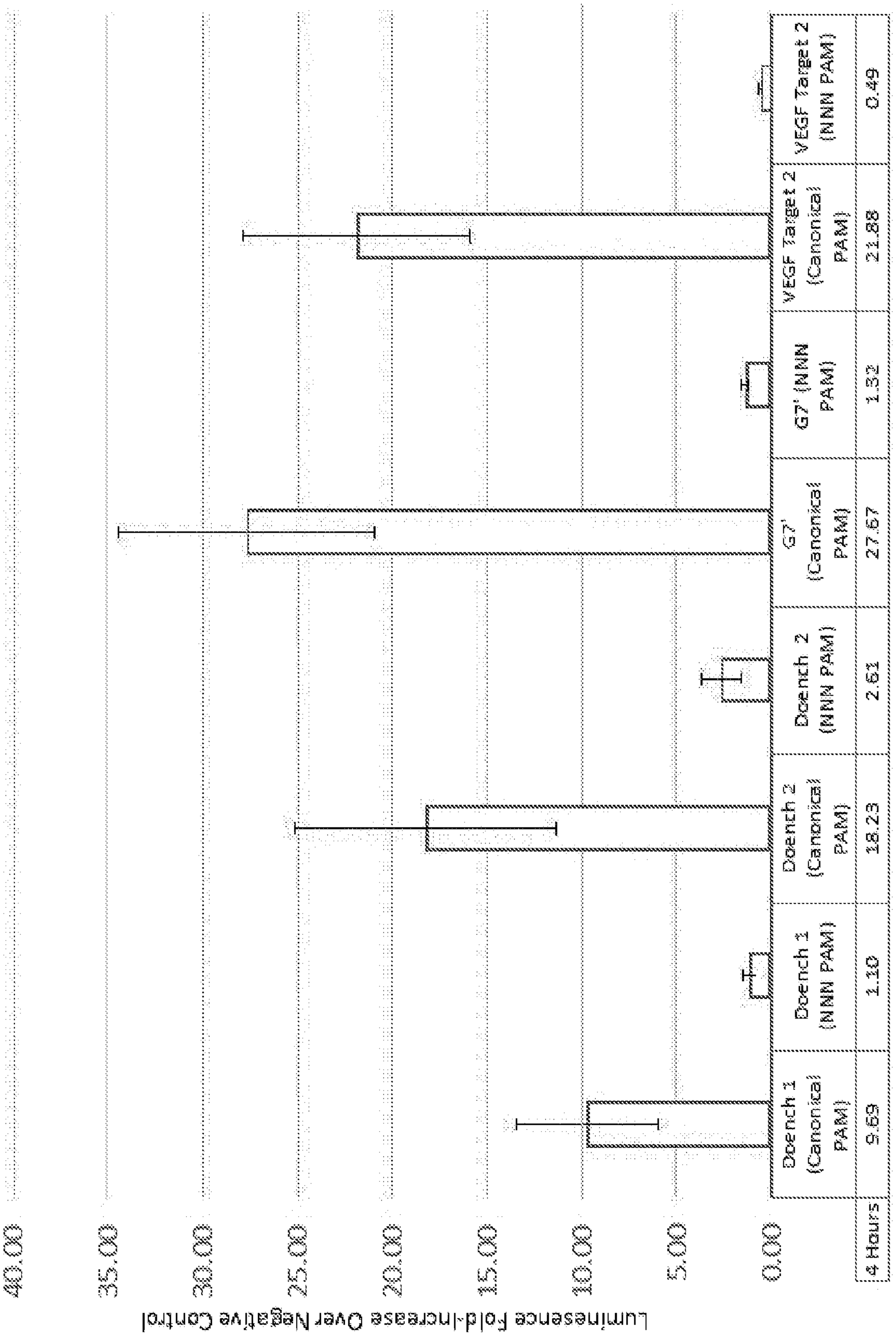

Luminescence Fold-Increase Over Negative Control
40.00
35.00
30.00
25.00
20.00
15.00
10.00
5.00
0.00
4 Hours
Doench 1 (Canonical PAM)
Doench 1 (NNN PAM)
Doench 2 (Canonical PAM)
Doench 2 (NNN PAM)
G7' (Canonical PAM)
G7' (NNN PAM)
VEGF Target 2 (Canonical PAM)
VEGF Target 2 (NNN PAM)
9.69
1.10
18.23
2.61
27.67
1.32
21.88
6.49

FIGURE 1

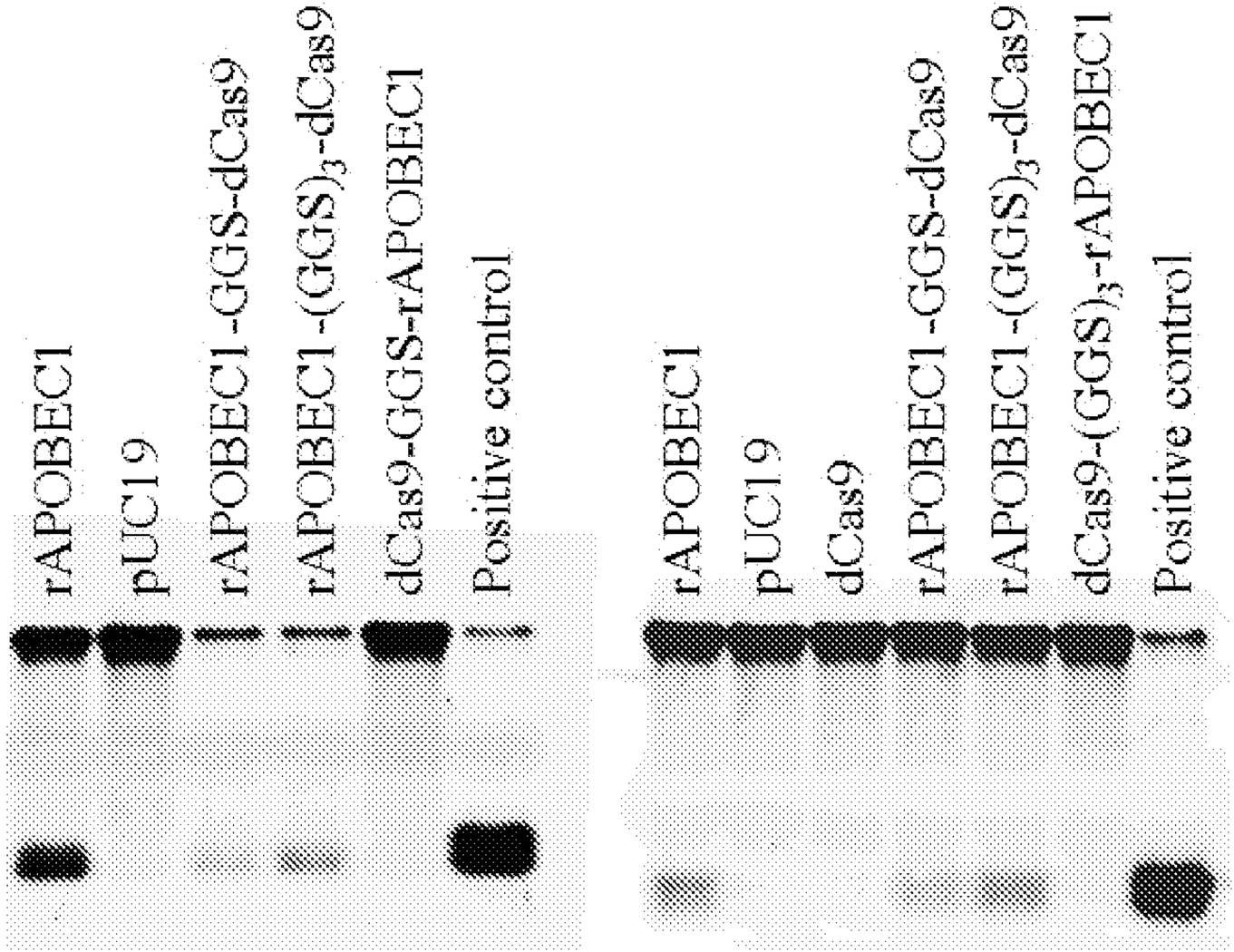

rAPOBEC1
pUC19
rAPOBEC1-GGS-dCas9
rAPOBEC1-(GGS)3-dCas
dCas9-GGS-rAPOBEC1
Positive control
rAPOBEC1
pUC19
dCas9
rAPOBEC1-GGS-dCas9
rAPOBEC1-(GGS)3-dCas
dCas9-(GGS)3-rAPOBEC
Positive control

FIGURE 2

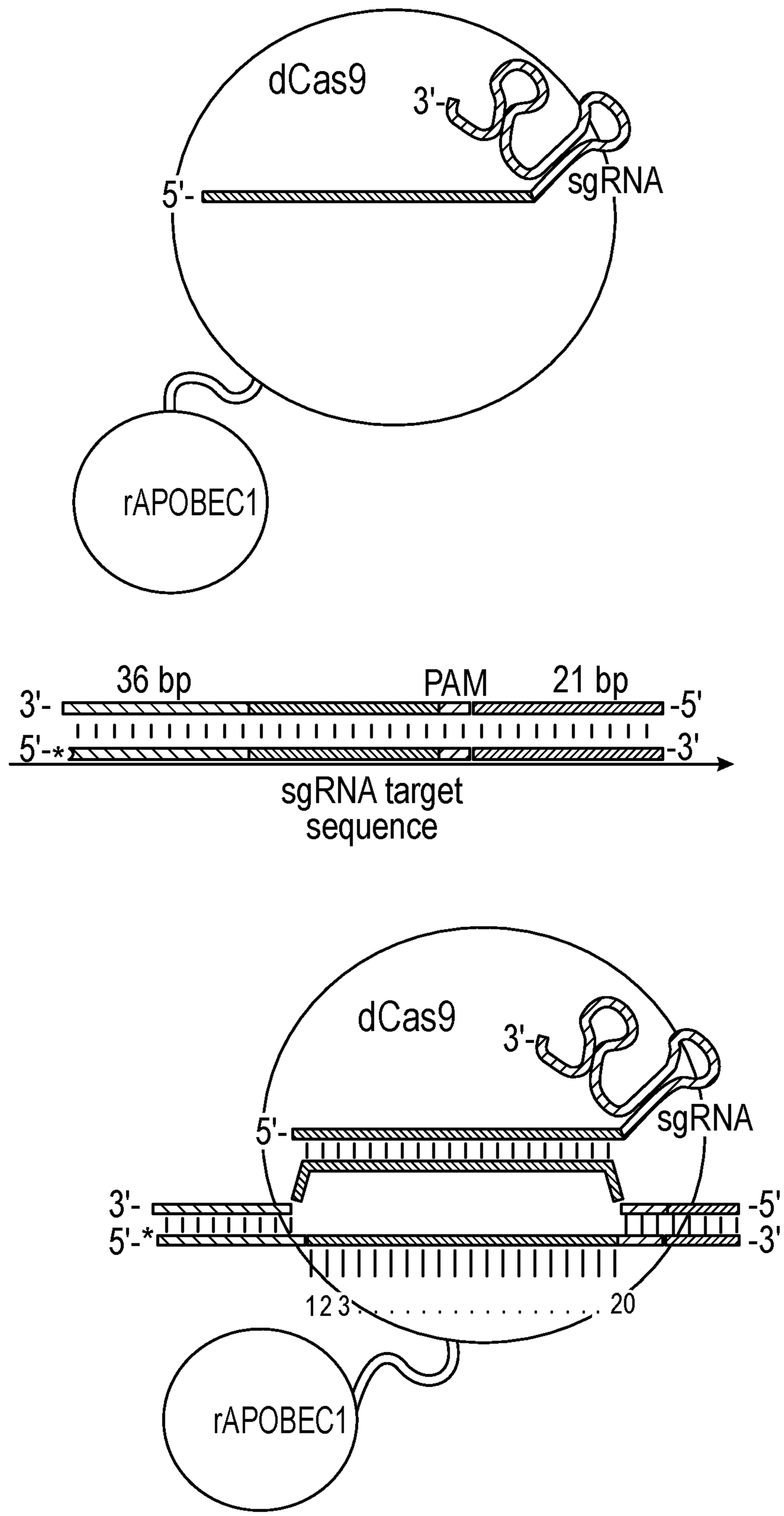

dCas9
3'-
5'-
sgRNA
rAPOBEC1
36 bp
PAM
21 bp
3'-
-5'
5'-*
-3'
sgRNA target sequence
dCas9
3'-
sgRNA
5'-
3'-
-5'
5'-*
-3'
1 2 3
20
rAPOBEC1

FIGURE 3

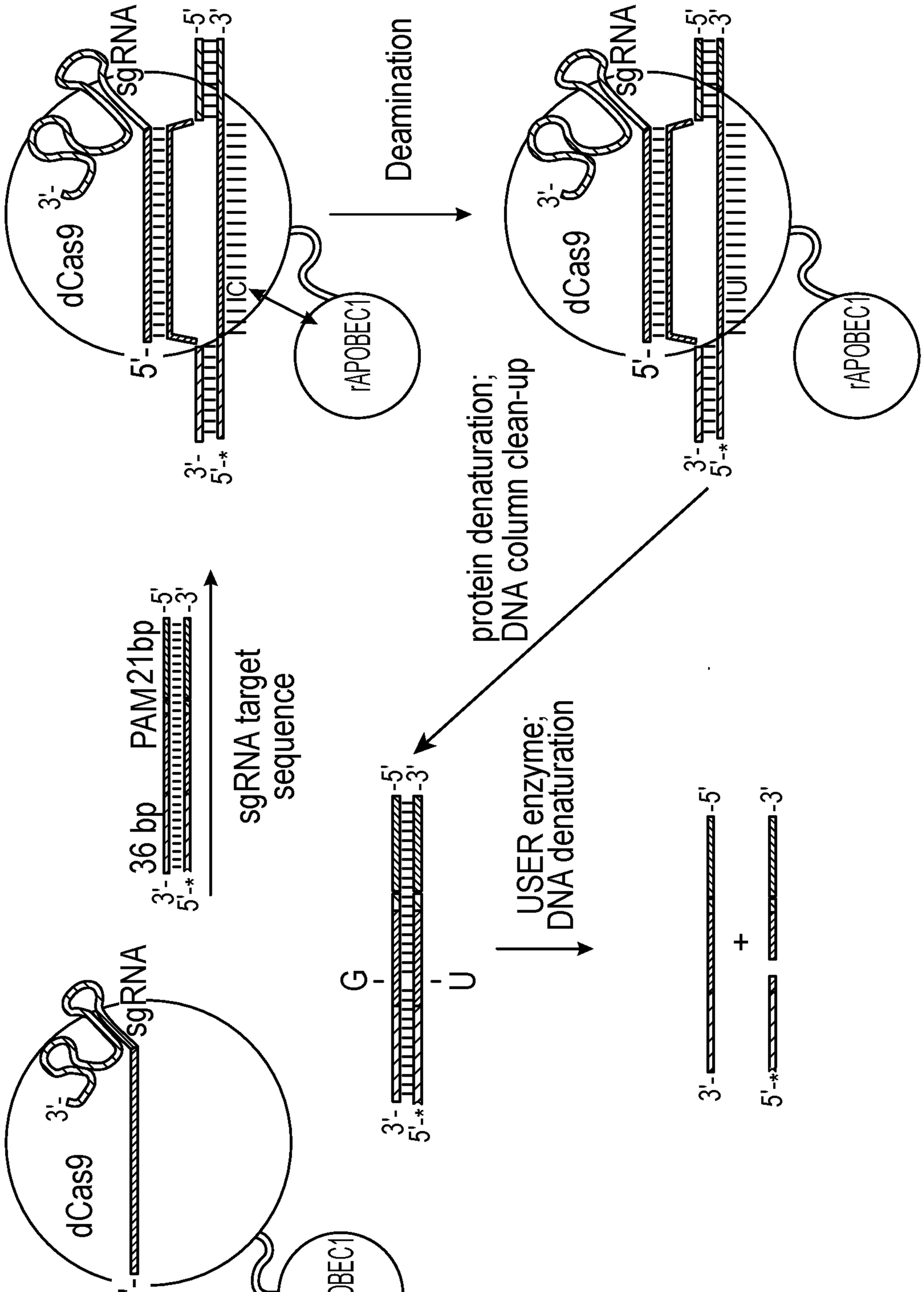

dCas9
sgRNA
3'-
5'-
5'-*
3'-
rAPOBEC1
Deamination
protein denaturation;
DNA column clean-up
USER enzyme;
DNA denaturation
36 bp
PAM21bp
sgRNA target
sequence
G
U

FIGURE 4

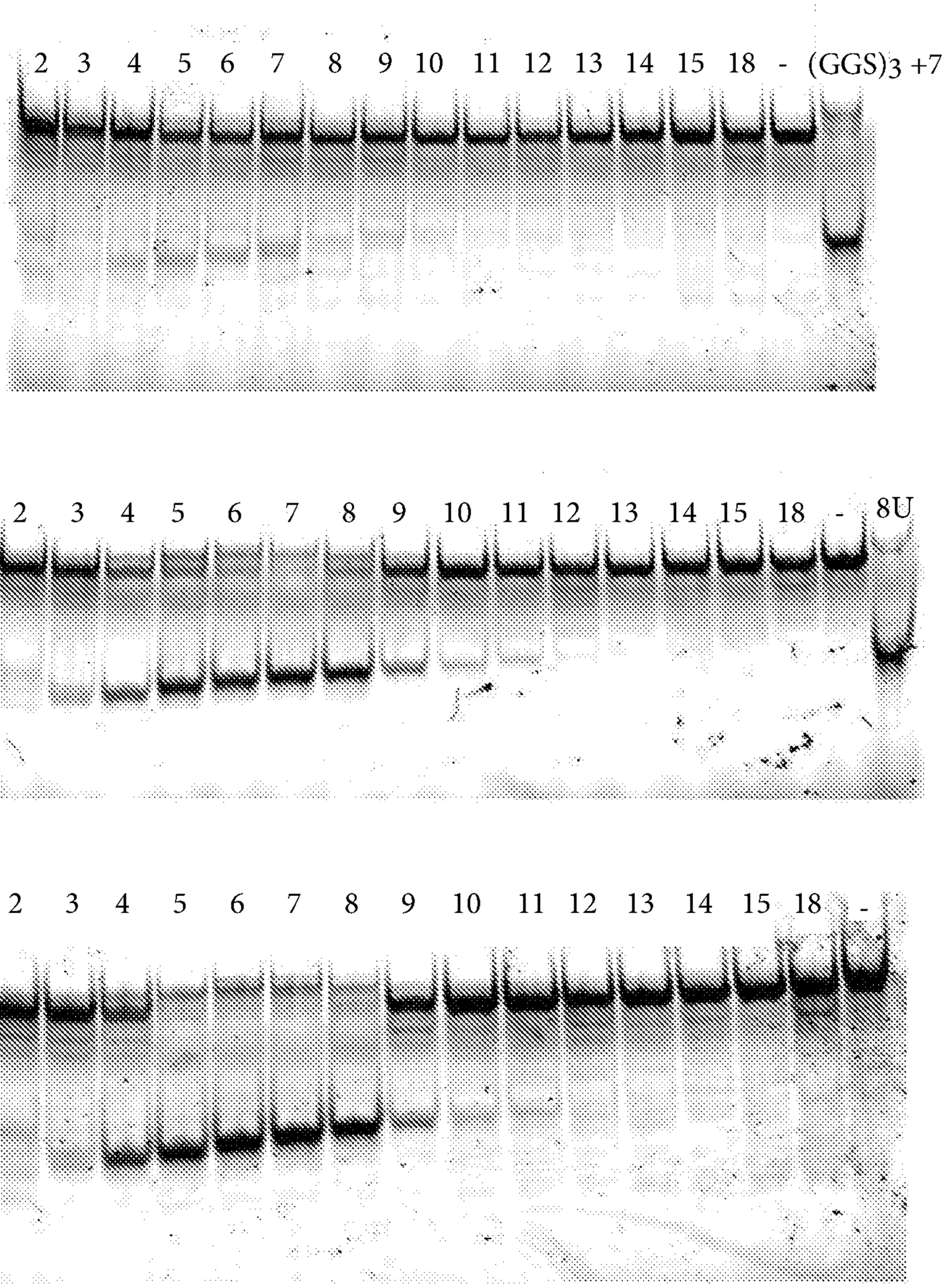

2 3 4 5 6 7 8 9 10 11 12 13 14 15 18 - (GGS)3 +7
2 3 4 5 6 7 8 9 10 11 12 13 14 15 18 - 8U
2 3 4 5 6 7 8 9 10 11 12 13 14 15 18 -

FIGURE 5

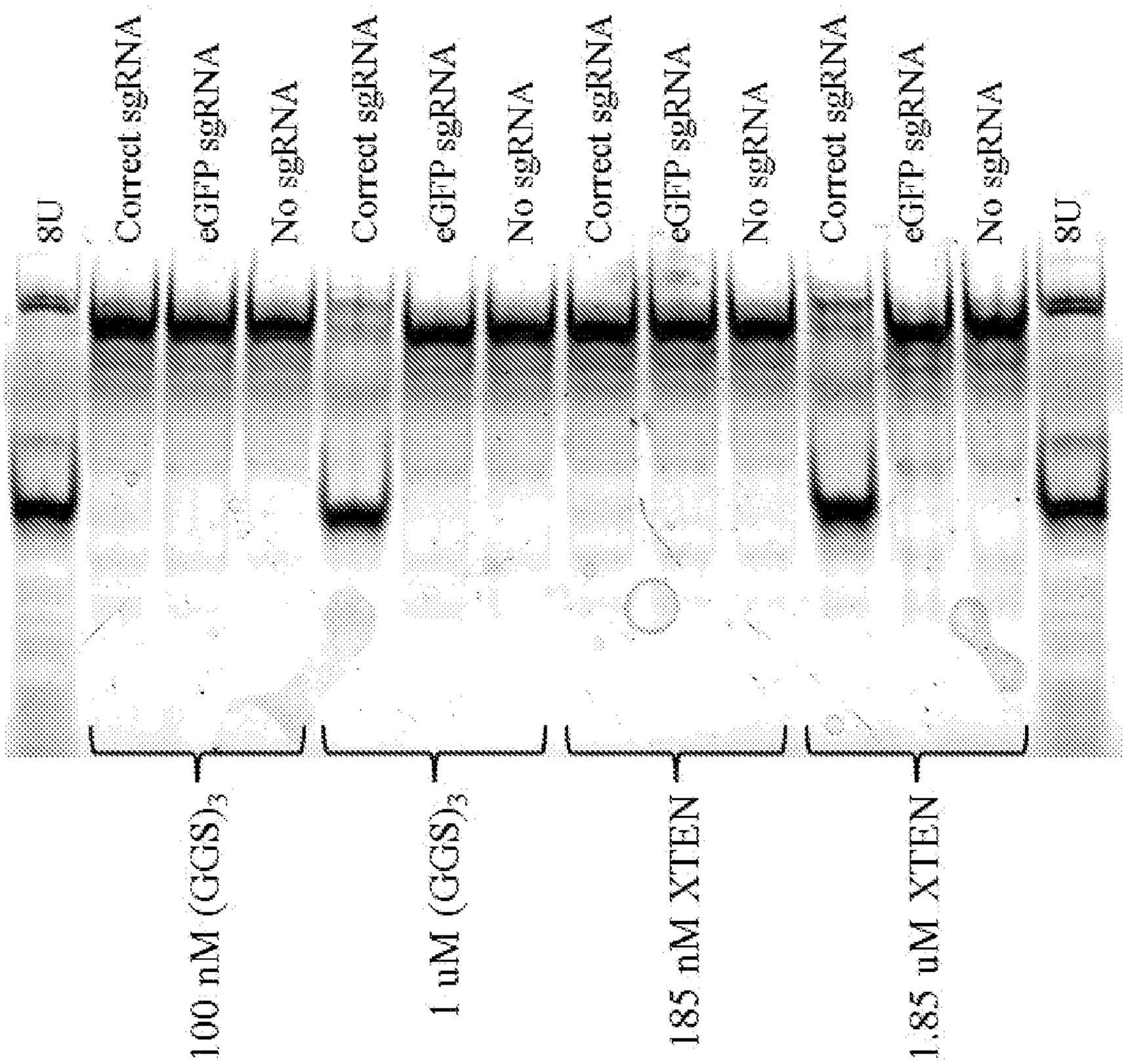
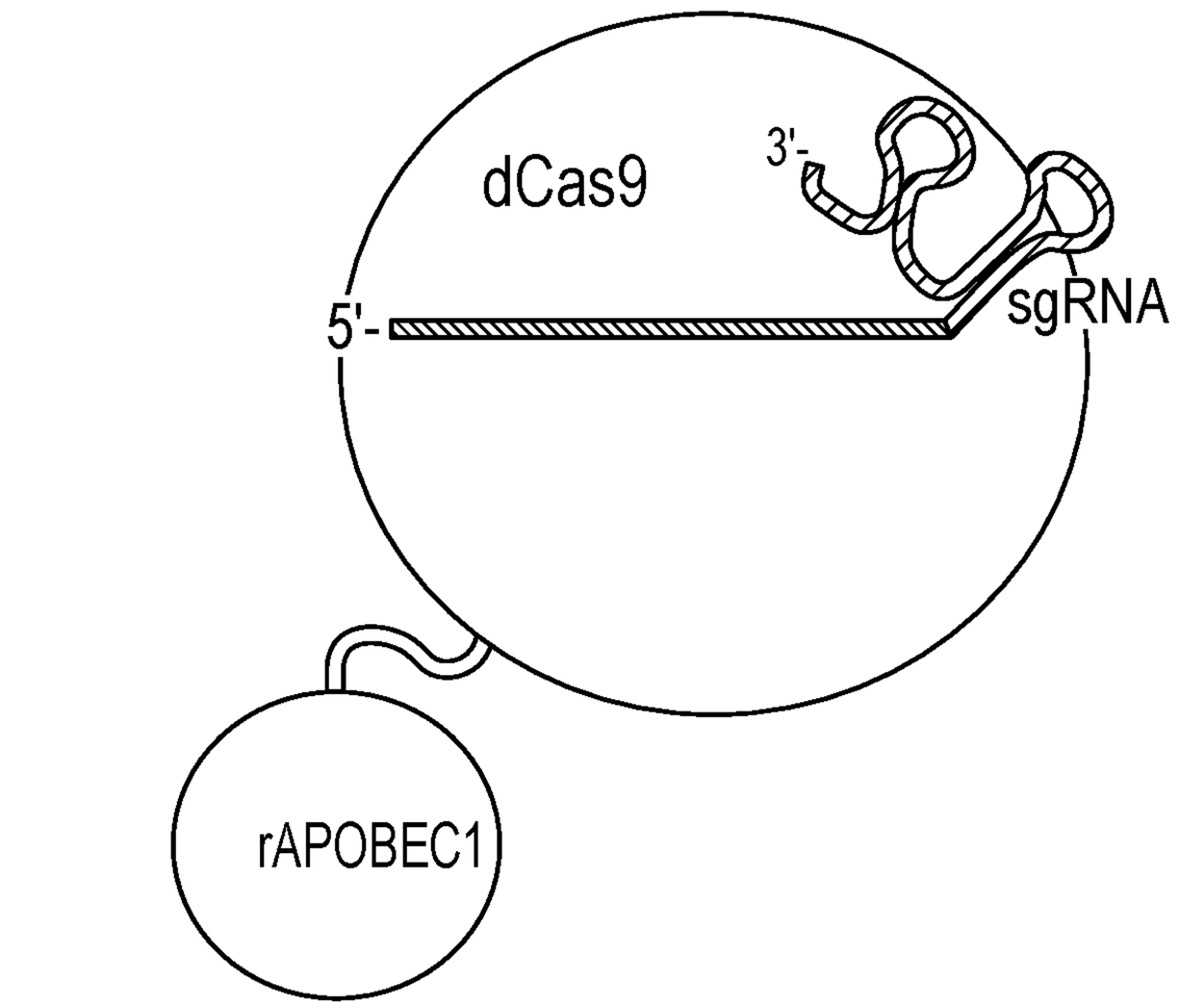
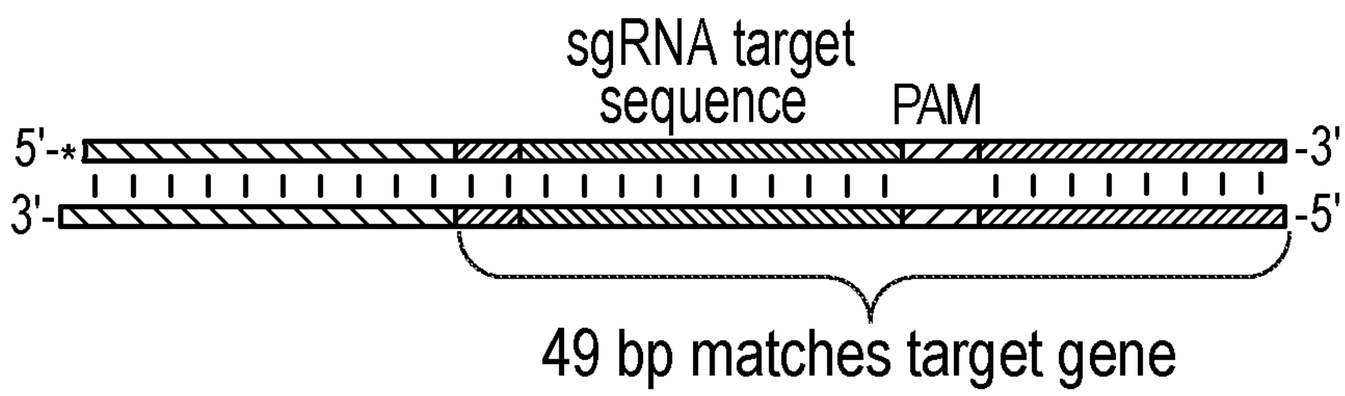

100 nM (GGS)3 8U
Correct sgRNA
eGFP sgRNA
No sgRNA
1 uM (GGS)3 8U
Correct sgRNA
eGFP sgRNA
No sgRNA
185 nM XTEN 8U
Correct sgRNA
eGFP sgRNA
No sgRNA
1.85 uM XTEN 8U
Correct sgRNA
eGFP sgRNA
No sgRNA

FIGURE 6


dCas9
3'-
5'-
sgRNA
rAPOBEC1


sgRNA target sequence
PAM
5'-*
-3'
3'-
-5'
49 bp matches target gene

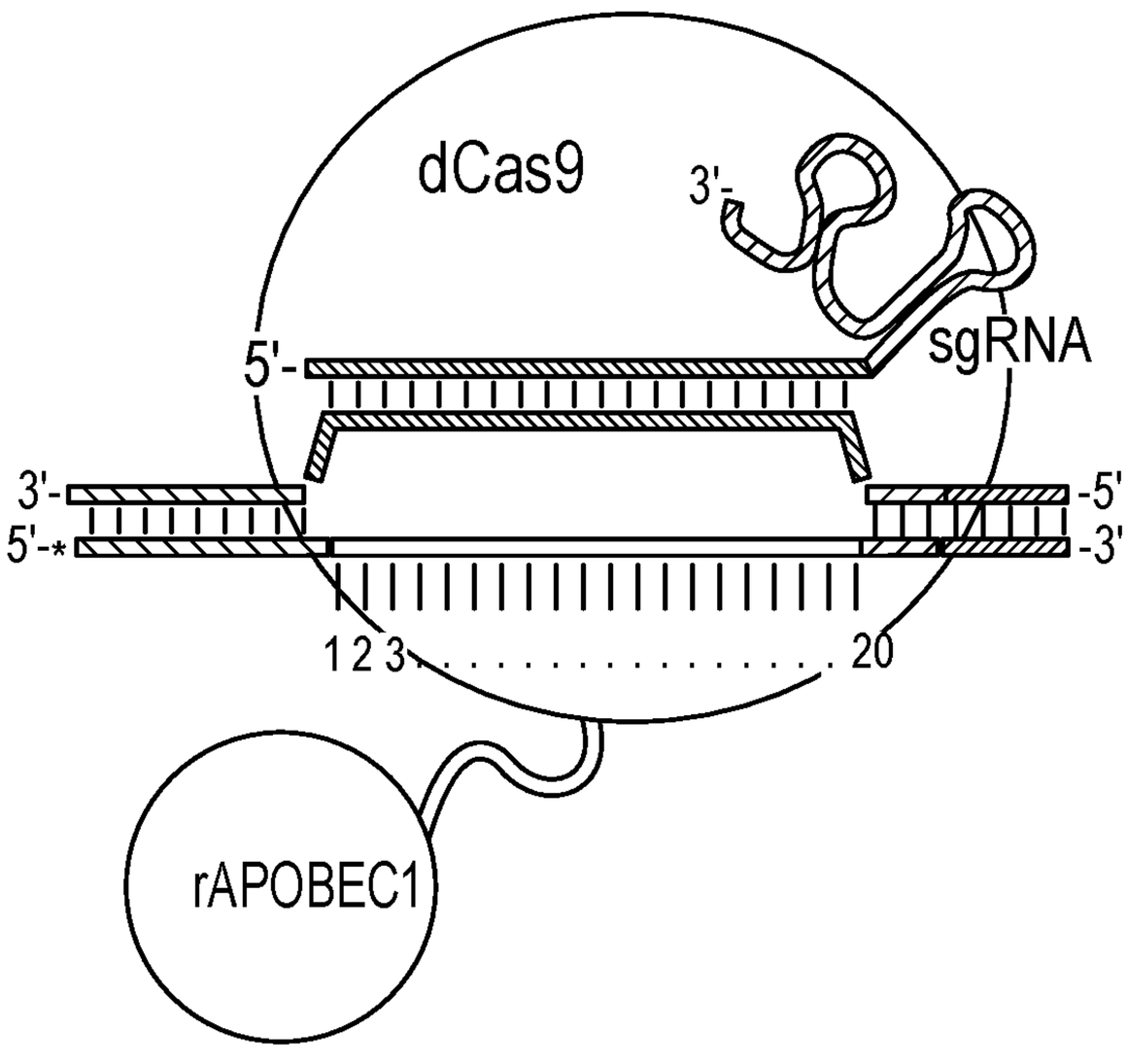

dCas9
3'-
5'-
sgRNA
3'-
-5'
5'-*
-3'
1 2 3 20
rAPOBEC1

FIGURE 7

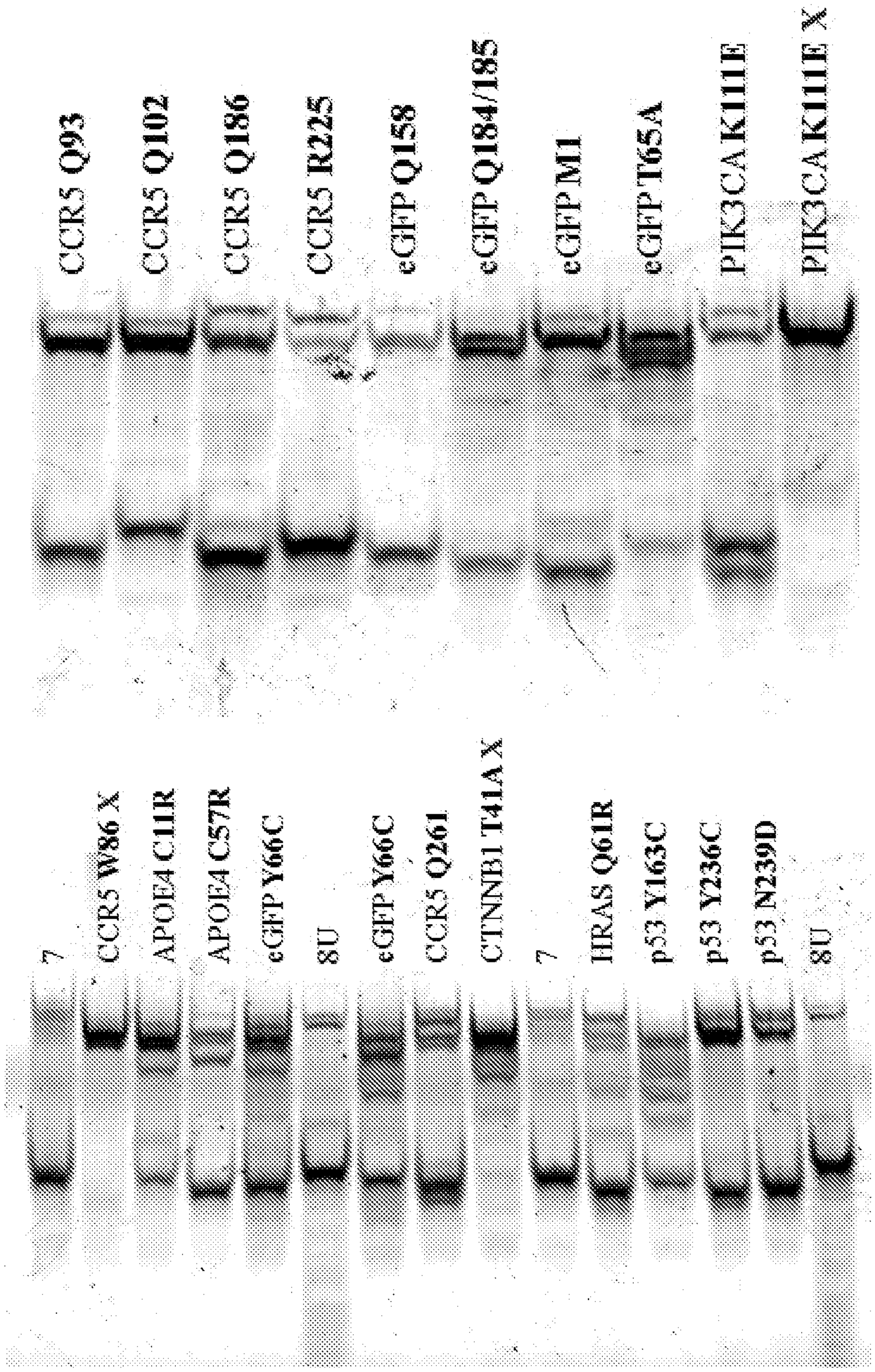

7
CCR5 W86 X
APOE4 C11R
APOE4 C57R
eGFP Y66C
8U
eGFP Y66C
CCR5 Q261
CTNNB1 T41A
7
HRAS Q61R
p53 Y163C
p53 Y236C
p53 N239D
8U
CCR5 Q93
CCR5 Q102
CCR5 Q186
CCR5 R225
eGFP Q158
eGFP Q184/185
eGFP M1
eGFP T65A
PIK3CA K111E
PIK3CA K111E X

FIGURE 8

EMX1		C_5	C_6	C_{10}
0 uM 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 uM 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 uM 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 uM 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 uM 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 uM 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 uM 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 uM 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 uM 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 uM 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 uM XTEN	A	0.1%	0.0%
	C	99.9%	99.9%
	G	0.0%	0.0%
	T	0.0%	0.0%
1.85 uM 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

rAPOBEC1
dCas9
sgRNA
5'
3'
Genomic DNA
binding
and opening
protospacer
PAM
Genomic DNA
Deamination
of target C
DNA replication
or repair
Nucleobase-edited DNA

FIGURE 11A

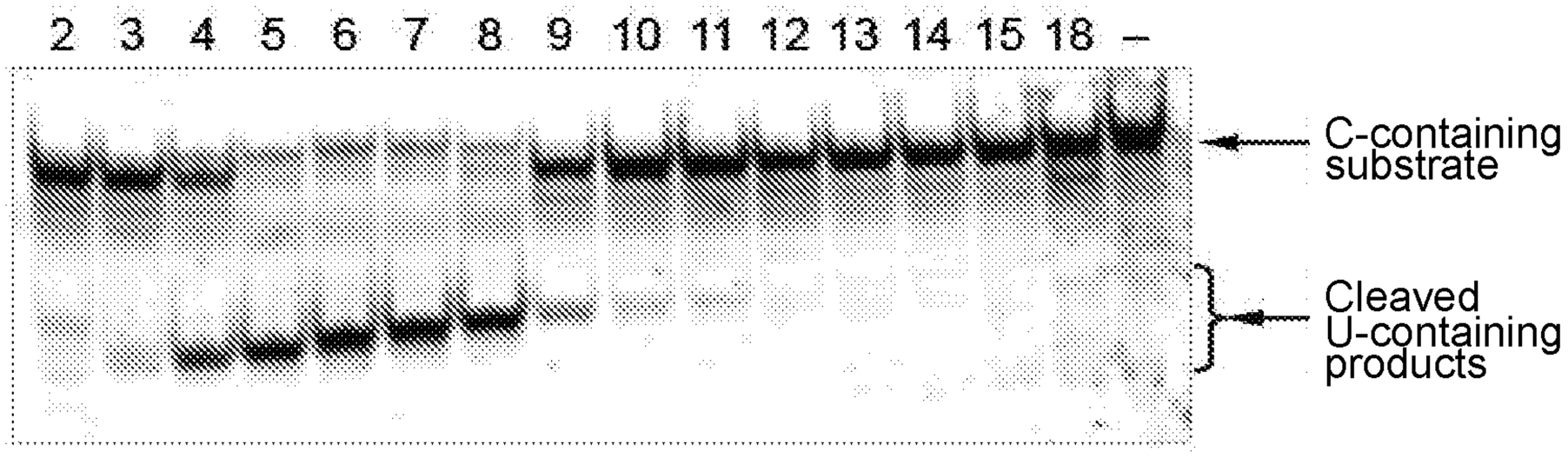


FIGURE 11B

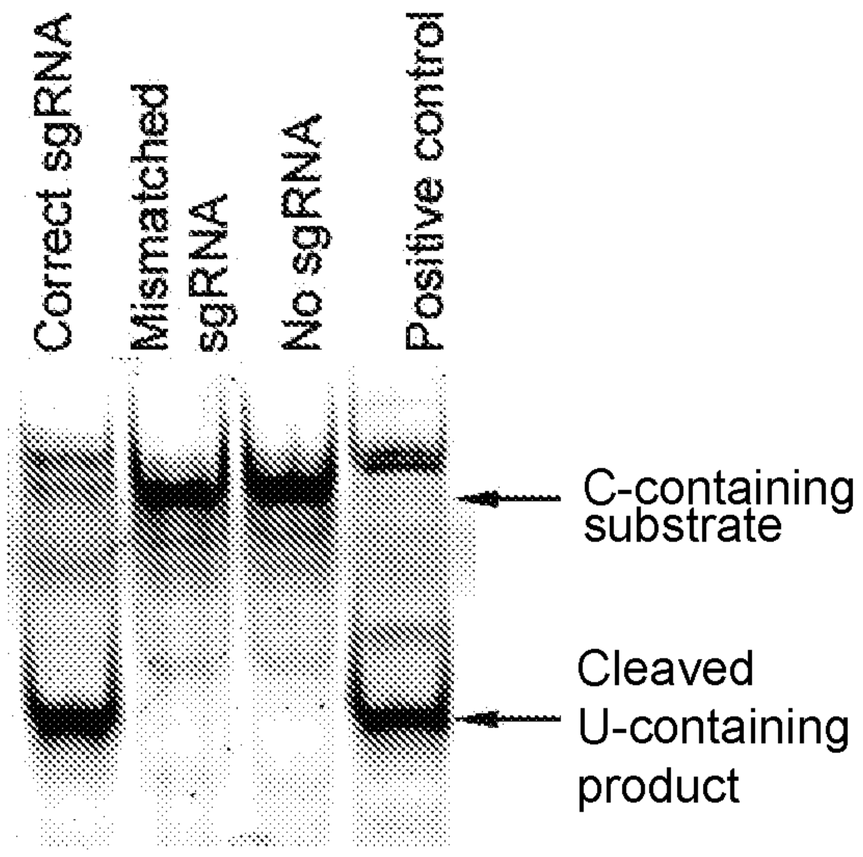


FIGURE 11C

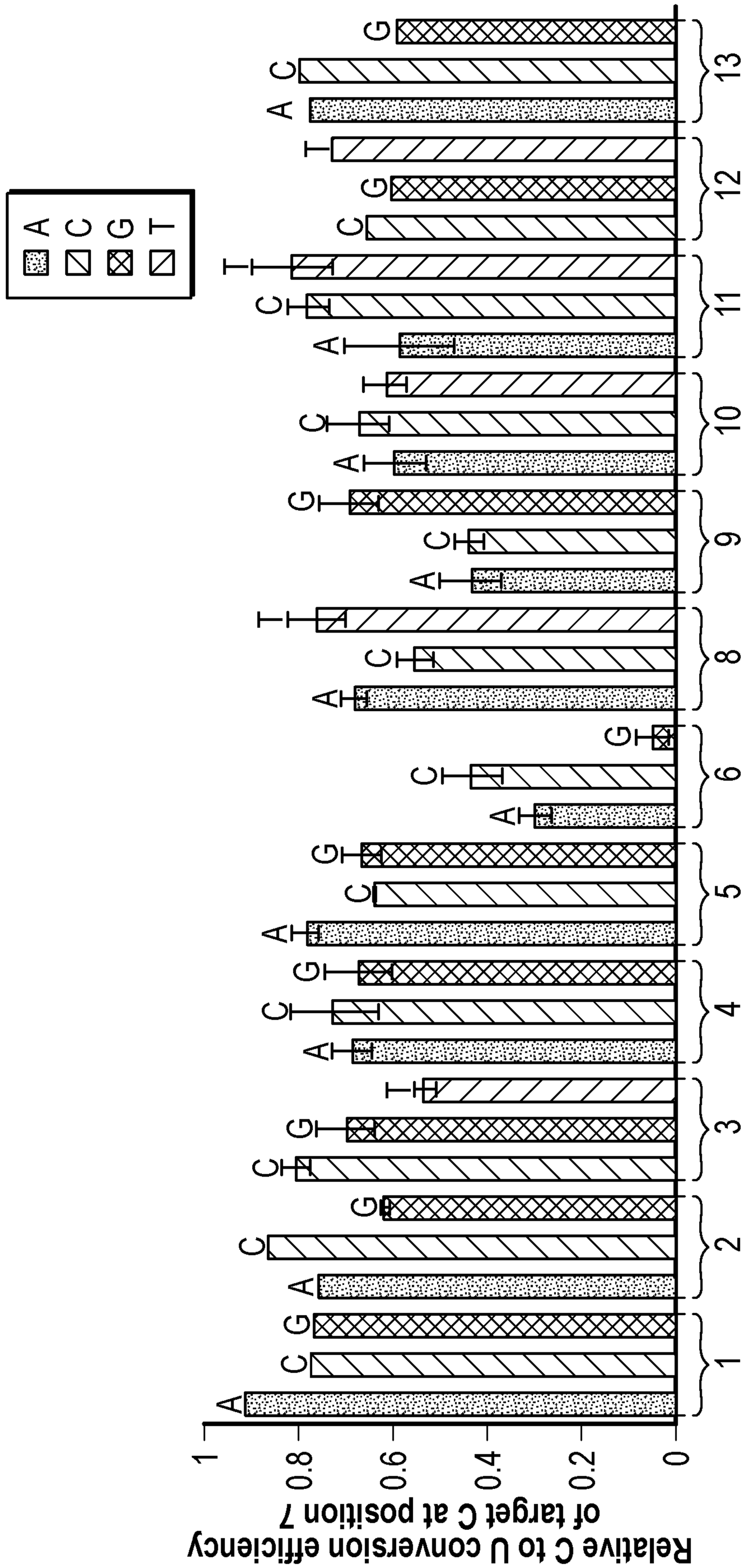

A
C
G
T
Relative C to U conversion efficiency of target C at position 7
1
0.8
0.6
0.4
0.2
0
Position of the varying base within the protospacer
1
2
3
4
5
6
8
9
10
11
12
13

