET (RULE 26)

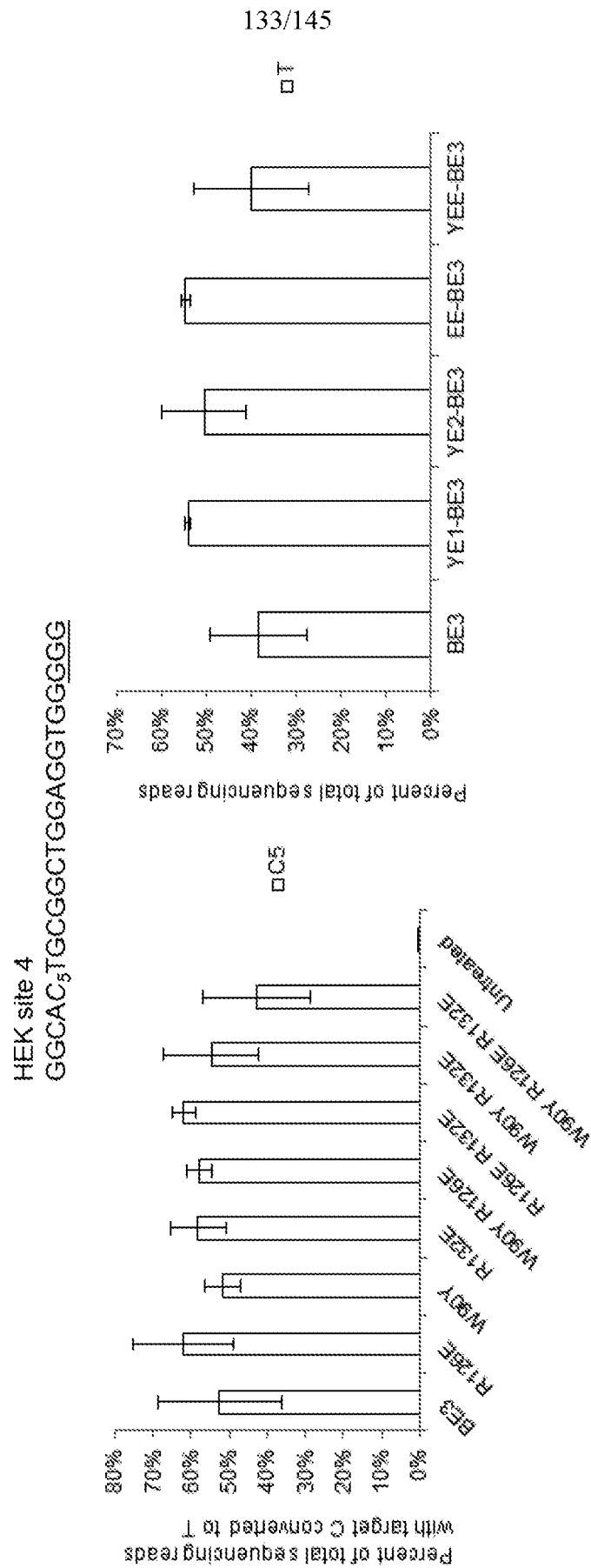


FIGURE 98

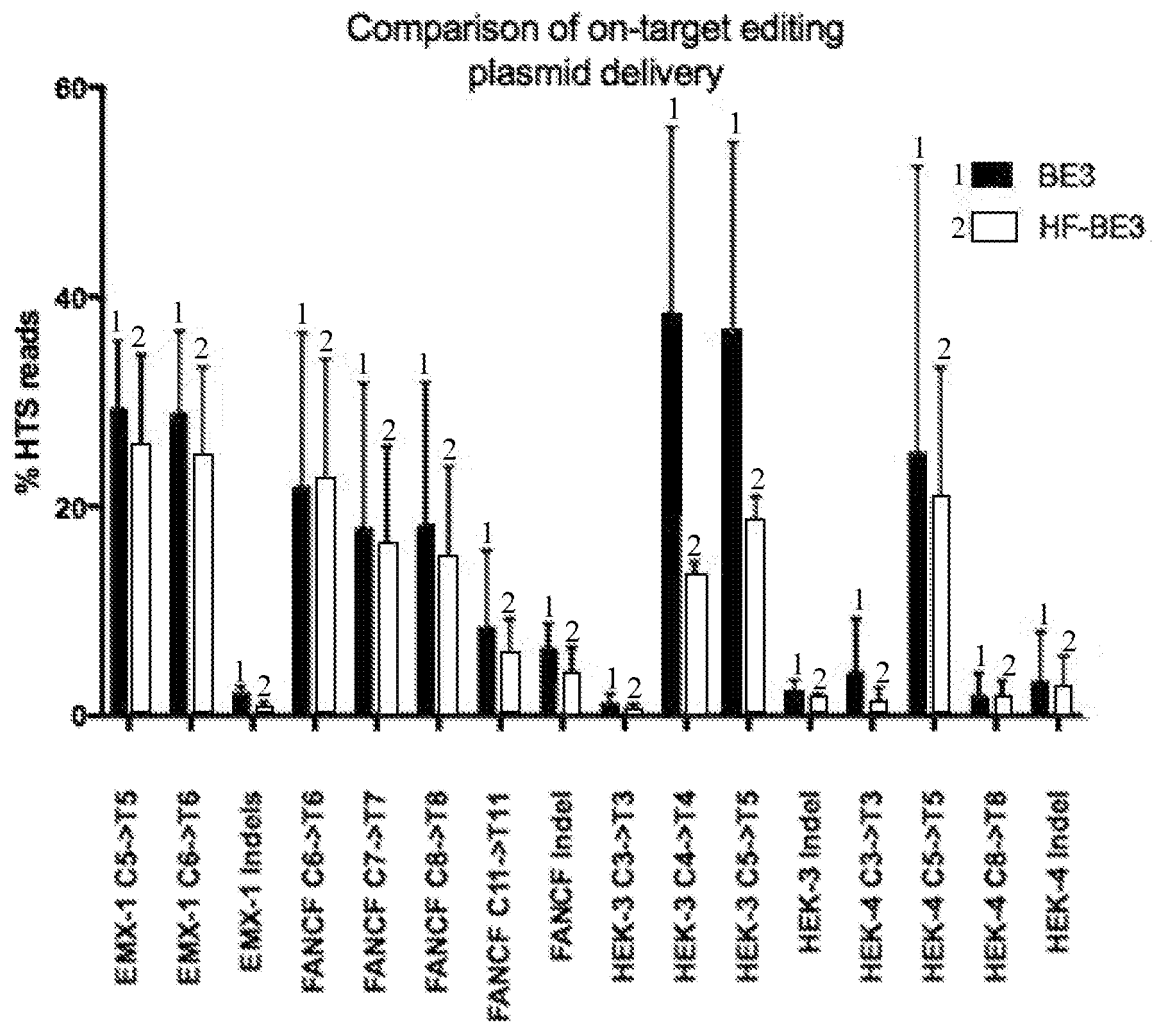


FIGURE 99

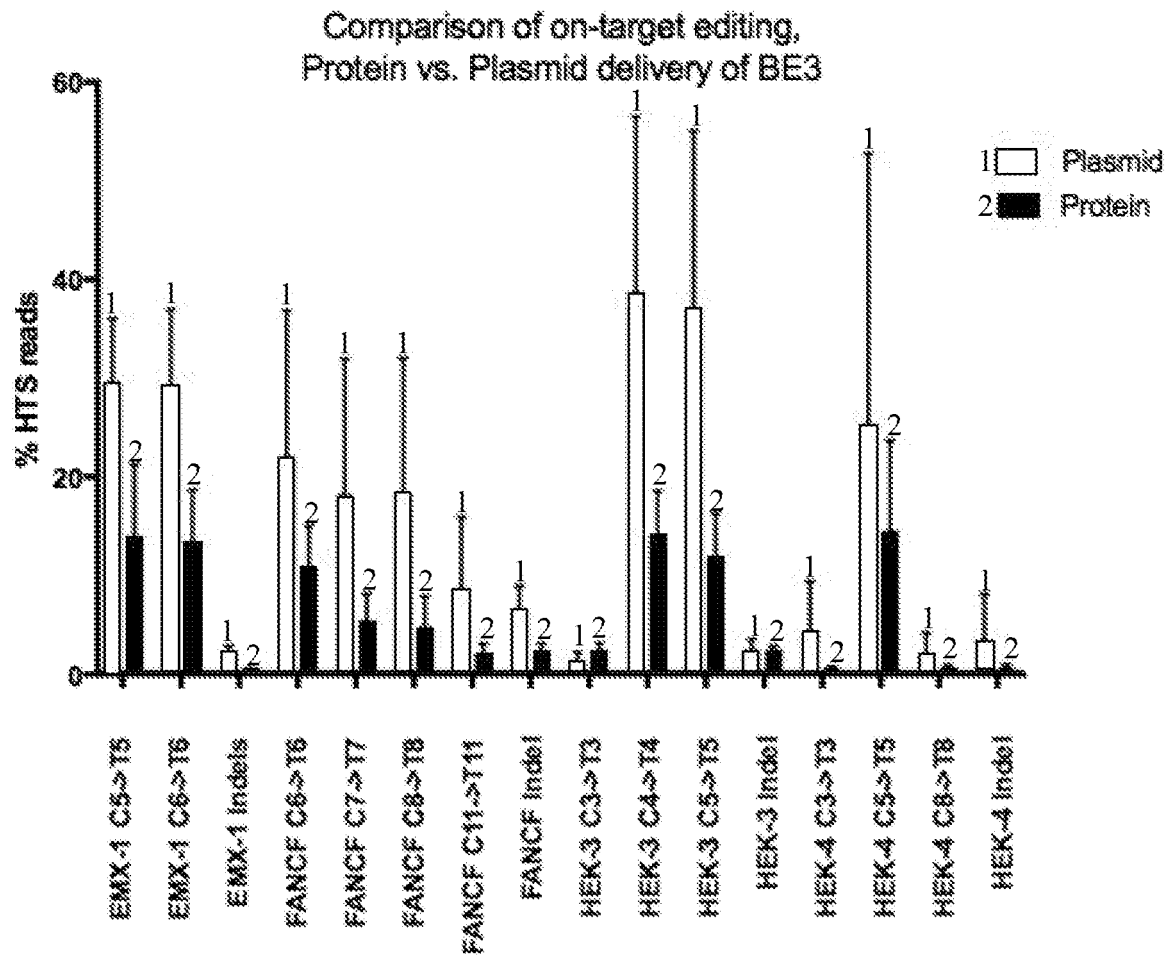


FIGURE 100

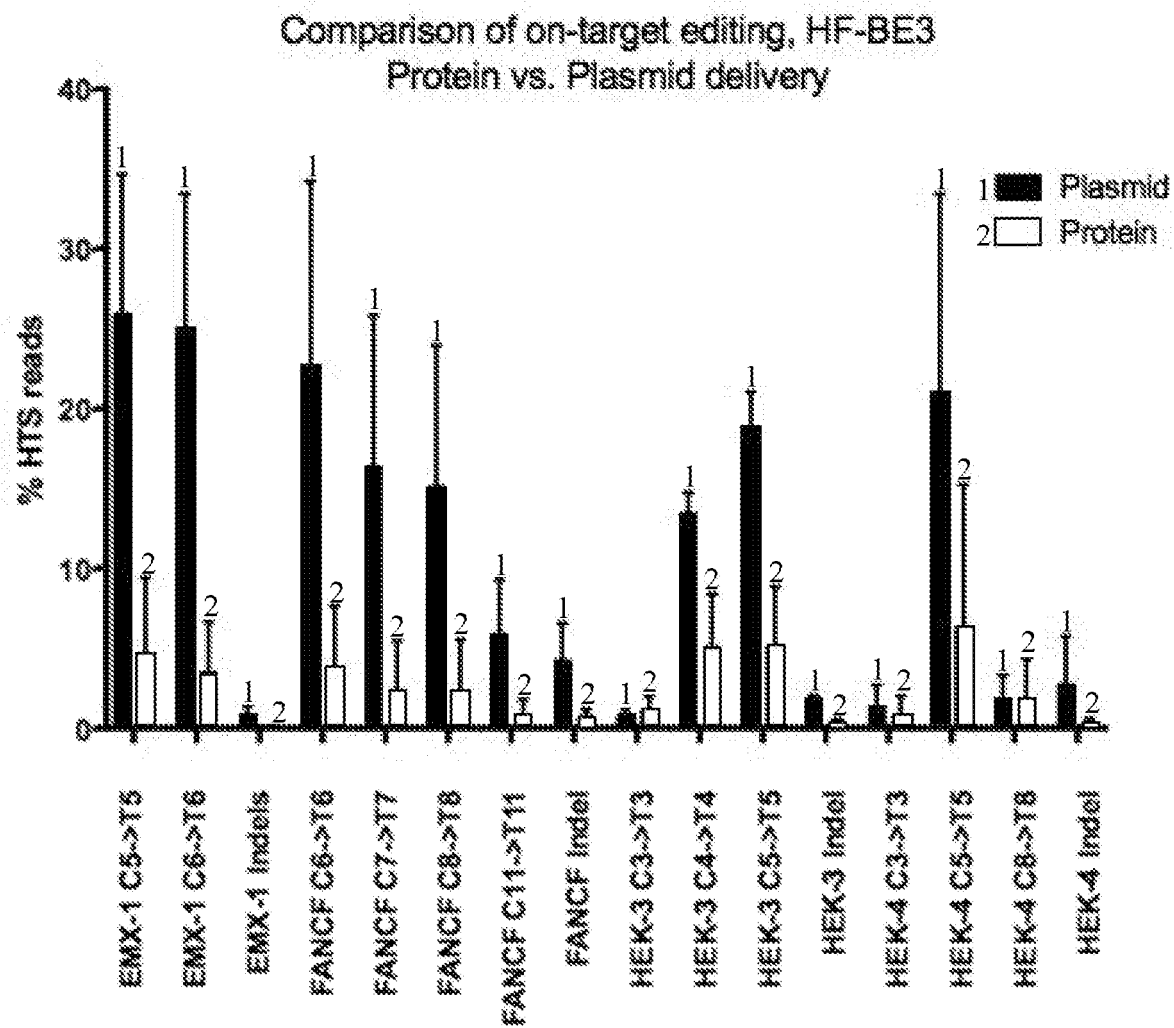


FIGURE 101