FIGURE 12A

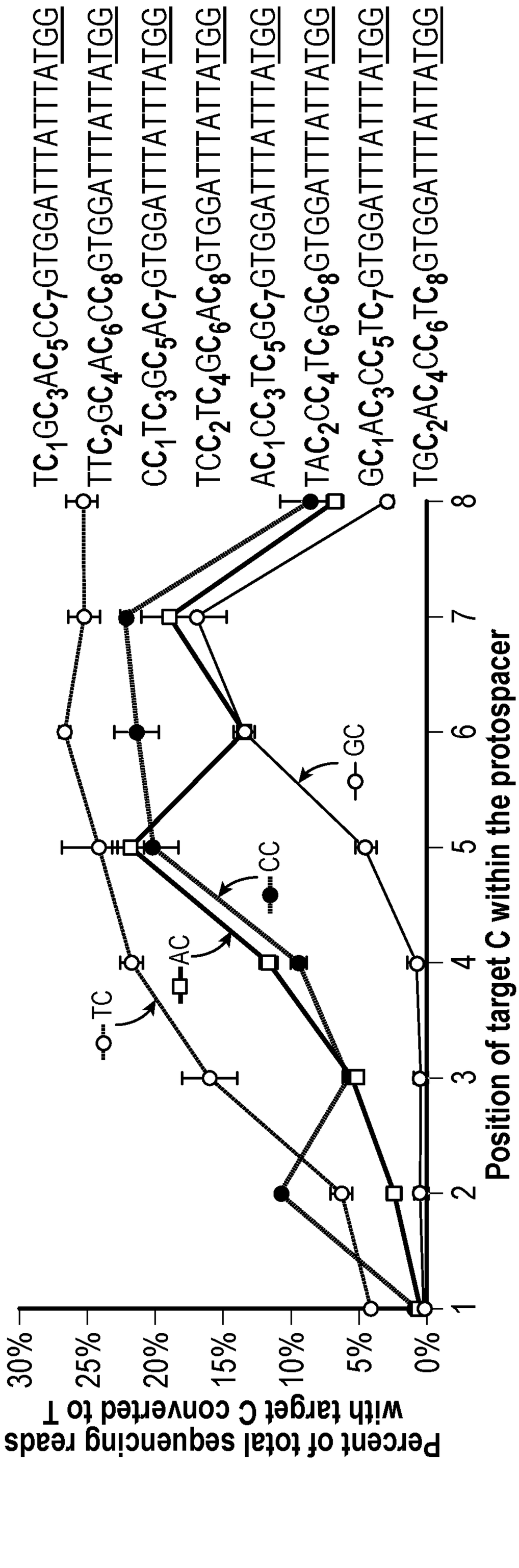

TTATTTATGG
TTTATTATGG
TTATTTATGG
TTTATTATGG
TTATTTATGG
TTTATTATGG
TTATTTATGG
TTTATTATGG
TC1GC3AC5CC7GTGGAT
TTC2GC4AC6CC8GTGGA
CC1TC3GC5AC7GTGGAT
TCC2TC4GC6AC8GTGGA
AC1CC3TC5GC7GTGGAT
TAC2CC4TC6GC8GTGGA
GC1AC3CC5TC7GTGGAT
TGC2AC4CC6TC8GTGGA
TC
AC
CC
GC
1
2
3
4
5
6
7
8
Position of target C within the protospacer
Percent of total sequencing reads with target C converted to T
0%
5%
10%
15%
20%
25%
30%

FIGURE 12B

EMX1:	GAGTC$_5$C$_6$GAGCAGAAGAAGAAGGG
FANCF:	GGAATC$_6$C$_7$C$_8$TTC$_{11}$TGCAGCACCTGG
HEK293 site 2:	GAAC$_4$AC$_6$AAAGCATAGACTGCGGG
HEK293 site 3:	GGCC$_4$C$_5$AGACTGAGCACGTGATGG
HEK293 site 4:	GGCAC$_5$TGCGGCTGGAGGTCCGGG
RNF2:	GTC$_3$ATC$_6$TTAGTC$_{12}$ATTACCTGAGG

FIGUIRE 13A

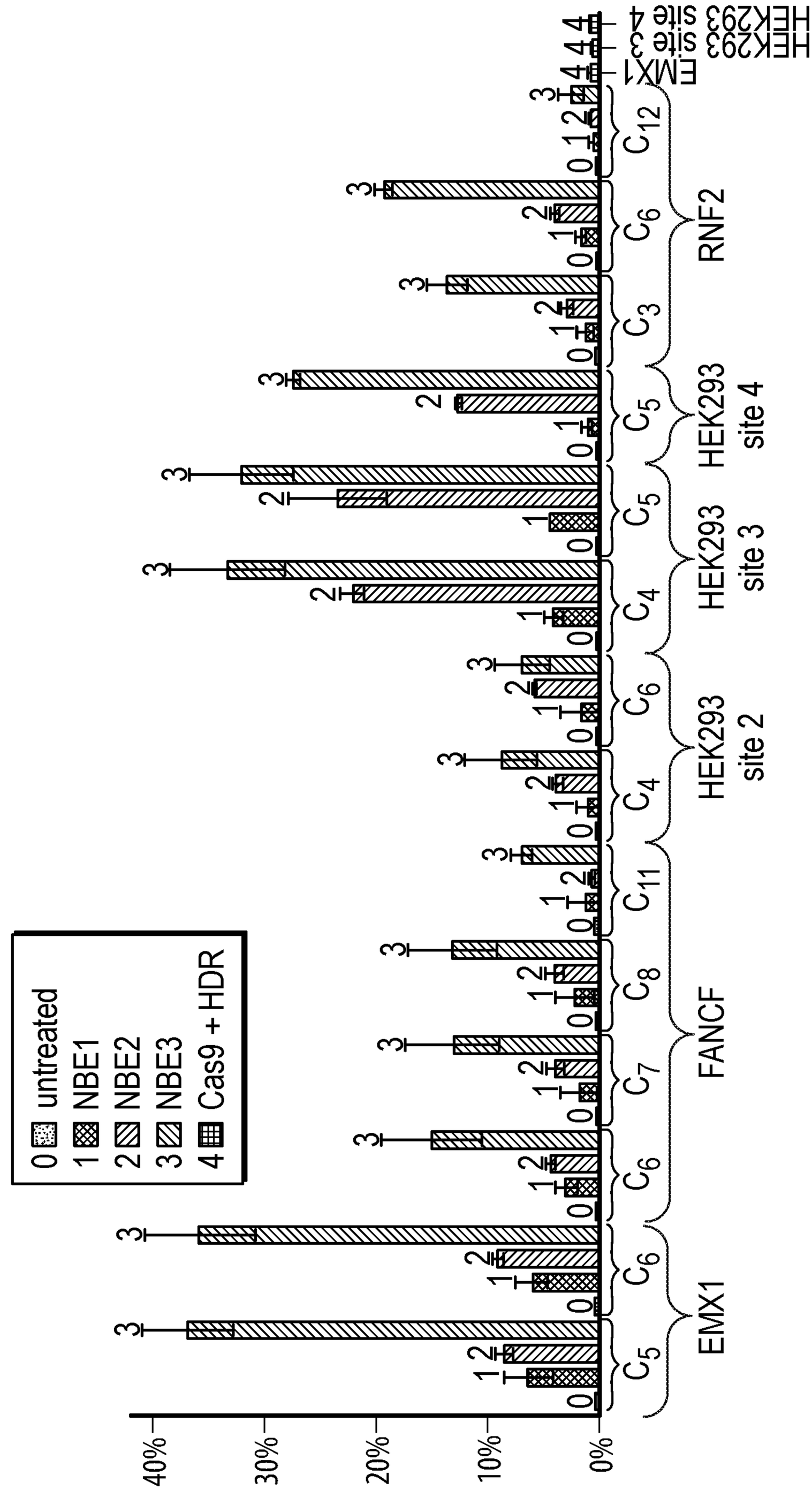

0 untreated
1 NBE1
2 NBE2
3 NBE3
4 Cas9 + HDR
Percent of total sequencing reads with target C converted to T
0%
10%
20%
30%
40%
EMX1
FANCF
HEK293 site 2
HEK293 site 3
HEK293 site 4
RNF2
HEK293 site 3
HEK293 site 4
EMX1

FIGURE 13B

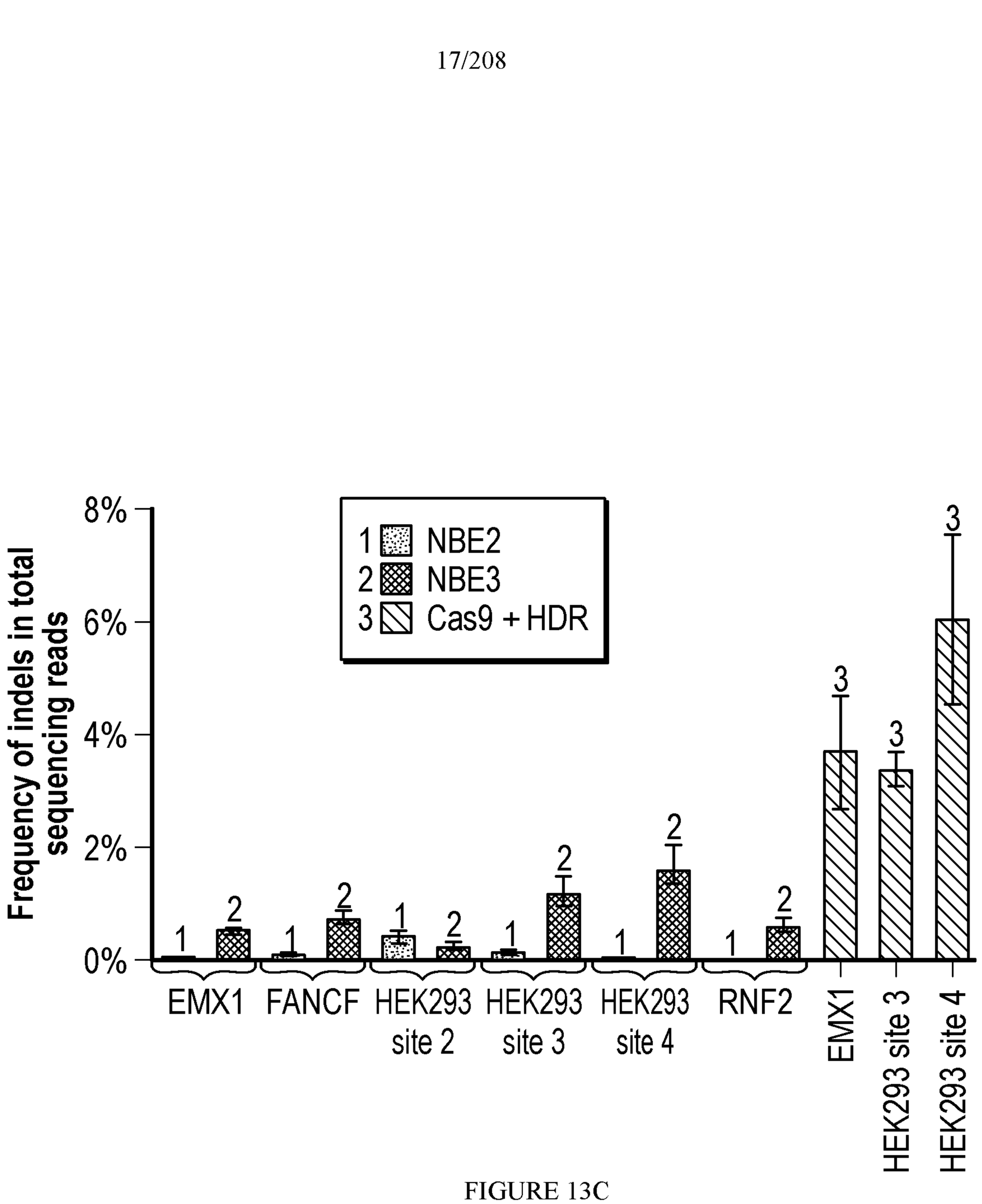

Frequency of indels in total sequencing reads
8%
6%
4%
2%
0%
1 NBE2
2 NBE3
3 Cas9 + HDR
1
2
3
EMX1
FANCF
HEK293 site 2
HEK293 site 3
HEK293 site 4
RNF2
EMX1
HEK293 site 3
HEK293 site 4

FIGURE 13C

		Lys			Arg → Cys			Leu → Leu			Ala			Val			Tyr			Gln			
APOE4 C158R	G	A	A	G	**C_5**	G	C	C	T	G	G	C	A	G	T	G	T	A	C	C	A	G	G
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	0.0	100.0	0.0	0.0	100.0	0.0	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	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	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	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0

FIGURE 14A

		His			Tyr			Asn			Tyr			Met			Cys			Asp → Asn			
TP53 N239D	C	C	A	C	T	A	C	A	A	C	T	A	C	A	T	G	T	G	T	**G_4**	A	C	A
A	0.0	0.0	100.0	0.0	0.0	100.0	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	0.0	0.0	100.0	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	100.0	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	0.0	100.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0

FIGURE 14B

		Arg			Ala			Met			Ala			Ile			Cys → Tyr			Lys			
TP53 Y163C	C	C	G	C	G	C	C	A	T	G	G	C	C	A	T	C	T	**G_6**	C	A	A	G	C
A	0.0	0.0	0.0	0.0	0.1	0.0	0.0	100.0	0.0	0.0	0.1	0.0	0.0	100.0	0.0	0.0	0.0	7.6	0.0	100.0	100.0	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	99.9	100.0	0.0	0.0	100.0	0.0	0.4	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	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	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	0.0	0.0

FIGURE 14C

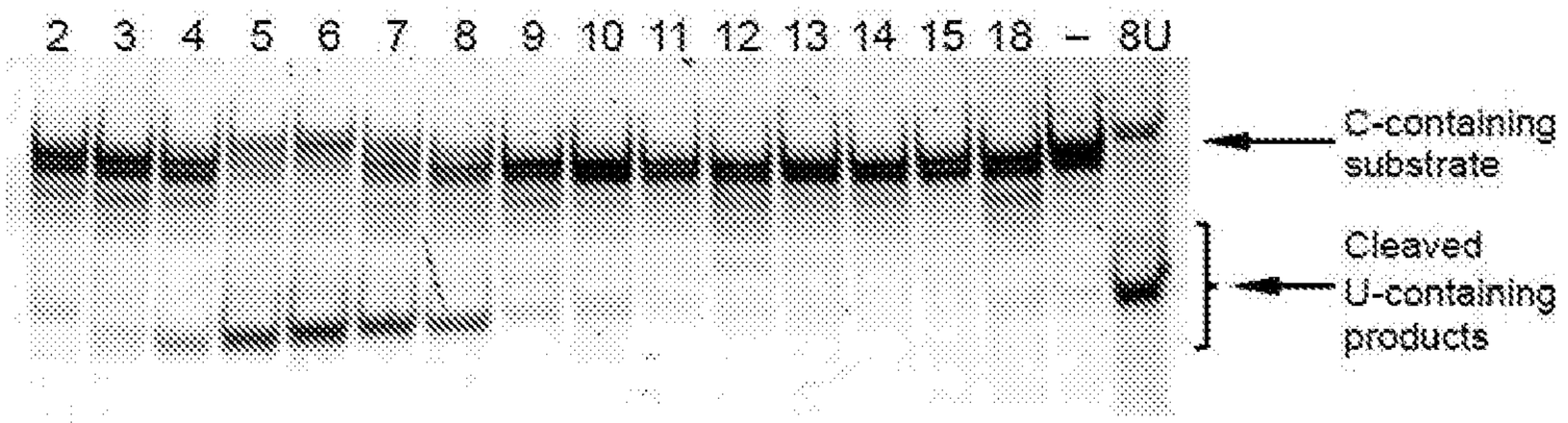


FIGURE 15A

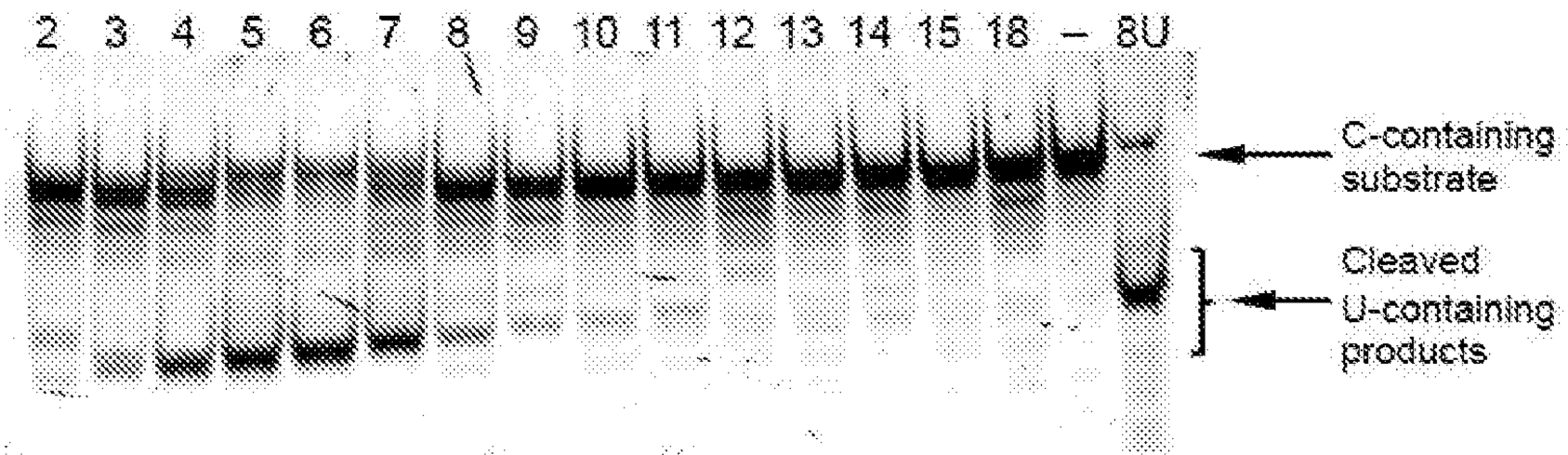


FIGURE 15B

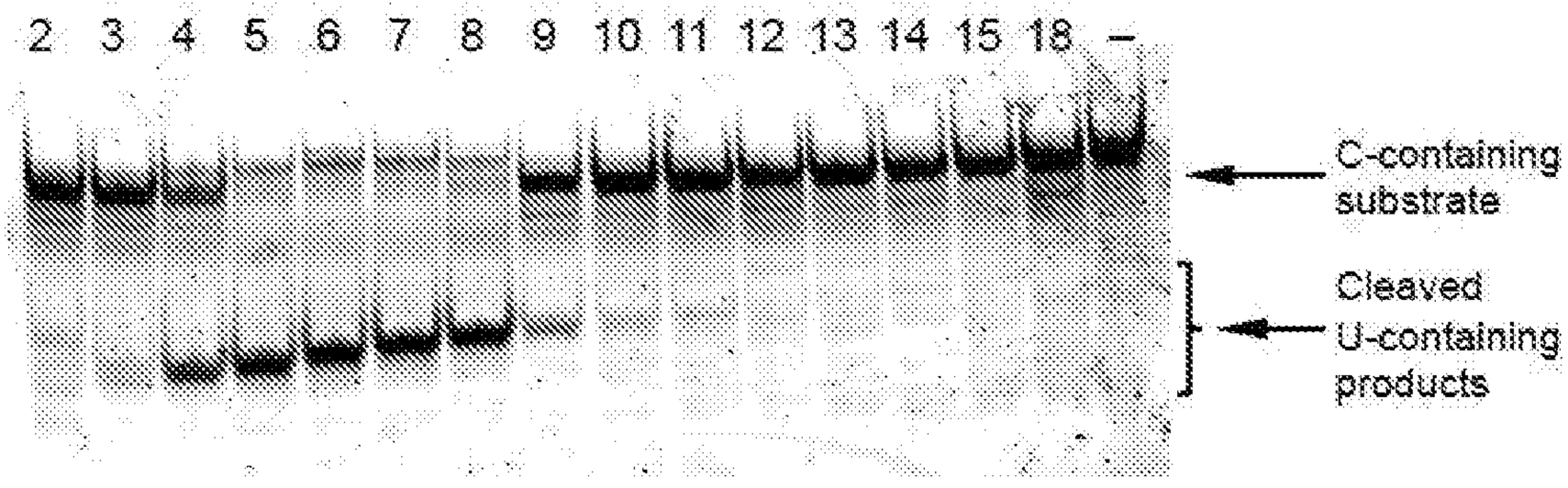


FIGURE 15C

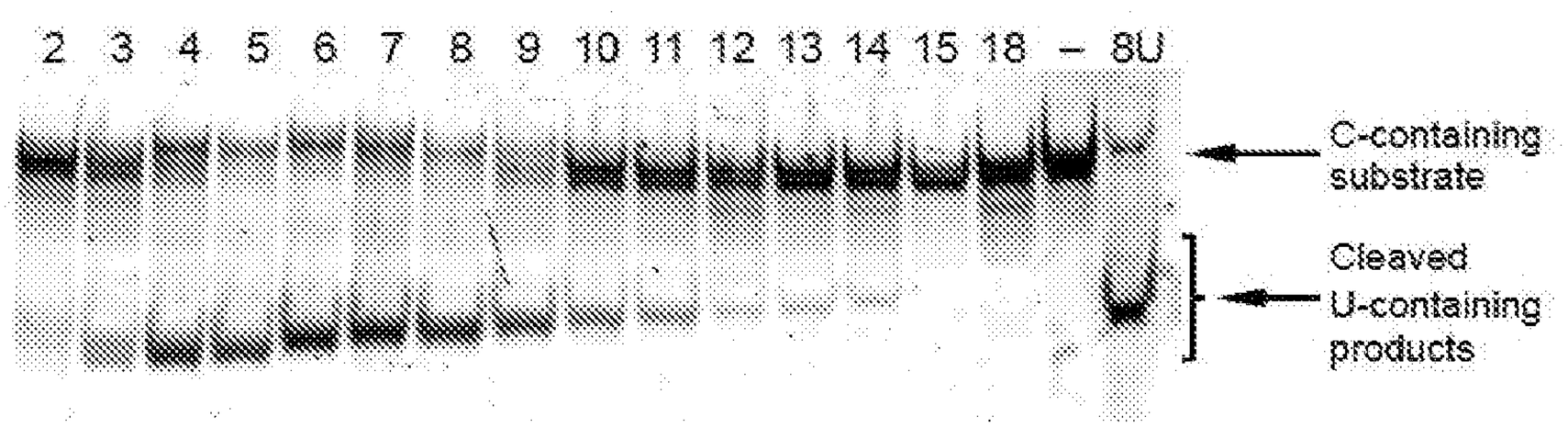


FIGURE 15D

APOE4 Cys112Arg:	5'-GGAGGACGTGC$_{11}$GCGGCCGCCTGG
APOE4 Cys158Arg:	5'-GAAGC$_5$GCCTGGCAGTGTACCAGG
CTNNB1 Thr41Ala:	5'-CTGTGGC$_7$AGTGGCACCAGAATGG
HRAS Gln61Arg:	5'-CCTCCC$_6$GGCCGGCGGTATCCAGG
p53 Tyr163Cys:	5'-GCTTGC$_6$AGATGGCCATGGCGCGG
p53 Tyr236Cys:	5'-ACACATGC$_8$AGTTGTAGTGGATGG
p53 Asn239Asp:	5'-TGTC$_4$ACACATGTAGTTGTAGTGG

FIGURE 16A

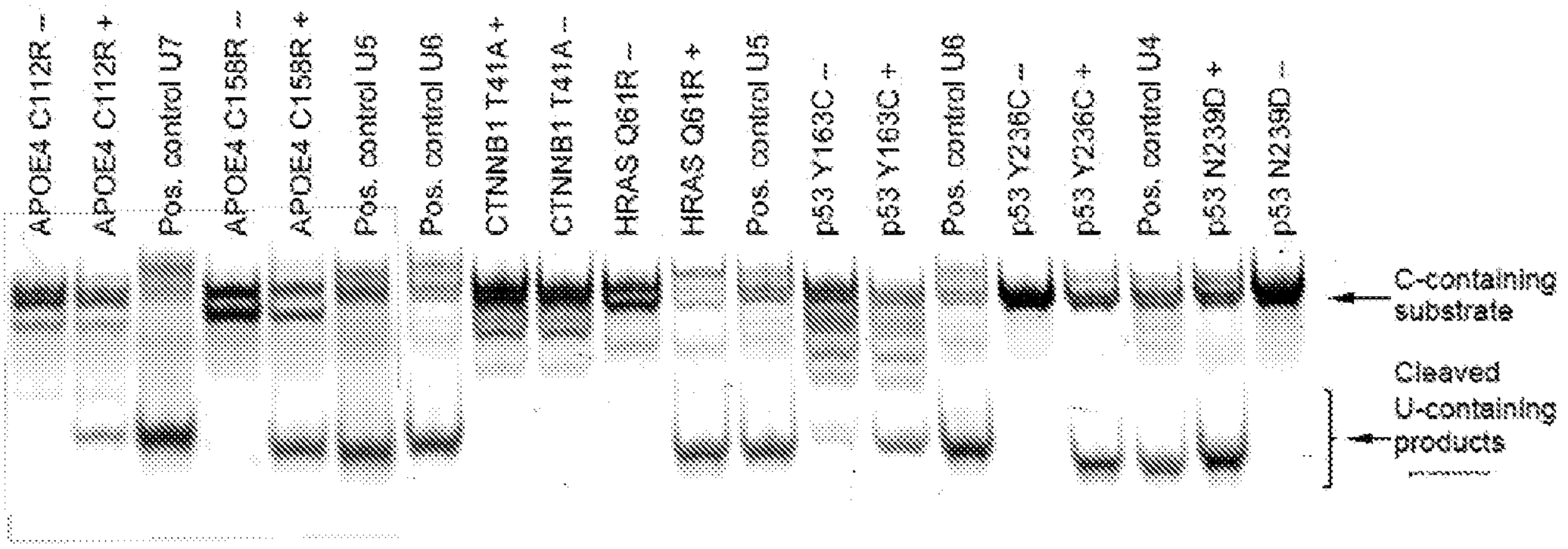


FIGURE 16B

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

EMX1: GAGTC$_5$C$_6$GAGCAGAAGAAGAAGGG
FANCF: GGAATC$_6$C$_7$C$_8$TTC$_{11}$TGCAGCACCTGG
HEK293 site 2: GAAC$_4$AC$_6$AAAGCATAGACTGCGGG
HEK293 site 3: GGCC$_4$C$_5$AGACTGAGCACGTGATGG
HEK293 site 4: GGCAC$_5$TGCGGCTGGAGGTCCGGG
RNF2: GTC$_3$ATC$_6$TTAGTCATTACCTGAGG

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

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_8
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

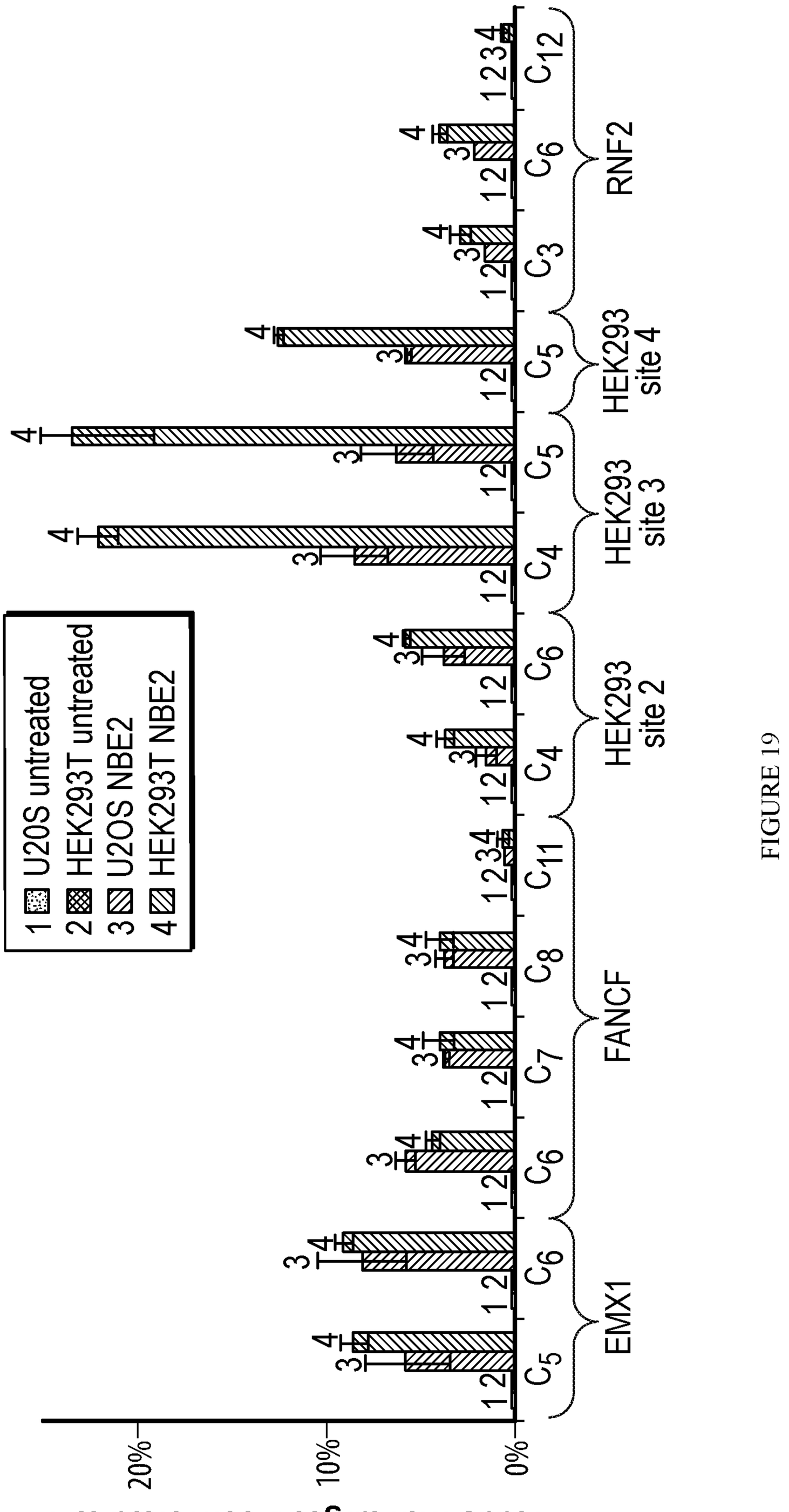

1 U2OS untreated
2 HEK293T untreated
3 U2OS NBE2
4 HEK293T NBE2
Percent of total DNA sequencing reads with target C converted to T
20%
10%
0%
EMX1
FANCF
RNF2
HEK293 site 2
HEK293 site 3
HEK293 site 4

FIGURE 19

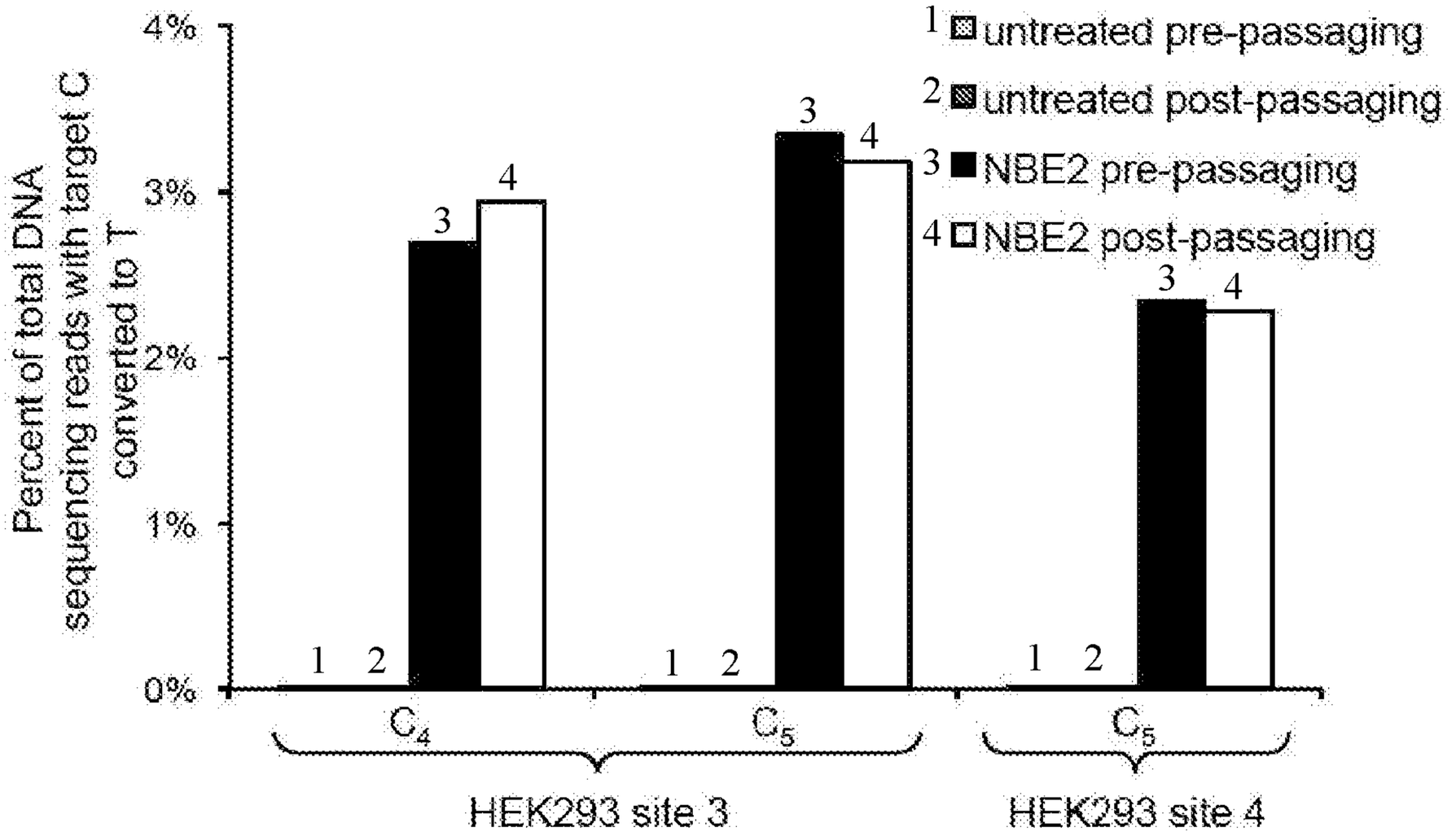


FIGURE 20

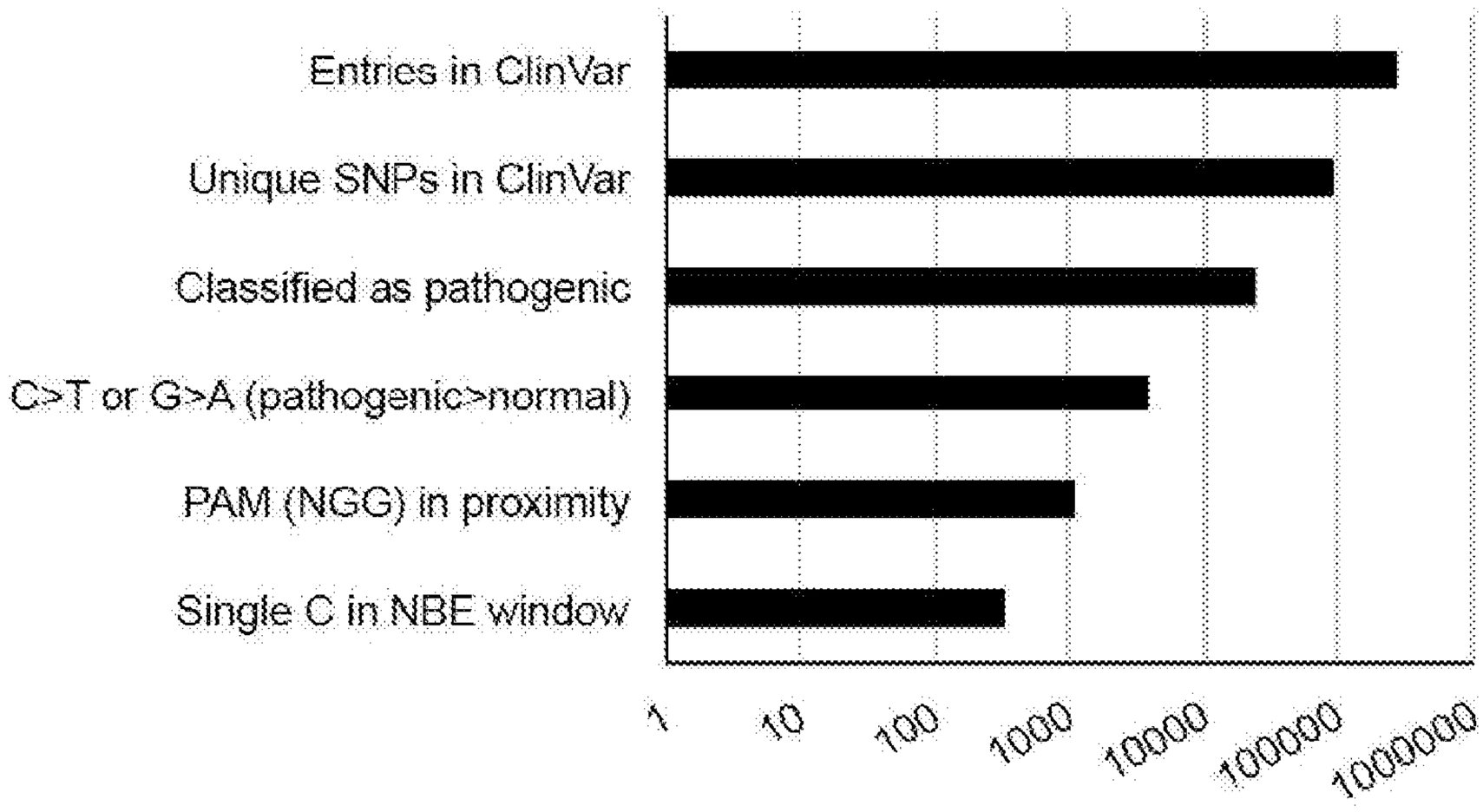


FIGURE 21

EMX1		G	A	G	T	C5	C6	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	G	G
1.85 uM NBE1	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	0.2	0.2
	C	0.0	0.0	0.0	0.0	60.4	61.0	0.0	0.0	0.0	92.1	0.0	0.0	0.0	0.2	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	99.6	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	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

FANCF		G	G	A	A	T	C6	C7	C8	T	T	C11	T	G	C	A	G	C	A	C	C	T	G	G
1.85 uM NBE1	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	0.2	95.0	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	0.0	99.8	0.2	0.0	99.7	0.2	0.0	0.1	0.0	0.0	99.6	99.5
	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	0.0	0.0	0.0	0.0	99.9	0.1	0.1

HEK293 site 2		G	A	A	C4	A	C6	A	A	A	G	C	A	T	A	G	A	C	T	G	C	G	G	G
1.85 uM NBE1	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	0.0	99.9	0.0	0.0	99.9	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	99.9	0.0	0.0	0.0	99.8	0.0	99.9	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	C4	C5	A	G	A	C	T	G	A	G	C	A	C	G	T	G	A	T	G	G
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	100.0	0.1	0.1	0.0	0.2	96.6	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	0.0	0.0	99.8	0.0	99.7	0.0	0.0	0.0	1.3	0.0	0.0	0.0
	G	99.7	99.6	0.0	0.0	0.0	0.0	99.8	0.0	0.0	0.0	99.6	0.0	99.8	0.0	0.0	0.0	99.8	0.0	99.8	0.0	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

FIGURE 22

HEK293 site 3		G	G	C	C4	C5	A	G	A	C	T	G	A	G	C	A	C	G	T	G	A	T	G	G
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	100.0	0.1	0.1	0.0	0.2	96.6	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	0.0	0.0	99.8	0.0	99.7	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	0.0	99.8	0.0	99.8	0.0	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	C5	T	G	C	G	G	C	T	G	G	A	G	G	T	G	G	C	C	C
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	100.0	0.1	0.1	0.0	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	93.4	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	C3	A	T	C6	T	T	A	G	T	C12	A	T	T	A	C	C	T	G	A	G	G
1.85 uM NBE1	A	0.1	0.0	0.1	99.9	0.0	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
	C	0.0	0.0	59.1	0.0	0.0	57.6	0.0	0.0	0.1	0.0	0.0	86.4	0.0	0.0	0.0	0.1	99.9	99.9	0.0	0.0	1.4	0.0	0.0
	G	99.9	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.8	0.0	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 22 (CONTINUED)

																						GUIDE-seq counts
EMX1 on target	G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	G	4521
untreated					0.1	0.0				0.0													
NBE1					4.2	4.4				0.0													
NBE2					9.1	9.3				0.0													
NBE3					26.0	26.6				0.0													
EMX1 off target 1	G	A	G	T	T	A	G	A	G	C	A	G	A	A	G	A	A	G	A	A	A	G	3123
untreated										0.0													
NBE1										0.0													
NBE2										0.0													
NBE3										0.0													
EMX1 off target 2	G	A	G	T	C	T	A	A	G	C	A	G	A	A	G	A	A	G	A	A	G	A	G	1445
untreated					0.0					0.0													
NBE1					1.0					0.0													
NBE2					3.6					0.0													
NBE3					8.5					0.0													

FIGURE 23

EMX1 off target 3	G	A	G	G	C	C	G	A	G	C	A	G	A	A	G	A	A	A	G	A	C	G	G
untreated					0.0	0.0				0.0											0.0		
NBE1					0.0	0.0				0.0											0.0		
NBE2					0.8	0.9				0.0											0.0		
NBE3					5.1	5.2				0.0											0.0		

EMX1 off target 4	G	A	G	T	C	C	T	A	G	C	A	G	G	A	G	A	A	G	A	A	G	A	G
untreated					0.0	0.0				0.0													
NBE1					0.2	0.2				0.0													
NBE2					0.5	0.5				0.0													
NBE3					2.2	2.2				0.0													

EMX1 off target 6	G	A	G	T	C	C	G	G	G	A	A	G	G	A	G	A	A	G	A	A	A	G	G
untreated					0.0	0.1																	
NBE1					0.1	0.1																	
NBE2					0.2	0.3																	
NBE3					1.0	1.0																	

700

390

216

FIGURE 23 (CONTINUED)

EMX1 off target 7	G	A	G	C	C	G	G	A	G	C	A	G	A	A	G	A	A	G	G	A	G	G	G	143
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														

EMX1 off target 8	A	A	G	T	C	C	G	A	G	G	A	G	A	G	G	A	A	G	A	A	A	G	G	102
untreated					0.0	0.0																		
NBE1					0.0	0.0																		
NBE2					0.0	0.0																		
NBE3					0.1	0.1																		

EMX1 off target 9	G	A	A	T	C	C	A	A	G	C	A	G	G	A	G	A	A	G	A	A	G	G	A	67
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														

EMX1 off target 10	A	C	G	T	C	T	G	A	G	C	A	G	A	A	G	A	A	G	A	A	T	G	G	38
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
FANCF on target	G	G	A	A	T	C	C	C	T	T	C	T	G	C	A	G	C	A	C	C	T	G	G	4816
untreated						0.0	0.0	0.0			0.0			0.0			0.0		0.0	0.0				
NBE1						3.7	3.2	3.4			2.4			0.0			0.0		0.0	0.0				
NBE2						4.1	3.5	3.5			0.4			0.0			0.0		0.0	0.0				
NBE3						19.1	16.0	16.7			6.8			0.1			0.0		0.0	0.0				
FANCF off target 1	G	G	A	A	C	C	C	C	G	T	C	T	G	C	A	G	C	A	C	C	A	G	G	2099
untreated					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			0.0			0.0		0.0	0.0				
NBE2					0.2	0.2	0.3	0.3			0.0			0.1			0.0		0.0	0.0				
NBE3					1.9	2.1	1.5	1.3			1.3			0.0			0.0		0.0	0.0				
FANCF off target 2	G	G	A	G	T	C	C	C	T	C	C	T	A	C	A	G	C	A	C	C	A	G	G	524
untreated						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				
NBE2						0.1	0.1	0.1		0.1	0.1			0.0			0.0		0.0	0.0				
NBE3						0.2	0.2	0.1		0.1	0.1			0.0			0.0		0.0	0.0				
FANCF off target 3	A	G	A	G	G	C	C	C	C	T	C	T	G	C	A	G	C	A	C	C	A	G	G	150
untreated						0.0	0.1	0.1	0.0		0.0			0.0			0.0		0.0	0.0				
NBE1						0.0	0.1	0.1	0.0		0.0			0.0			0.0		0.0	0.0				
NBE2						0.0	0.1	0.1	0.0		0.0			0.0			0.1		0.0	0.0				
NBE3						0.0	0.0	0.0	0.0		0.0			0.0			0.0		0.0	0.0				
FANCF off target 4	A	C	C	A	T	C	C	C	T	C	C	T	G	C	A	G	C	A	C	C	A	G	G	125
untreated		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	0.0			0.0			0.0		0.0	0.2				
NBE2		0.0	0.0			0.1	0.1	0.1		0.2	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			0.0			0.0		0.0	0.0				

FIGURE 24

FANCF off target 5	G	G	A	T	T	G	C	C	A	T	C	G	G	C	A	G	C	A	C	C	T	G	G	101
untreated							0.1	0.0			0.0	0.0		0.0			0.0		0.0	0.0				
NBE1							0.1	0.0			0.0	0.1		0.0			0.0		0.0	0.0				
NBE2							0.1	0.0			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	0.0				