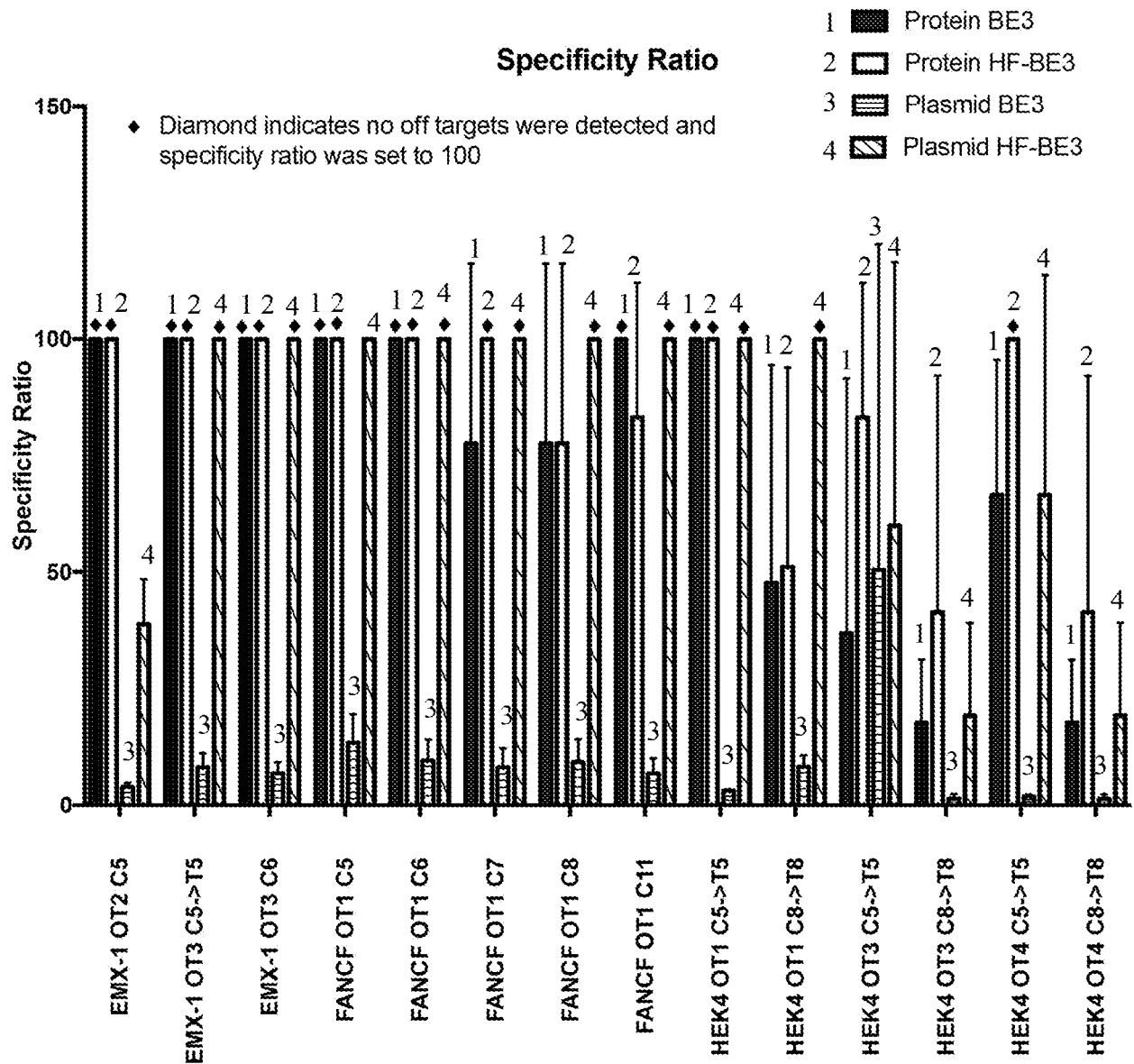


FIGURE 102

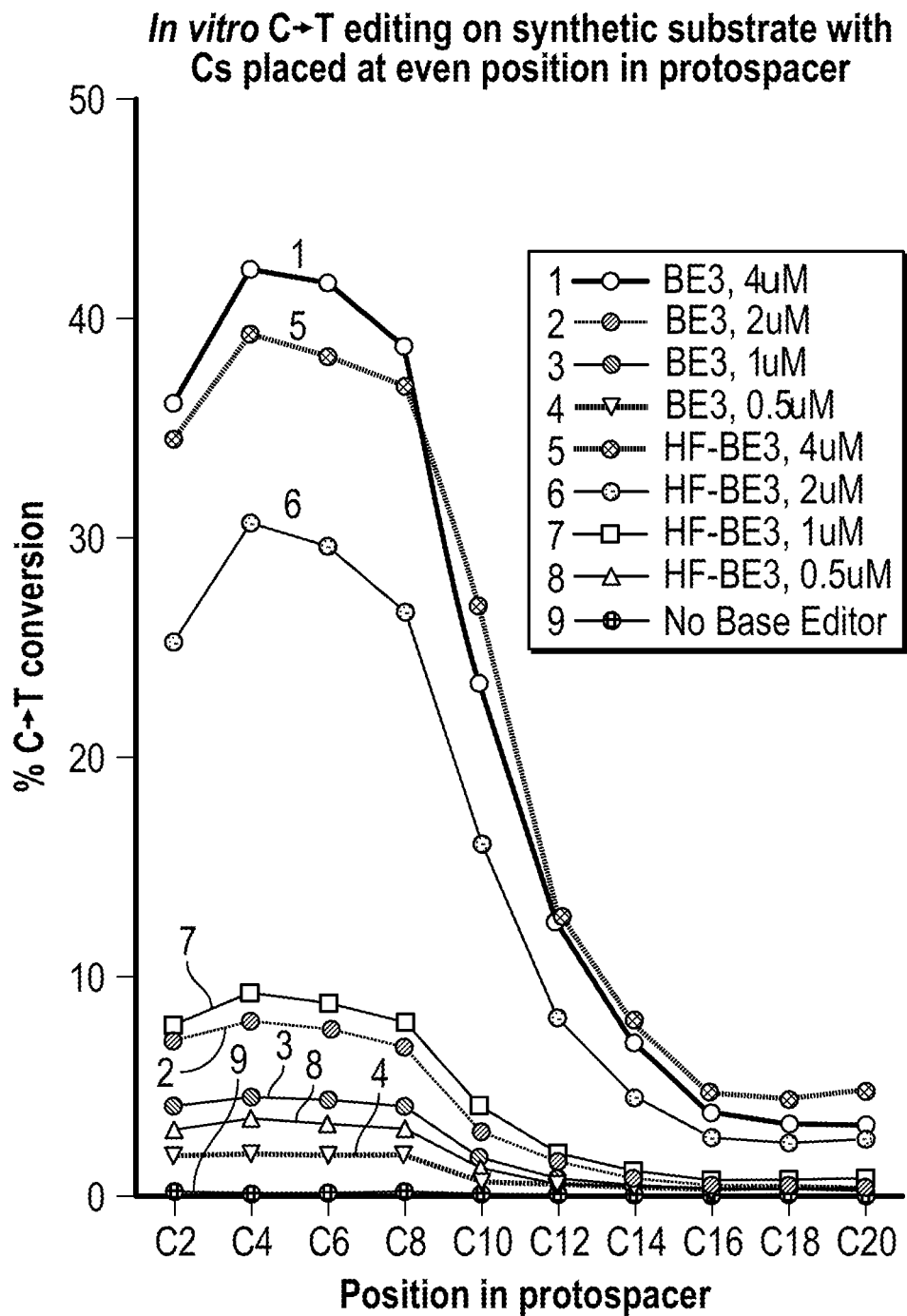


FIGURE 103

***In vitro* C→T editing on synthetic substrate with
Cs placed at odd positions in protospacer**

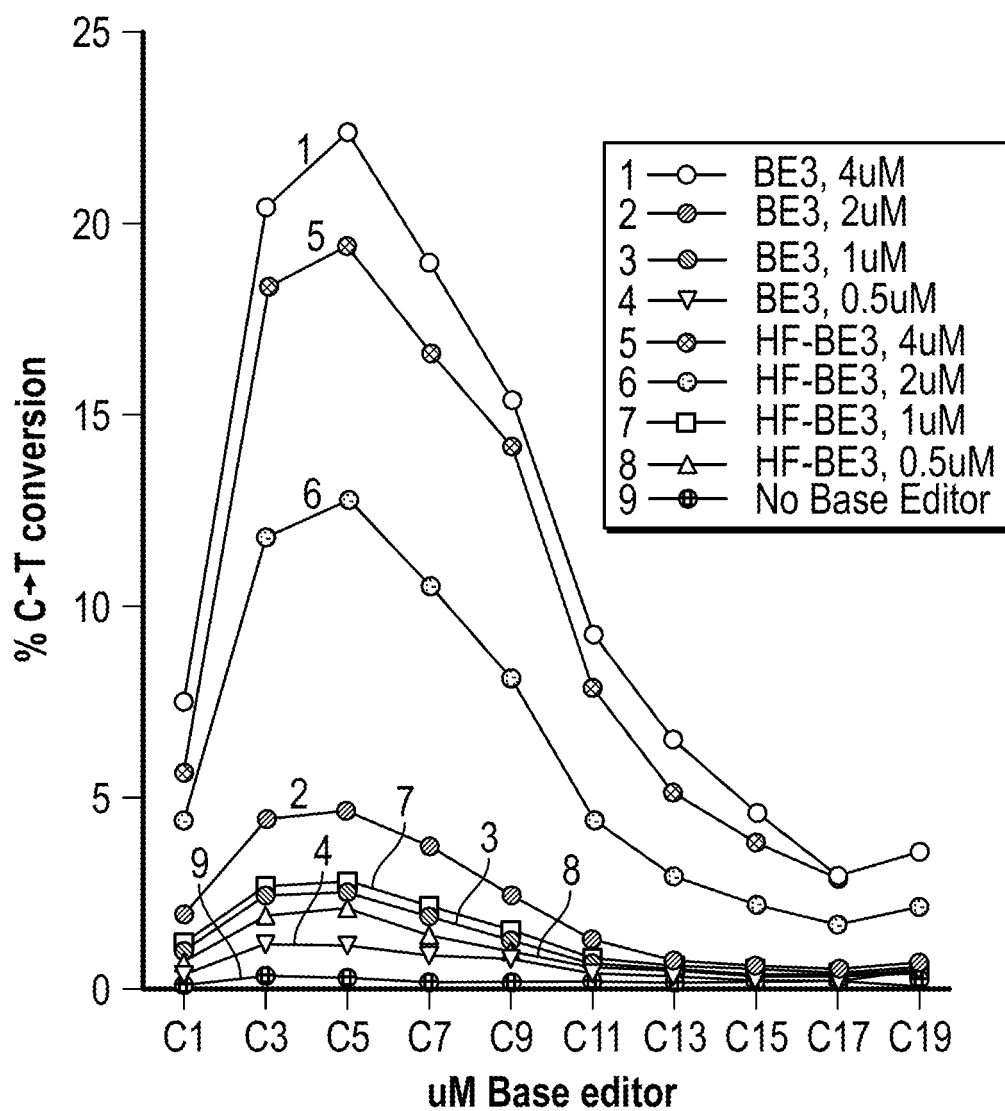