FANCF off target 6	T	G	A	A	T	C	C	C	A	T	C	T	C	C	A	G	C	A	C	C	A	G	G	78
untreated						0.0	0.0	0.0			0.0		0.1	0.1			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				
NBE2						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	G	G	A	G	T	C	C	C	T	C	C	T	A	C	A	G	C	A	C	C	A	G	G	77
untreated						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				
NBE2						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	0.0				

FANCF off target 8	G	G	A	G	T	C	C	C	T	C	C	T	G	C	A	G	C	A	C	C	T	G	A	4
untreated						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				
NBE2						1.4	0.5	0.5		0.4	0.5			0.0			0.0		0.0	0.0				
NBE3						0.1	0.1	0.0		0.0	0.0			0.0			0.0		0.0	0.0				

FIGURE 24 (CONTINUED)

																						GUIDE-seq counts
HEK site 2 on target	G	A	A	C	A	C	A	A	A	G	C	A	T	A	G	A	C	T	G	C	G	G	G	1670
untreated				0.0		0.0					0.0						0.0			0.0				
NBE1				1.8		2.9					0.0						0.0			0.0				
NBE2				8.5		10.5					0.0						0.0			0.0				
NBE3				17.6		14.3					0.0						0.0			0.1				
HEK site 2 off target 1	G	A	A	C	A	C	A	A	T	G	C	A	T	A	G	A	T	T	G	C	C	G	G	99
untreated				0.0		0.0					0.0									0.1	0.0			
NBE1				0.0		0.0					0.1									0.1	0.2			
NBE2				0.0		0.4					0.0									0.1	0.0			
NBE3				0.2		0.6					0.0									0.1	0.0			
HEK site 2 off target 2	A	A	A	C	A	T	A	A	A	G	C	A	T	A	G	A	C	T	G	C	A	A	A	4
untreated				0.0							0.0						0.0			0.0				
NBE1				0.0							0.0						0.0			0.0				
NBE2				0.0							0.0						0.0			0.0				
NBE3				0.0							0.0						0.0			0.0				

FIGURE 25

																						GUIDE-seq counts
HEK site 3 on target	G	G	C	C	C	A	G	A	C	T	G	A	G	C	A	C	G	T	G	A	T	G	G	2074
untreated			0.1	0.1	0.1				0.0					0.0		0.0								
NBE1			0.1	4.6	4.3				0.0					0.0		0.0								
NBE2			3.6	21.3	20.4				0.0					0.0		0.0								
NBE3			0.5	33.4	33.1				0.5					0.0		0.2								
HEK site 3 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	327
untreated	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				
NBE2	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				
HEK site 3 off target 2	G	A	C	A	C	A	G	A	C	T	G	G	G	C	A	C	G	T	G	A	G	G	G	306
untreated			0.0		0.0				0.0					0.0		0.0								
NBE1			0.0		0.0				0.0					0.0		0.0								
NBE2			0.0		0.0				0.0					0.0		0.0								
NBE3			0.0		0.0				0.0					0.0		0.0								
HEK site 3 off target 3	A	G	C	T	C	A	G	A	C	T	G	A	G	C	A	A	G	T	G	A	G	G	G	136
untreated			0.0		0.0				0.0					0.0										
NBE1			0.0		0.0				0.0					0.0										
NBE2			0.0		0.0				0.0					0.0										
NBE3			0.0		0.9				0.0					0.0										
HEK site 3 off target 4	A	G	A	C	C	A	G	A	C	T	G	A	G	C	A	A	G	A	G	A	G	G	G	10
untreated				0.0	0.0				0.0					0.0										
NBE1				0.0	0.0				0.0					0.1										
NBE2				0.0	0.0				0.0					0.0										
NBE3				0.0	0.0				0.0					0.0										
HEK site 3 off target 5	G	A	G	C	C	A	G	A	A	T	G	A	G	C	A	C	G	T	G	A	G	G	G	2
untreated				0.0	0.0									0.0		0.0								
NBE1				0.0	0.0									0.0		0.0								
NBE2				0.0	0.0									0.0		0.0								
NBE3				0.0	0.0									0.0		0.0								

FIGURE 26

																						GUIDE-seq counts
HEK site 4 on target	G	G	C	A	C	T	G	C	G	G	C	T	G	G	A	G	G	T	G	G	G	G	1054
untreated			0.0		0.0			0.1			0.0												
NBE1			0.0		0.4			0.1			0.0												
NBE2			0.1		12.7			0.1			0.0												
NBE3			1.5		22.3			1.0			0.0												
HEK site 4 off target 1	T	G	C	A	C	T	G	C	G	G	C	C	G	G	A	G	G	A	G	G	T	G	G	2475
untreated			0.0		0.0			0.0			0.0	0.0											
NBE1			0.0		0.6			0.1			0.1	0.0											
NBE2			0.3		3.3			0.3			0.0	0.0											
NBE3			0.2		10.2			0.3			0.0	0.0											
HEK site 4 off target 2	G	G	C	T	C	T	G	C	G	G	C	T	G	G	A	G	G	G	G	G	T	G	G	2020
untreated			0.0		0.0			0.1			0.0												
NBE1			0.0		0.6			0.1			0.0												
NBE2			0.0		0.4			0.1			0.1												
NBE3			0.0		3.3			0.1			0.0												
HEK site 4 off target 3	G	G	C	A	C	G	A	C	G	G	C	T	G	G	A	G	G	T	G	G	G	G	G	1375
untreated			0.0		0.0			0.0			0.0												
NBE1			0.1		11.6			4.0			0.0												
NBE2			0.0		9.6			3.9			0.0												
NBE3			0.1		19.0			1.9			0.1												
HEK site 4 off target 4	G	G	C	A	T	C	A	C	G	G	C	T	G	G	A	G	G	T	G	G	A	G	G	1097
untreated			0.0			0.0		0.0			0.0												
NBE1			0.0			0.2		0.3			0.0												
NBE2			0.5			5.3		2.7			0.0												
NBE3			0.2			18.1		3.1			0.0												

FIGURE 27

HEK site 4 off target 5	G	G	C	G	C	T	G	C	G	G	C	G	G	G	A	G	G	T	G	G	A	G	G	1002
untreated			0.0		0.0			0.1			0.0													
NBE1			0.0		0.0			0.0			0.0													
NBE2			0.0		0.0			0.1			0.0													
NBE3			0.1		0.1			0.1			0.0													

HEK site 4 off target 6	G	G	C	A	C	T	G	A	G	A	C	T	G	G	G	G	G	T	G	G	G	G	G	982
untreated			0.0		0.0						0.0													
NBE1			0.0		0.5						0.3													
NBE2			0.8		3.6						0.0													
NBE3			0.0		6.8						0.0													

HEK site 4 off target 7	A	G	C	A	G	T	G	C	G	G	C	T	A	G	A	G	G	T	G	G	T	G	G	981
untreated			0.0					0.1			0.0													
NBE1			0.0					0.1			0.0													
NBE2			0.0					0.1			0.0													
NBE3			0.0					0.2			0.0													

HEK site 4 off target 8	G	G	C	A	C	T	G	C	T	A	C	T	G	G	G	G	G	T	G	G	T	G	G	789
untreated			0.0		0.0			0.0			0.0													
NBE1			0.0		2.1			0.0			0.0													
NBE2			0.2		5.1			0.5			0.0													
NBE3			0.2		8.2			0.1			0.0													

HEK site 4 off target 9	G	G	C	A	C	T	G	G	G	G	C	T	G	G	G	G	G	A	G	G	G	G	G	712
untreated			0.0		0.0						0.0													
NBE1			0.0		0.3						0.0													
NBE2			0.0		0.4						0.0													
NBE3			0.0		0.9						0.0													

HEK site 4 off target 10	G	G	C	A	C	T	G	G	G	G	T	T	G	G	A	G	G	T	G	G	G	G	G	664
untreated			0.0		0.0																			
NBE1			0.0		0.0																			
NBE2			0.6		3.5																			
NBE3			0.3		10.0																			

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

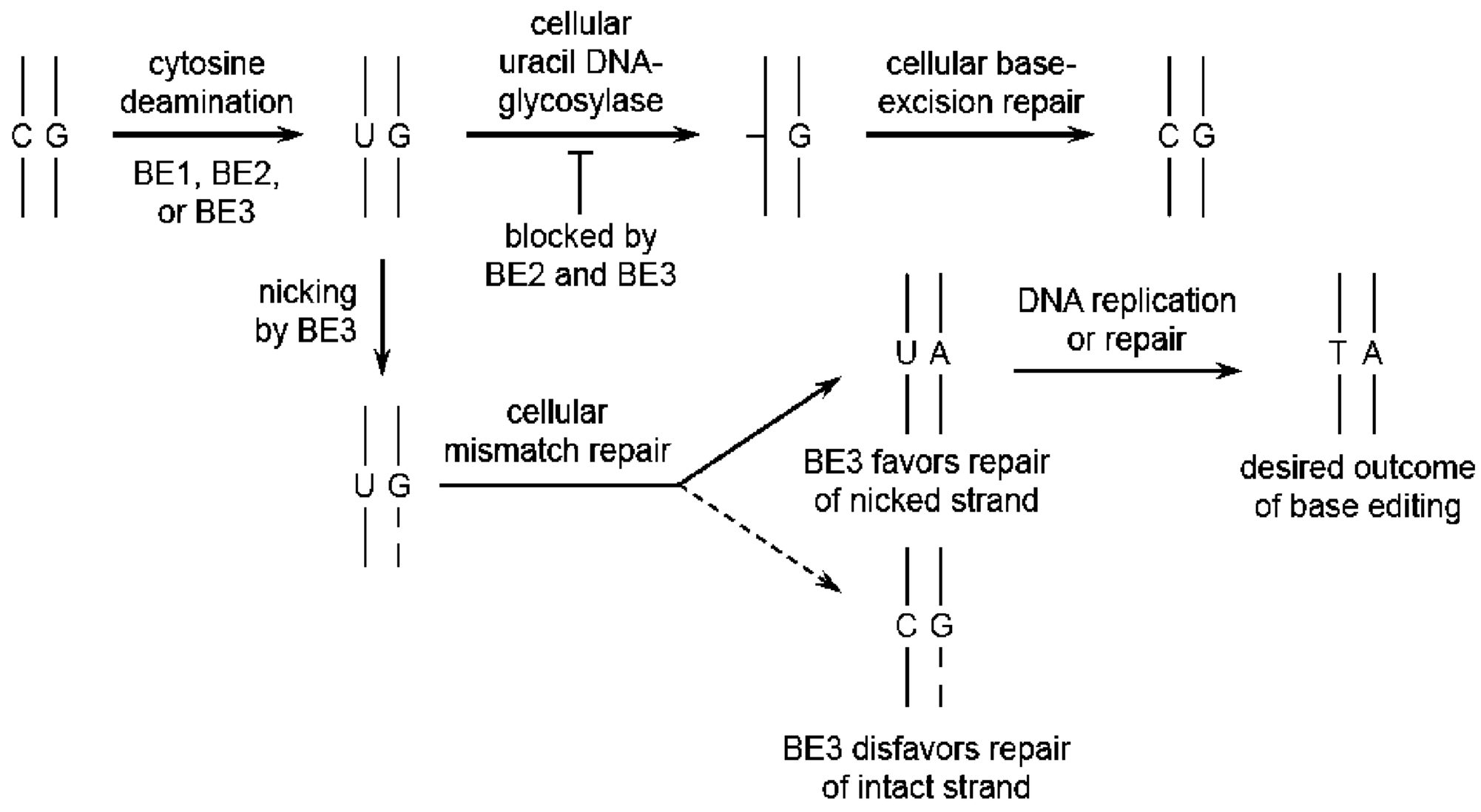


FIGURE 29A

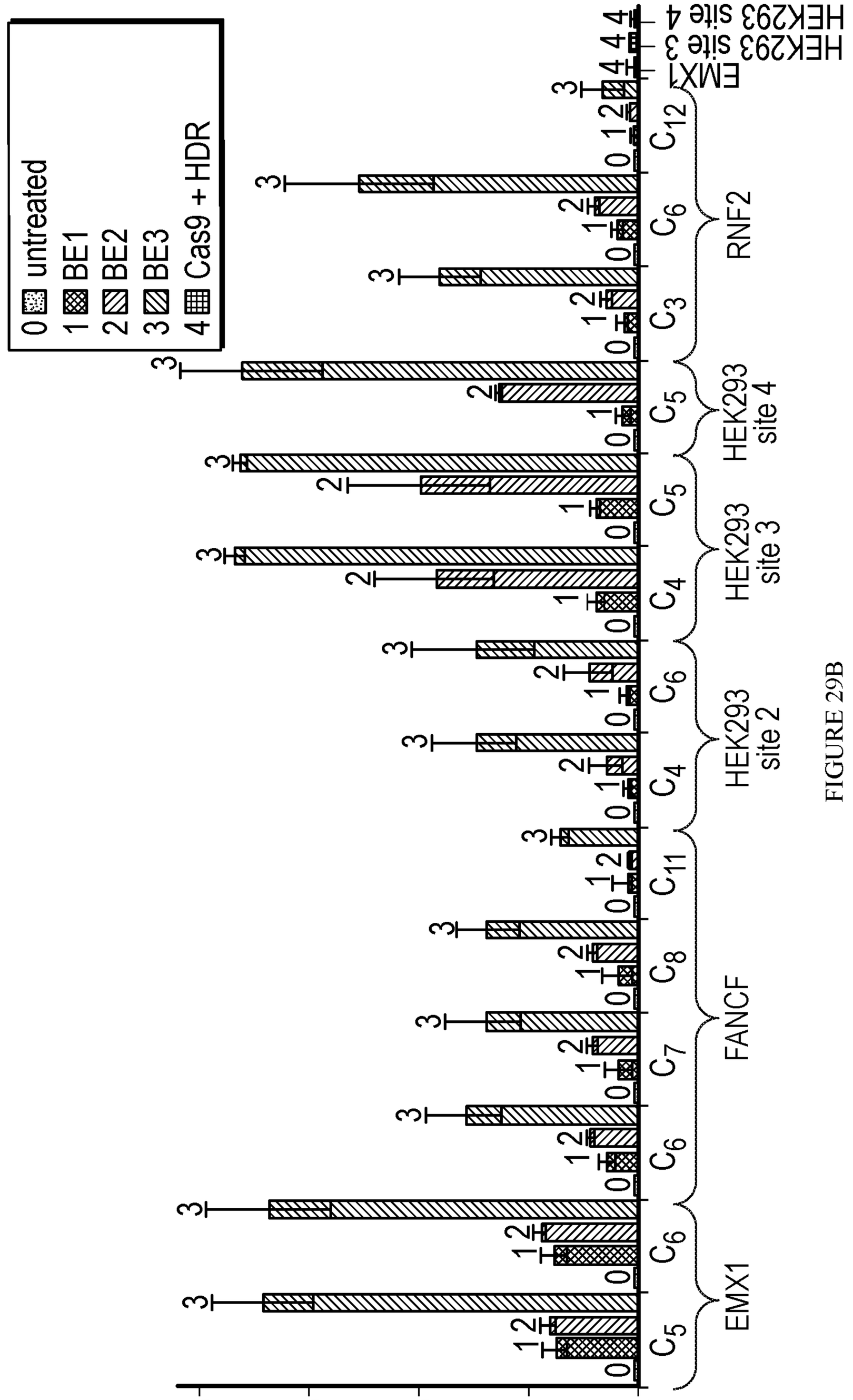

0 untreated
1 BE1
2 BE2
3 BE3
4 Cas9 + HDR
percent of total sequencing reads with target C converted to T
40%
30%
20%
10%
0%
EMX1
FANCF
RNF2
HEK293 site 2
HEK293 site 3
HEK293 site 4
EMX1
C5
C6
C11
C7
C8
C4
C3
C12
C6
C5
C5
C4
C6
C6

FIGURE 29B

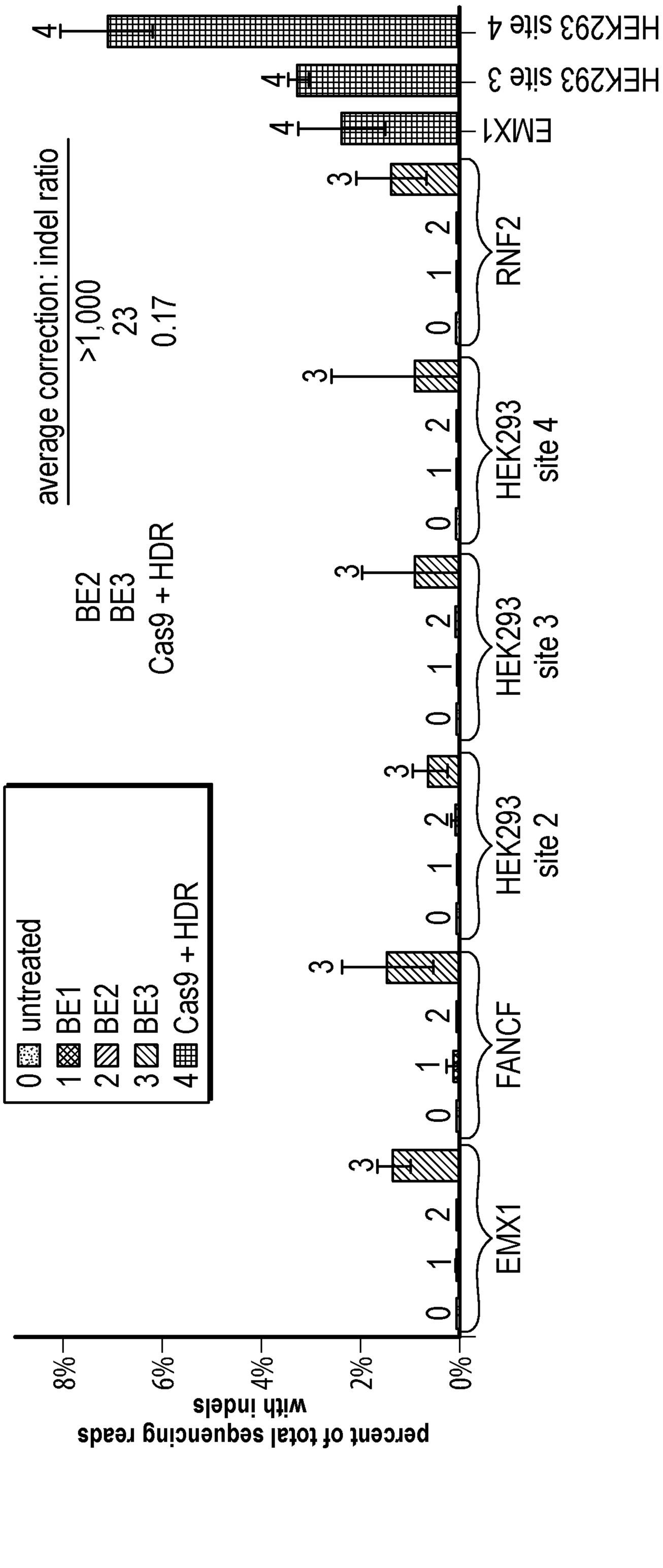

average correction: indel ratio
>1,000
23
0.17
BE2
BE3
Cas9 + HDR
0 untreated
1 BE1
2 BE2
3 BE3
4 Cas9 + HDR
percent of total sequencing reads with indels
8%
6%
4%
2%
0%
EMX1
HEK293 site 3
HEK293 site 4
RNF2
HEK293 site 2
FANCF
HEK293 site 4

FIGURE 29C

untreated		Lys			Arg			Leu			Ala			Val			Tyr				Gln			indel %
APOE4 C158R	G	A	A	G	C_5	G	C	C	T	G	G	C	A	G	T	G	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	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	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	100.0	0.0	0.0	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	0.0	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	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	0.0	

BE3 treated		Lys			Arg → Cys			Leu → Leu			Ala			Val			Tyr				Gln			indel %
APOE4 C158R	G	A	A	G	C_5	G	C	C	T	G	G	C	A	G	T	G	T	A	C	C	A	G	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	0.0	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	92.9	0.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0	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	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	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	

Cas9 + HDR		Lys			Arg → Cys			Leu			Ala			Val			Tyr				Gln			indel %
APOE4 C158R	G	A	A	G	C_5	G	C	C	T	G	G	C	A	G	T	G	T	A	C	C	A	G	G	28.1
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	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	0.0	
G	100.0	0.0	0.0	100.0	0.0	100.0	0.0	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	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	

FIGURE 30A

untreated			Arg			Ala			Met			Ala			Ile		Cys				Lys			indel %
TP53 Y163C	C	C	G	C	G	C	C	A	T	G	G	C	C	A	T	C	T	G*	C	A	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	0.1	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	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	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	100.0	99.9	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	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	

BE3 treated			Arg			Ala			Met			Ala			Ile		Cys → Tyr				Lys			indel %
TP53 Y163C	C	C	G	C	G	C	C	A	T	G	G	C	C	A	T	C	T	G*	C	A	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	0.1	0.0	0.0	100.0	0.0	0.0	0.0	7.6	0.0	100.0	100.0	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	99.9	100.0	0.0	0.0	100.0	0.0	0.4	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	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	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	0.0	0.0	

Cas9 + HDR			Arg			Ala			Met			Ala			Ile		Cys → Tyr				Lys			indel %
TP53 Y163C	C	C	G	C	G	C	C	A	T	G	G	C	C	A	T	C	T	G*	C	A	A	G	C	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	100.0	0.0	0.0	0.0	0.0	0.0	99.9	100.0	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	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	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	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	0.0	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	

FIGURE 30B

																						GUIDE-seq counts/ ChIP-seq intensity
HEK site 2 on target	G	A	A	C	A	C	A	A	A	G	C	A	T	A	G	A	C	T	G	C	G	G	G	1670/ 117
untreated				0.0		0.0					0.0						0.0			0.0				
BE1				1.8		2.9					0.0						0.0			0.0				
BE2				8.5		10.5					0.0						0.0			0.0				
BE3				17.6		14.9					0.0						0.0			0.1				
HEK site 2 GUIDE-seq off target 1	G	A	A	C	A	C	A	A	T	G	C	A	T	A	G	A	T	T	G	C	C	G	G	99
untreated				0.0		0.0					0.0									0.1	0.0			
BE1				0.0		0.0					0.1									0.1	0.2			
BE2				0.0		0.4					0.0									0.1	0.0			
BE3				0.2		0.6					0.0									0.1	0.0			
HEK site 2 GUIDE-seq off target 2	A	A	A	C	A	T	A	A	A	G	C	A	T	A	G	A	C	T	G	C	A	A	A	4
untreated				0.0							0.0						0.0			0.0				
BE1				0.0							0.0						0.0			0.0				
BE2				0.0							0.0						0.0			0.0				
BE3				0.0							0.0						0.0			0.0				
HEK site 2 ChIP-seq off target 1	T	C	A	G	G	G	T	G	A	G	C	A	T	A	G	A	C	T	G	C	C	G	G	31
untreated		0.0									0.0						0.0			0.0	0.0			
BE1		0.0									0.0						0.0			0.1	0.0			
BE2		0.0									0.0						0.0			0.1	0.0			
BE3		0.0									0.0						0.0			0.1	0.0			

FIGURE 31

HEK site 2 ChIP-seq off target 2	G	A	A	T	C	G	G	G	A	G	G	G	G	A	G	A	C	T	G	C	G	G	G	28
untreated					0.0												0.0			0.0				
BE1					0.0												0.0			0.1				
BE2					0.0												0.0			0.1				
BE3					0.0												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	23
untreated											0.0						0.0			0.0				
BE1											0.0						0.0			0.1				
BE2											0.0						0.0			0.0				
BE3											0.0						0.0			0.0				

HEK site 2 ChIP-seq off target 4	G	G	A	G	A	G	A	G	A	G	C	A	T	A	G	A	C	T	G	C	T	G	G	16
untreated											0.0						0.0			0.0				
BE1											0.0						0.0			0.0				
BE2											0.0						0.0			0.0				
BE3											0.0						0.0			0.0				

HEK site 2 ChIP-seq off target 5	C	C	A	A	A	C	A	A	A	A	C	A	T	A	G	A	C	T	G	C	T	G	G	10
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
HEK site 3 on target	G	G	C	C	C	A	G	A	C	T	G	A	G	C	A	C	G	T	G	A	T	G	G	2074/ 163
untreated			0.1	0.1	0.1				0.0					0.0		0.0								
BE1			0.1	4.8	4.3				0.0					0.0		0.0								
BE2			3.6	21.3	20.4				0.0					0.0		0.0								
BE3			0.5	34.4	33.1				0.5					0.0		0.2								
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	327
untreated	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				
BE2	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				
HEK site 3 GUIDE-seq off target 2	G	A	C	A	C	A	G	A	C	T	G	G	G	C	A	C	G	T	G	A	G	G	G	306
untreated			0.0		0.0				0.0					0.0		0.0								
BE1			0.0		0.0				0.0					0.0		0.0								
BE2			0.0		0.0				0.0					0.0		0.0								
BE3			0.0		0.0				0.0					0.0		0.0								
HEK site 3 GUIDE-seq off target 3	A	G	C	T	C	A	G	A	C	T	G	A	G	C	A	A	G	T	G	A	G	G	G	136
untreated			0.0		0.0				0.0					0.0										
BE1			0.0		0.0				0.0					0.0										
BE2			0.0		0.0				0.0					0.0										
BE3			0.0		0.9				0.0					0.0										
HEK site 3 GUIDE-seq off target 4	A	G	A	C	C	A	G	A	C	T	G	A	G	C	A	A	G	A	G	A	G	G	G	10
untreated				0.0	0.0				0.0					0.0										
BE1				0.0	0.0				0.0					0.1										
BE2				0.0	0.0				0.0					0.0										
BE3				0.0	0.0				0.0					0.0										

FIGURE 32

HEK site 3 GUIDE-seq off target 5	G	A	G	C	C	A	G	A	A	T	G	A	G	C	A	C	G	T	G	A	G	G	G	2
untreated				0.0	0.0									0.0		0.0								
BE1				0.0	0.0									0.0		0.0								
BE2				0.0	0.0									0.0		0.0								
BE3				0.0	0.0									0.0		0.0								
HEK site 3 ChIP-seq off target 1	C	A	G	G	A	A	G	C	T	G	G	A	G	C	A	C	G	T	G	A	G	G	G	47
untreated	0.0							0.0						0.0		0.0								
BE1	0.0							0.0						0.0		0.0								
BE2	0.0							0.0						0.0		0.0								
BE3	0.0							0.0						0.0		0.0								
HEK site 3 ChIP-seq off target 2	A	A	G	G	C	T	G	A	G	G	G	A	G	C	A	C	G	T	G	A	A	G	G	46
untreated					0.0									0.0		0.0								
BE1					0.0									0.0		0.0								
BE2					0.0									0.0		0.0								
BE3					0.0									0.0		0.0								
HEK site 3 ChIP-seq off target 3	G	T	C	A	G	G	G	G	A	A	G	A	G	C	A	C	G	T	G	A	C	G	G	33
untreated			0.0											0.0		0.0					0.0			
BE1			0.0											0.0		0.0					0.0			
BE2			0.0											0.0		0.0					0.0			
BE3			0.0											0.0		0.0					0.0			
HEK site 3 ChIP-seq off target 4	G	T	T	G	T	G	A	A	C	T	G	A	G	C	A	C	G	T	G	A	G	G	G	31
untreated									0.0					0.0		1.7								
BE1									0.0					0.0		0.7								
BE2									0.0					0.0		0.4								
BE3									0.0					0.0		0.4								
HEK site 3 ChIP-seq off target 5	A	T	A	T	T	T	G	C	T	G	G	A	G	C	A	C	G	T	G	A	A	G	G	31
untreated								0.0						0.0		0.0								
BE1								0.0						0.0		0.0								
BE2								0.0						0.0		0.0								
BE3								0.0						0.0		0.0								

FIGURE 32 (CONTINUED)

																						GUIDE-seq counts/ ChIP-seq intensity
HEK site 4 on target	G	G	C	A	C	T	G	C	G	G	C	T	G	G	A	G	G	T	G	G	G	G	1054/ 49
untreated			0.0		0.0			0.1			0.0												
BE1			0.0		0.4			0.1			0.0												
BE2			0.1		12.7			0.1			0.0												
BE3			1.5		22.3			1.0			0.0												
HEK site 4 GUIDE-seq off target 1	T	G	C	A	C	T	G	C	G	G	C	C	G	G	A	G	G	A	G	G	T	G	G	2475
untreated			0.0		0.0			0.0			0.0	0.0												
BE1			0.0		0.5			0.1			0.1	0.0												
BE2			0.3		3.3			0.3			0.0	0.0												
BE3			0.2		10.2			0.3			0.0	0.0												
HEK site 4 GUIDE-seq off target 2	G	G	C	T	C	T	G	C	G	G	C	T	G	G	A	G	G	G	G	G	T	G	G	2020
untreated			0.0		0.0			0.1			0.0													
BE1			0.0		0.6			0.1			0.0													
BE2			0.0		0.4			0.1			0.1													
BE3			0.0		3.3			0.1			0.0													
HEK site 4 GUIDE-seq off target 3	G	G	C	A	C	G	A	C	G	G	C	T	G	G	A	G	G	T	G	G	G	G	G	1375
untreated			0.0		0.0			0.0			0.0													
BE1			0.1		11.6			4.0			0.0													
BE2			0.0		2.6			3.9			0.0													
BE3			0.1		19.6			1.9			0.1													
HEK site 4 GUIDE-seq off target 4	G	G	C	A	T	C	A	C	G	G	C	T	G	G	A	G	G	T	G	G	A	G	G	1097
untreated			0.0			0.0		0.0			0.0													
BE1			0.0			0.2		0.3			0.0													
BE2			0.5			5.3		2.7			0.0													
BE3			0.2			18.1		3.1			0.0													

FIGURE 33

HEK site 4 GUIDE-seq off target 5	G	G	C	G	C	T	G	C	G	G	C	G	G	G	A	G	G	T	G	G	A	G	G	1002
untreated			0.0		0.0			0.1			0.0													
BE1			0.0		0.0			0.0			0.0													
BE2			0.0		0.0			0.1			0.0													
BE3			0.1		0.1			0.1			0.0													

HEK site 4 GUIDE-seq off target 6	G	G	C	A	C	T	G	A	G	A	C	T	G	G	G	G	G	T	G	G	G	G	G	982
untreated			0.0		0.0						0.0													
BE1			0.0		0.5						0.3													
BE2			0.8		3.6						0.0													
BE3			0.0		6.8						0.0													

HEK site 4 GUIDE-seq off target 7	A	G	C	A	G	T	G	C	G	G	C	T	A	G	A	G	G	T	G	G	T	G	G	981
untreated			0.0					0.1			0.0													
BE1			0.0					0.1			0.0													
BE2			0.0					0.1			0.0													
BE3			0.0					0.2			0.0													

HEK site 4 GUIDE-seq off target 8	G	G	C	A	C	T	G	C	T	A	C	T	G	G	G	G	G	T	G	G	T	G	G	789
untreated			0.0		0.0			0.0			0.0													
BE1			0.0		2.1			0.0			0.0													
BE2			0.2		5.1			0.5			0.0													
BE3			0.2		8.2			0.1			0.0													

HEK site 4 GUIDE-seq off target 9	G	G	C	A	C	T	G	G	G	G	C	T	G	G	G	G	G	A	G	G	G	G	G	712
untreated			0.0		0.0						0.0													
BE1			0.0		0.3						0.0													
BE2			0.0		0.4						0.0													
BE3			0.0		0.9						0.0													

FIGURE 33 (CONTINUED)

HEK site 4 GUIDE-seq off target 10	G	G	C	A	C	T	G	G	G	G	T	T	G	G	A	G	G	T	G	G	G	G	G
untreated			0.0		0.0																		
BE1			0.0		0.0																		
BE2			0.6		3.5																		
BE3			0.3		10.0																		

664

HEK site 4 ChIP-seq off target 1	G	T	G	G	C	T	G	G	A	G	G	T	G	G	A	G	G	T	G	G	G	G	G
untreated					0.0																		
BE1					0.0																		
BE2					0.0																		
BE3					0.0																		

110

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

89

FIGURE 33 (CONTINUED)

APOE4	C50	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	0.1±0.1	100±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	100±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	100±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	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	100±0.1	0±0	0.1±0.1	0±0	100±0.1	0.1±0.1	0±0	100±0.1	0.1±0.1	0.1±0.1	0±0	0.1±0.1	0±0	100±0.1	0.1±0.1	0.1±0.1	100±0.1
G	0.1±0.1	0.1±0.1	0±0	0±0	0.1±0.1	100±0.1	0±0	99.9±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0±0	0±0	100±0.1	0.1±0.1	100±0.1	0±0	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	100±0.1	0±0
T	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	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
BE3 + on-target sgRNA																									
A	0±0	100±0.1	0±0	0.1±0.1	0.1±0.1	0.1±0.1	0±0	0.1±0.1	0.1±0.1	100±0.1	100±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±0	100±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	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	100±0.1	0.1±0.1	0.1±0.1	0±0	100±0.1	0.1±0.1	0±0	100±0.1	0±0	0.1±0.1	0±0	0.1±0.1	0.1±0.1	100±0.1	0±0	0±0	100±0.1
G	0.1±0.1	0.1±0.1	0±0	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	0±0	0.1±0.1	0.1±0.1	100±0.1	0±0	0.1±0.1	100±0.1	0.1±0.1	100±0.1	0±0	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
T	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	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
BE3 + off-target sgRNA																									
A	0±0	100±0.1	0±0	0±0	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0±0	100±0.1	100±0.1	0.1±0.1	0±0	0±0	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	0.1±0.1	0.1±0.1	0.1±0.1	0±0
C	100±0.1	0.1±0.1	100±0.1	100±0.1	0.1±0.1	0±0	100±0.1	0.1±0.1	100±0	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	0±0	0.1±0.1	0.1±0.1	0.1±0.1	0±0	100±0.1	0.1±0.1	0±0	100±0.1
G	0±0	0.1±0.1	0±0	0±0	0±0	100±0.1	0.1±0.1	100±0.1	0±0	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	0±0	100±0.1	0±0	100±0.1	0±0	0.1±0.1	0.1±0.1	100±0.1	0±0	100±0.1	100±0.1	0±0
T	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±0	0±0	0±0	0.1±0.1	0±0	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0±0	0.1±0.1	0.1±0.1	0.1±0.1	0±0	0.1±0.1	0.1±0.1

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	0.1±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	100±0.1	0±0	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	100±0.1	0±0	0.1±0.1	0.1±0.1	0.1±0.1	0±0	100±0.1
C	0.1±0.1	100±0	100±0.1	0.1±0.1	100±0.1	100±0.1	0±0	100±0.1	0.1±0.1	0±0	0.1±0.1	0±0	100±0.1	100±0.1	0±0	0±0	0.1±0.1	0±0	0±0	100±0.1	100±0.1	0.1±0.1	0±0	100±0.1	0.1±0.1
G	0±0	0±0	0±0	0.1±0.1	0±0	0.1±0.1	100±0.1	0.1±0.1	100±0.1	0±0	0±0	100±0.1	0.1±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±0	0±0	100±0.1	0±0	0.1±0.1
T	100±0.1	0±0	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	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	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1
BE3 + on-target sgRNA																									
A	0±0	0±0	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0±0	0.1±0.1	0±0	0.1±0.1	0.2±0.1	100±0.1	0.1±0.1	0.2±0.1	99.9±0.2	0±0	0.1±0.1	0.2±0.2	0.1±0.1	0.1±0.1	99.9±0.2
C	0.1±0.1	99.9±0.1	100±0.1	0.1±0.1	99.5±0.1	100±0.1	0.1±0.1	100±0.1	0±0	0±0	0.1±0.1	0±0	100±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0±0	100±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	0.2±0.2
G	0±0	0±0	0.1±0.1	0±0	0.1±0.1	0±0	100±0.1	0±0	100±0.1	0.1±0.1	0±0	100±0.1	0.1±0.1	0.1±0.1	99.9±0.1	0.1±0.1	0±0	99.9±0.1	0.2±0.2	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1
T	100±0.1	0.2±0.1	0.1±0.1	100±0.1	0.5±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	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	99.9±0.2	0.1±0.1	0.1±0.1	0.1±0.1
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	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0±0	0.1±0.1	0.1±0.1	0±0	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	100±0.1
C	0.1±0.1	100±0.1	100±0.1	0.1±0.1	100±0.1	100±0.1	0±0	100±0.1	0±0	0.1±0.1	0.1±0.1	0±0	100±0.1	100±0.1	0±0	0.1±0.1	0.1±0.1	0±0	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
G	0±0	0±0	0±0	0.1±0.1	0±0	0.1±0.1	100±0.1	0±0	100±0.1	0.1±0.1	0±0	100±0.1	0±0	0±0	100±0.1	0.1±0.1	0±0	100±0.1	0.1±0.1	0±0	0±0	0±0	100±0.1	0.1±0.1	0.1±0.1
T	100±0.1	0.1±0.1	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±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	100±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±0

FIGURE 34

APOE4	A-1	G-2	G-3	C-4	C-5	G-6	G-7	G-8	G-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	100±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	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	0.1±0.1	99.9±0.1	0.1±0.1	0.1±0.1	100±0.2	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±0	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.2	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	100±0.1	0.1±0.1	0.1±0.1	0.2±0.1	0.2±0.2	0.2±0.1	0.2±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	0.1±0.1	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	0±0	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	0.1±0.1	0.2±0.2	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±0	0.1±0.1	0.1±0.1	0.2±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±0	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±0	100±0.1	0±0	0.1±0.1	0.1±0.1	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±0	0.1±0.1	100±0.1	100±0.1	100±0.1	100±0.1	0±0	0±0	0±0	99.9±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	100±0.1	100±0.1	0.1±0.1	99.9±0.1	0±0	0±0	100±0.1	0±0
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±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±0	0±0	0.1±0.1	0±0	0.1±0.1	0±0	0.1±0.1	0.1±0.1	0.1±0.1	0.1±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	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
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	99.6±0.1	0.1±0.1	100±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±0	0.1±0.1
G	100±0.1	0.1±0.1	99.9±0.2	0.1±0.1	100±0.1	100±0.1	0±0	0±0	0±0	0±0	0.1±0.1	100±0.1	0.1±0.1	99.9±0.1	0±0	0±0	0.1±0.1	0.5±0.1	0.1±0.1	0.1±0.1	99.9±0.2	0±0	99.7±0.1	0.1±0.1	100±0.1
T	0.1±0.1	0.1±0.1	0.2±0.2	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	0.3±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±0.2	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±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	100±0.1	0.1±0.1	0.1±0.1	0.2±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
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	99.9±0.1	0±0	0±0	99.7±0.1	0.1±0.1	100±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±0	0.2±0.2
G	100±0.1	0.1±0.1	100±0.1	0±0	100±0.1	100±0.1	0.1±0.1	0±0	0.1±0.1	0±0	0.1±0.1	100±0.1	0.1±0.1	99.8±0.2	0.1±0.1	0±0	0.1±0.1	0.5±0.5	0±0	0±0	100±0.1	0.1±0.1	99.6±0.4	0.1±0.1	99.9±0.2
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±0	100±0.1	0.2±0.1	0.1±0.1	0.1±0.1	0.4±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	99.6±0.5	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.4±0.3	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±0	0±0	100±0.1	0±0	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
C	0.1±0.1	100±0.1	0±0	100±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	0±0	99.6±0.1	0.1±0.1	100±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±0	0.1±0.1
G	100±0.1	0.1±0.1	100±0.1	0±0	100±0.1	100±0.1	0±0	0±0	0±0	0±0	0.1±0.1	100±0.1	0.1±0.1	99.9±0.1	0±0	0±0	0.1±0.1	0.4±0.1	0±0	0±0	100±0.1	0±0	99.7±0.2	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±0	0.1±0.1	0±0	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.2±0.2	0.1±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±0.2	0±0	0.1±0.1

FIGURE 34 (CONTINUED)

TP53	C-50	C-49	T-48	G-47	T-46	G-45	C-44	A-43	G-42	C-41	T-40	G-39	T-38	G-37	G-36	G-35	T-34	T-33	G-32	A-31	T-30	T-29	C-28	C-27	A-26
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	0.1±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	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	100±0.1
C	100±0.1	100±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	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	100±0.1	100±0.1	0.1±0.1
G	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	100±0.1	0.1±0.1	100±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
T	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	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	100±0.1	0.1±0.1	0.1±0.1	100±0.1	100±0.1	0.1±0.1	0.1±0.1	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	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	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1
C	100±0.1	100±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	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	100±0.1	100±0.1	0.1±0.1
G	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	100±0.1	0.1±0.1	100±0.1	100±0.1	100±0.1	0.1±0.1	0.1±0.1	99.8±0.3	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1
T	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	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	100±0.1	0.3±0.3	0.1±0.1	100±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1
BE3 + off-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	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	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1
C	100±0.1	100±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	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	100±0.1	100±0.1	0.1±0.1
G	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	100±0.1	0.1±0.1	100±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
T	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	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	100±0.1	0.1±0.1	0.1±0.1	100±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1

TP53	C-25	A-24	C-23	C-22	C-21	C-20	C-19	G-18	C-17	C-16	C-15	G-14	G-13	C-12	A-11	C-10	C-9	C-8	G-7	C-6	G-5	T-4	C-3	C-2	G-1
Untreated																									
A	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	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	0.1±0.1	0.1±0.1	0.1±0.1
C	100±0.1	0.1±0.1	100±0.1	100±0.1	100±0.1	100±0.1	100±0.1	0.1±0.1	100±0.1	100±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	100±0.1	100±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	100±0.1	0.1±0.1
G	0.1±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	100±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	100±0.1	0.1±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	0.1±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
BE3 + on-target sgRNA																									
A	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	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	0.1±0.1	0.1±0.1	0.1±0.1
C	100±0.1	0.1±0.1	100±0.1	100±0.1	100±0.1	100±0.1	100±0.1	0.1±0.1	100±0.1	100±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	100±0.1	99.9±0.2	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	100±0.1	0.1±0.1
G	0.1±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	100±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	100±0.1	0.1±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	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.2±0.2	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
BE3 + off-target sgRNA																									
A	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	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.5±0.7	0.1±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	100±0.1	0.1±0.1	100±0.1	100±0.1	100±0.1	100±0.1	100±0.1	0.1±0.1	100±0.1	100±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1	100±0.1	99.6±0.6	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	100±0.1	100±0.1	0.1±0.1
G	0.1±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	100±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	100±0.1	0.1±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	0.1±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

FIGURE 35

TP53	A1	G2	T3	C4	A5	C6	A7	G8	C9	A10	C11	A12	T13	G14	A15	C16	G17	G18	A19	G20	G21	T22	T23	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	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
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	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
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	100±0.1	0.1±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
BE3 + 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	0.1±0.1	0.3±0.4	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
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	0.1±0.1	100±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1	0.5±0.7	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	100±0.1	0.1±0.1	0.1±0.1	100±0.1	99.8±0.4	0.1±0.1	100±0.1	99.6±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
BE3 + 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	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
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	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
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	100±0.1	0.1±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
Untreated																									
A	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	0.1±0.1	0.1±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	100±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	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	100±0.1	100±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	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1
G	100±0.1	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	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	100±0.1	0.1±0.1	100±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	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	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
BE3 + on-target sgRNA																									
A	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	0.1±0.1	0.2±0.3	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	100±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	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	100±0.1	100±0.1	99.9±0.3	100±0.1	0.1±0.1	100±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	100±0.1
G	100±0.1	0.1±0.1	99.7±0.6	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	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	0.1±0.1	100±0.1	0.1±0.1
T	0.1±0.1	0.1±0.1	0.4±0.5	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	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
BE3 + off-target sgRNA																									
A	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	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	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
C	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	0.1±0.1	0.1±0.1	100±0.1	100±0.1	100±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	0.1±0.1	0.1±0.1	0.1±0.1	100±0.1	0.1±0.1	100±0.1
G	100±0.1	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	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	100±0.1	0.1±0.1	100±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	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	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

FIGURE 35 (CONTINUED)