FIGURE 104

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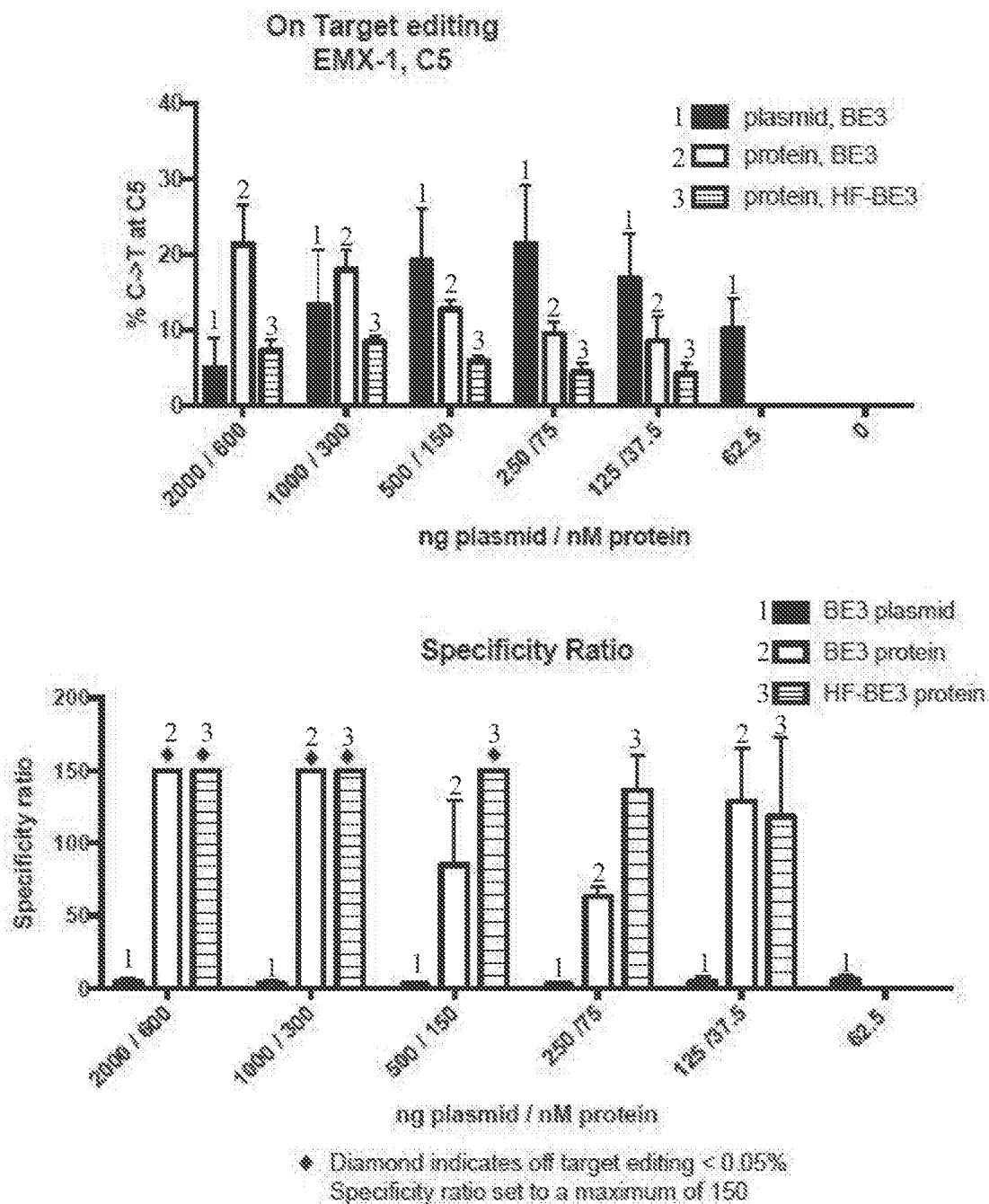


FIGURE 105

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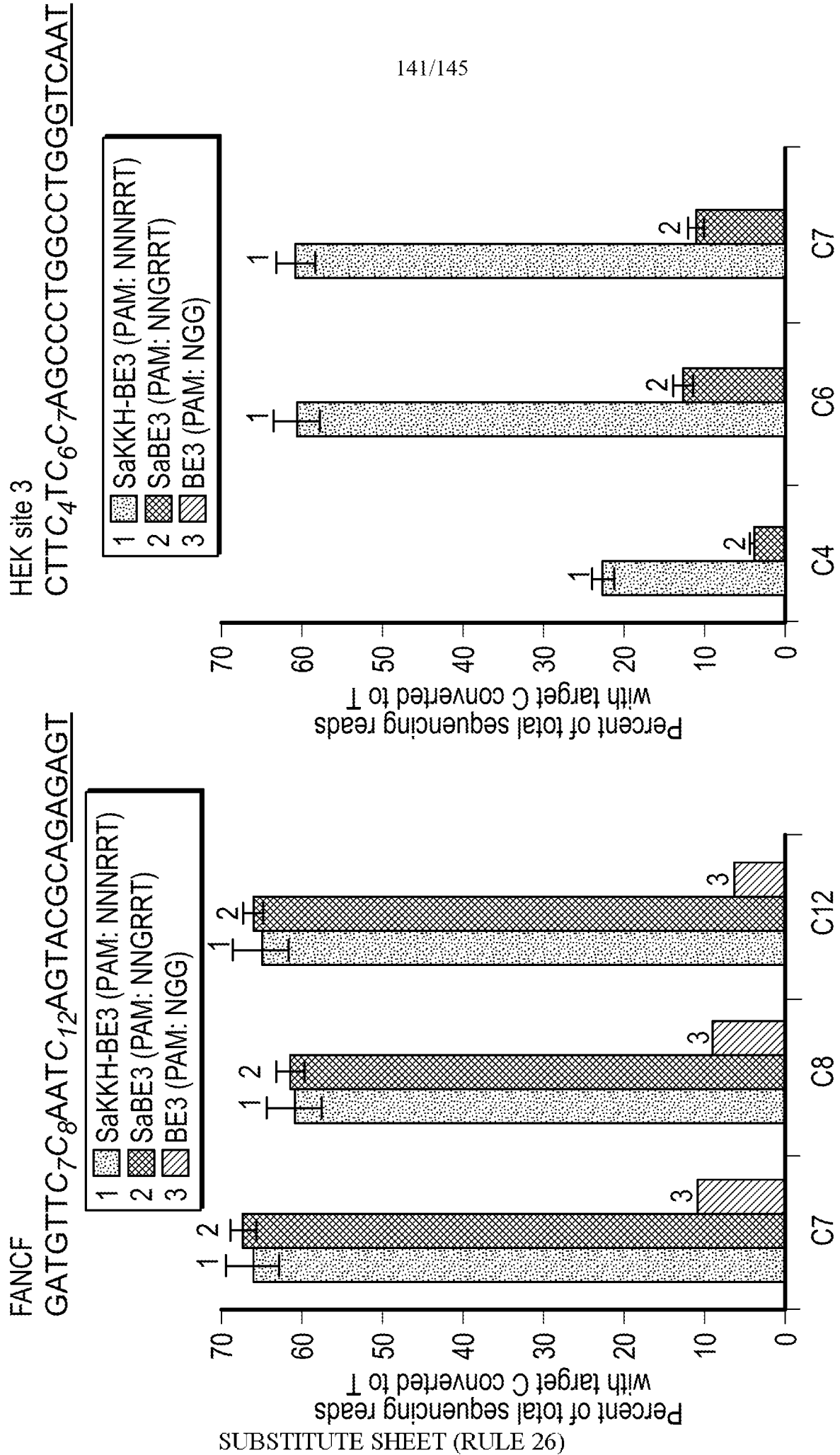