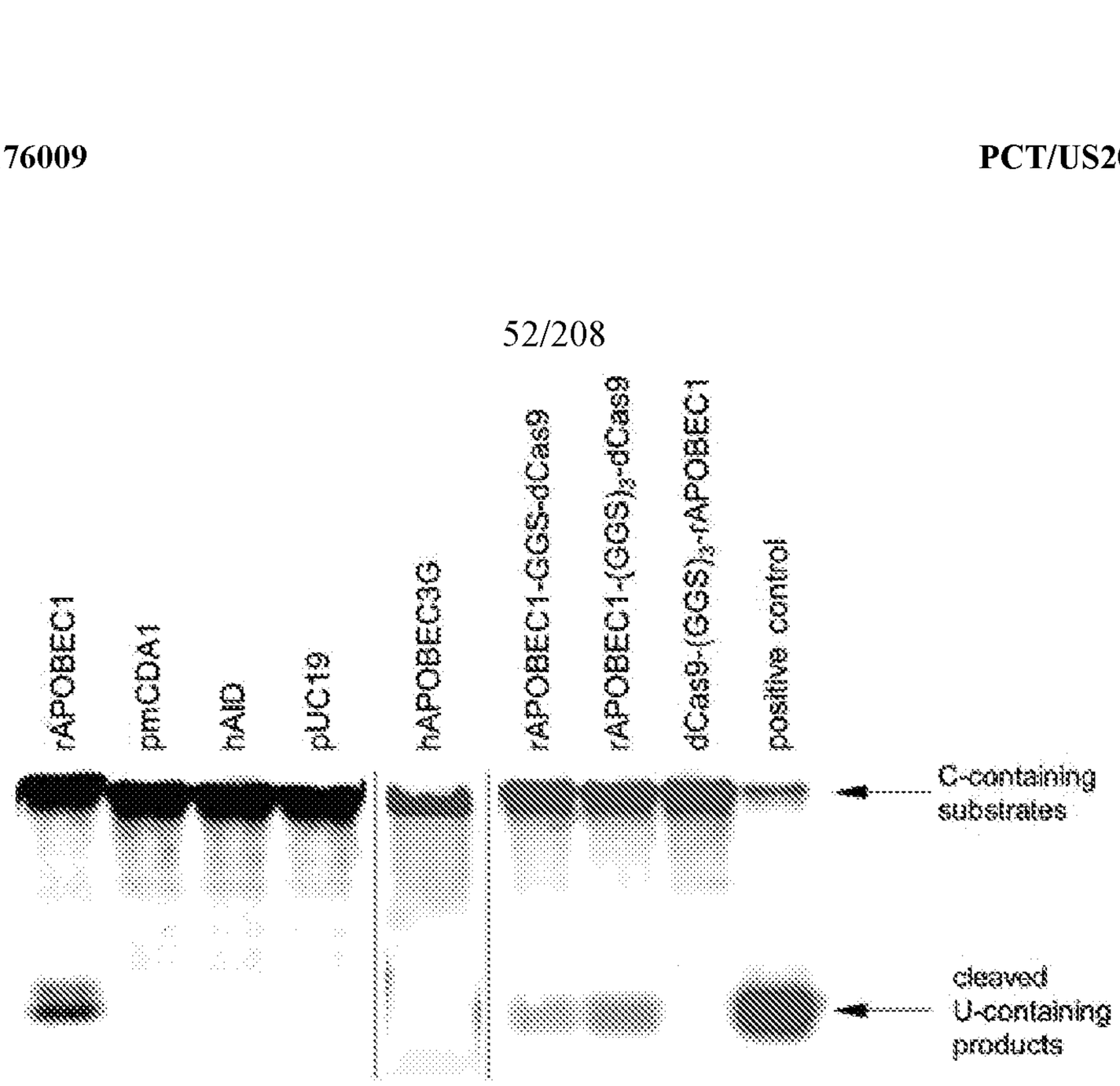


FIGURE 36A

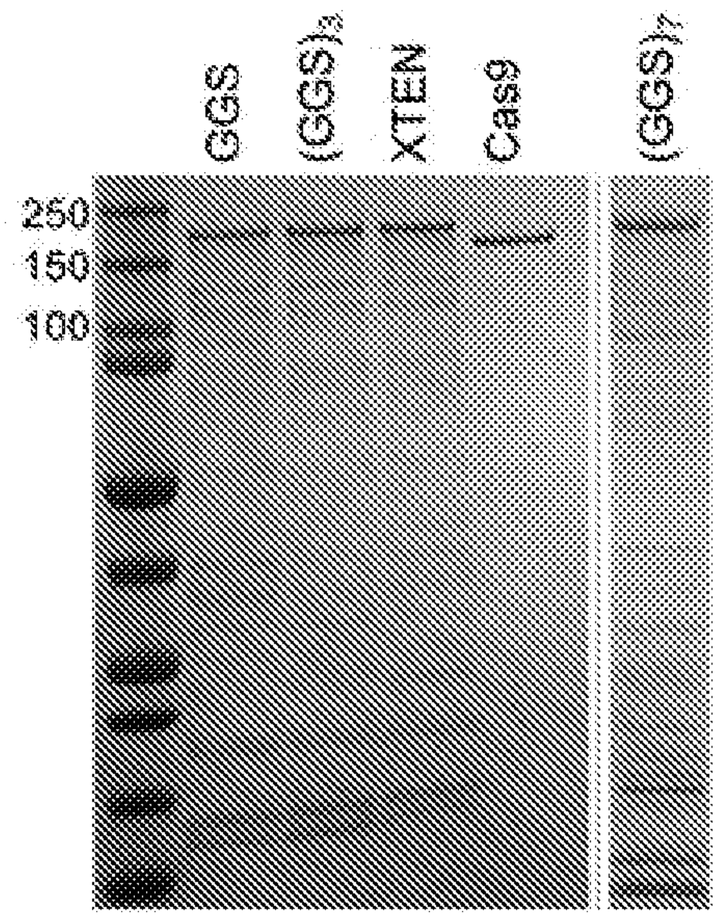


FIGURE 36B

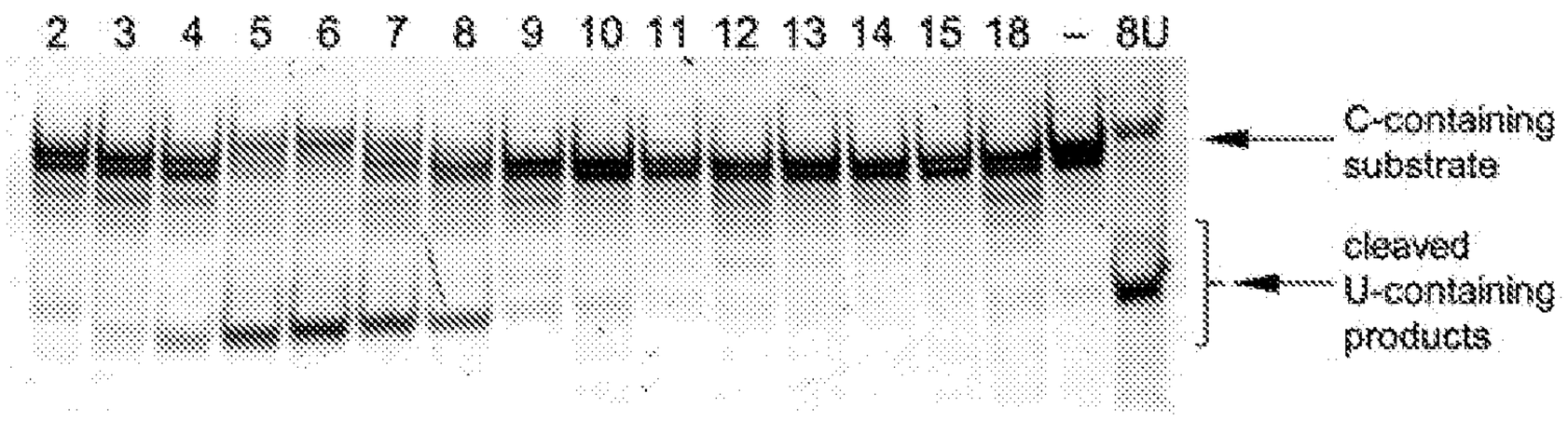


FIGURE 36C

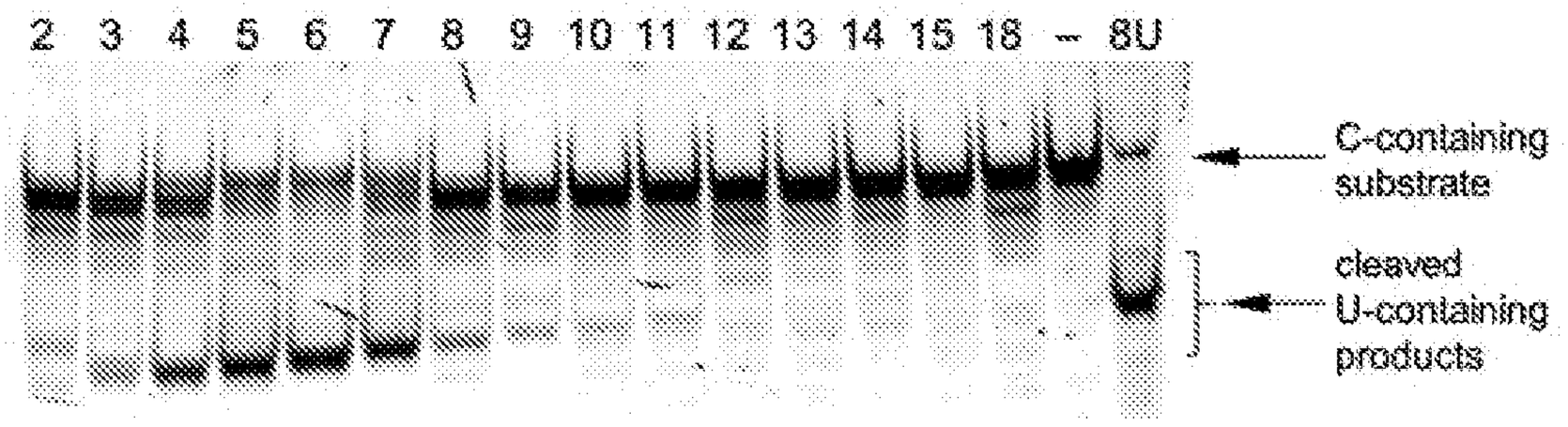


FIGURE 36D

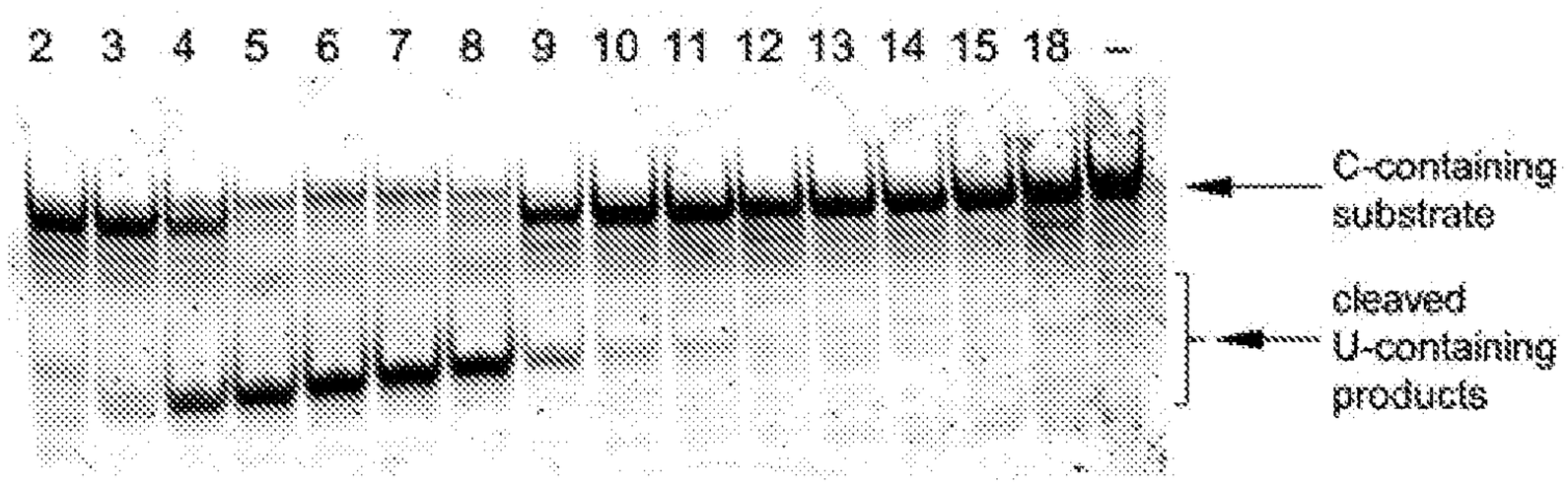


FIGURE 36E

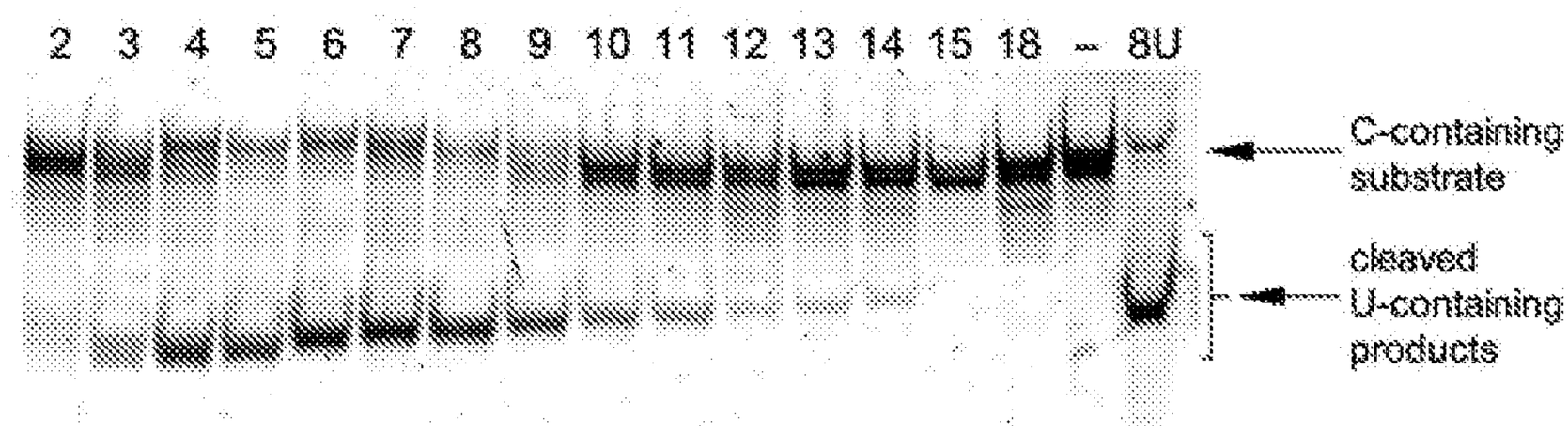


FIGURE 36F

EMX1: GAGTC_5C_6GAGCAGAAGAAGAAGGG

FANCF: GGAAT$C_6C_7C_8$TTC_{11}TGCAGCACCTGG

HEK293 site 2: GAAC_4AC_6AAAGCATAGACTGCGGG

HEK293 site 3: GGCC_4C_5AGACTGAGCACGTGATGG

HEK293 site 4: GGCAC_5TGCGGCTGGAGGTCCGGG

RNF2: GTC_3ATC_6TTAGTC_{12}ATTACCTGAGG

FIGURE 37A

EMX1		G	A	G	T	C_5	C_6	G	A	G	C	A	G	A	A	G	A	A	G	A	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	0.2	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	0.0	0.2	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	39.5	39.0	0.0	0.0	0.0	0.7	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

FANCF		G	G	A	A	T	C_6	C_7	C_8	T	T	C_{11}	T	G	C	A	G	C	A	C	C	T	G	G
1.85 uM BE1	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	0.2	95.0	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	0.0	99.8	0.2	0.0	99.7	0.2	0.0	0.1	0.0	0.0	99.8	99.5
	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	0.0	0.0	0.0	0.0	99.9	0.1	0.1

HEK293 site 2		G	A	A	C_4	A	C_6	A	A	A	G	C	A	T	A	G	A	C	T	G	C	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	0.0	99.9	0.0	0.0	99.9	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	99.6	0.0	0.0	0.1	0.0	99.8	0.0	0.0	0.0	99.8	0.0	99.5	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_4	C_5	A	G	A	C	T	G	A	G	C	A	C	G	T	G	A	T	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	86.6	0.0	0.0	0.0	0.0	99.8	0.0	99.7	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	0.0	99.8	0.0	99.8	0.0	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_5	T	G	C	G	G	C	T	G	G	A	G	G	T	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	0.2	0.1	0.0	0.3	0.5	100.0	0.1	0.1	0.0	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_2	A	T	C_6	T	T	A	G	T	C_{12}	A	T	T	A	C	C	T	G	A	G	G
1.85 uM BE1	A	0.1	0.0	0.1	99.9	0.0	0.0	0.0	0.0	99.9	0.1	0.0	0.1	99.9	0.0	0.0	99.8	0.1	0.0	0.0	0.1	98.6	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	0.0	0.1	99.9	99.9	0.0	0.0	1.4	0.0	0.0
	G	99.9	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.8	0.0	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

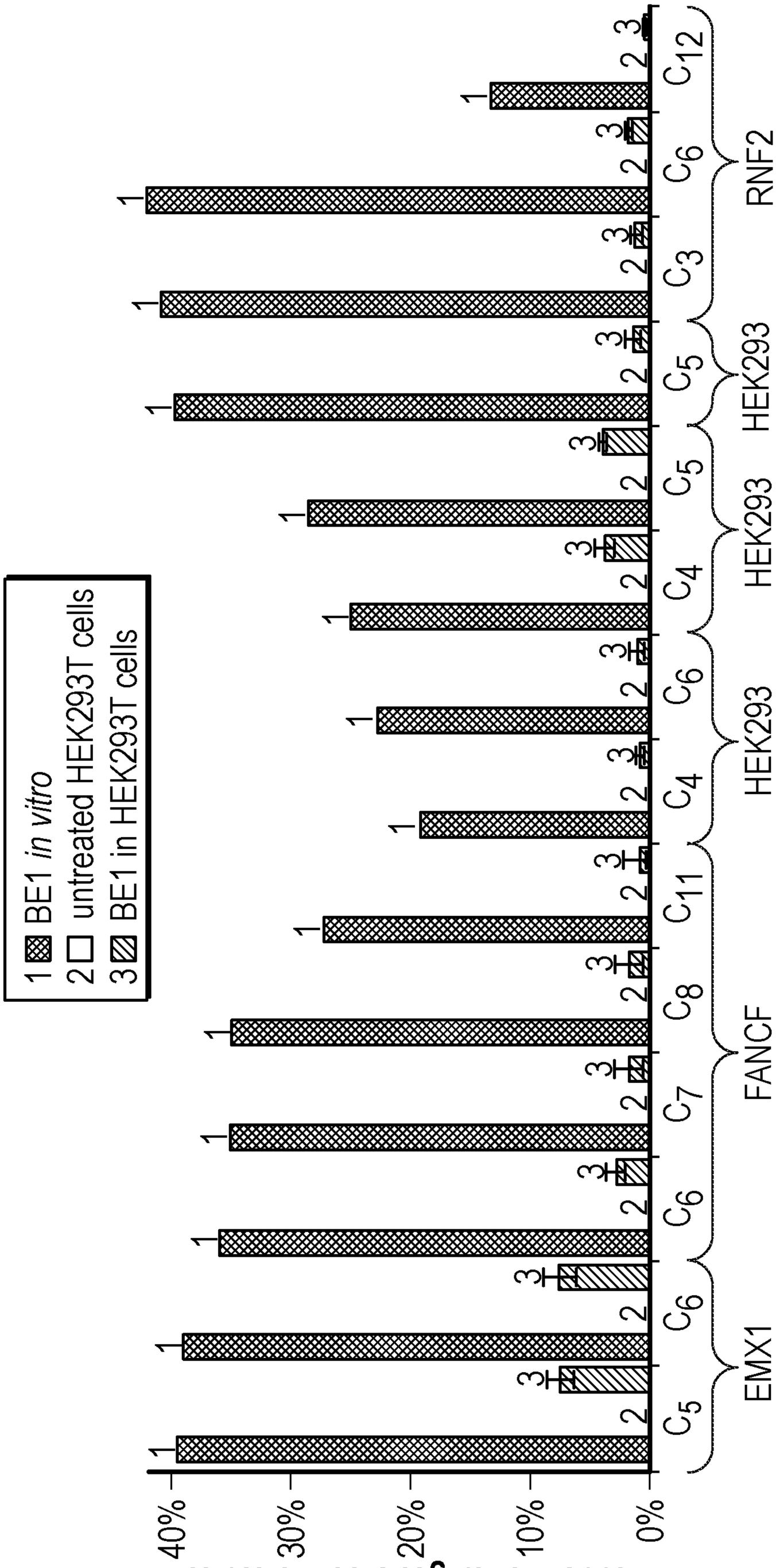

1 BE1 in vitro
2 untreated HEK293T cells
3 BE1 in HEK293T cells
percent of total sequencing reads with target C converted to T
40%
30%
20%
10%
0%
EMX1
FANCF
HEK293 site 2
HEK293 site 3
HEK293 site 4
RNF2
C5
C6
C4
C7
C8
C11
C3
C12

FIGURE 37C

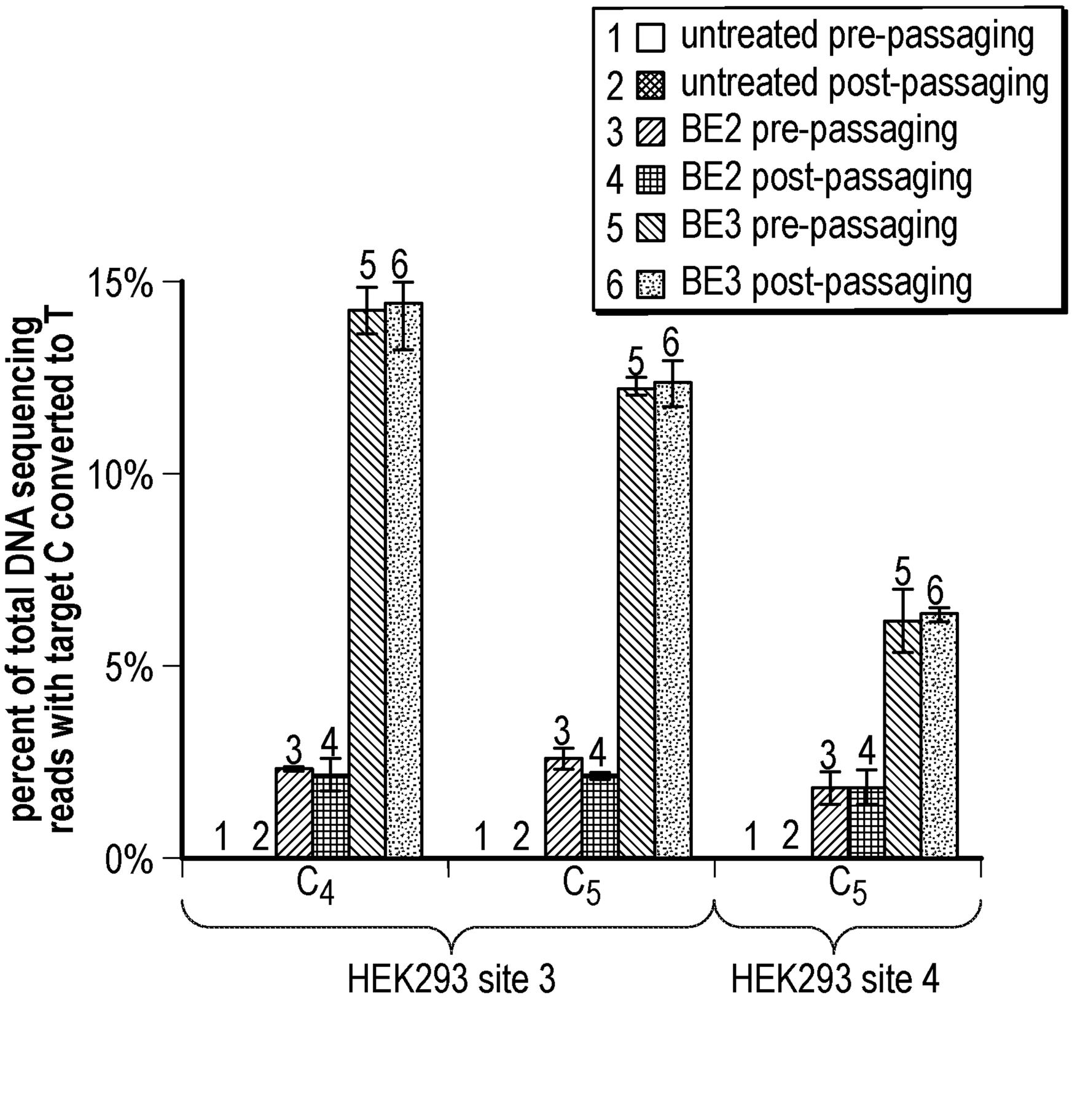

1 untreated pre-passaging
2 untreated post-passaging
3 BE2 pre-passaging
4 BE2 post-passaging
5 BE3 pre-passaging
6 BE3 post-passaging
percent of total DNA sequencing reads with target C converted to T
15%
10%
5%
0%
C4
C5
C5
HEK293 site 3
HEK293 site 4

FIGURE 38

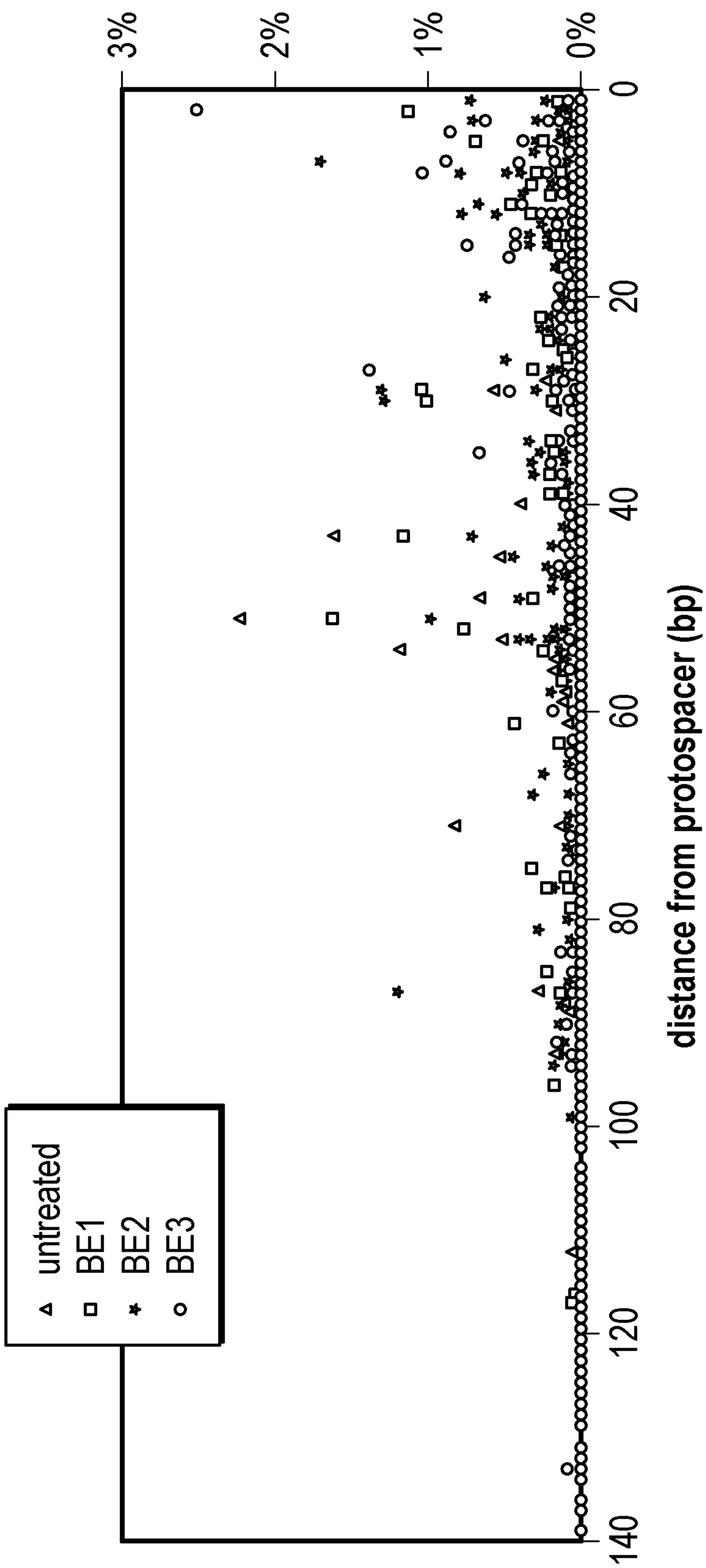

percent of total sequencing reads with non-protospacer C/G converted to T/A
3%
2%
1%
0%
0
20
40
60
80
100
120
140
distance from protospacer (bp)
untreated
BE1
BE2
BE3

FIGURE 39A

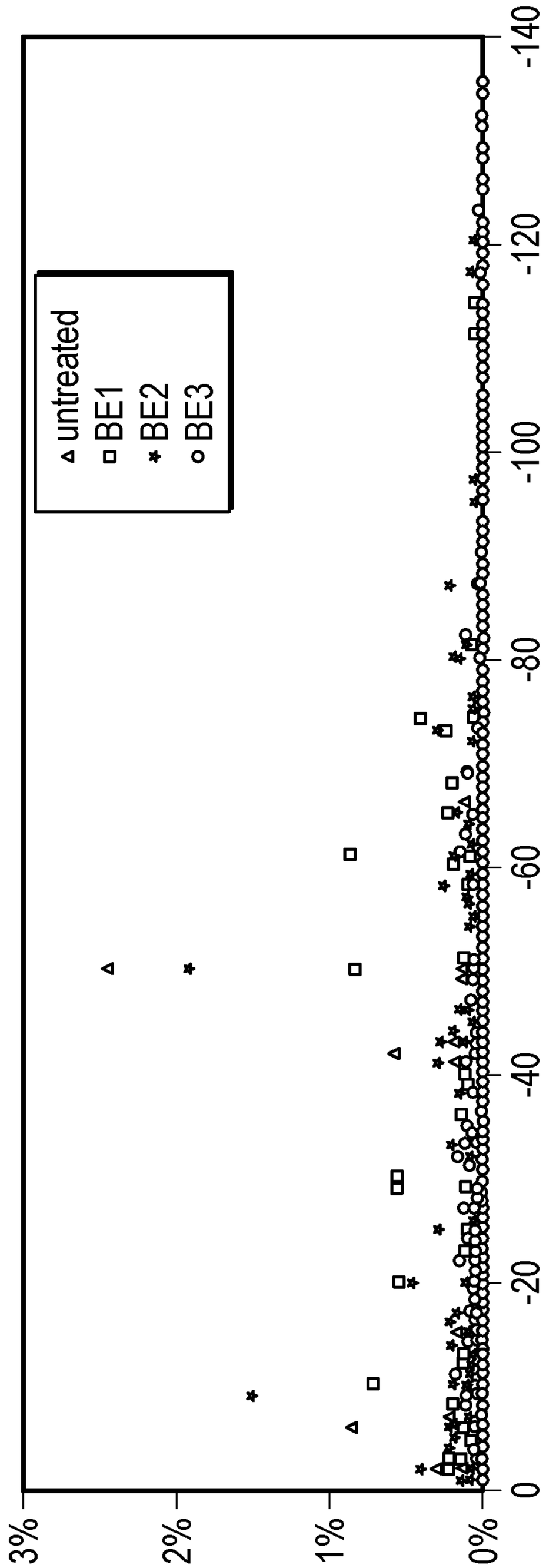

untreated
BE1
BE2
BE3
-140
-120
-100
-80
-60
-40
-20
0
distance from protospacer (bp)
3%
2%
1%
0%
percent of total sequencing reads with non-protospacer C/G converted to T/A

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	1.84
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		Lys			Arg			Leu			Ala			Val			Tyr			Gln			indel %
APOE4 C158R	G	A	A	G	C_5	G	C	C	T	G	G	C	A	G	T	G	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	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	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	100.0	100.0	0.0	0.0	0.0	
G	100.0	0.0	0.0	99.9	0.0	100.0	0.0	0.0	0.0	100.0	99.9	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	99.9	100.0	
T	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	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.1	0.0	

BE3 + on-target sgRNA		Lys			Arg → Cys			Leu → Leu			Ala			Val			Tyr			Gln			indel %
APOE4 C158R	G	A	A	G	C_5	G	C	C	T	G	G	C	A	G	T	G	T	A	C	C	A	G	G	6.1
A	0.1	100.0	100.0	0.0	1.0	0.0	1.6	0.8	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	0.1	
C	0.0	0.0	0.0	0.0	39.1	0.0	62.0	61.3	0.0	0.0	0.0	59.9	0.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0	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	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	58.2	0.1	35.7	37.5	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	0.0	

BE3 + off-target sgRNA		Lys			Arg			Leu			Ala			Val			Tyr			Gln			indel %
APOE4 C158R	G	A	A	G	C_5	G	C	C	T	G	G	C	A	G	T	G	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	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	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	100.0	0.0	0.0	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	0.0	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	100.0	100.0	
T	0.0	0.0	0.0	0.0	0.1	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	

Cas9 + HDR		Lys			Arg → Cys			Leu			Ala			Val			Tyr			Gln			indel %
APOE4 C158R	G	A	A	G	C_5	G	C	C	T	G	G	C	A	G	T	G	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	99.8	0.0	0.0	0.0	0.0	99.1	0.1	0.5	98.8	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	0.5	99.7	99.6	0.7	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	0.0	0.0	99.4	100.0	
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	

FIGURE 40A

untreated		Arg			Ala			Met			Ala			Ile			Cys			Lys				indel %
TP53 Y163C	C	C	G	C	G	C	C	A	T	G	G	C	C	A	T	C	T	G_6	C	A	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	0.1	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	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	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	100.0	99.9	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	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	

BE3 + on-target sgRNA		Arg			Ala			Met			Ala			Ile			Cys → Tyr			Lys				indel %
TP53 Y163C	C	C	G	C	G	C	C	A	T	G	G	C	C	A	T	C	T	G_6	C	A	A	G	C	0.0
A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.1	0.0	0.0	100.0	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	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	99.9	0.0	0.0	0.0	0.0	100.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	96.2	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	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	100.0	0.5	0.0	0.0	0.0	0.0	0.0	

BE3 + off-target sgRNA		Arg			Ala			Met			Ala			Ile			Cys			Lys				indel %
TP53 Y163C	C	C	G	C	G	C	C	A	T	G	G	C	C	A	T	C	T	G_6	C	A	A	G	C	0.0
A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.1	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	99.9	99.9	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	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	99.9	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	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	0.0	0.0	0.0	0.1	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	

Cas9 + HDR		Arg			Ala			Met			Ala			Ile			Cys → Tyr			Lys				indel %
TP53 Y163C	C	C	G	C	G	C	C	A	T	G	G	C	C	A	T	C	T	G_6	C	A	A	G	C	8.0
A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.1	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	99.9	100.0	0.0	0.4	
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	100.0	0.0	0.0	0.0	99.6	
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	0.0	100.0	0.0	0.0	0.0	100.0	0.0	
T	0.0	0.0	0.0	0.0	0.1	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	

FIGURE 40B

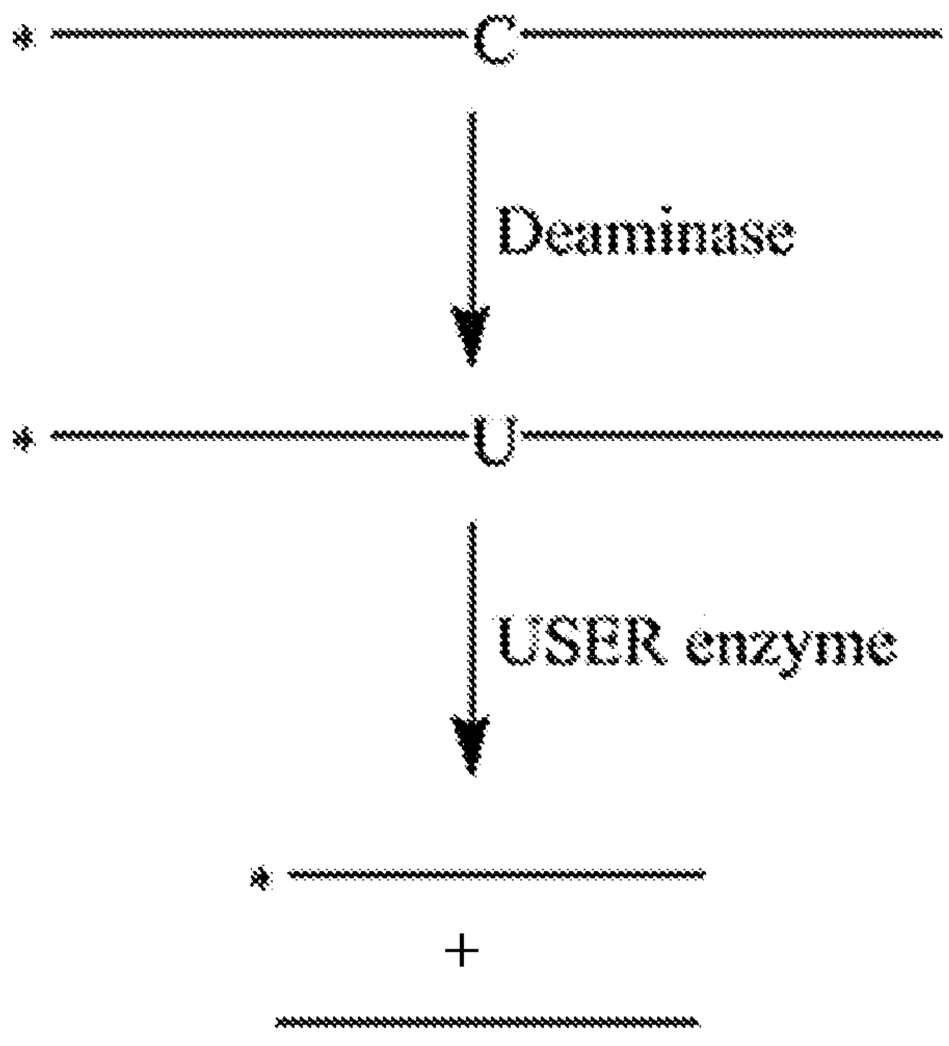
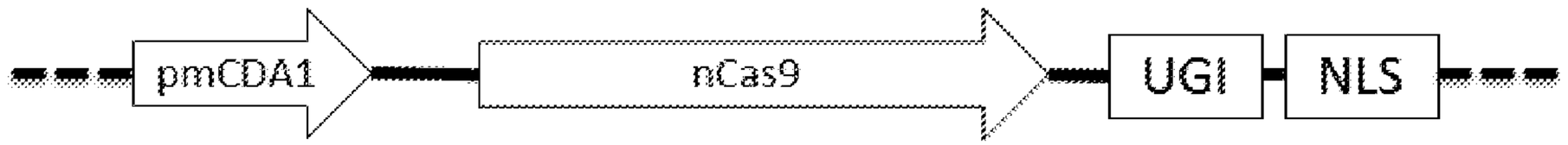
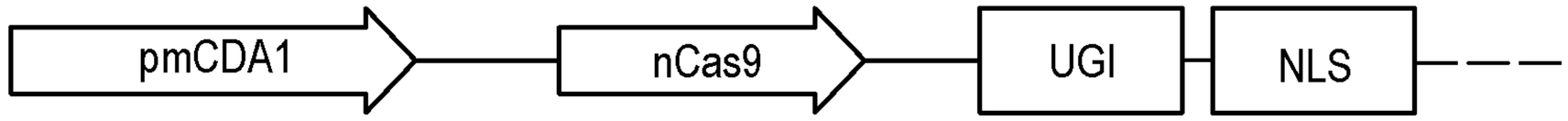


FIGURE 41



			P	A	M	20	19	18	17	16	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1	-1	-2	-3
	T	G	C	C	A	T	C	A	C	G	T	G	C	T	C	A	A	T	C	G	G	G	G	C	C	C	C	A
CDA																												
A	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	99.9%	0.0%	0.0%	0.0%	0.5%	0.0%	0.0%	0.1%	100.0%	5.8%	0.0%	0.0%	0.0%	33.9%	33.9%	33.1%	0.0%	0.0%	0.0%	0.0%	100.0%
C	0.0%	0.0%	99.9%	99.9%	0.0%	0.0%	99.9%	0.0%	100.0%	0.0%	0.0%	0.0%	100.0%	0.0%	99.9%	0.0%	1.0%	0.0%	99.9%	0.0%	0.0%	0.0%	0.0%	100.0%	100.0%	99.9%	99.9%	0.0%
G	0.0%	99.9%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%	99.5%	0.0%	0.0%	0.0%	0.0%	91.8%	0.0%	0.0%	0.0%	65.7%	65.0%	65.2%	0.0%	0.0%	0.0%	0.0%	0.0%
T	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%	100.0%	0.0%	0.0%	1.5%	100.0%	0.0%	100.0%	0.3%	1.1%	1.7%	0.0%	0.0%	0.0%	0.0%	0.0%
rAPOBEC1																												
A	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	99.9%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	100.0%	0.8%	0.0%	0.0%	0.0%	38.5%	41.9%	1.4%	0.0%	0.0%	0.1%	0.0%	100.0%
C	0.0%	0.0%	99.9%	99.9%	0.0%	0.0%	99.9%	0.0%	100.0%	0.0%	0.0%	0.0%	100.0%	0.0%	99.9%	0.0%	0.1%	0.0%	99.9%	0.0%	8.1%	0.7%	0.0%	100.0%	99.9%	99.9%	100.0%	0.0%
G	0.0%	99.9%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	99.9%	0.0%	99.9%	0.0%	0.0%	0.0%	0.0%	99.0%	0.0%	0.0%	0.0%	51.3%	56.7%	98.6%	0.0%	0.0%	0.0%	0.0%	0.0%
T	100.0%	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%	0.1%	100.0%	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%	100.0%	0.0%	100.0%	2.2%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
untreated																												
A	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%	0.1%	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	100.0%	0.0%	0.0%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%
C	0.0%	0.0%	99.9%	99.9%	0.0%	0.0%	99.9%	0.0%	100.0%	0.0%	0.0%	0.0%	100.0%	0.0%	99.9%	0.0%	0.0%	0.0%	99.9%	0.0%	0.0%	0.0%	0.0%	100.0%	100.0%	99.9%	100.0%	0.0%
G	0.0%	99.9%	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%	100.0%	0.0%	0.0%	0.0%	99.9%	99.9%	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%
T	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%	100.0%	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%

FIGURE 42



Hek-2 site, shown: coding strand (G→A), target: template stand (C→T)

	P	A	M	20	19	18	17	16	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1	-1	-2	-3
	C	G	C	C	C	C	G	C	A	G	T	C	T	A	T	G	C	T	T	T	G	T	G	T	T	C	C	A	G
CDA																													
A	0.0%	0.0%	0.0%	0.2%	0.0%	0.5%	0.2%	0.0%	99.9%	0.0%	0.0%	0.0%	0.0%	99.9%	0.0%	19.2%	0.0%	0.0%	0.0%	0.0%	32.6%	0.0%	33.6%	0.0%	0.0%	0.0%	0.0%	99.9%	0.8%
C	99.9%	0.0%	100.0%	99.7%	99.9%	99.5%	0.0%	99.9%	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%	0.1%	0.0%	0.0%	99.8%	99.6%	0.0%	0.3%
G	0.0%	99.9%	0.0%	0.0%	0.0%	0.0%	99.7%	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%	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%	0.0%	100.0%	0.0%	100.0%	0.0%	100.0%	0.3%	0.0%	100.0%	100.0%	100.0%	2.4%	100.0%	8.0%	100.0%	100.0%	0.2%	0.4%	0.0%	0.1%

rAPOBEC1

A	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.0%	99.9%	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%	20.9%	0.0%	0.0%	0.0%	0.0%	99.9%	0.0%
C	99.9%	0.0%	100.0%	100.0%	99.9%	99.9%	0.0%	100.0%	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%	38.6%	0.0%	0.4%	0.0%	0.0%	99.9%	99.9%	0.0%	0.0%
G	0.0%	99.9%	0.0%	0.0%	0.0%	0.0%	99.9%	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	99.3%	0.0%	0.0%	0.0%	0.0%	42.3%	0.0%	77.6%	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%	0.0%	100.0%	0.0%	100.0%	0.0%	100.0%	0.0%	0.0%	100.0%	100.0%	100.0%	0.7%	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%	0.0%	0.1%	0.0%	99.9%	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%	99.9%	0.0%
C	99.9%	0.0%	100.0%	100.0%	99.9%	99.9%	0.0%	100.0%	0.0%	0.0%	0.0%	99.9%	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%	99.9%	99.9%	0.0%	0.0%
G	0.0%	99.9%	0.0%	0.0%	0.0%	0.0%	99.9%	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%	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%	0.0%	100.0%	0.0%	100.0%	0.0%	100.0%	0.0%	0.0%	100.0%	100.0%	100.0%	0.0%	100.0%	0.1%	100.0%	100.0%	0.0%	0.0%	0.0%	0.0%

FIGURE 43

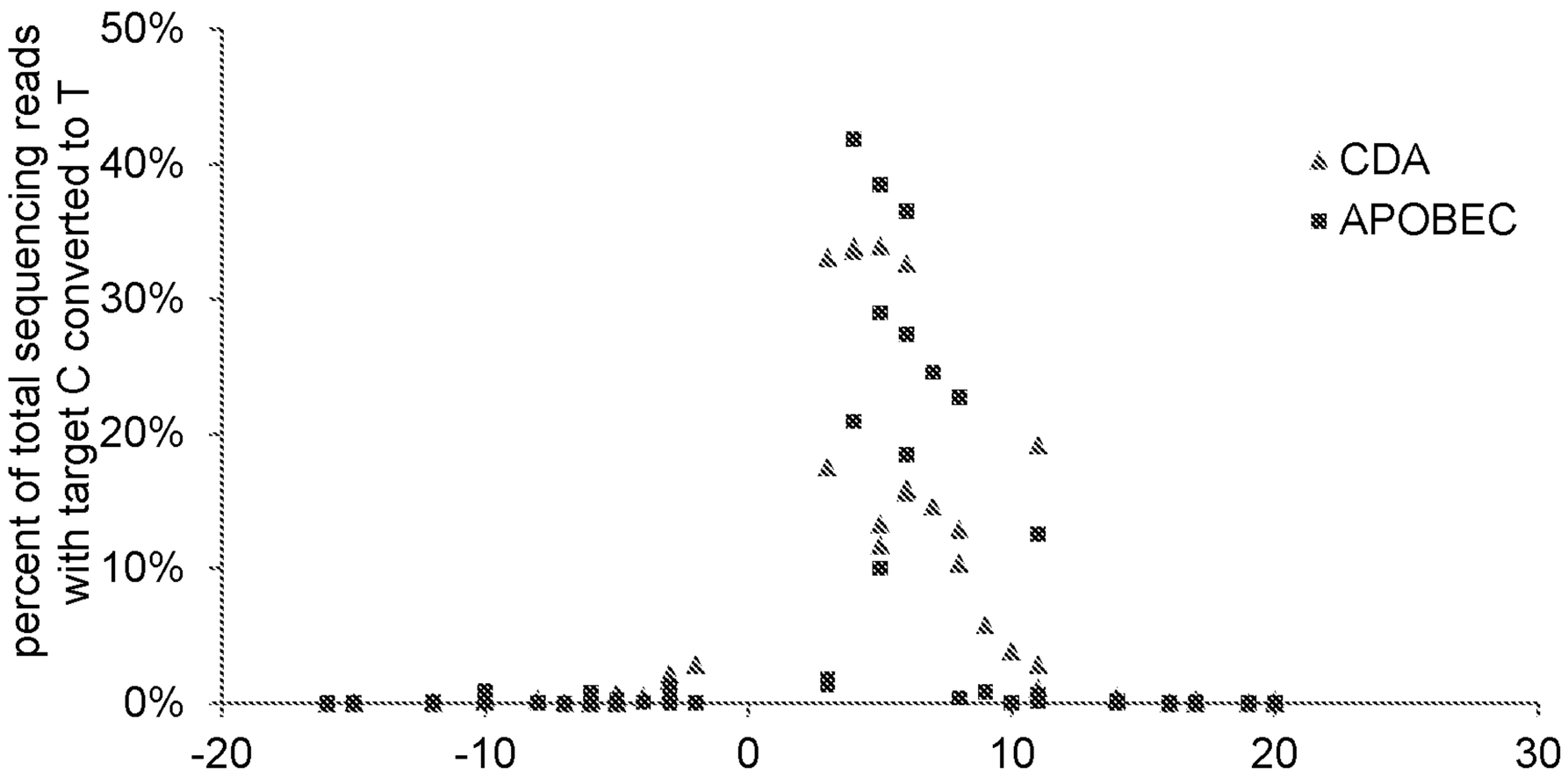


FIGURE 44

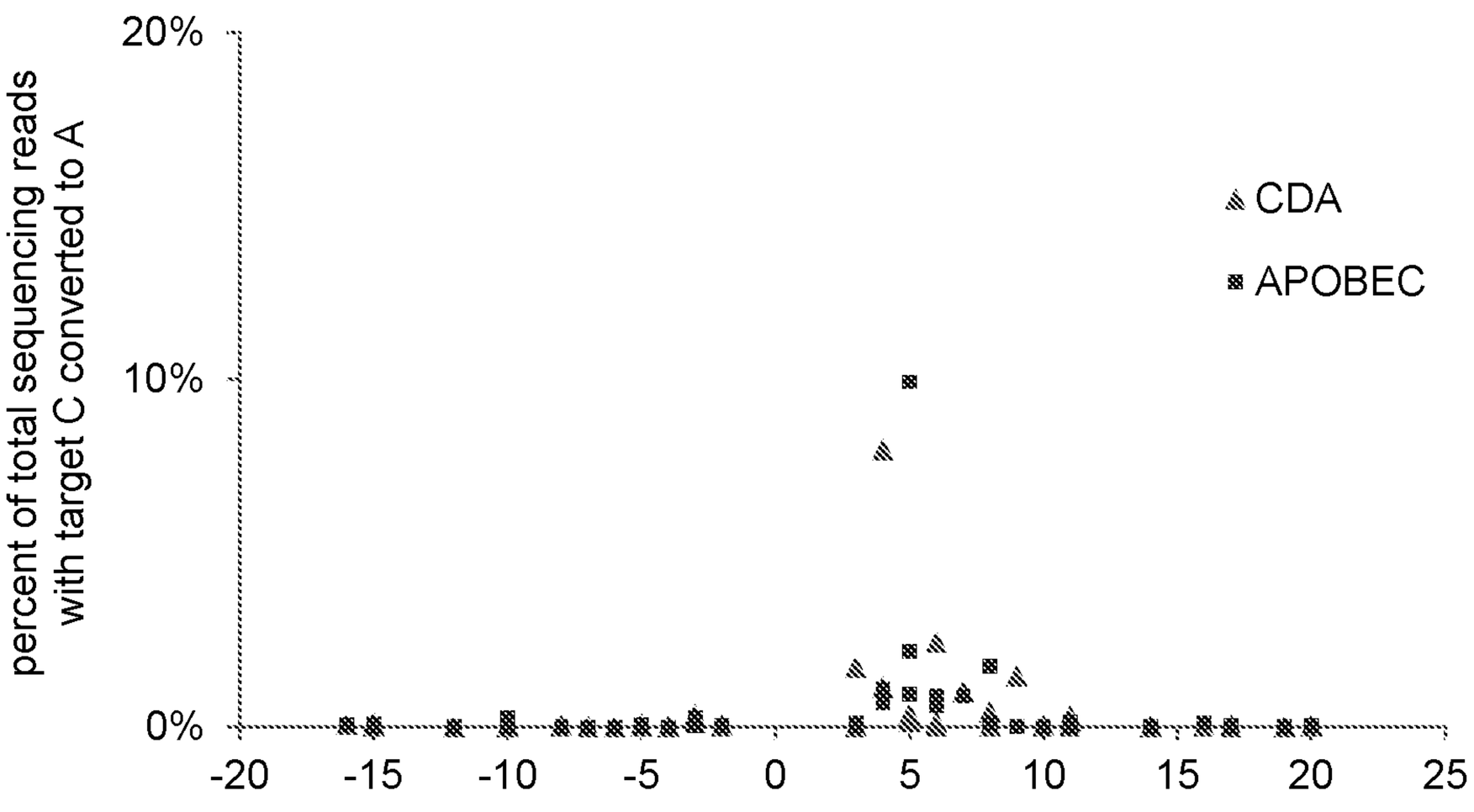


FIGURE 45

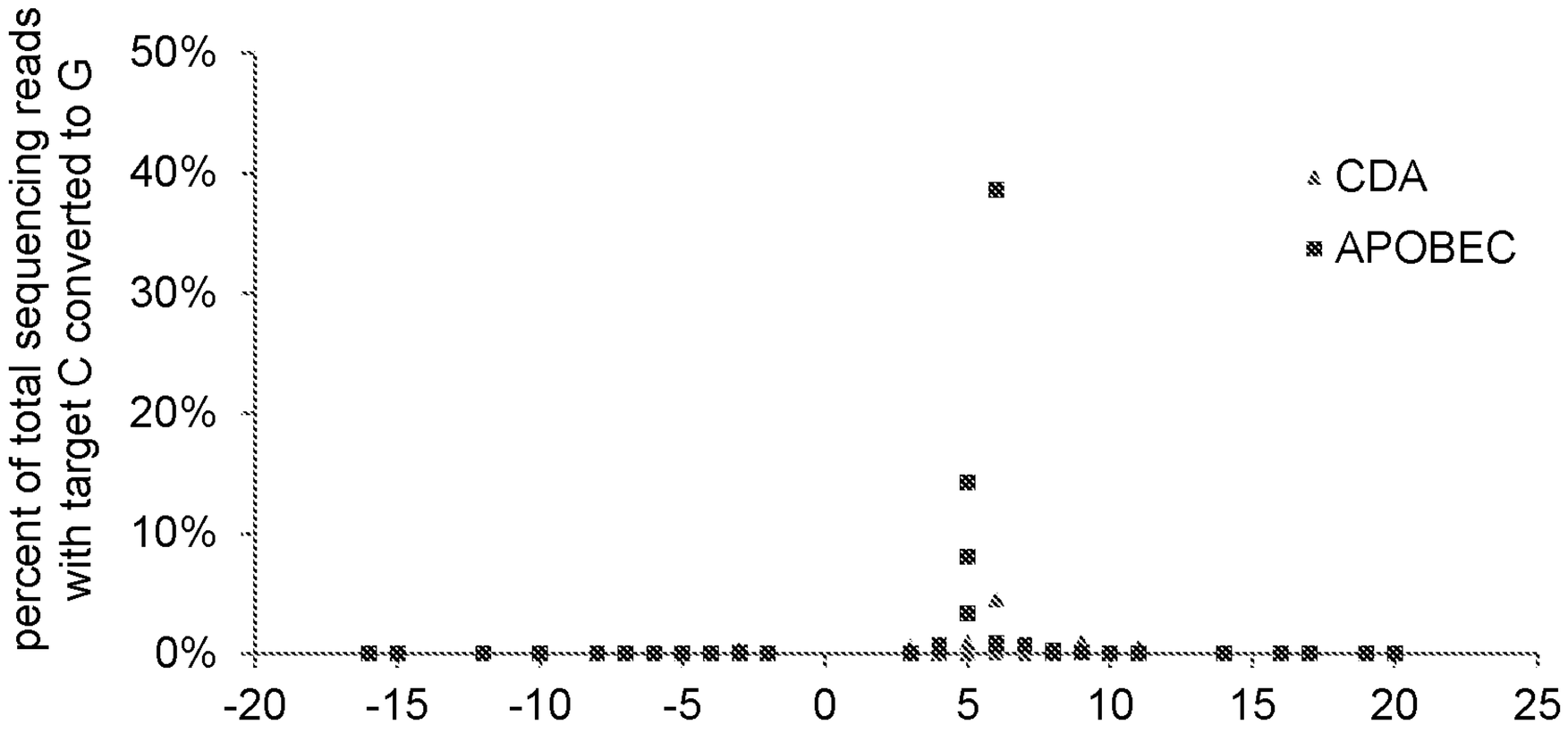
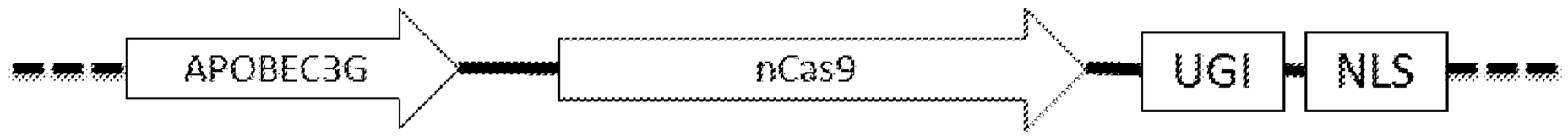
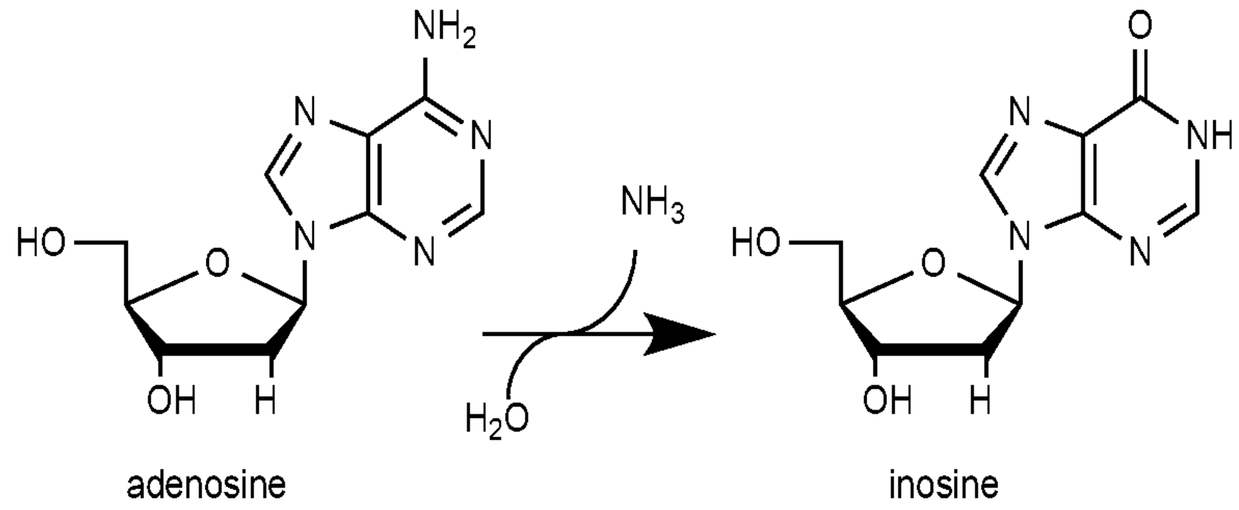

percent of total sequencing reads with target C converted to G
50%
40%
30%
20%
10%
0%
-20
-15
-10
-5
0
5
10
15
20
25
CDA
APOBEC

FIGURE 46

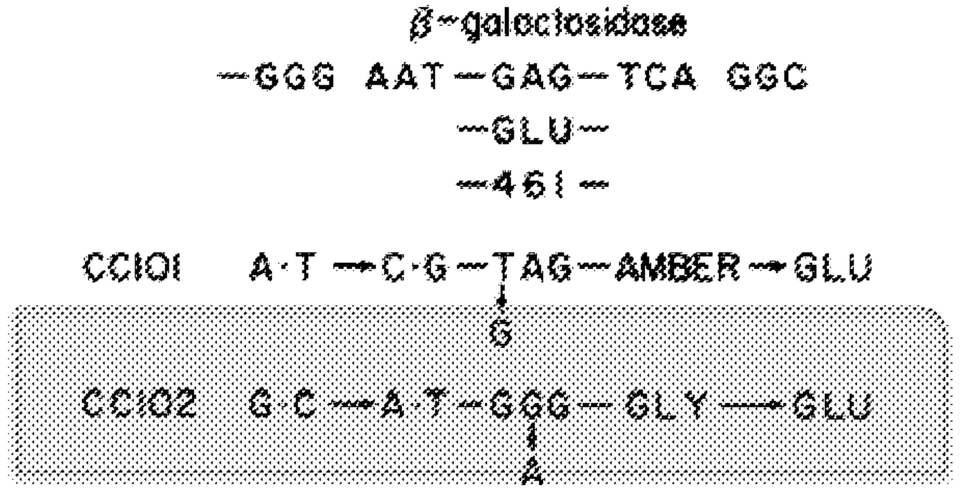


	P	A	M	20	19	18	17	16	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1
	C	C	C	G	C	A	G	T	C	T	A	T	G	C	T	T	T	G	T	G	T	T	C
rAPOBEC1																							
A	0.02%	0.02%	0.01%	0.02%	0.02%	0.02%	0.05%	0.01%	99.96%	0.09%	0.00%	0.01%	0.00%	99.96%	0.01%	0.02%	0.01%	0.00%	0.00%	0.00%	9.30%	0.01%	10.87%	0.00%	0.01%	0.01%
C	99.96%	0.00%	99.98%	99.97%	99.97%	99.97%	0.00%	99.98%	0.02%	0.01%	0.01%	99.98%	0.01%	0.01%	0.01%	0.01%	99.98%	0.01%	0.01%	0.01%	18.14%	0.01%	0.54%	0.01%	0.01%	99.95
G	0.00%	99.96%	0.00%	0.00%	0.00%	0.00%	99.93%	0.00%	0.01%	99.86%	0.00%	0.00%	0.00%	0.01%	0.00%	99.96%	0.00%	0.00%	0.00%	0.00%	72.40%	0.00%	88.10%	0.00%	0.00%	0.01%
T	0.02%	0.02%	0.01%	0.01%	0.01%	0.01%	0.02%	0.01%	0.01%	0.03%	99.99%	0.01%	99.99%	0.02%	99.98%	0.01%	0.01%	99.99%	99.98%	99.99%	0.17%	99.98%	0.49%	99.98%	99.98%	0.03%
APOBEC3G	0.01%	0.01%	0.01%	0.01%	0.02%	0.01%	0.05%	0.01%	99.97%	0.01%	0.00%	0.00%	0.00%	99.97%	0.01%	0.01%	0.00%	0.00%	0.01%	0.00%	2.18%	0.01%	0.34%	0.00%	0.00%	0.01%
A	99.97%	0.01%	99.98%	99.98%	99.96%	99.98%	0.00%	99.99%	0.02%	0.00%	0.01%	99.99%	0.01%	0.01%	0.01%	0.00%	99.98%	0.01%	0.01%	0.01%	5.34%	0.01%	0.15%	0.01%	0.02%	99.98
C	0.00%	99.97%	0.00%	0.00%	0.00%	0.00%	99.93%	0.00%	0.01%	99.98%	0.00%	0.00%	0.00%	0.00%	0.00%	99.98%	0.00%	0.00%	0.00%	0.00%	92.44%	0.00%	99.46%	0.00%	0.00%	0.00%
G	0.02%	0.01%	0.01%	0.01%	0.02%	0.01%	0.02%	0.00%	0.00%	0.01%	99.99%	0.01%	99.99%	0.02%	99.98%	0.01%	0.01%	99.99%	99.98%	99.99%	0.04%	99.98%	0.05%	99.98%	99.98%	0.01%
T																										
APOBEC3G_RR	0.01%	0.02%	0.01%	0.01%	0.02%	0.01%	0.05%	0.01%	99.97%	0.01%	0.00%	0.00%	0.00%	99.97%	0.01%	0.04%	0.01%	0.00%	0.01%	0.00%	2.18%	0.01%	6.12%	0.00%	0.00%	0.01%
A	99.97%	0.00%	99.98%	99.99%	99.97%	99.97%	0.00%	99.98%	0.02%	0.00%	0.01%	99.99%	0.01%	0.01%	0.01%	0.01%	99.98%	0.01%	0.01%	0.01%	4.98%	0.01%	2.49%	0.01%	0.02%	99.99
C	0.00%	99.96%	0.00%	0.00%	0.00%	0.00%	99.92%	0.00%	0.01%	99.98%	0.00%	0.00%	0.00%	0.01%	0.00%	99.94%	0.00%	0.00%	0.00%	0.00%	92.80%	0.00%	91.04%	0.00%	0.00%	0.00%
G	0.02%	0.02%	0.01%	0.01%	0.01%	0.02%	0.02%	0.01%	0.00%	0.01%	99.99%	0.01%	99.99%	0.01%	99.98%	0.01%	0.01%	99.99%	99.99%	99.98%	0.05%	99.98%	0.35%	99.98%	99.98%	0.01%
T																										
untreated																										
A	0.02%	0.02%	0.00%	0.01%	0.02%	0.01%	0.05%	0.01%	99.98%	0.00%	0.00%	0.01%	0.00%	99.97%	0.01%	0.00%	0.01%	0.00%	0.00%	0.00%	0.01%	0.01%	0.01%	0.00%	0.01%	0.01%
C	99.96%	0.00%	99.99%	99.98%	99.97%	99.97%	0.00%	99.98%	0.01%	0.00%	0.01%	99.99%	0.01%	0.01%	0.01%	0.00%	99.98%	0.01%	0.01%	0.01%	0.01%	0.01%	0.00%	0.01%	0.01%	99.98
G	0.00%	99.96%	0.00%	0.00%	0.00%	0.00%	99.91%	0.00%	0.01%	99.98%	0.00%	0.00%	0.00%	0.00%	0.00%	99.98%	0.00%	0.00%	0.00%	0.00%	99.96%	0.00%	99.96%	0.00%	0.00%	0.00%
T	0.02%	0.02%	0.01%	0.01%	0.01%	0.02%	0.03%	0.01%	0.00%	0.01%	99.99%	0.01%	99.99%	0.02%	99.98%	0.01%	0.01%	99.99%	99.99%	99.99%	0.02%	99.98%	0.02%	99.98%	99.98%	0.01%

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

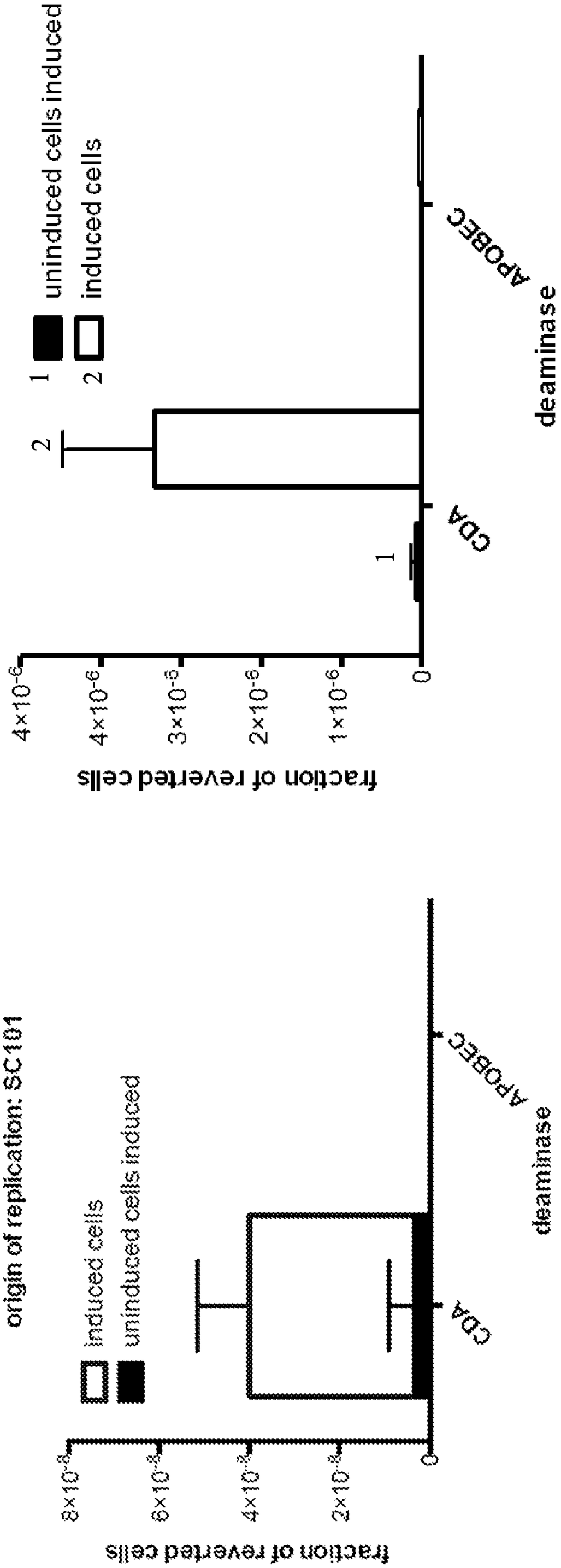

origin of replication: SC101
induced cells
uninduced cells
fraction of reverted cells
0
2×10-8
4×10-8
6×10-8
8×10-8
CDA
APOBEC
deaminase
1
2
origin of replication: SC101
uninduced cells induced
induced cells
fraction of reverted cells
0
1×10-6
2×10-6
3×10-6
4×10-6
4×10-6
CDA
APOBEC
deaminase
1
2

FIGURE 49

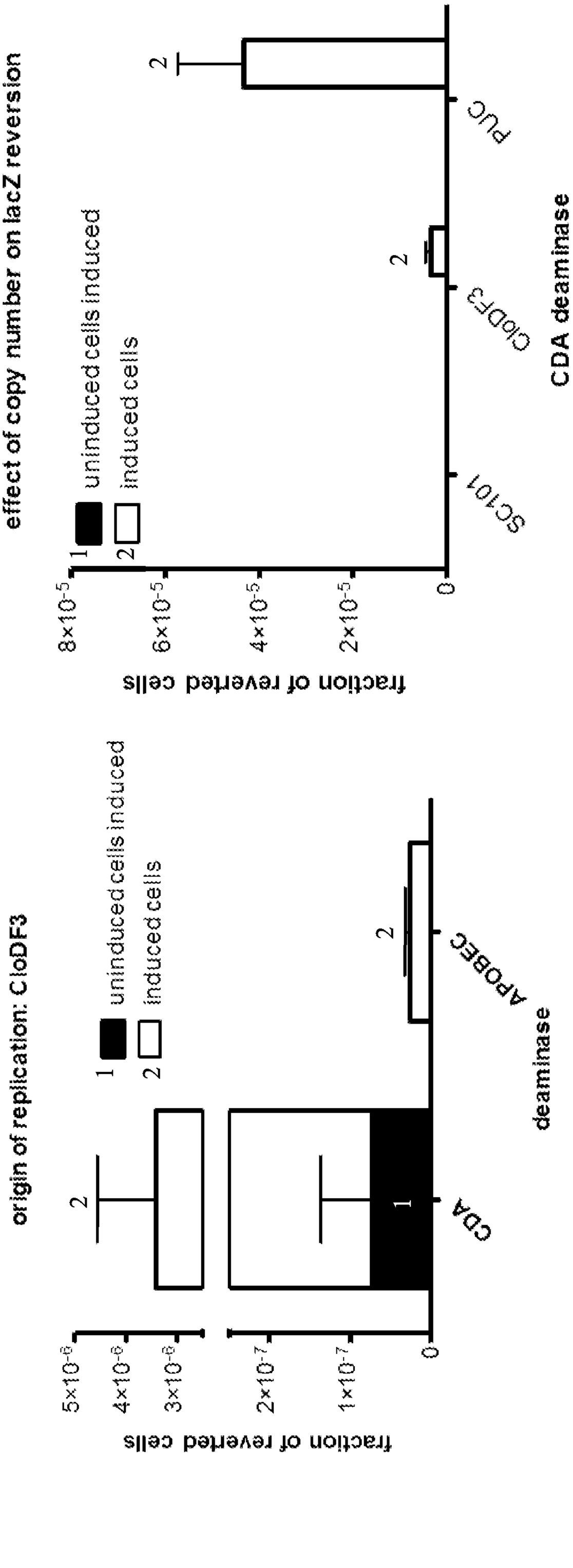


FIGURE 49 (CONTINUED)

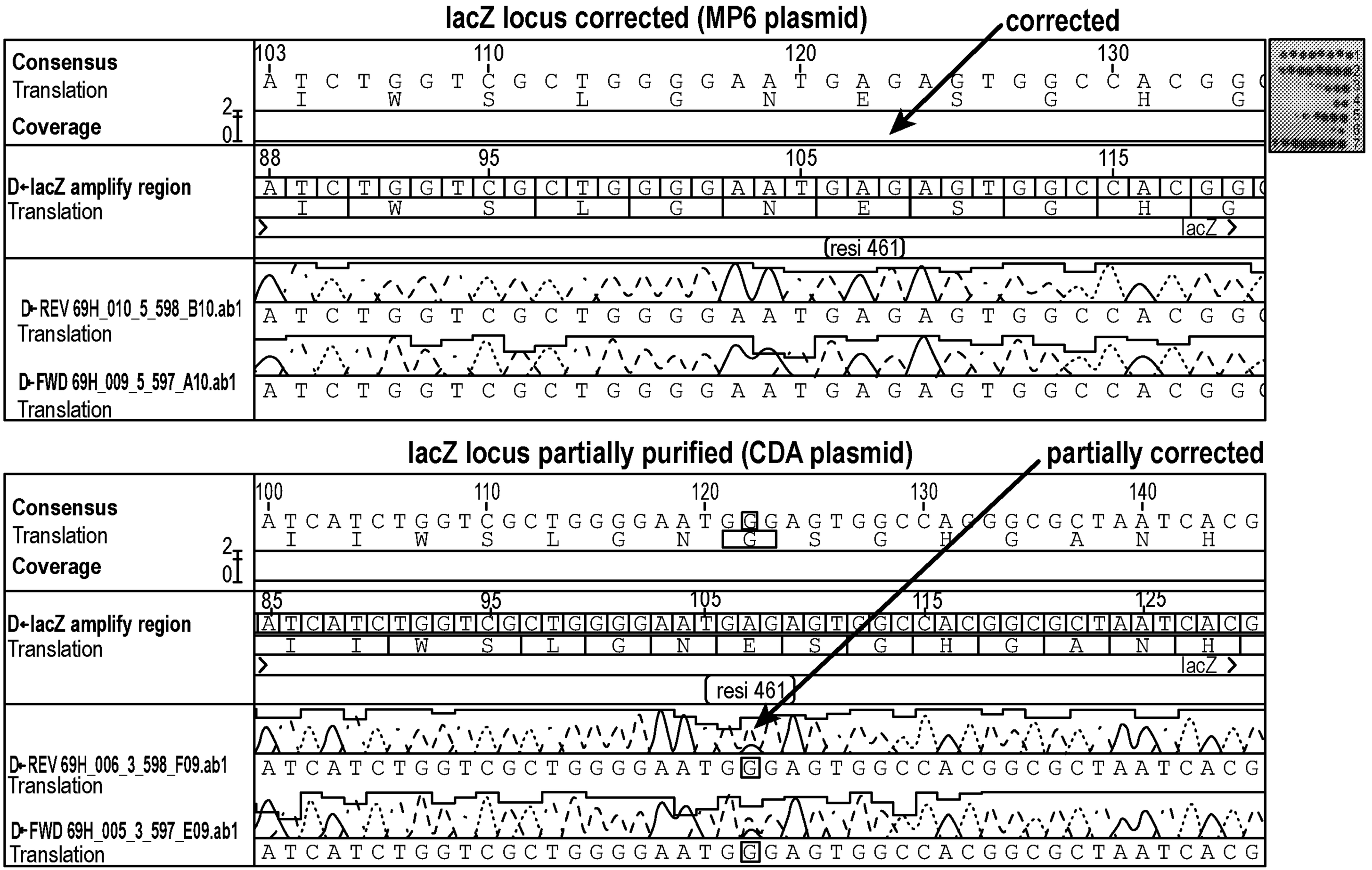

lacZ locus corrected (MP6 plasmid)
corrected
Consensus
Translation
Coverage
D←lacZ amplify region
Translation
lacZ
(resi 461)
D←REV 69H_010_5_598_B10.ab1
Translation
D←FWD 69H_009_5_597_A10.ab1
Translation
lacZ locus partially purified (CDA plasmid)
partially corrected
Consensus
Translation
Coverage
D←lacZ amplify region
Translation
lacZ
resi 461
D←REV 69H_006_3_598_F09.ab1
Translation
D←FWD 69H_005_3_597_E09.ab1
Translation

FIGURE 50

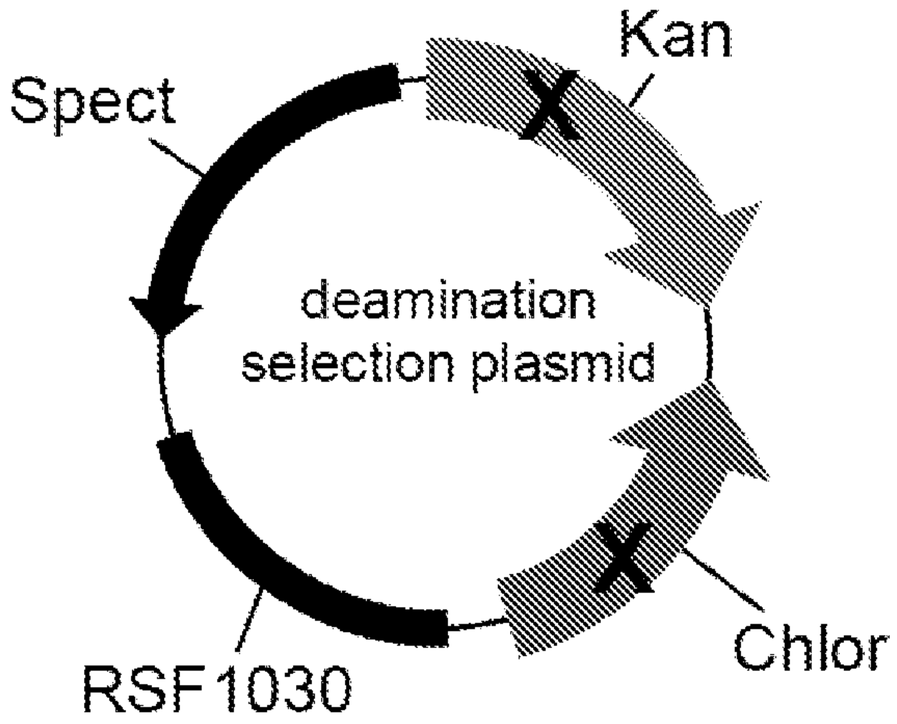
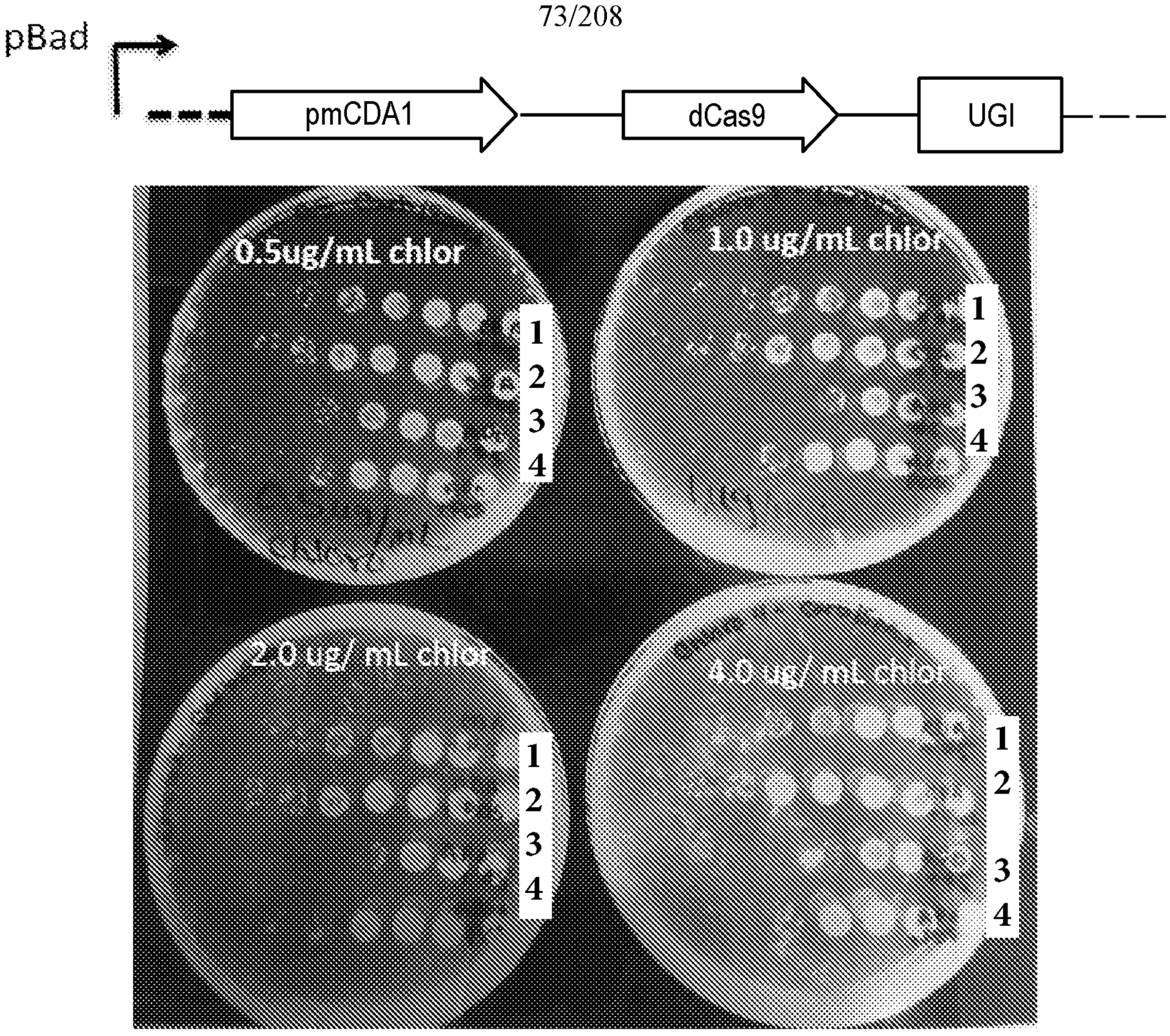


FIGURE 51



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

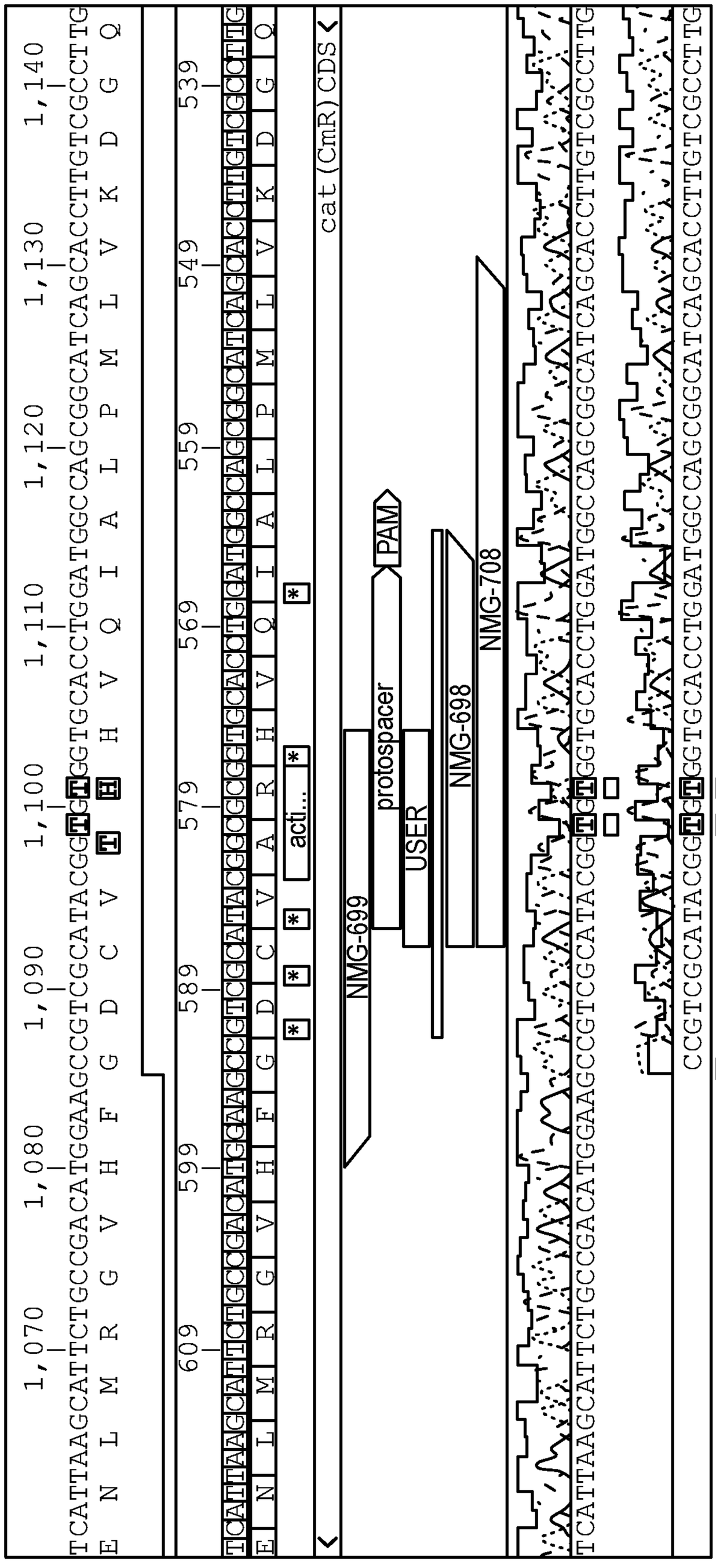

rAPOBEC-XTEN-dCas9-UGI on 8 ug/mL chlor
1,080
1,090
1,100
1,110
1,120
1,130
1,140
1,070
599
589
579
569
559
549
539
609
protospacer
PAM
NMG-699
USER
NMG-698
NMG-708
acti...
cat(CmR)CDS

FIGURE 53A

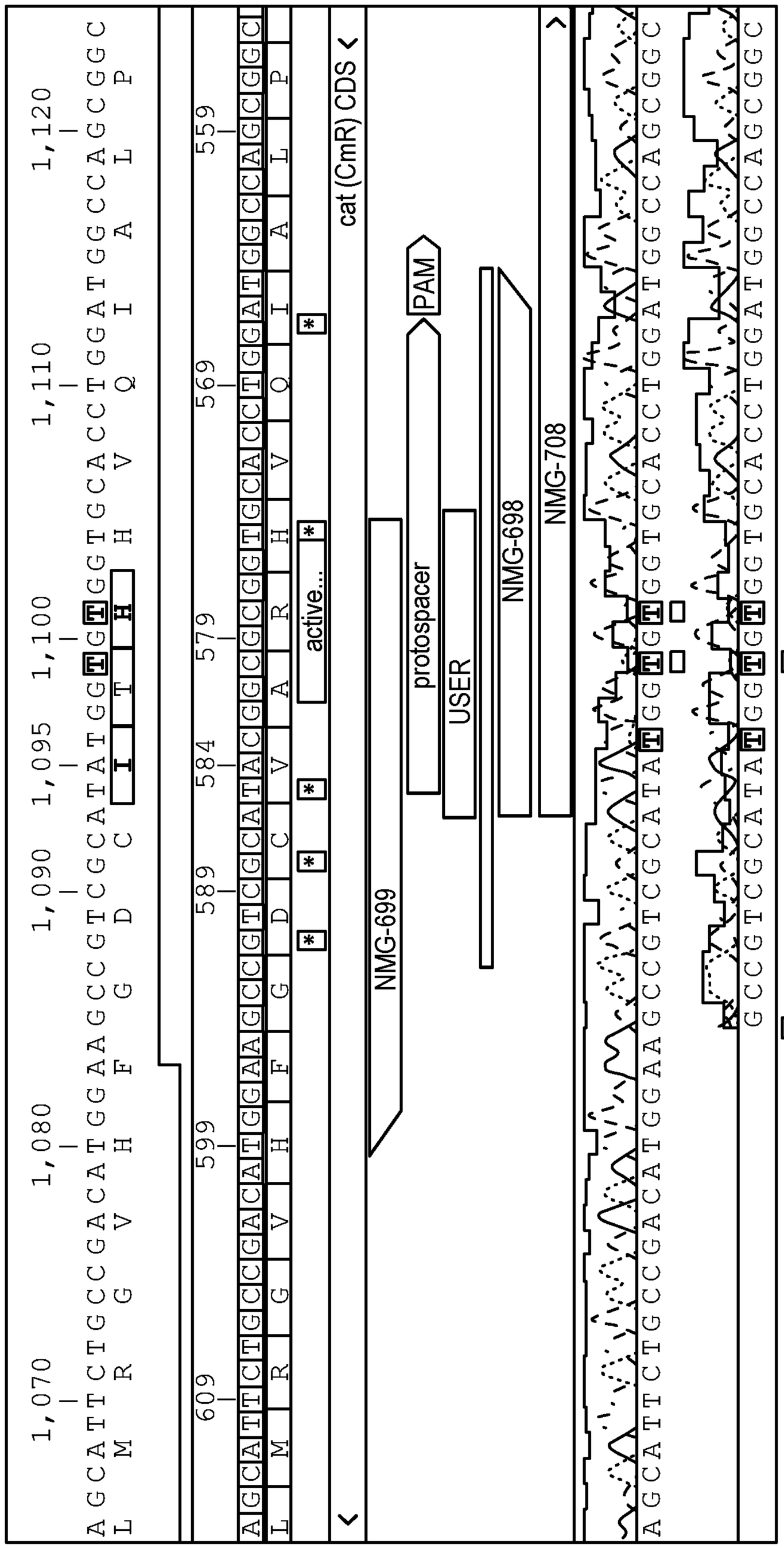

CDA-XTEN-dCas9-UGI: survival on 8 ug/mL chloramphenicol
cat (CmR) CDS
protospacer
PAM
NMG-708
NMG-699
NMG-698

FIGURE 53B

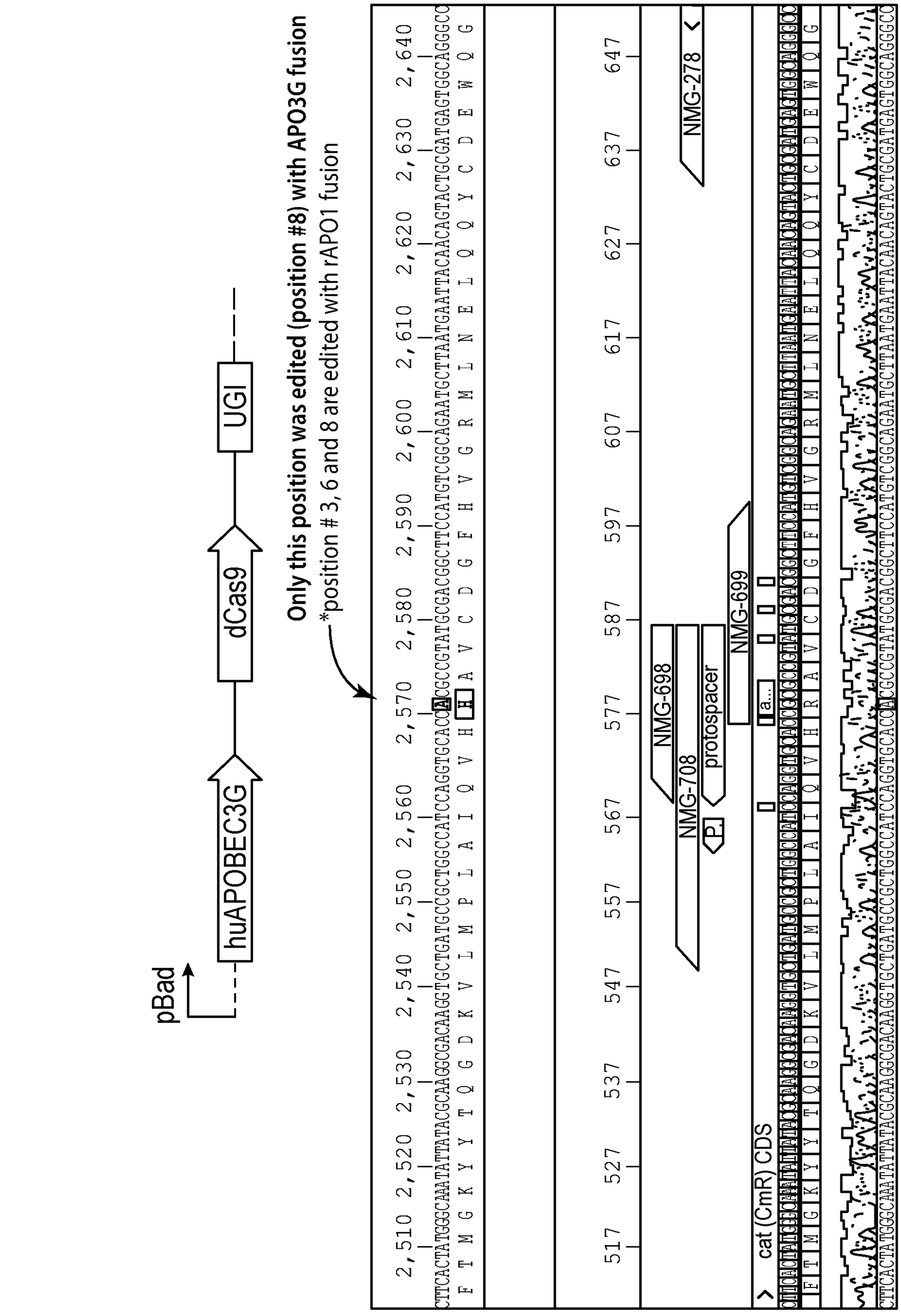

pBad
huAPOBEC3G
UGI
dCas9
Only this position was edited (position #8) with APO3G fusion
*position # 3, 6 and 8 are edited with rAPO1 fusion
NMG-278
NMG-698
NMG-708
protospacer
NMG-699
cat (CmR) CDS

FIGURE 54

EMX1 on target	G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	G	G
untreated					0±0	0±0				0±0													
BE3					42.6±5.3	41.9±5.5				0±0													
HF-BE3					49.3±5.5	40.7±5.6				0±0													
EMX1 off target 1	G	A	G	T	T	A	G	A	G	C	A	G	A	A	G	A	A	G	A	A	A	G	G
untreated										0±0													
BE3										0±0													
HF-BE3										0±0													
EMX1 off target 2	G	A	G	T	C	T	A	A	G	C	A	G	A	A	G	A	A	G	A	A	G	A	G
untreated					0±0					0±0													
BE3					12.1±0.9					0±0													
HF-BE3					1.7±0.3					0±0													
EMX1 off target 3	G	A	G	G	C	C	G	A	G	C	A	G	A	A	G	A	A	A	G	A	C	G	G
untreated					0±0	0±0				0±0													
BE3					6.8±2	8.1±2.5				0.2±0													
HF-BE3					0±0	0±0				0±0													
EMX1 off target 4	G	A	G	T	C	C	T	A	G	C	A	G	G	A	G	A	A	G	A	A	G	A	G
untreated					0±0	0±0				0±0													
BE3					1.3±0.1	1.3±0.1				0±0													
HF-BE3					0.1±0	0.2±0				0±0													