FIGURE 106A

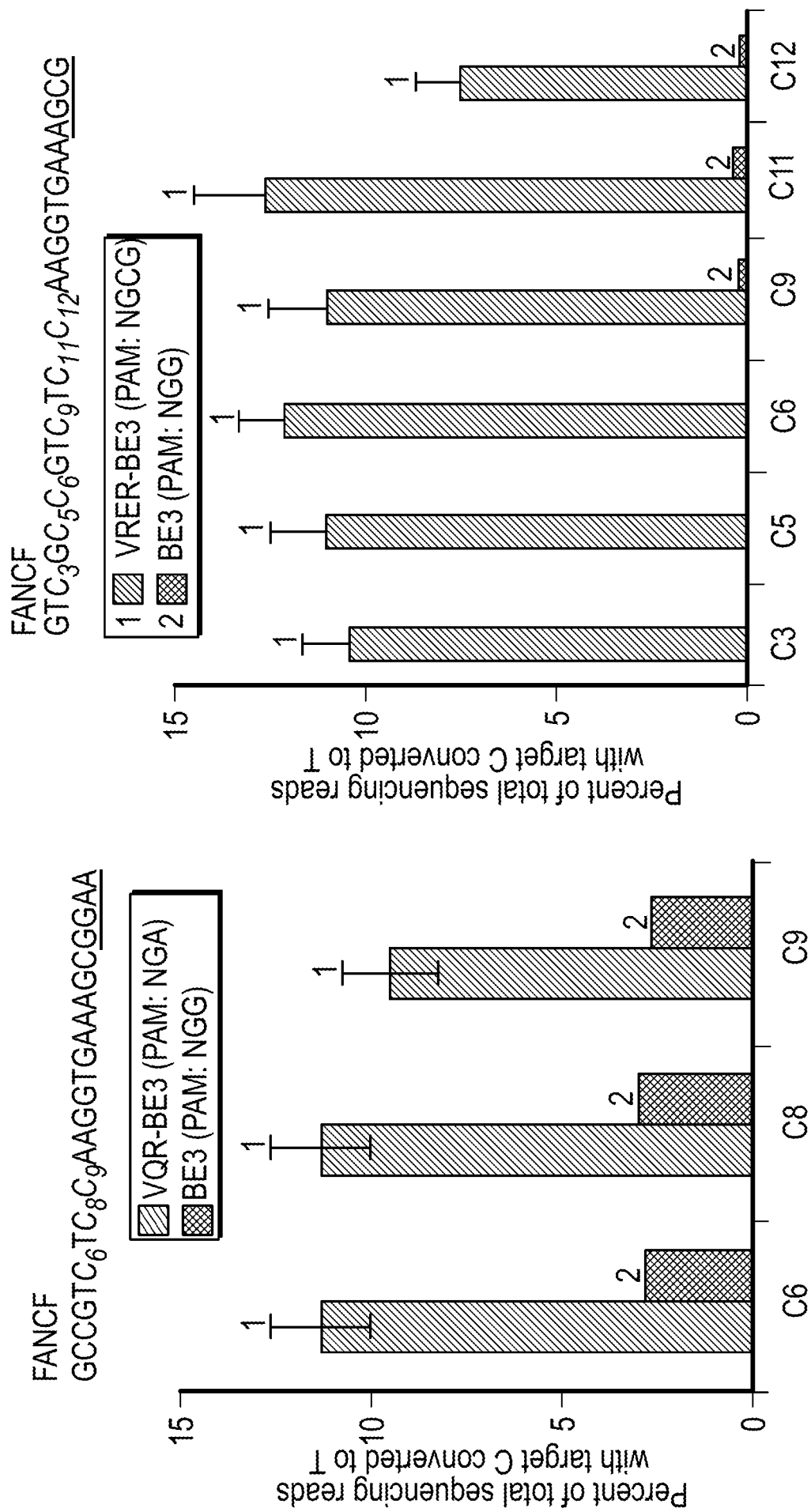


FIGURE 106B

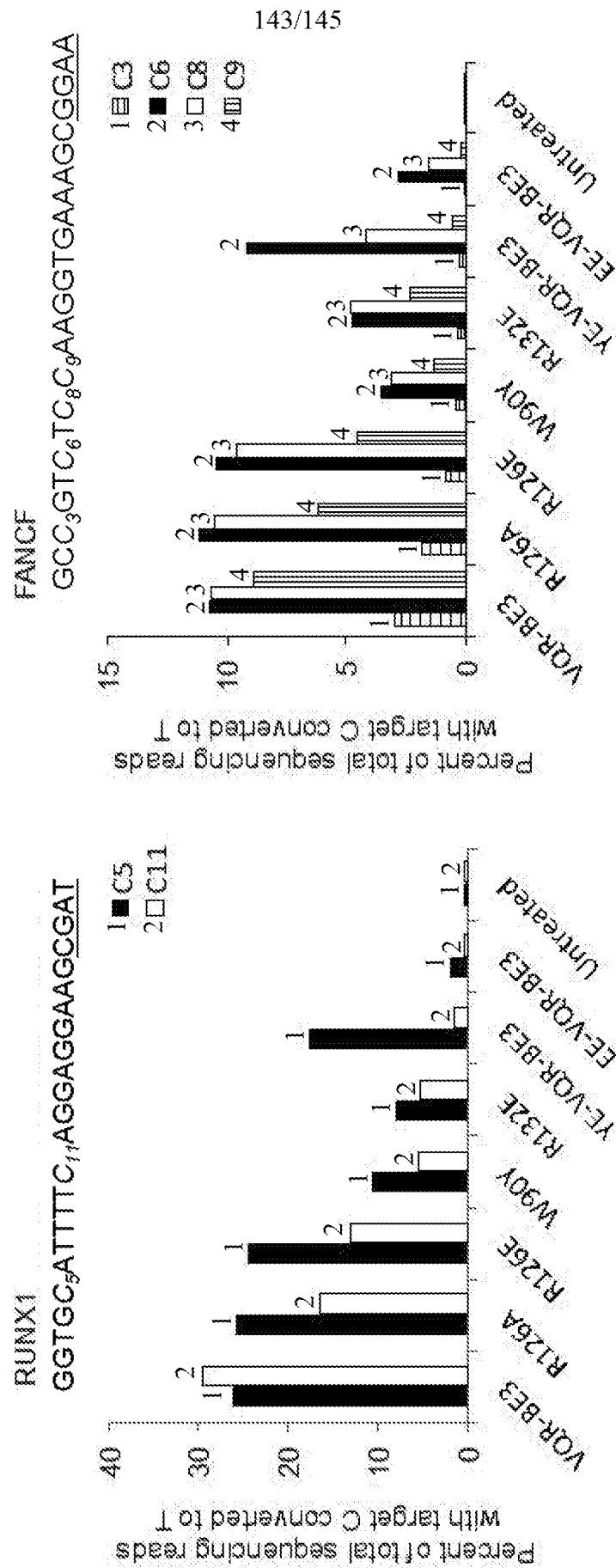