FIGURE 55

EMX1 off target 6	G	A	G	T	C	C	G	G	G	A	A	G	G	A	G	A	A	G	A	A	A	G	G
untreated					0±0	0±0																	
BE3					0.4±0	0.4±0																	
HF-BE3					0±0	0±0																	

EMX1 off target 7	G	A	G	C	C	G	G	A	G	C	A	G	A	A	G	A	A	G	G	A	G	G	G
untreated				0±0	0±0					0±0													
BE3				0±0	0±0					0±0													
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	G	A	A	G	A	A	A	G	G
untreated					0±0	0±0																	
BE3					0±0	0±0																	
HF-BE3					0±0	0±0																	

EMX1 off target 9	G	A	A	T	C	C	A	A	G	C	A	G	G	A	G	A	A	G	A	A	G	G	A
untreated					0±0	0±0				0±0													
BE3					0.1±0	0.1±0				0±0													
HF-BE3					0±0	0±0				0±0													

EMX1 off target 10	A	C	G	T	C	T	G	A	G	C	A	G	A	A	G	A	A	G	A	A	T	G	G
untreated		0±0			0±0					0±0													
BE3		0±0			1.5±0.1					0±0													
HF-BE3		0±0			1.1±0.2					0±0													

FIGURE 55 (CONTINUED)

EMX1		C_3	C_6	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	

FANCF		C_6	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	38.5 ± 7.2	36.5 ± 6.5	14.4 ± 2.2	

RNF2		C_3	C_6	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	

HEK3		C_6	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	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	
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_6	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	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	

FIGURE 56

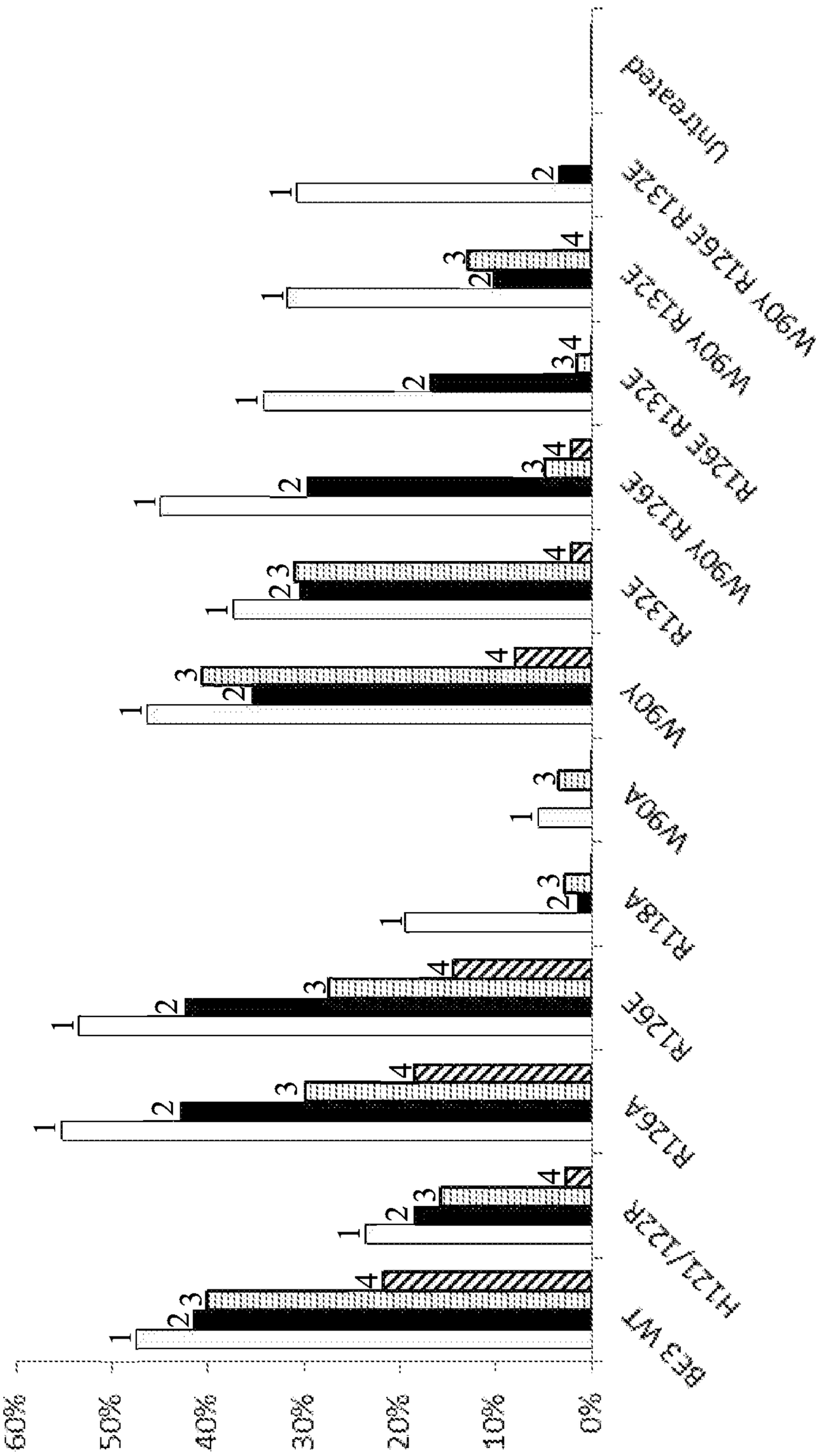
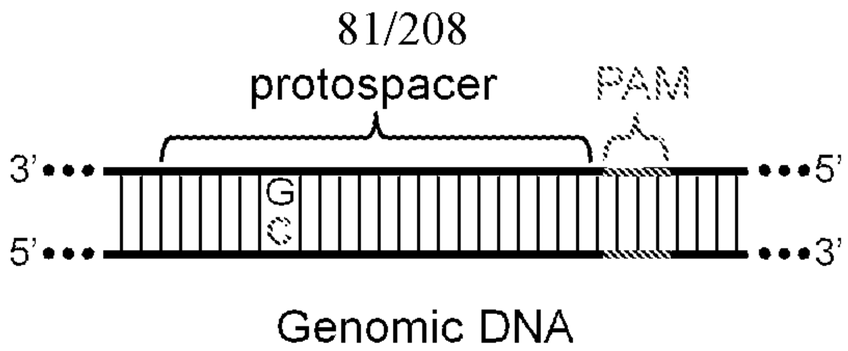

1 C6
2 C7
3 C8
4 C11
Untreated
W/90Y R1.26E R132E
W/90Y R132E
R1.26E R132E
W/90Y R1.26E
R132E
W/90Y
W/90A
R1.18A
R1.26E
R1.26A
H123/1122R
BE3 WT
60%
50%
40%
30%
20%
10%
0%
BASE EDITED

FIGURE 57



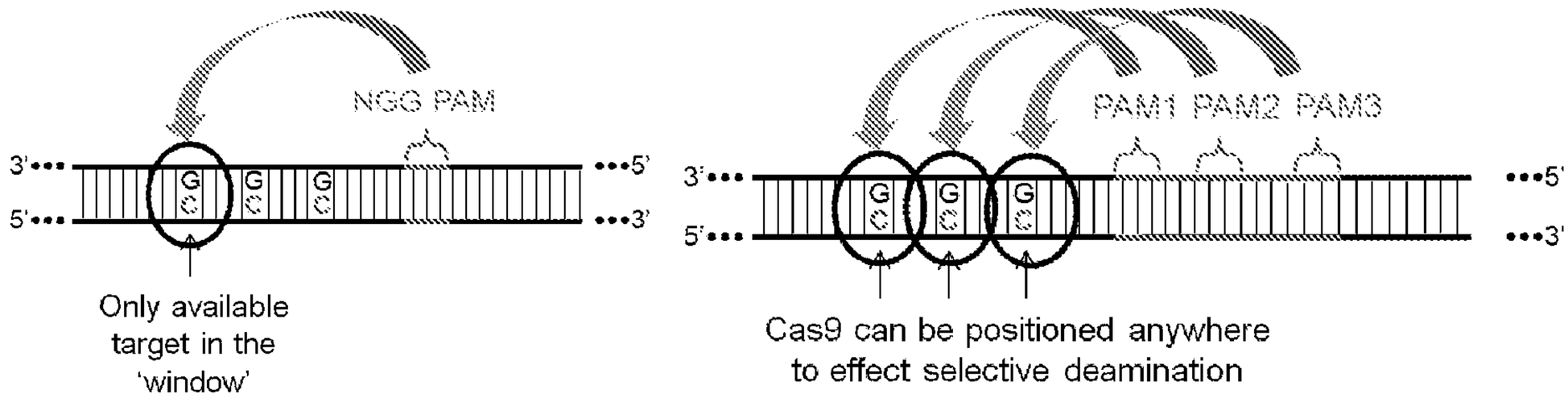


FIGURE 58

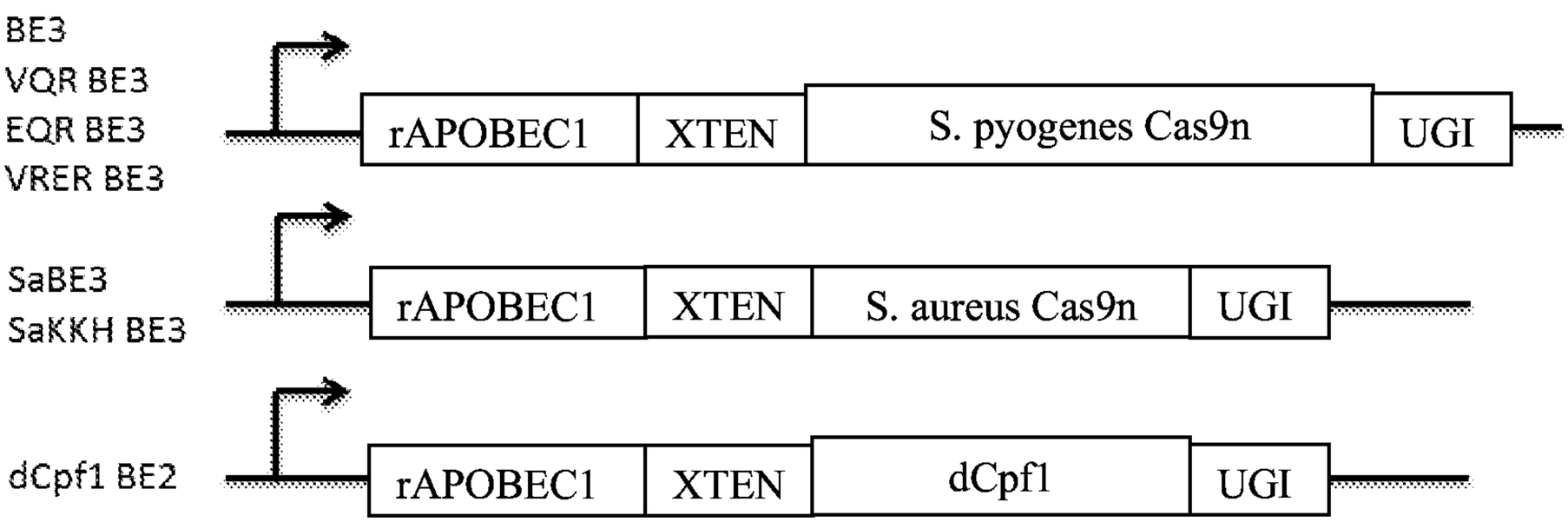


FIGURE 59

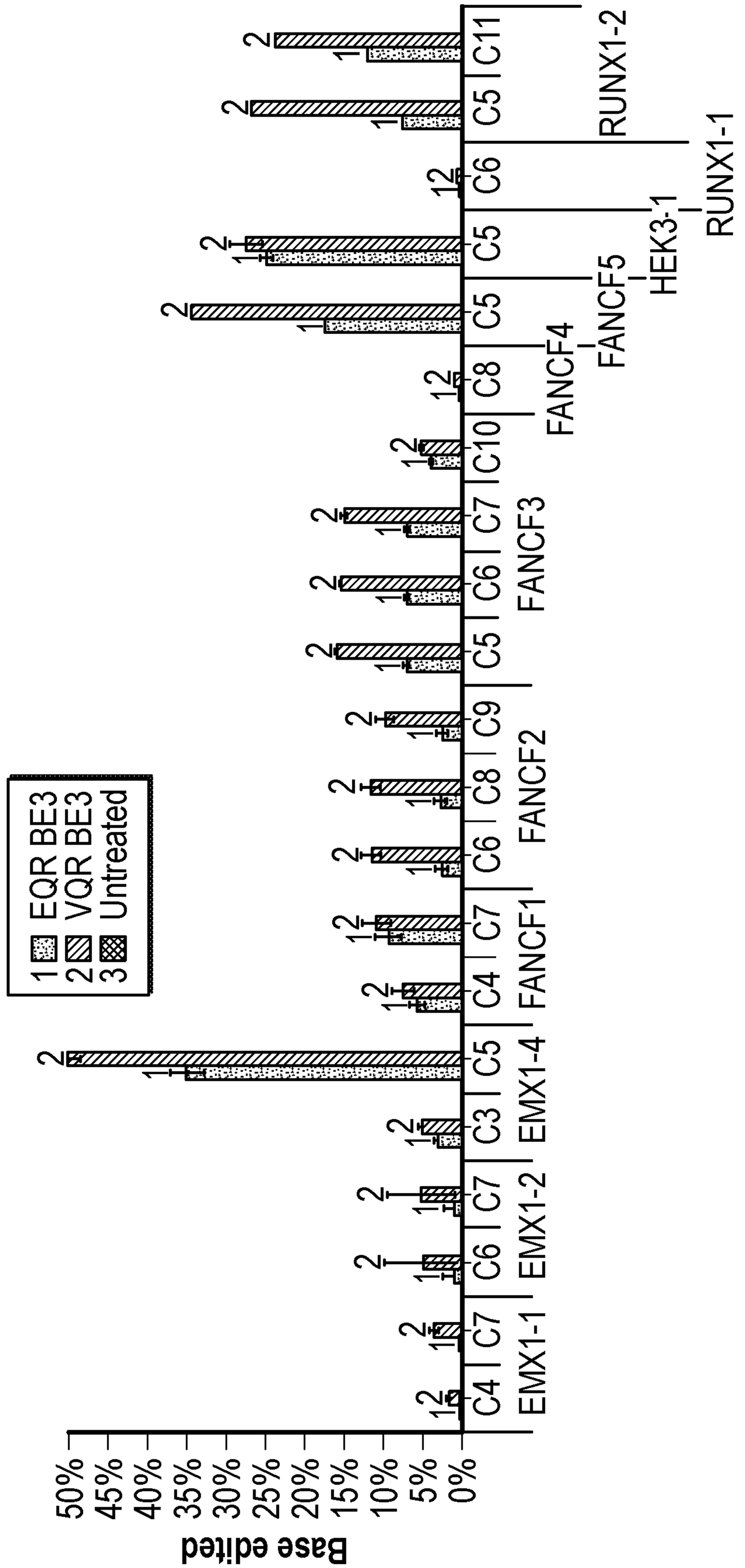

Base edited
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
1 EQR BE3
2 VQR BE3
3 Untreated
EMX1-1
EMX1-2
EMX1-3
EMX1-4
FANCF1
FANCF2
FANCF3
FANCF4
FANCF5
HEK3-1
RUNX1-1
RUNX1-2

FIGURE 60

NGCG PAM EMX (VRER BE3)

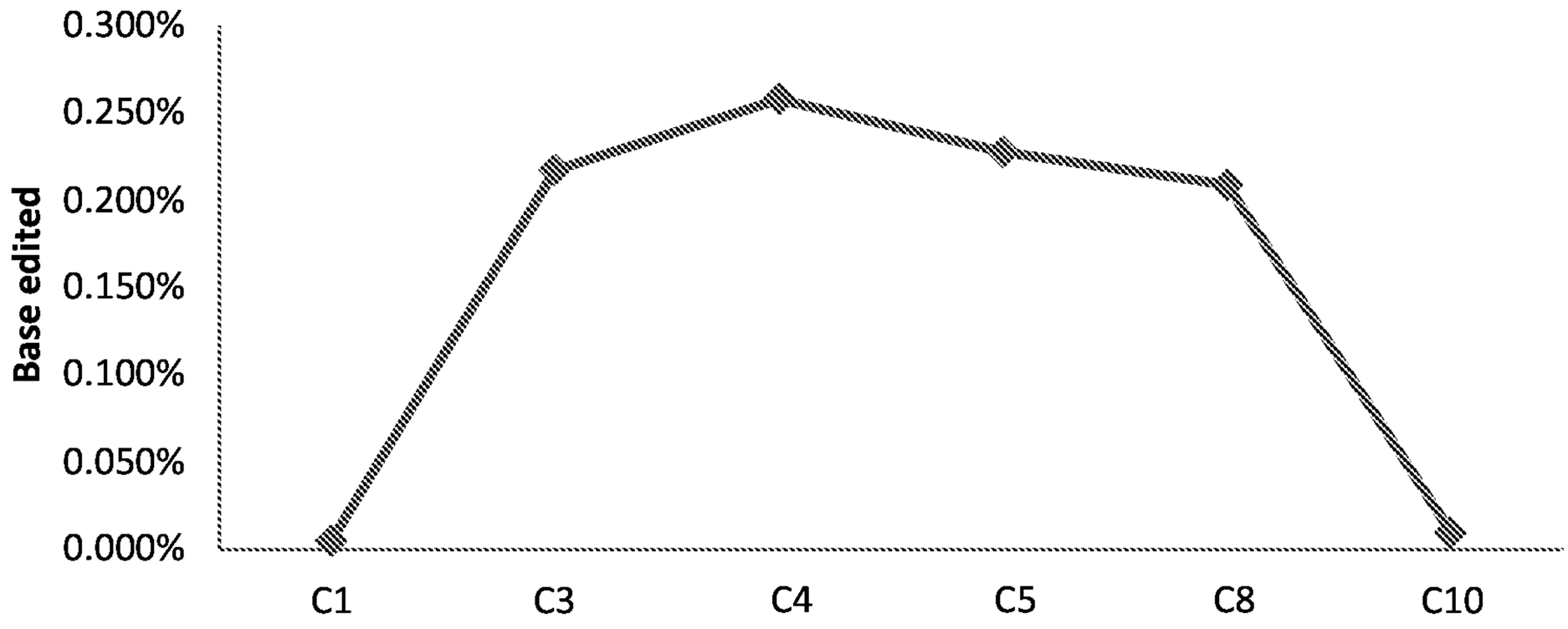


FIGURE 61

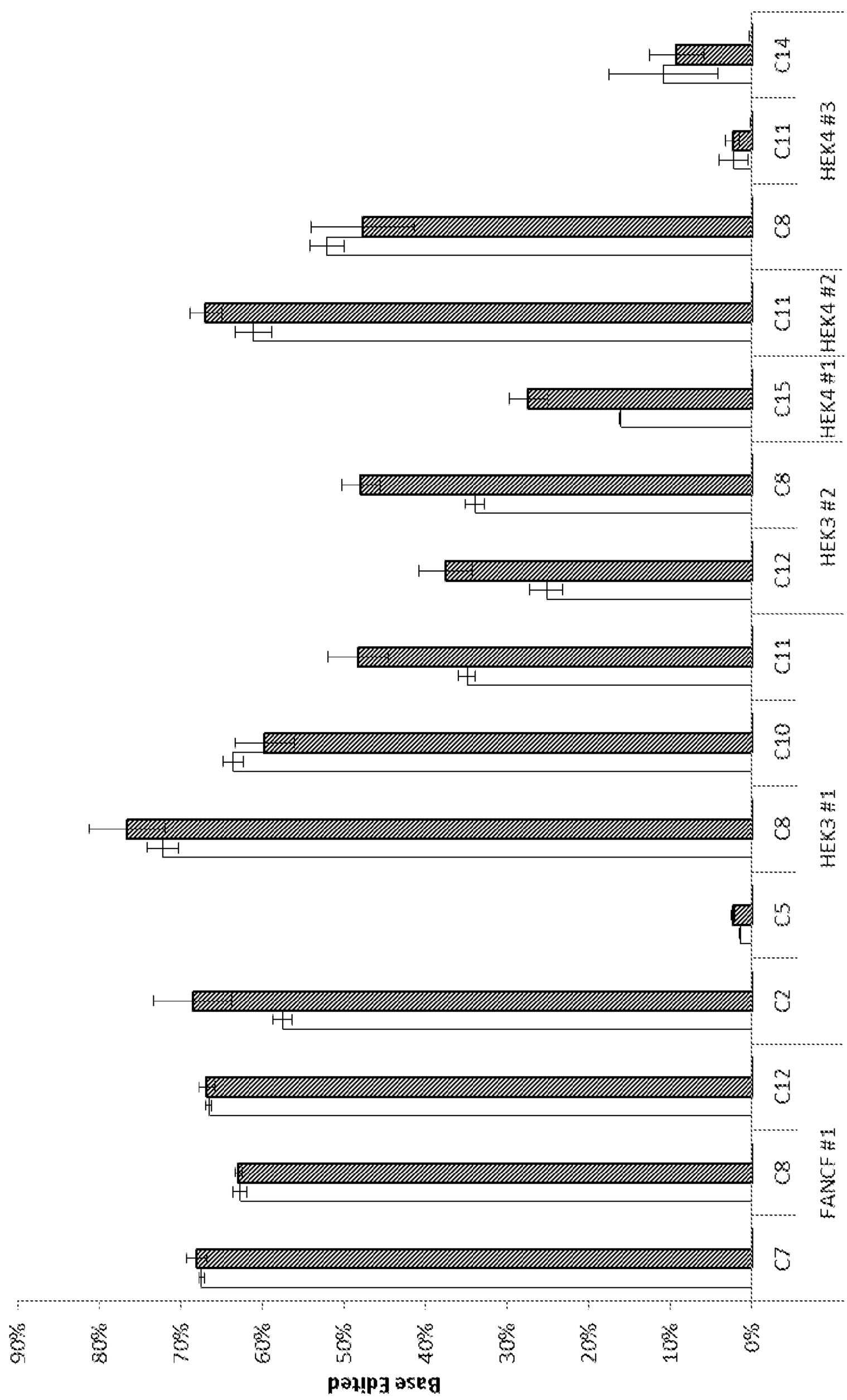

SaKKH BE3
SaBE3
Untreated
Base Edited
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
C12
C8
C11
C15
C8
C11
C5
C2
C12
C8
C10
C11
C7
HEK3 #2
HEK4 #1
HEK4 #2
HEK3 #1
FANCF #1
HEK4 #3

FIGURE 62

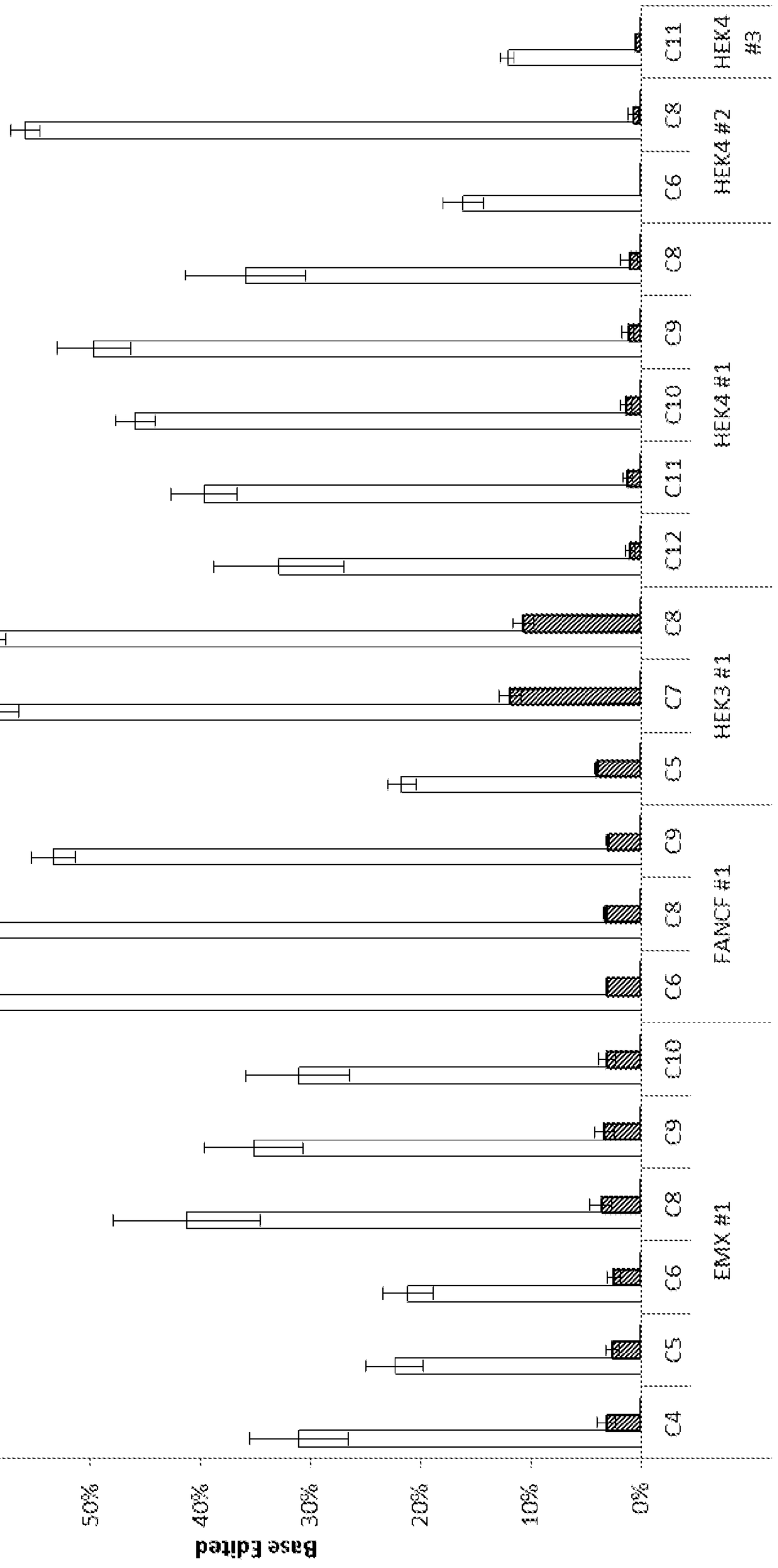

SaKKH BE3
SaBE3
Untreated
Base Edited
70%
60%
50%
40%
30%
20%
10%
0%
C4
C5
C6
C8
C10
EMX #1
C4
C5
C6
C8
C9
C10
C11
C12
FAMCF #1
C5
C7
C8
HEK3 #1
C6
C8
C9
C10
C11
HEK4 #1
C6
C8
HEK4 #2
C11
HEK4 #3

FIGURE 63

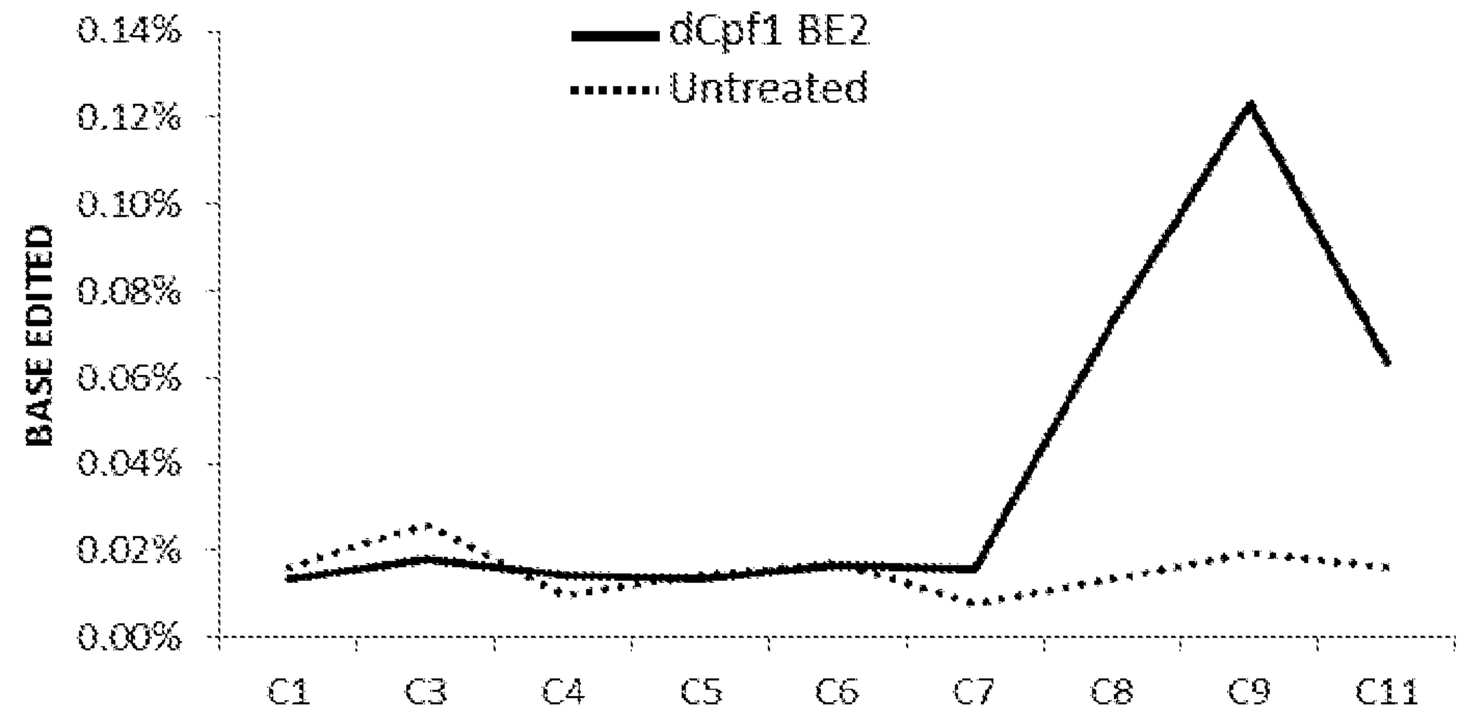


FIGURE 64A

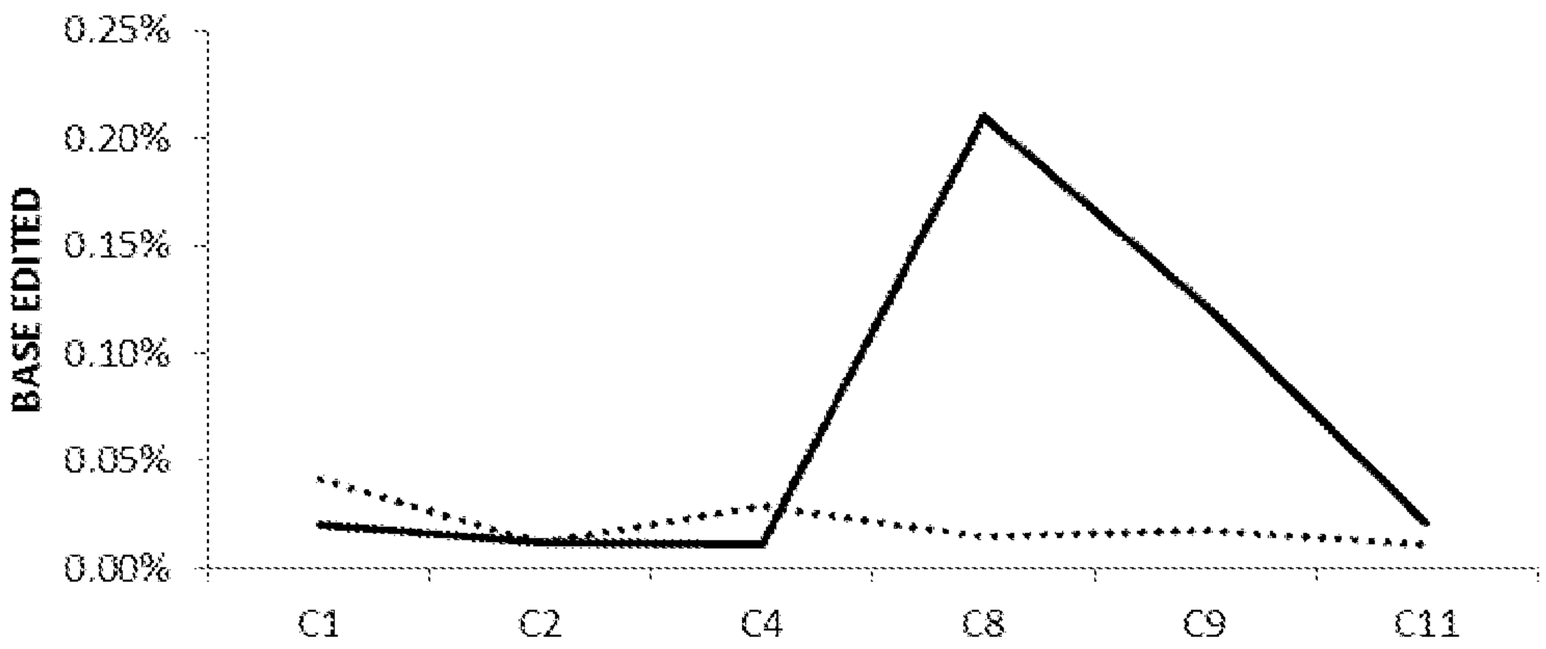


FIGURE 64B

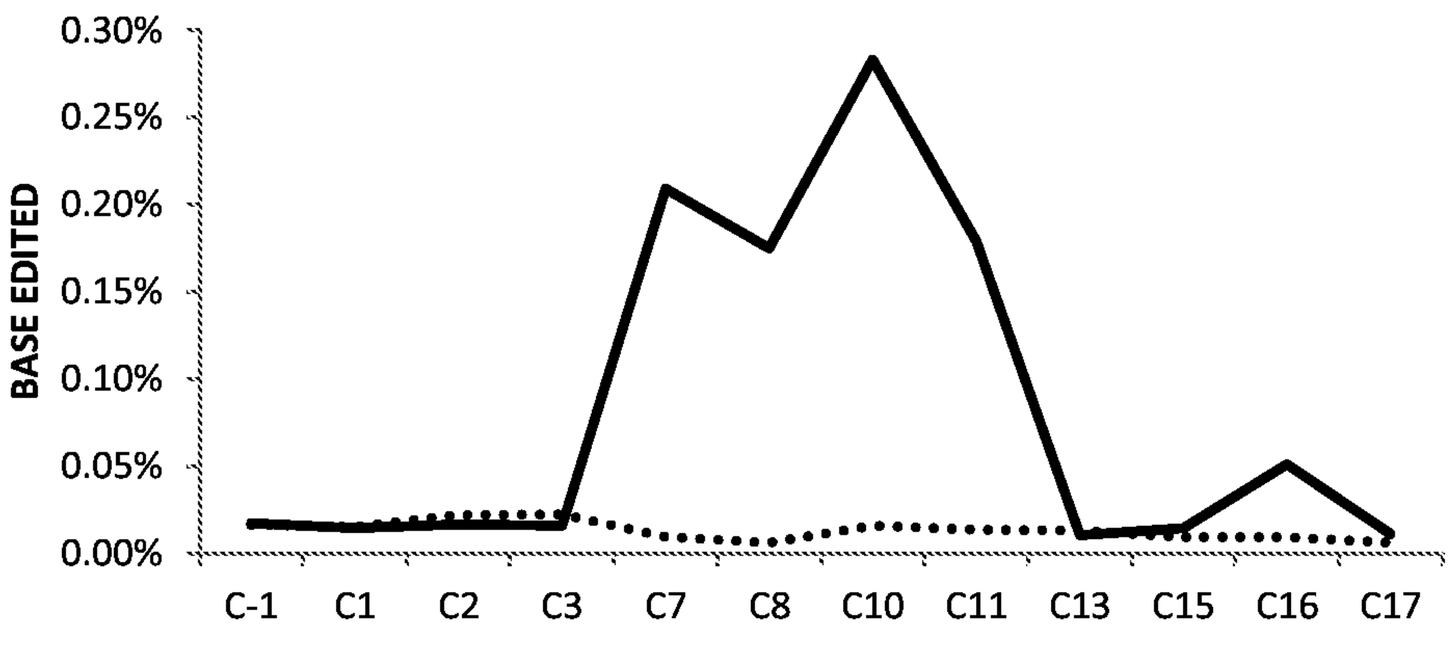


FIGURE 64C

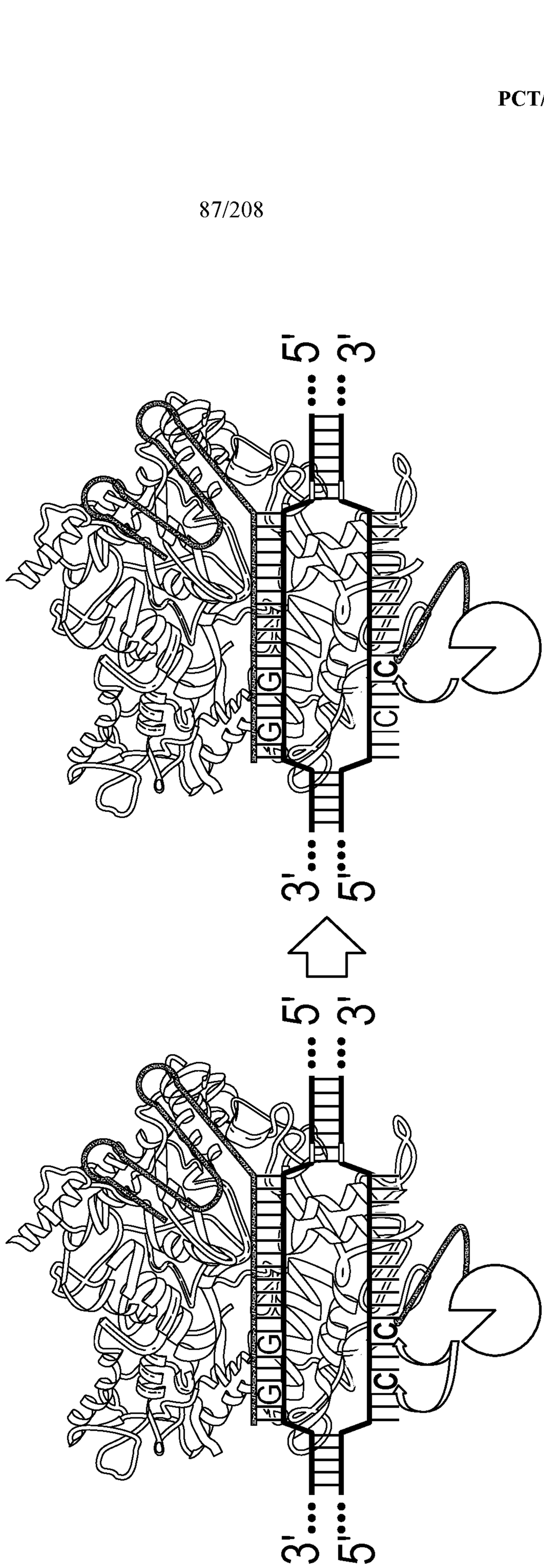


FIGURE 6

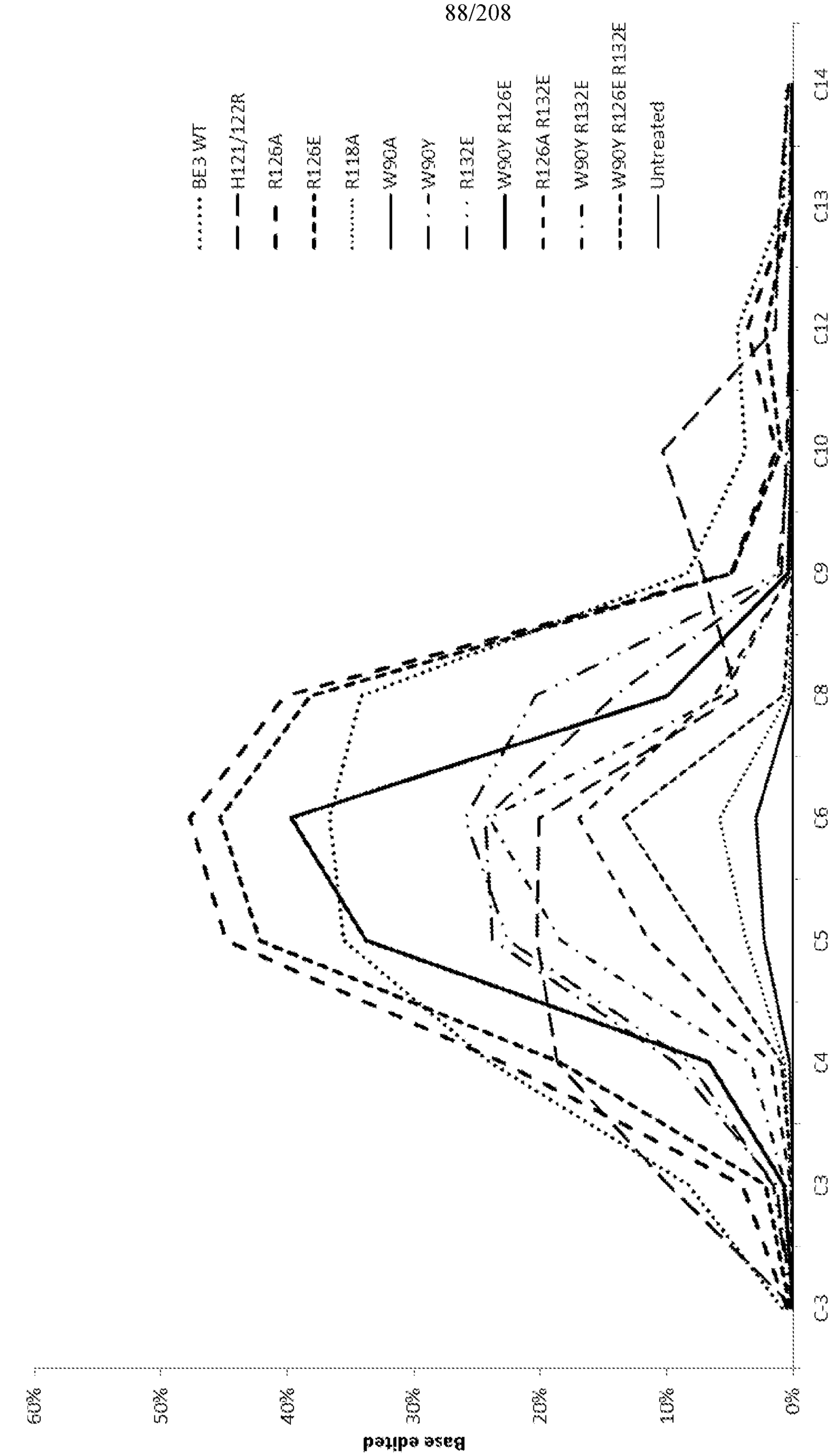

BE3 WT
H121/122R
R126A
R126E
R118A
W90A
W90Y
R132E
W90Y R126E
R126A R132E
W90Y R132E
W90Y R126E R132E
Untreated
C-3
C3
C4
C5
C6
C8
C9
C10
C12
C13
C14
Base edited
0%
10%
20%
30%
40%
50%
60%

FIGURE 66

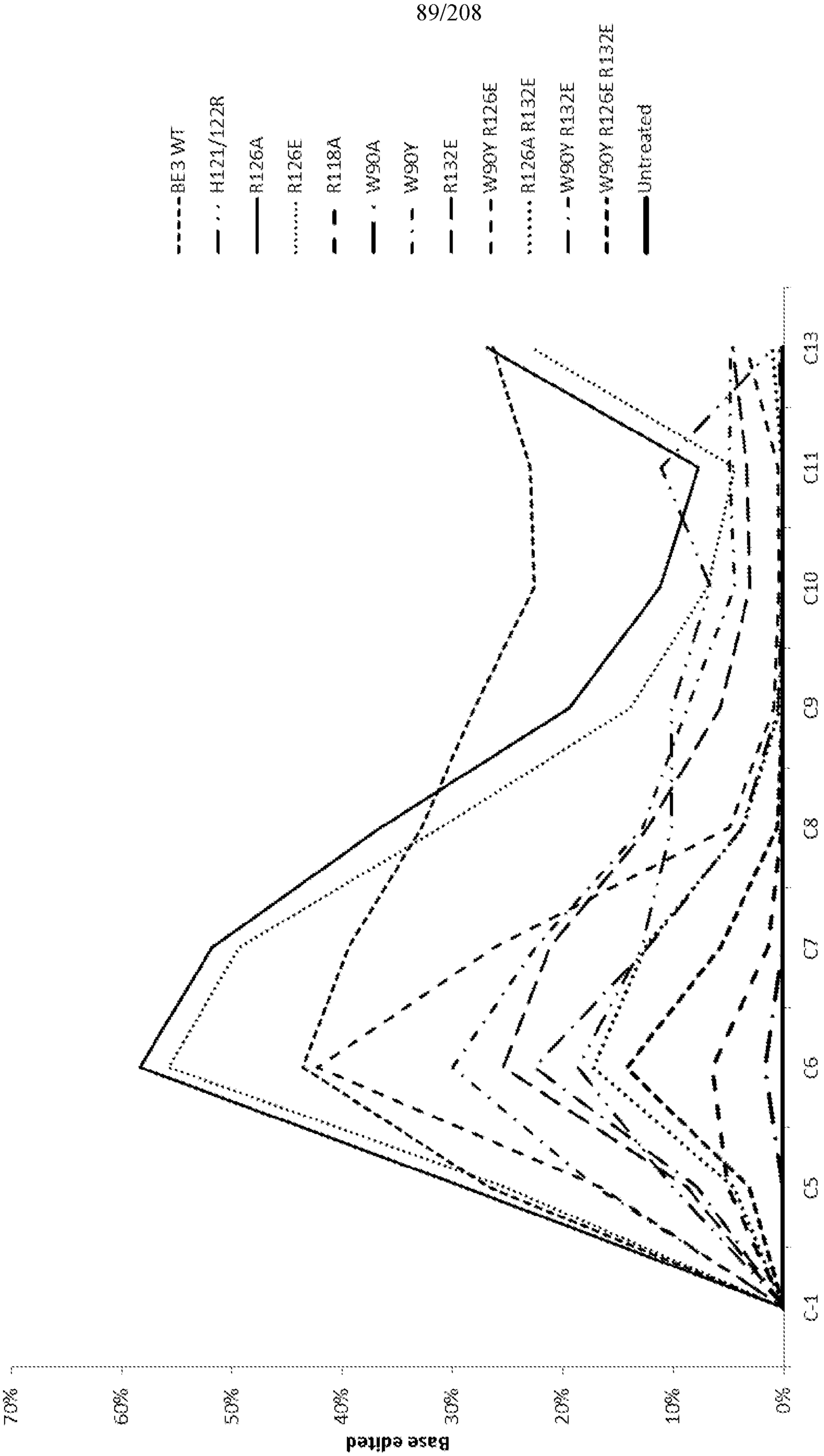

BE3 WT
H121/122R
R126A
R126E
R118A
W90A
W90Y
R132E
W90Y R126E
R126A R132E
W90Y R132E
W90Y R126E R132E
Untreated
C18
C13
C11
C9
C8
C7
C6
C5
C-1
70%
60%
50%
40%
30%
20%
10%
0%
Base edited

FIGURE 67

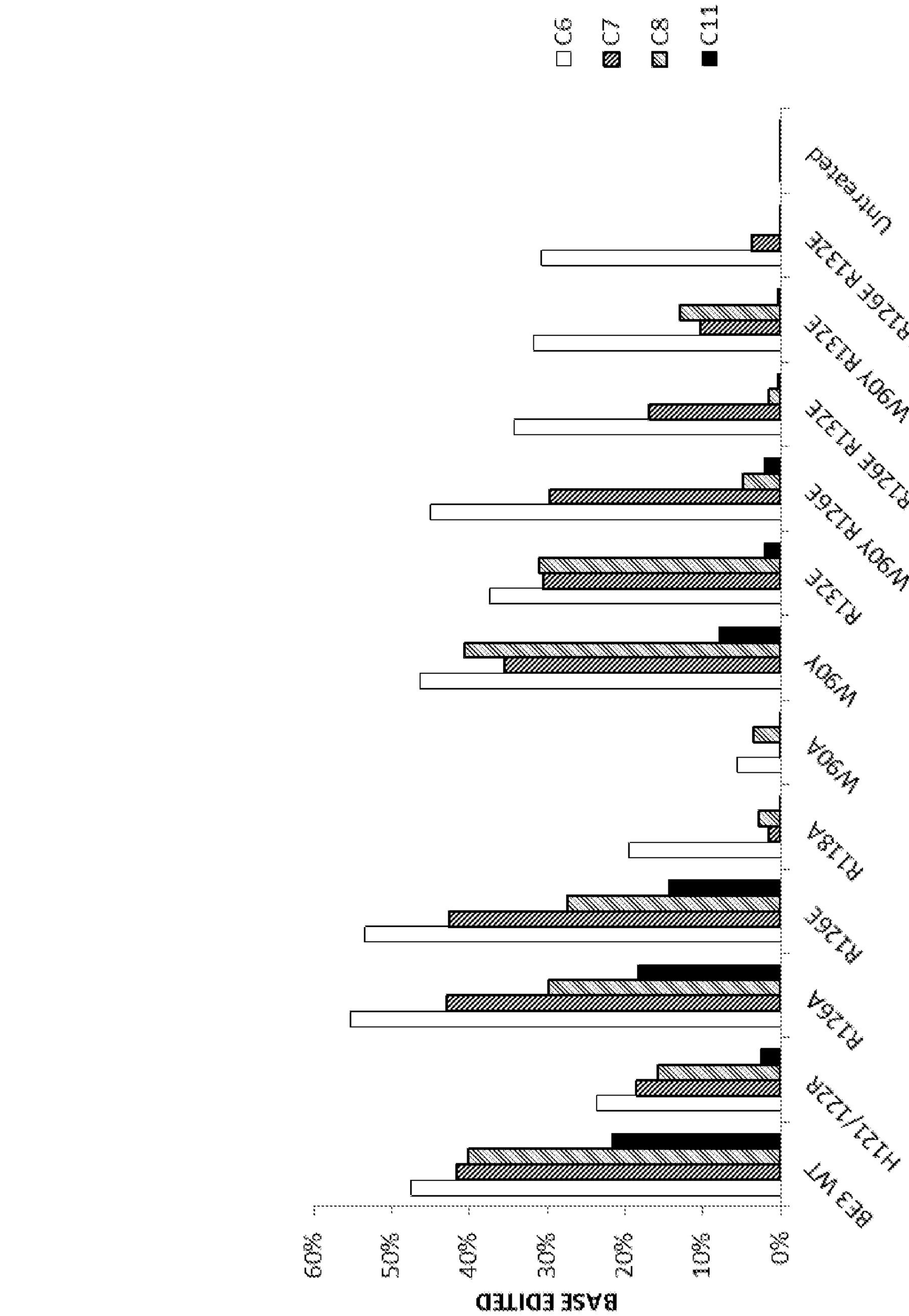

C6
C7
C8
C11
Untreated
W90Y R126E R132E
W90Y R132E
R126E R132E
W90Y R126E
R132E
W90Y
W90A
R138A
R126E
R126A
H121/L122R
BE3 WT
60%
50%
40%
30%
20%
10%
0%
BASE EDITED

FIGURE 89

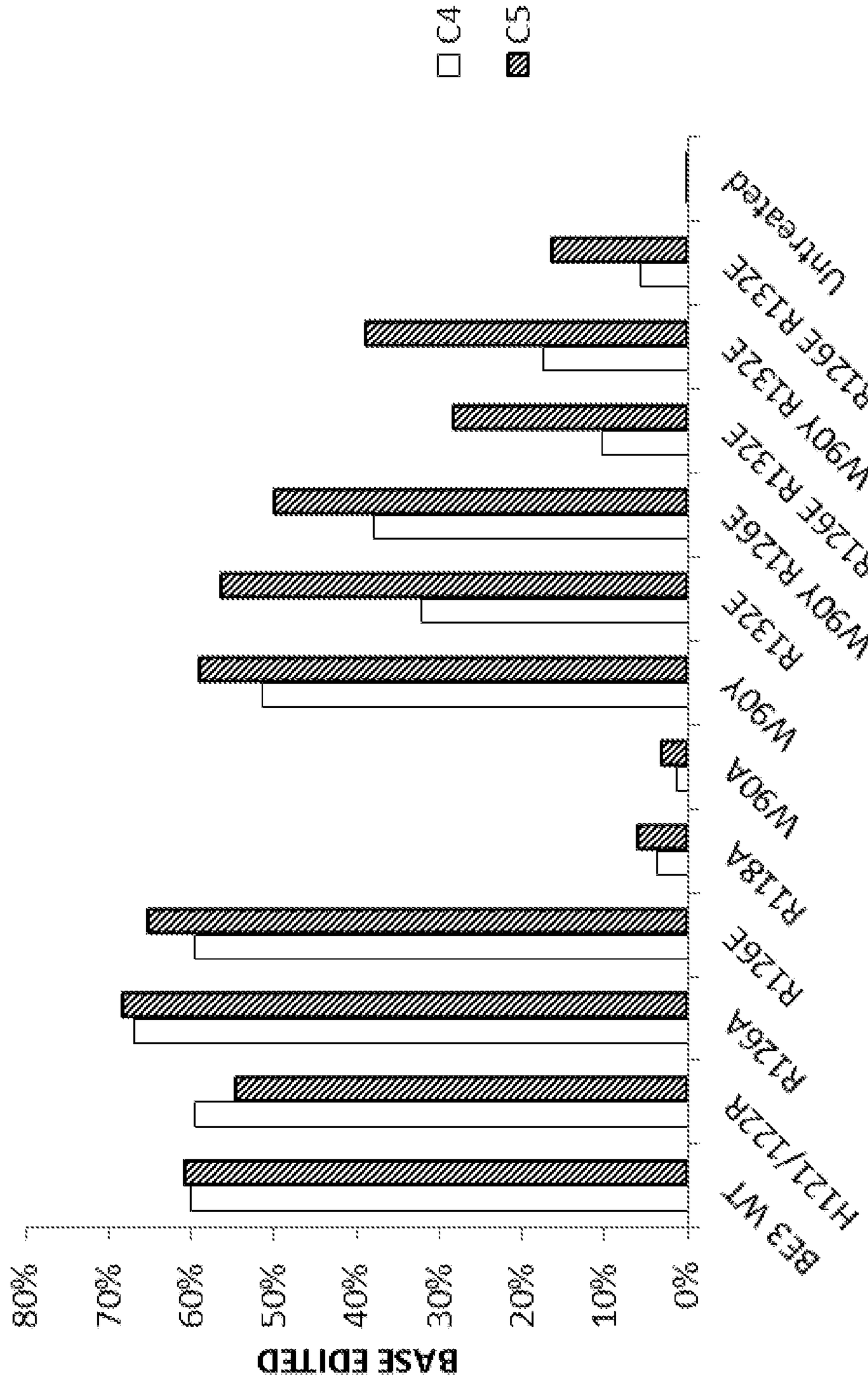

C4
C5
Untreated
W90Y R126E R132E
W90Y R132E
R126E R132E
W90Y R126E
R132E
W90Y
W90A
R118A
R126E
R126A
H221/132R
BE3 WT
0%
10%
20%
30%
40%
50%
60%
70%
80%
BASE EDITED

FIGURE 69

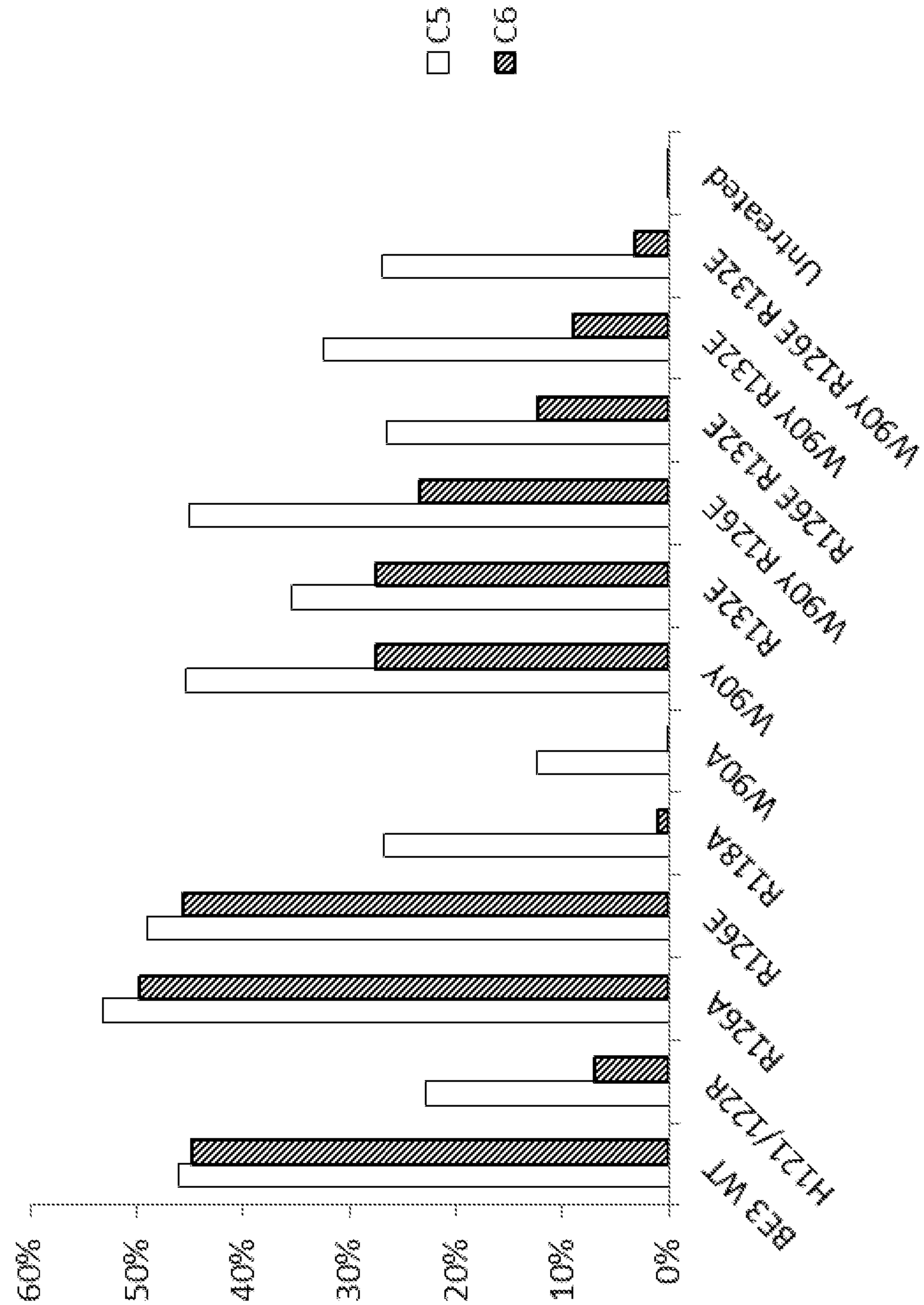

C5
C6
Untreated
W90Y R126E R132E
W90Y R132E
R126E R132E
W90Y R126E
R132E
W90Y
W90A
R118A
R126E
R126A
H121/122R
BE3 WT
60%
50%
40%
30%
20%
10%
0%
BASE EDITED

FIGURE 70

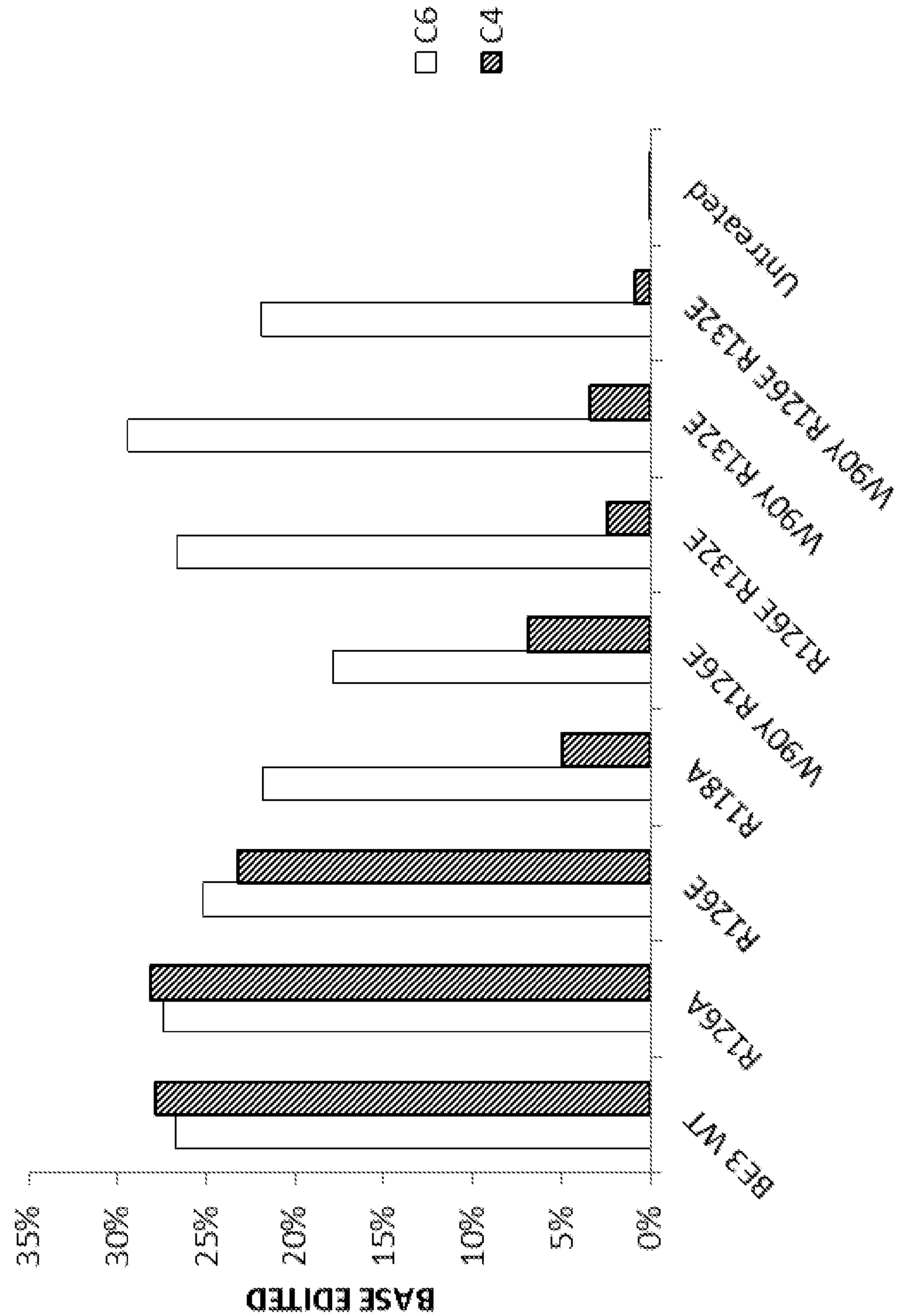

C6
C4
Untreated
W90Y R126E R132E
W90Y R132E
R126E R132E
W90Y R126E
R118A
W90Y R126E
R126E
R126A
BE3 WT
35%
30%
25%
20%
15%
10%
5%
0%
BASE EDITED

FIGURE 71

BE3

		Lys			Arg → Cys			Leu → Leu			Ala			Tyr			Gln			
Base	G	A	A	G	C	G	C	C	T	G	G	C	A	G	T	G	T	A	C	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	0.1	99.9	0.1	0.0
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	0.0	99.9	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	0.0	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	0.0	0.1	0.1

BE3 W90Y R132E

		Lys			Arg → Cys			Leu → Leu			Ala			Tyr			Gln			
Base	G	A	A	G	C	G	C	C	T	G	G	C	A	G	T	G	T	A	C	C
A	0.0	99.9	99.9	0.0	0.5	0.1	0.3	0.1	0.0	0.0	0.0	0.1	99.8	0.0	0.0	0.0	0.1	99.9	0.1	0.0
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	0.0	99.9	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	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	0.0	0.0

FIGURE 72

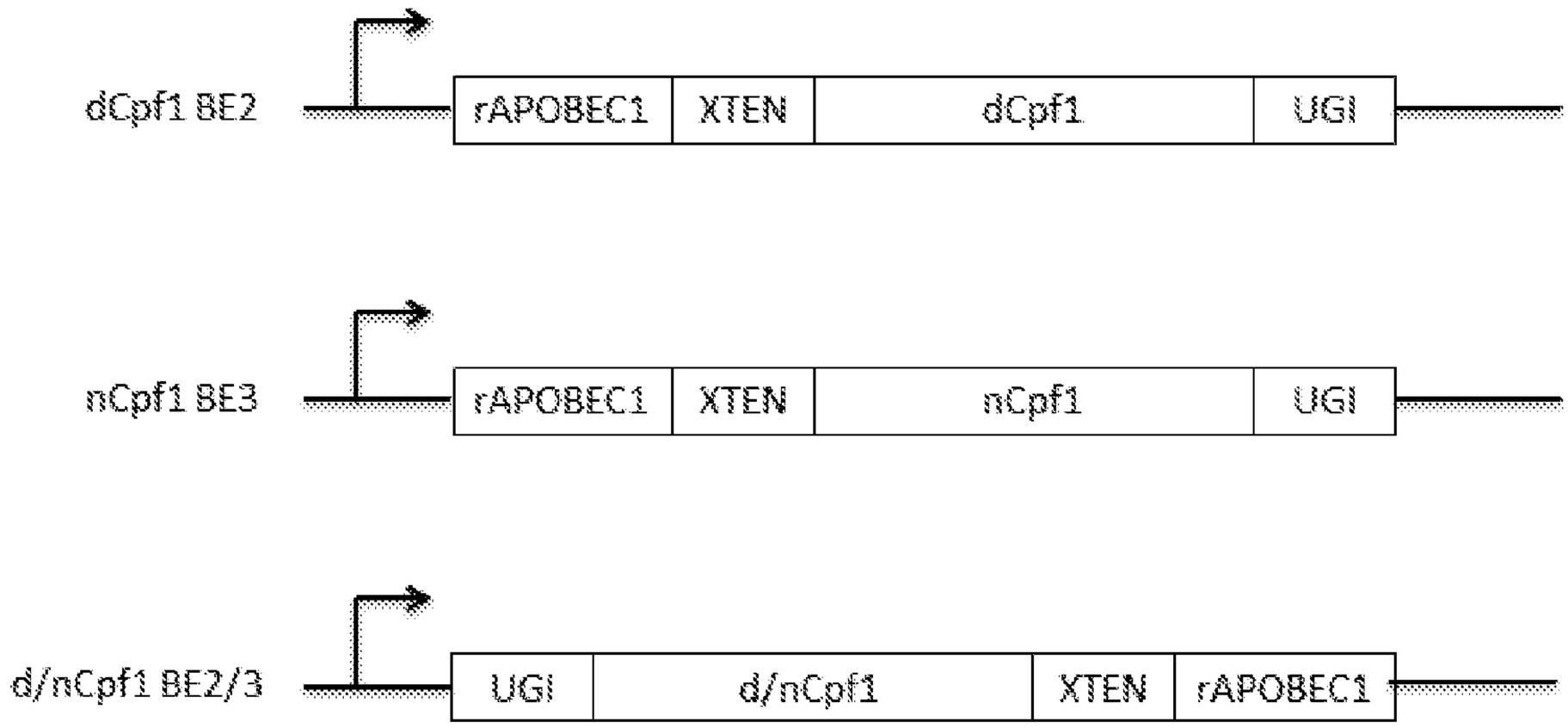
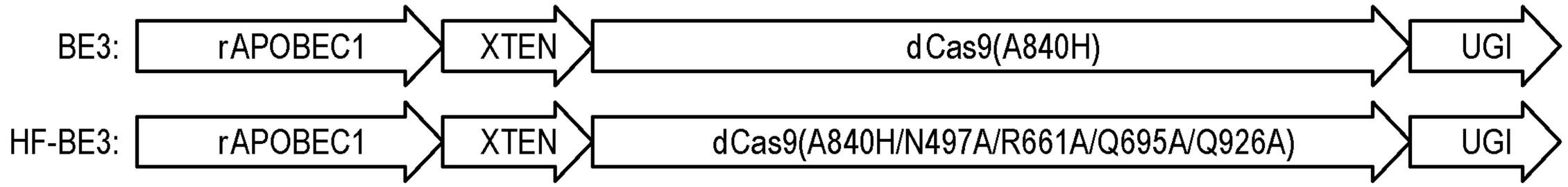

dCpf1 BE2
rAPOBEC1
XTEN
dCpf1
UGI
nCpf1 BE3
rAPOBEC1
XTEN
nCpf1
UGI
d/nCpf1 BE2/3
UGI
d/nCpf1
XTEN
rAPOBEC1

FIGURE 73



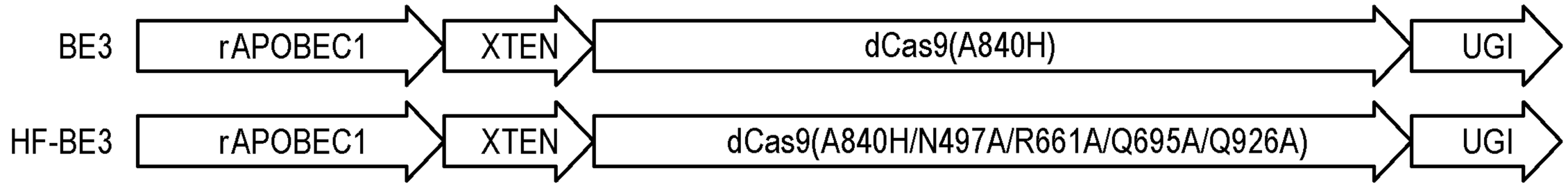
EMX1		C_3	C_6	C_{12}	indel%
untreated	A	0 ± 0	0 ± 0	0 ± 0	0 ± 0
	C	99.9±0	99.9±0	99.9±0	
	G	0 ± 0	0 ± 0	0 ± 0	
	T	0 ± 0	0 ± 0	0 ± 0	
BE3	A	1.3 ± 0.1	0.7 ± 0.2	0 ± 0	2.6±0.3
	C	51.7 ± 1	55.2±0.1	99.9 ± 0	
	G	4 ± 0.7	1.9 ± 0.4	0 ± 0	
	T	42.8 ± 0.2	41.9 ± 0.4	0 ± 0	
HF BE3	A	1.5 ± 0.7	0.5 ± 0.1	0 ± 0	1 ± 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	

FANCF		C_6	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	

RNF2		C_3	C_6	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	

numbers are μ ± σ from three independent replicates

FIGURE 74



HEK3		C_6	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	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	
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_6	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	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

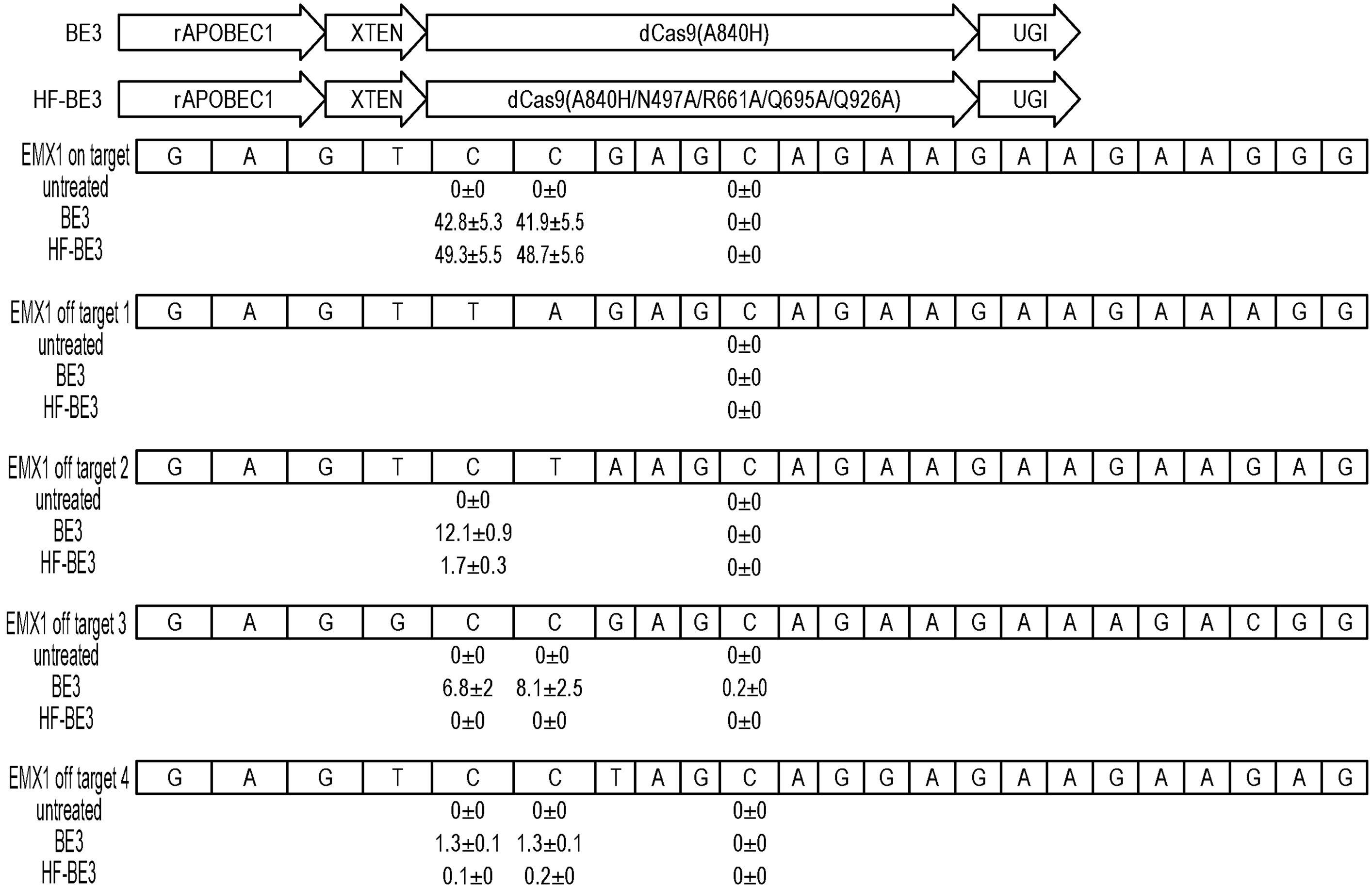

BE3
rAPOBEC1
XTEN
dCas9(A840H)
UGI
HF-BE3
rAPOBEC1
XTEN
dCas9(A840H/N497A/R661A/Q695A/Q926A)
UGI
EMX1 on target
G A G T C C G A G C A G A A G A A G G G
untreated 0±0 0±0 0±0
BE3 42.8±5.3 41.9±5.5 0±0
HF-BE3 49.3±5.5 48.7±5.6 0±0
EMX1 off target 1
G A G T T A G A G C A G A A G A A A G G
untreated 0±0
BE3 0±0
HF-BE3 0±0
EMX1 off target 2
G A G T C T A A G C A G A A G A A G A G
untreated 0±0 0±0
BE3 12.1±0.9 0±0
HF-BE3 1.7±0.3 0±0
EMX1 off target 3
G A G G C C G A G C A G A A G A A A G A C G G
untreated 0±0 0±0 0±0
BE3 6.8±2 8.1±2.5 0.2±0
HF-BE3 0±0 0±0 0±0
EMX1 off target 4
G A G T C C T A G C A G G A G A A G A A G A G
untreated 0±0 0±0 0±0
BE3 1.3±0.1 1.3±0.1 0±0
HF-BE3 0.1±0 0.2±0 0±0

FIGURE 76

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

numbers are μ ± σ from three independent replicates

FIGURE 76 (CONTINUED)

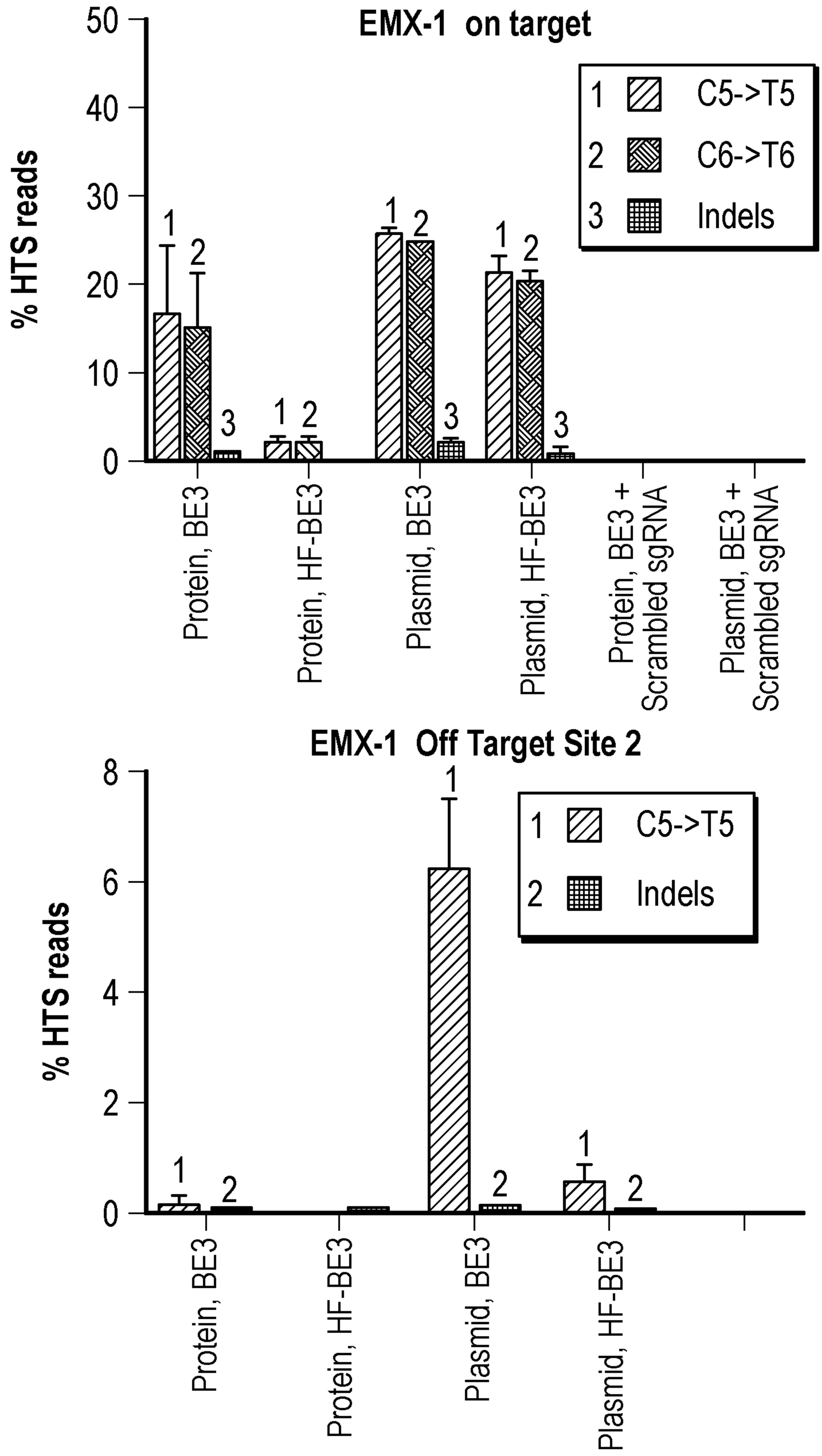

EMX-1 on target
% HTS reads
50
40
30
20
10
0
1
2
3
C5->T5
C6->T6
Indels
Protein, BE3
Protein, HF-BE3
Plasmid, BE3
Plasmid, HF-BE3
Protein, BE3 + scrambled sgRNA
Plasmid, BE3 + scrambled sgRNA
EMX-1 Off Target Site 2
% HTS reads
8
6
4
2
0
1
2
C5->T5
Indels
Protein, BE3
Protein, HF-BE3
Plasmid, BE3
Plasmid, HF-BE3

FIGURE 77

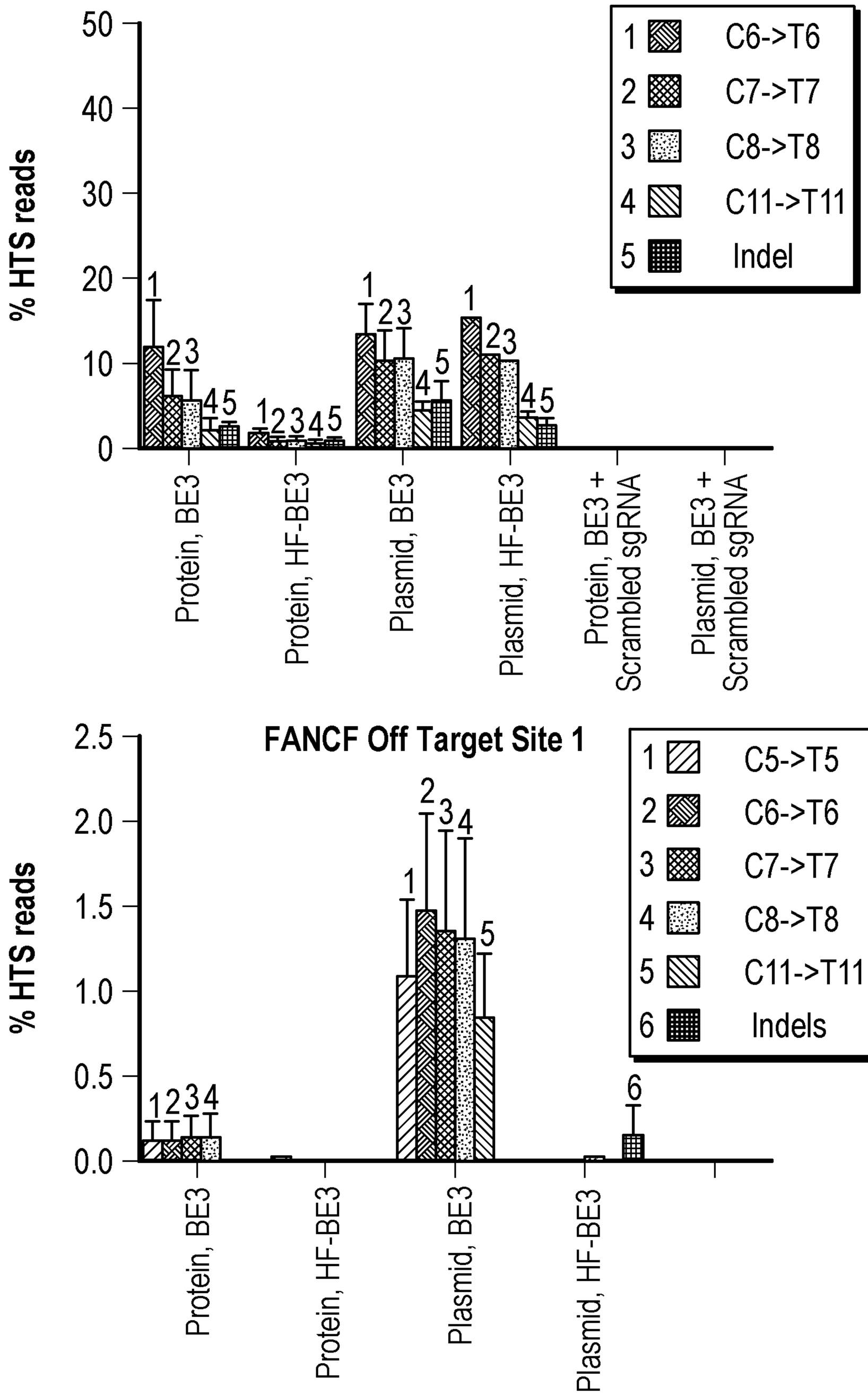

FANCF on target
% HTS reads
50
40
30
20
10
0
1 C6->T6
2 C7->T7
3 C8->T8
4 C11->T11
5 Indel
Protein, BE3
Protein, HF-BE3
Plasmid, BE3
Plasmid, HF-BE3
Protein, BE3 + crambled sgRNA
Plasmid, BE3 + crambled sgRNA
FANCF Off Target Site 1
% HTS reads
2.5
2.0
1.5
1.0
0.5
0.0
1 C5->T5
2 C6->T6
3 C7->T7
4 C8->T8
5 C11->T11
6 Indels
Protein, BE3
Protein, HF-BE3
Plasmid, BE3
Plasmid, HF-BE3

FIGURE 78

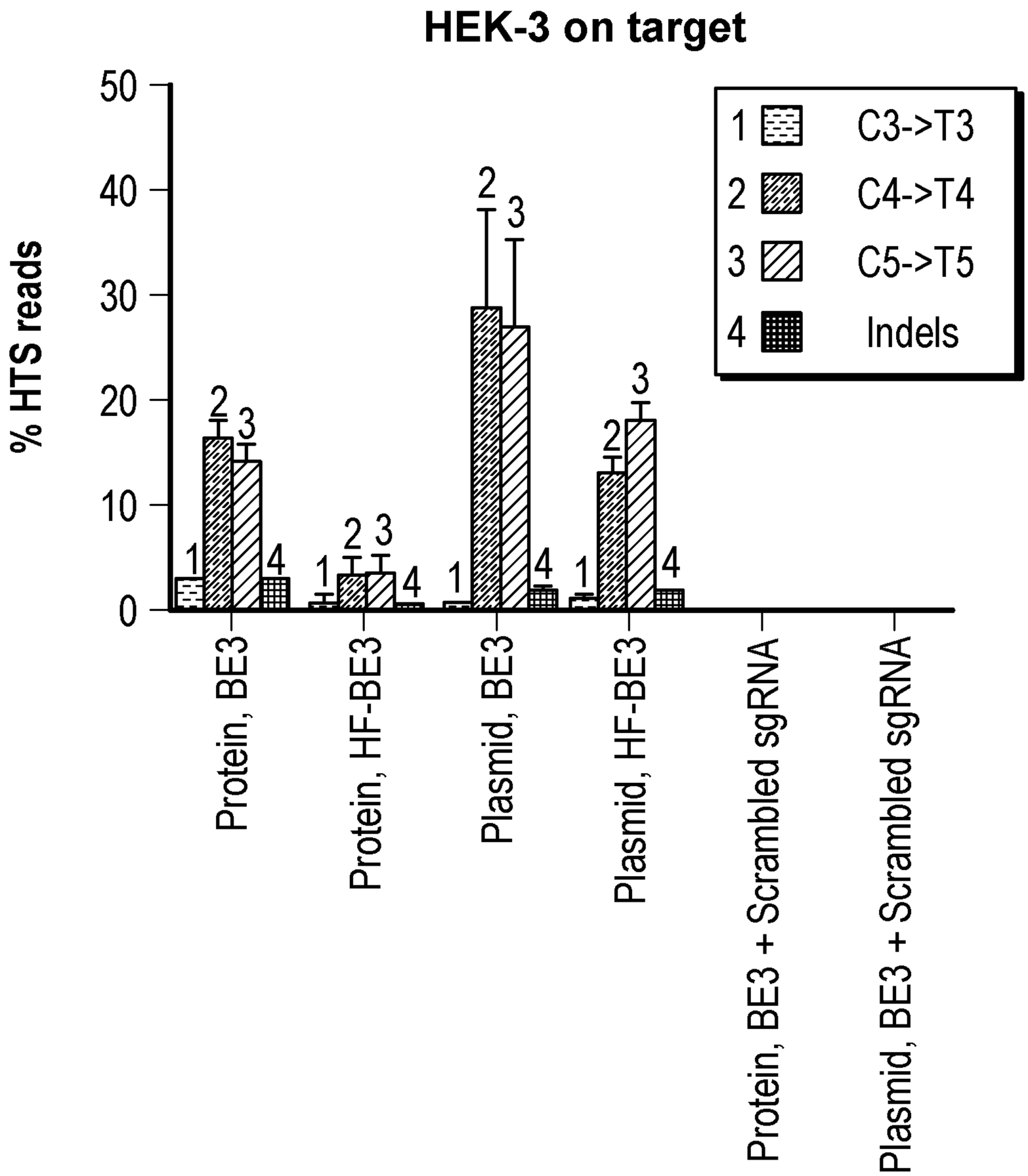

HEK-3 on target
% HTS reads
50
40
30
20
10
0
1 C3->T3
2 C4->T4
3 C5->T5
4 Indels
Protein, BE3
Protein, HF-BE3
Plasmid, BE3
Plasmid, HF-BE3
BE3 + Scrambled sgRNA
BE3 + Scrambled sgRNA

FIGURE 79

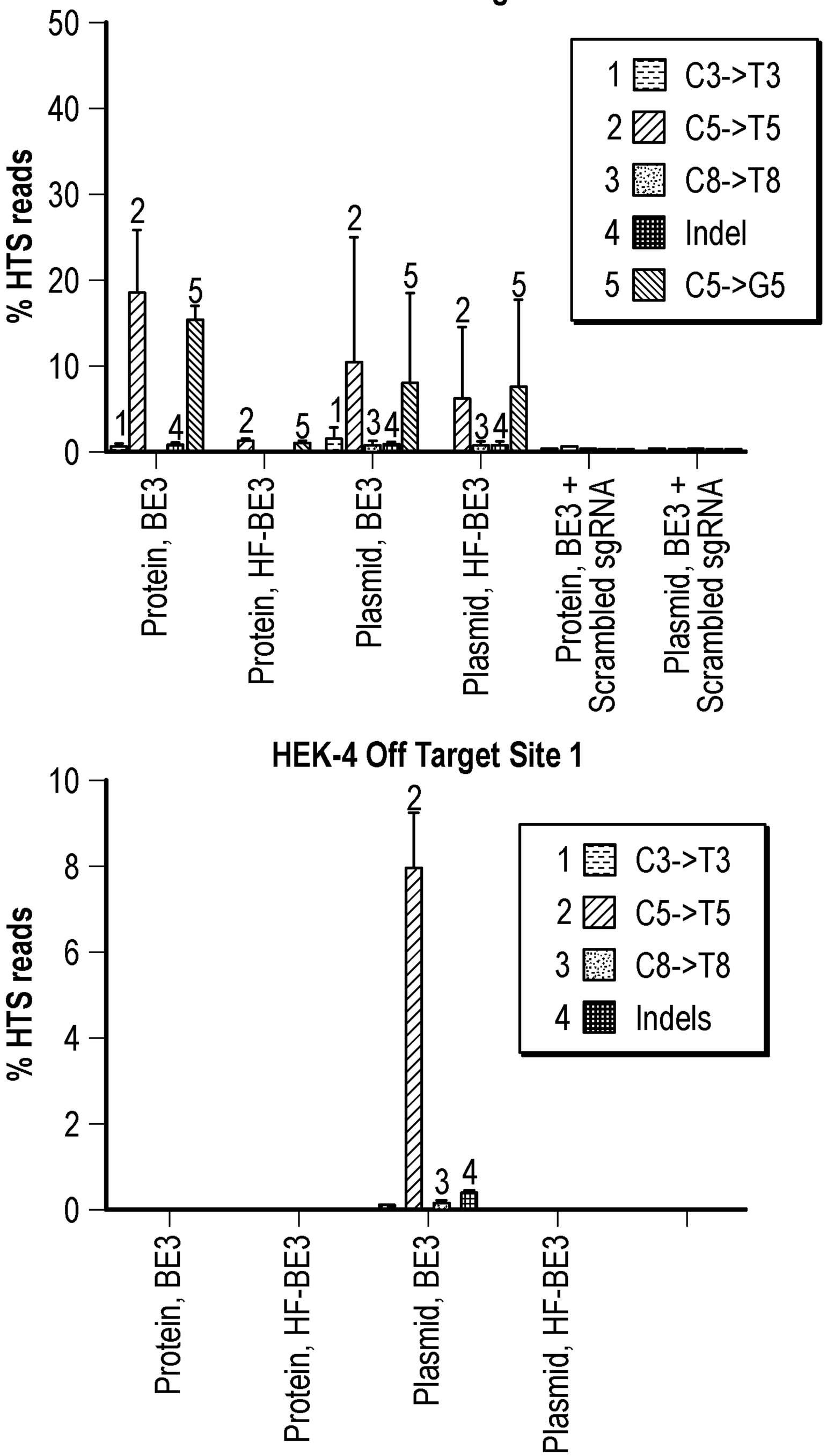

HEK-4 on target
% HTS reads
50
40
30
20
10
0
1 C3->T3
2 C5->T5
3 C8->T8
4 Indel
5 C5->G5
Protein, BE3
Protein, HF-BE3
Plasmid, BE3
Plasmid, HF-BE3
Protein, BE3 + scrambled sgRNA
Plasmid, BE3 + scrambled sgRNA
HEK-4 Off Target Site 1
% HTS reads
10
8
6
4
2
0
1 C3->T3
2 C5->T5
3 C8->T8
4 Indels
Protein, BE3
Protein, HF-BE3
Plasmid, BE3
Plasmid, HF-BE3