FIGURE 107A

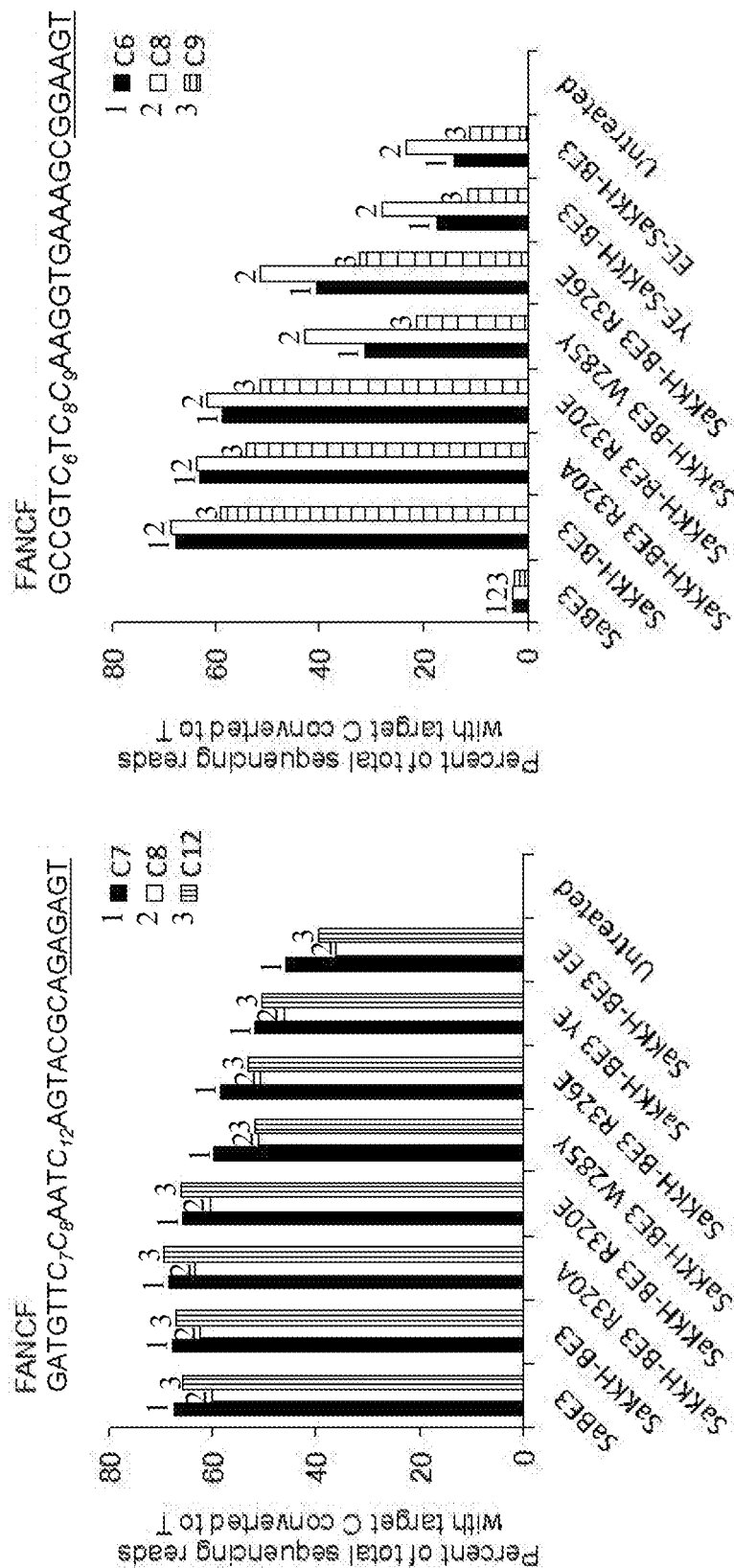


FIGURE 107B

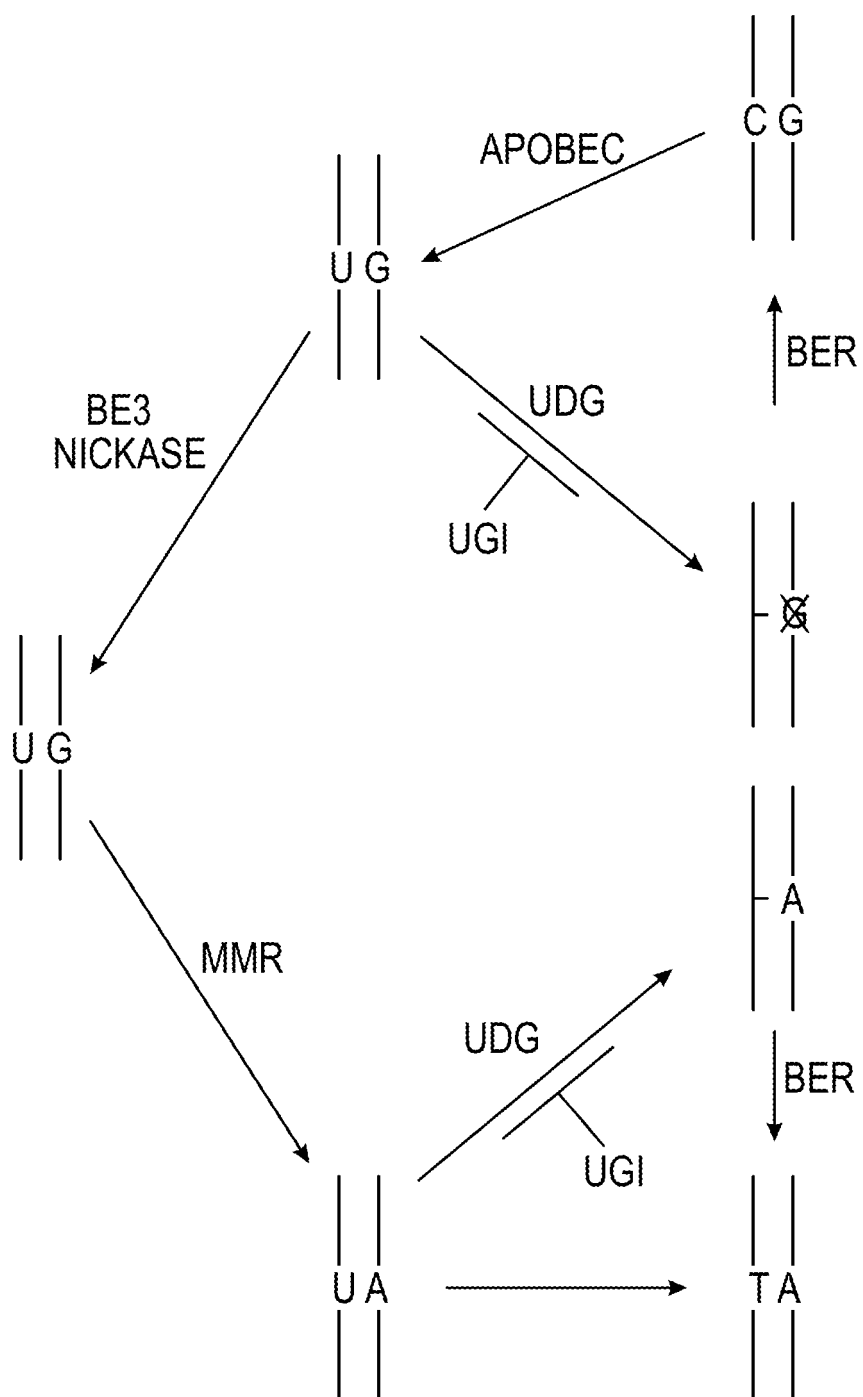


FIGURE 108