FIGURE 80

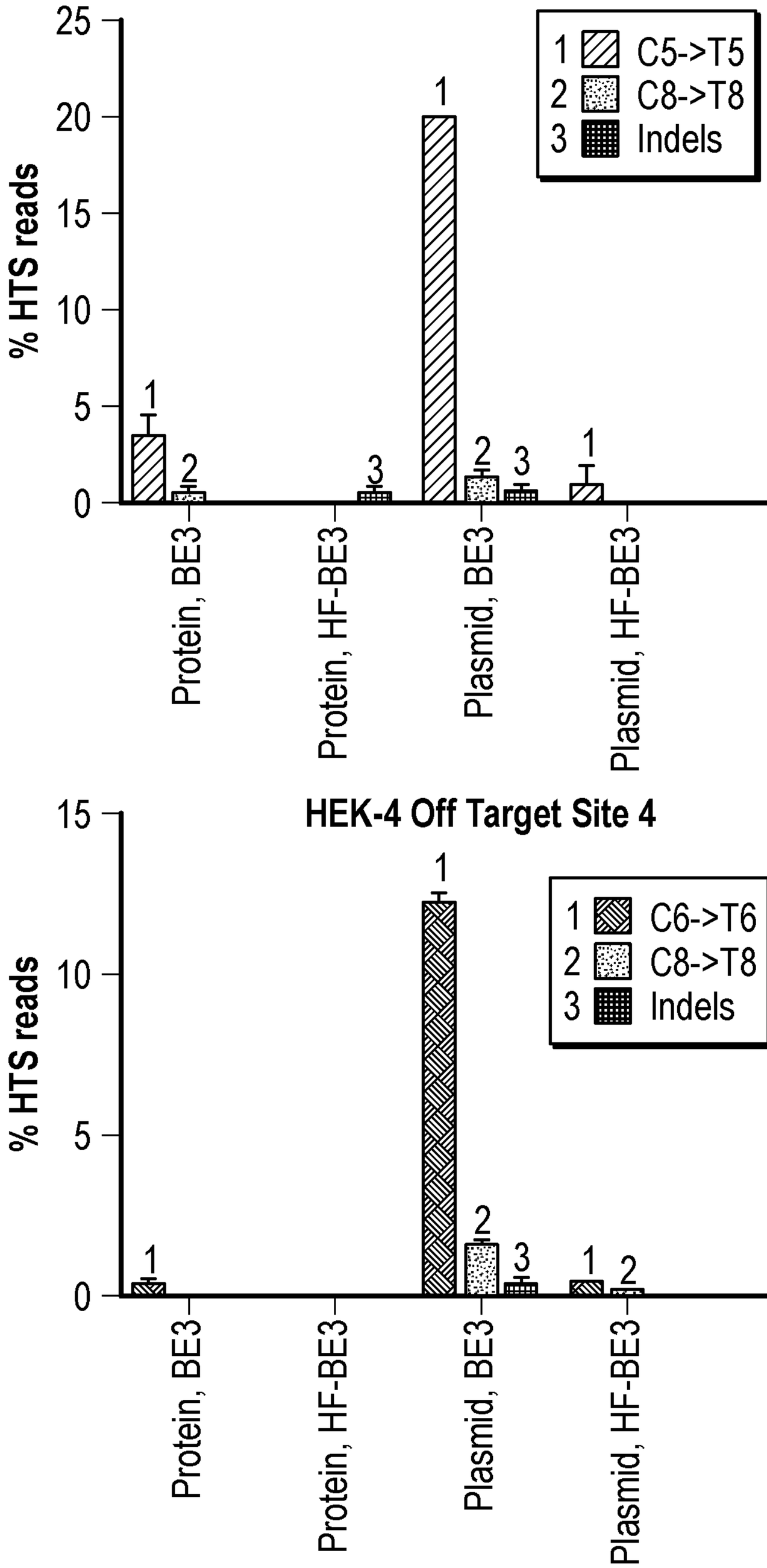
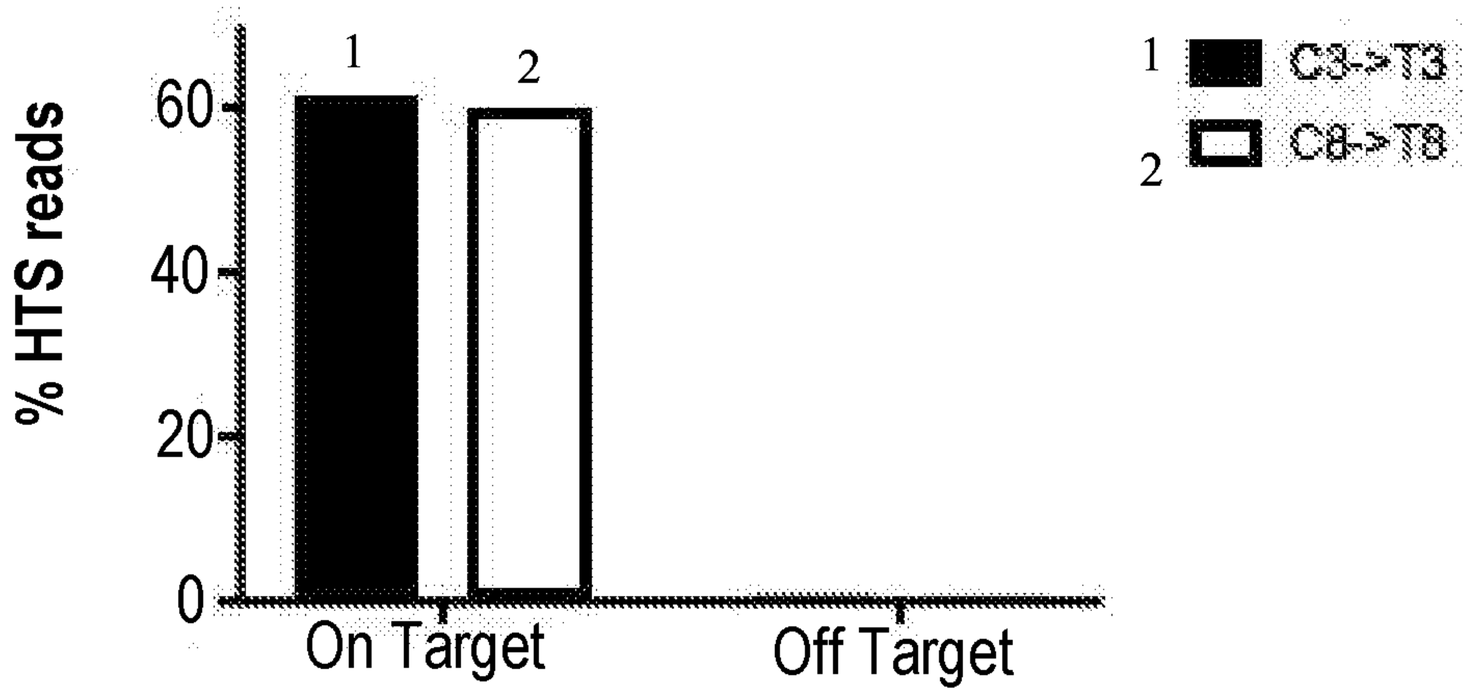
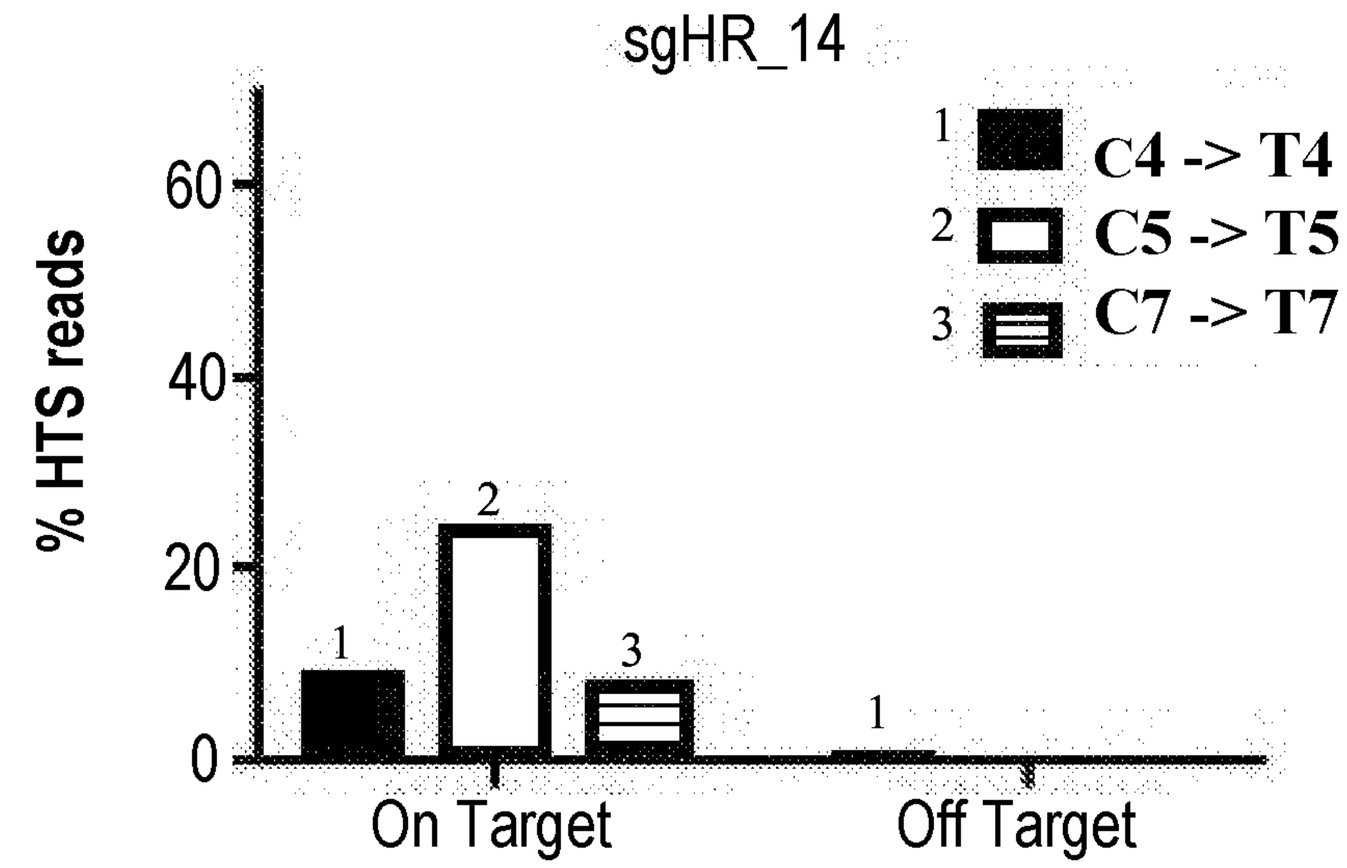


FIGURE 80 (CONTINUED)


sgHR_13
% HTS reads
60
40
20
0
1
2
On Target
Off Target
1 C3->T3
2 C8->T8


sgHR_14
% HTS reads
60
40
20
0
1
2
3
On Target
Off Target
1 C4 -> T4
2 C5 -> T5
3 C7 -> T7

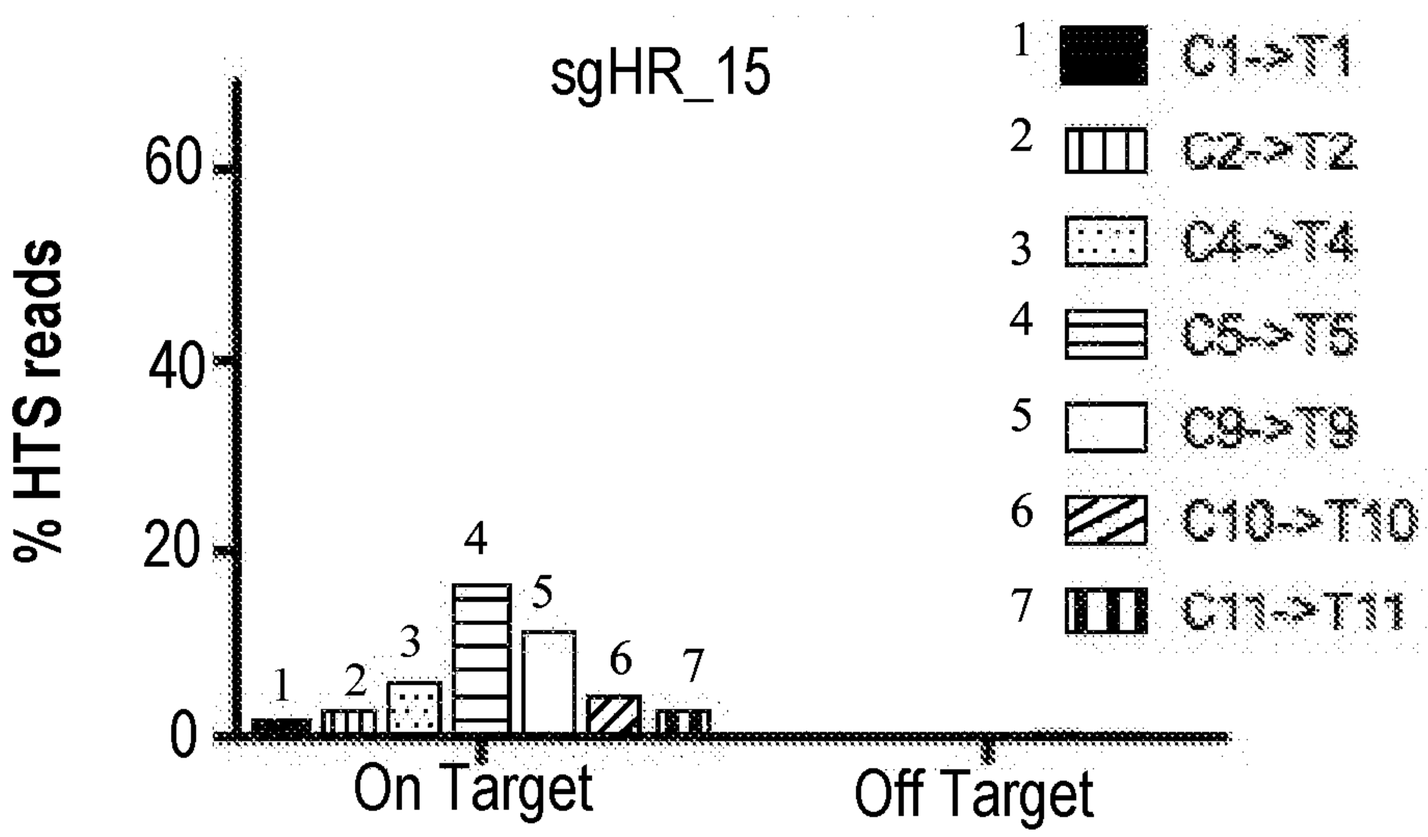
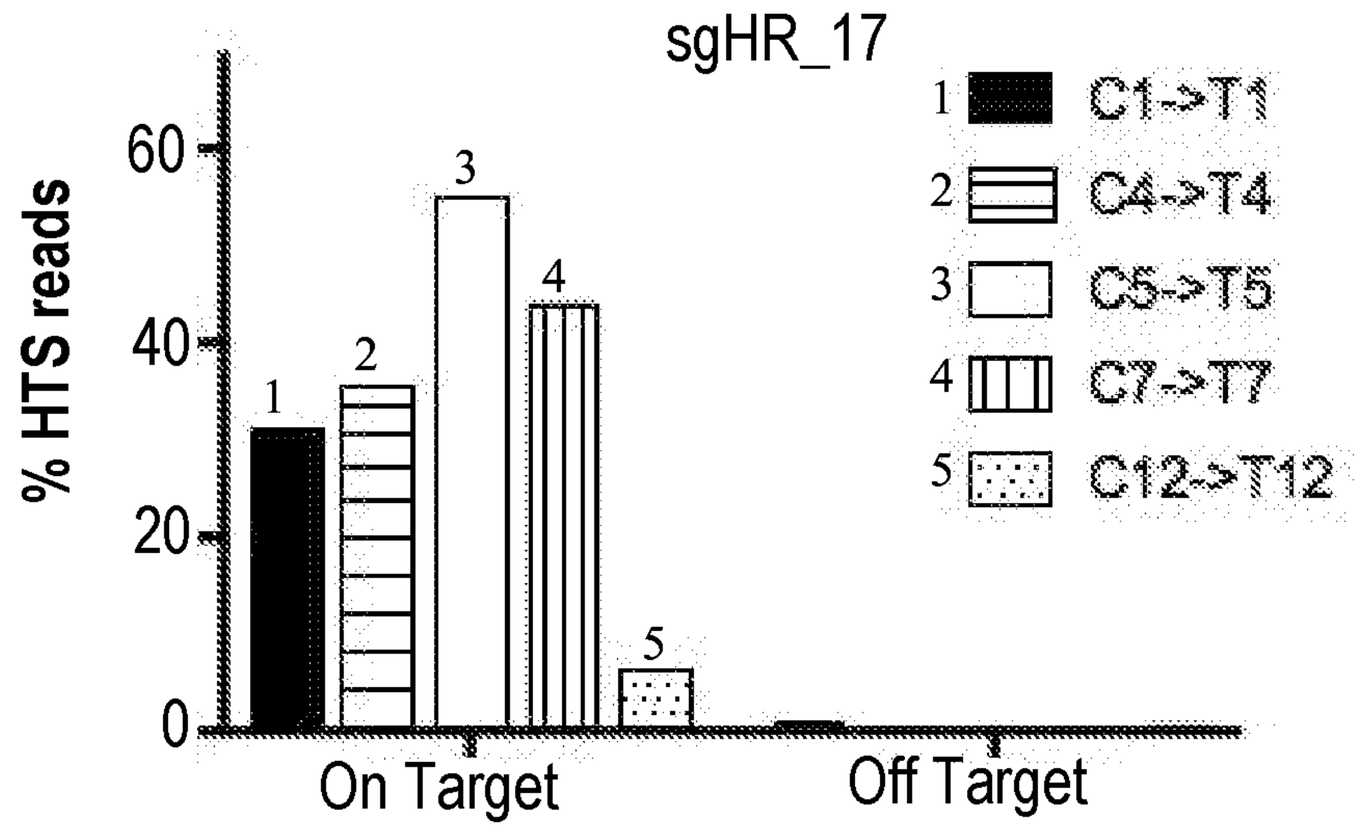

sgHR_15
% HTS reads
60
40
20
0
1
2
3
4
5
6
7
On Target
Off Target
1 C1->T1
2 C2->T2
3 C4->T4
4 C5->T5
5 C9->T9
6 C10->T10
7 C11->T11

FIGURE 81


sgHR_17
% HTS reads
60
40
20
0
1
2
3
4
5
On Target
Off Target
1 C1->T1
2 C4->T4
3 C5->T5
4 C7->T7
5 C12->T12

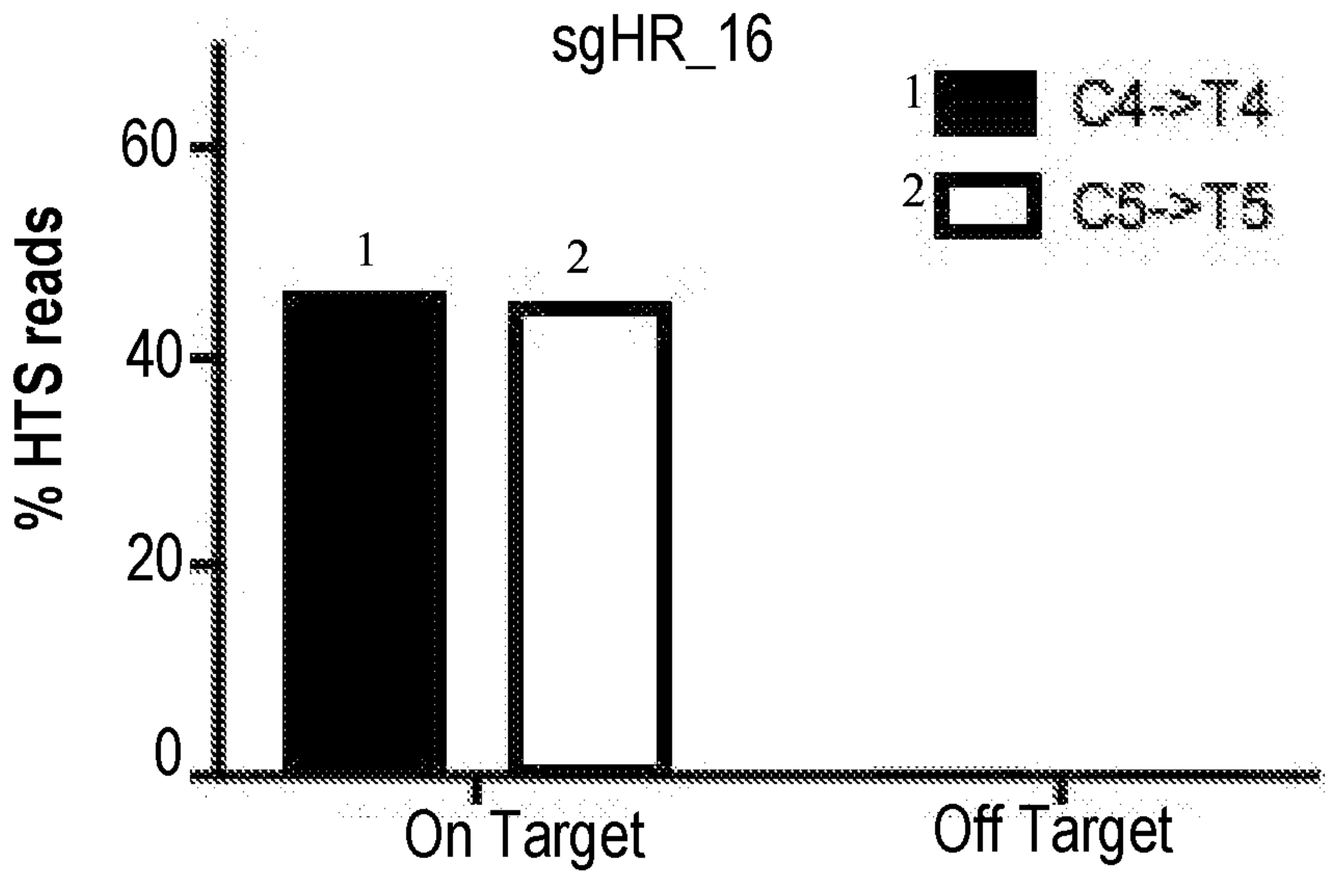

sgHR_16
% HTS reads
60
40
20
0
1
2
On Target
Off Target
1 C4->T4
2 C5->T5

FIGURE 82

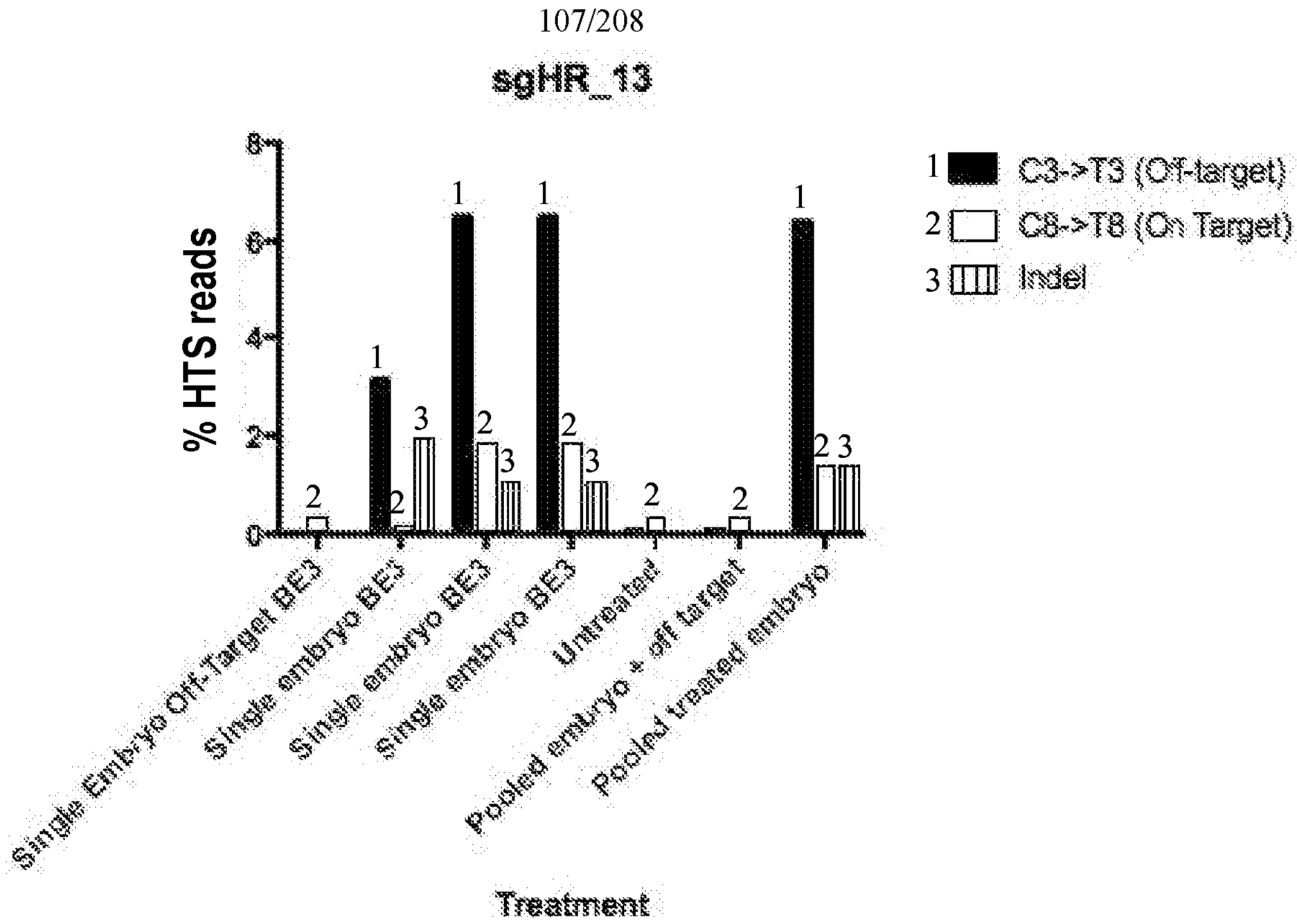


FIGURE 83

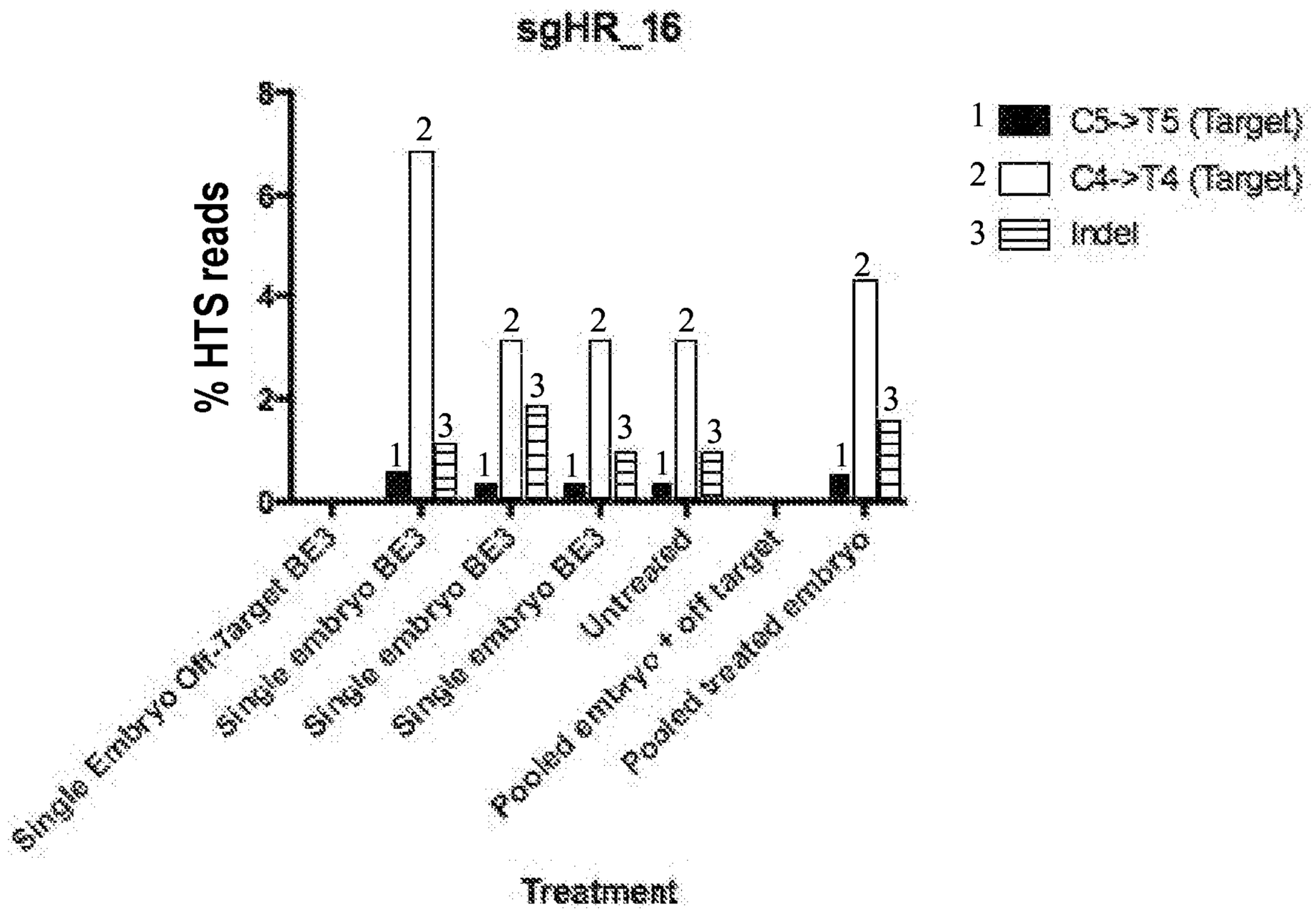


FIGURE 84

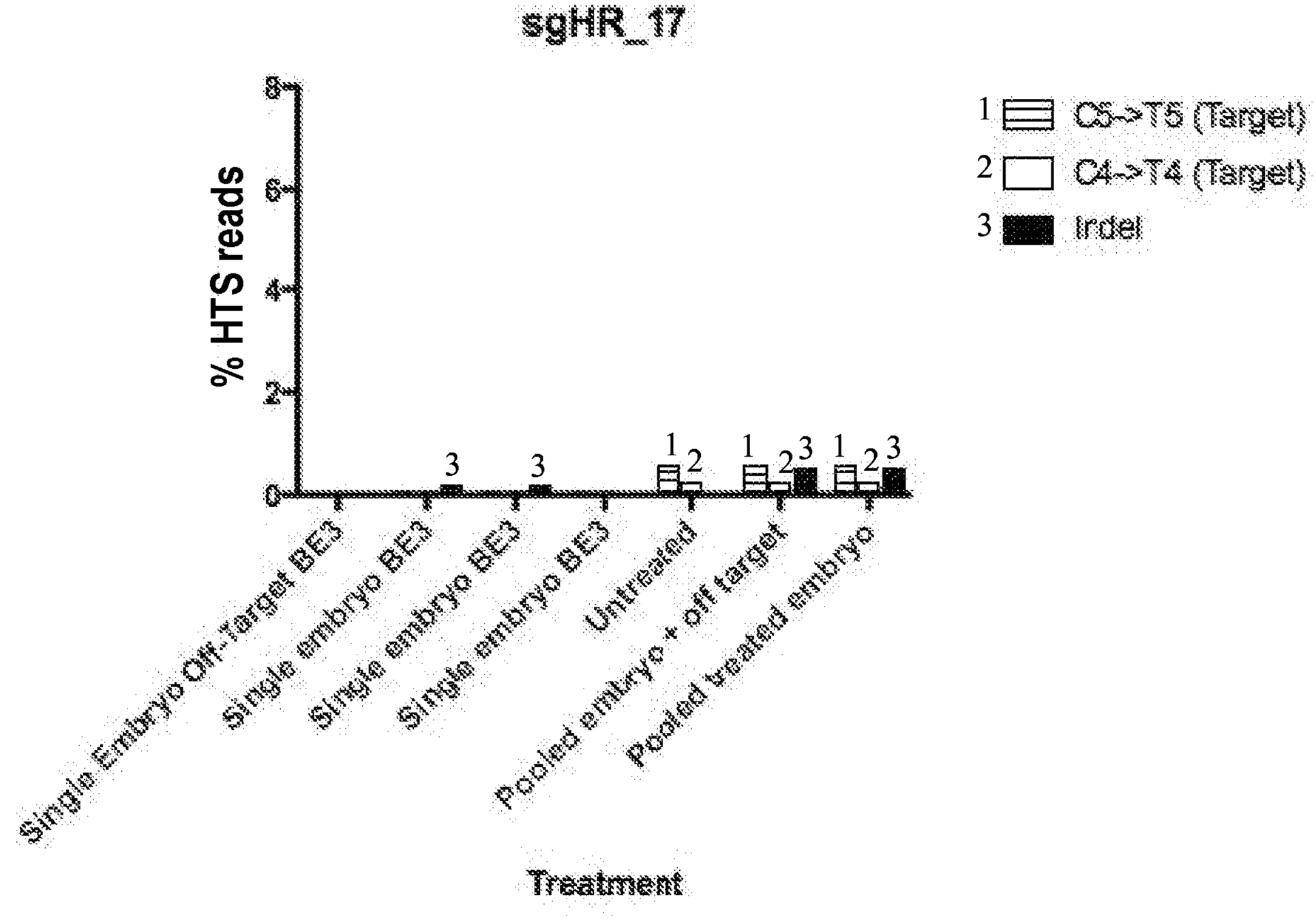

sgHR_17
% HTS reads
0
2
4
6
8
1 C5->T5 (Target)
2 C4->T4 (Target)
3 Indel
3
3
1 2
1 2 3
1 2 3
Single Embryo Off-Target BE3
Single embryo BE3
Single embryo BE3
Single embryo BE3
Untreated
Pooled embryo + off target
Pooled treated embryo
Treatment

FIGURE 85

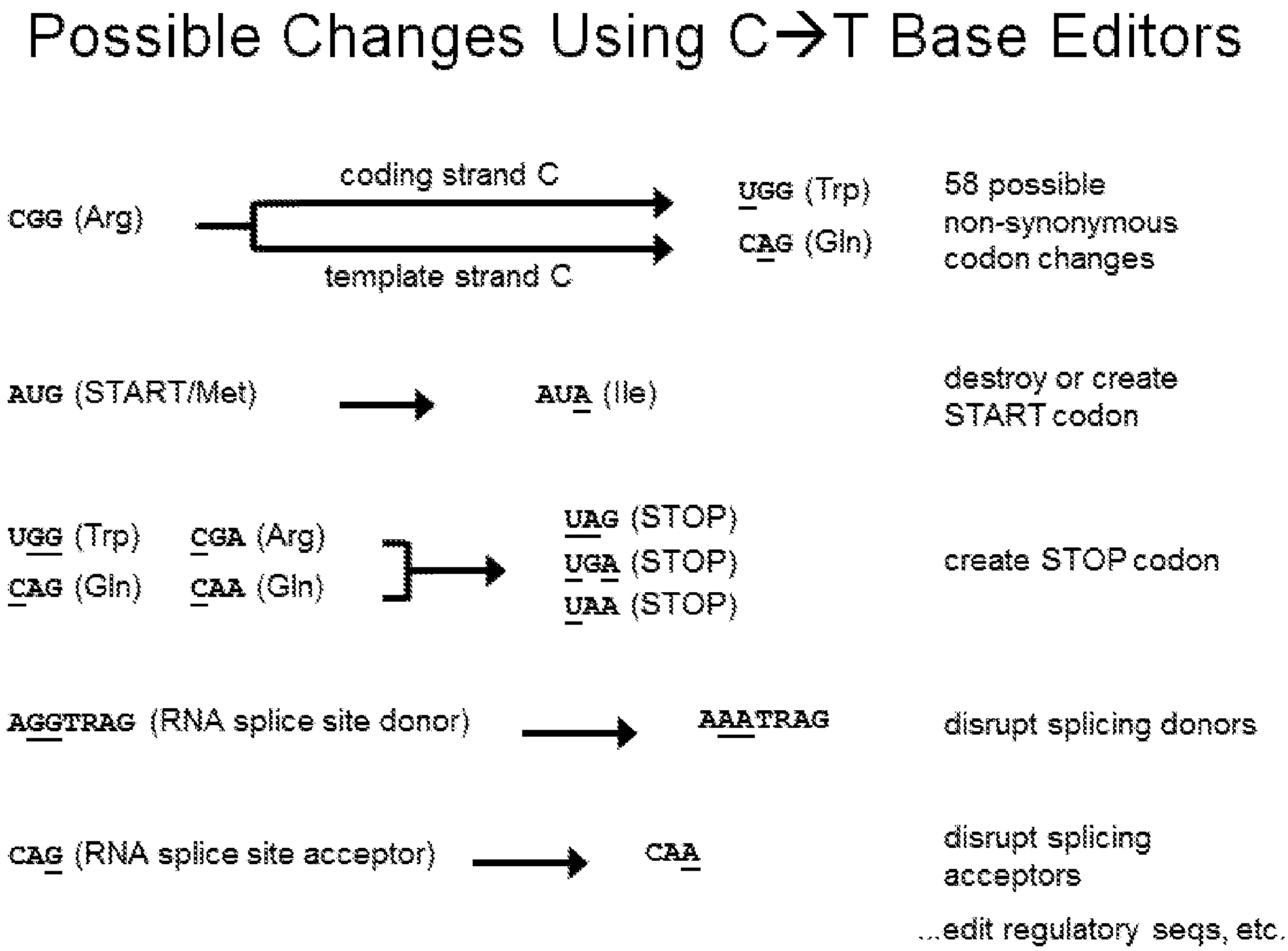
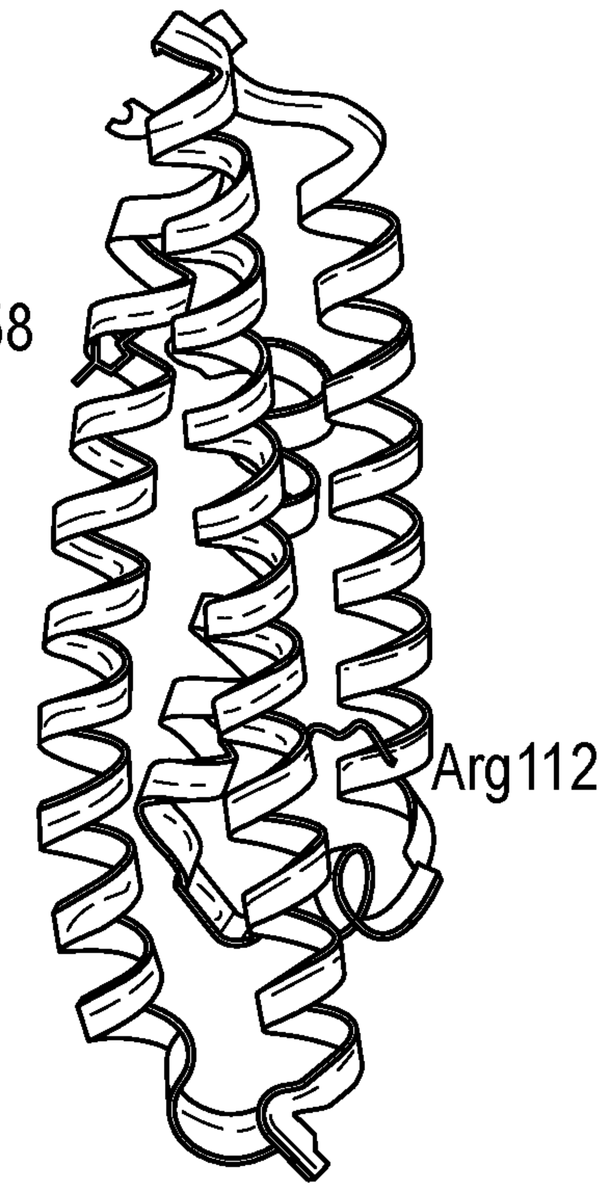

Possible Changes Using C→T Base Editors
coding strand C
CGG (Arg)
template strand C
UGG (Trp)
CAG (Gln)
58 possible non-synonymous codon changes
AUG (START/Met)
AUA (Ile)
destroy or create START codon
UGG (Trp)
CGA (Arg)
CAG (Gln)
CAA (Gln)
UAG (STOP)
UGA (STOP)
UAA (STOP)
create STOP codon
AGGTRAG (RNA splice site donor)
AAATRAG
disrupt splicing donors
CAG (RNA splice site acceptor)
CAA
disrupt splicing acceptors
...edit regulatory seqs, etc.

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 CGC	high

BE3

FIGURE 87

untreated		Lys			Arg 158			Leu			Ala			Val			Tyr			Gln				indel %
APOE4 C158R	G	A	A	G	C_5	G	C	C	T	G	G	C	A	G	T	G	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	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	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	100.0	0.0	0.0	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	0.0	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	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	0.0	

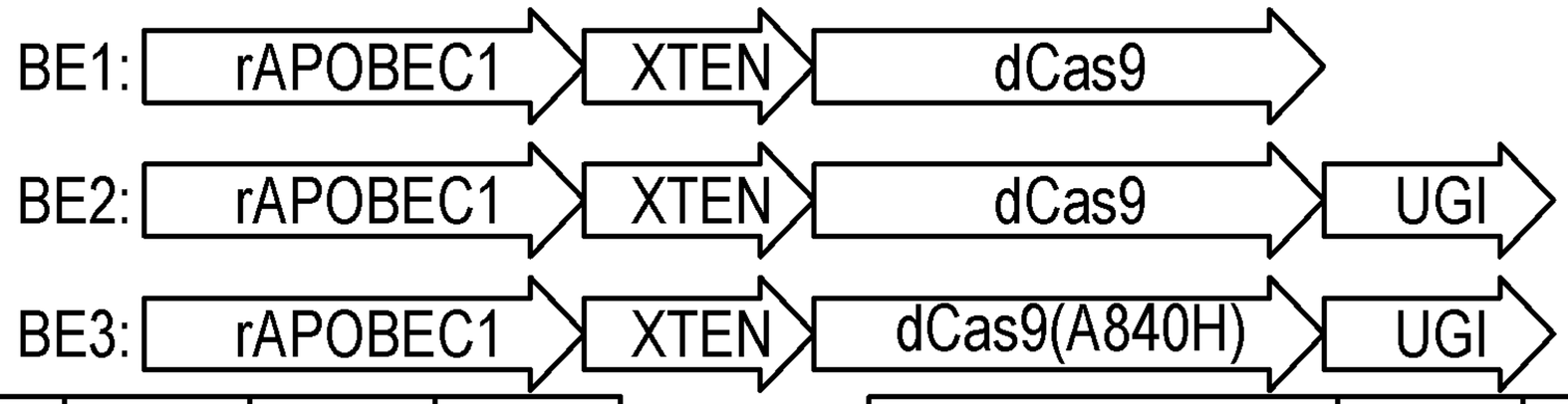
Cas9 + HDR		Lys			Arg 158 → Cys			Leu			Ala			Val			Tyr			Gln				indel%
APOE4 C158R	G	A	A	G	C_5	G	C	C	T	G	G	C	A	G	T	G	T	A	C	C	A	G	G	**26.1**
A	0.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.4	0.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	
C	0.0	0.0	0.0	0.0	99.7	0.0	99.9	99.9	0.0	0.0	0.0	100.0	0.5	0.0	0.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0	0.0	
G	100.0	0.0	0.0	100.0	0.0	100.0	0.0	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	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%
APOE4 C158R	G	A	A	G	C_5	G	C_7	C_8	T	G	G	C	A	G	T	G	T	A	C	C	A	G	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	0.0	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	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	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	0.0	

FIGURE 88

BE3-treated	Gly			*Ser* → *Ser*			*Arg 37* → *Stop*			Tyr			Pro			Gly			Glu				
PRNP R37X	G	G	C	A	G	C_7	C_8	G	A	T	A	C	C	C	G	G	G	G	C	A	G	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	0.0	100.0	0.0	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	0.0	100.0	0.0	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	100.0	0.0	0.0	100.0	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	0.0	0.0

FIGURE 89



EMX1-parental		C_5	C_6	C_{10}	indel %
untreated	A	0.0%	0.0%	0.0%	0.01%
	C	100.0%	100.0%	100.0%	
	G	0.0%	0.0%	0.0%	
	T	0.0%	0.0%	0.0%	
BE1	A	0.4%	0.1%	0.0%	0.18%
	C	95.8%	97.4%	100.0%	
	G	0.9%	0.2%	0.0%	
	T	2.9%	2.3%	0.0%	
BE2	A	0.3%	0.1%	0.0%	0.15%
	C	94.9%	95.7%	100.0%	
	G	1.0%	0.1%	0.0%	
	T	3.8%	4.0%	0.0%	
BE3	A	1.4%	0.8%	0.0%	2.54%
	C	78.5%	84.7%	100.0%	
	G	3.0%	1.4%	0.0%	
	T	17.1%	13.0%	0.0%	

EMX1-UDG KO		C_5	C_6	C_{10}	indel %
untreated	A	0.0%	0.0%	0.0%	0.01%
	C	99.9%	99.9%	100.0%	
	G	0.0%	0.0%	0.0%	
	T	0.1%	0.1%	0.0%	
BE1	A	0.0%	0.0%	0.0%	0.04%
	C	76.5%	76.6%	100.0%	
	G	0.0%	0.0%	0.0%	
	T	23.5%	23.4%	0.0%	
BE2	A	0.0%	0.0%	0.0%	0.02%
	C	96.3%	96.3%	100.0%	
	G	0.0%	0.0%	0.0%	
	T	3.7%	3.7%	0.0%	
BE3	A	0.0%	0.0%	0.0%	0.04%
	C	84.5%	86.8%	100.0%	
	G	0.0%	0.0%	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%	
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	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	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%	

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	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	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	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%	

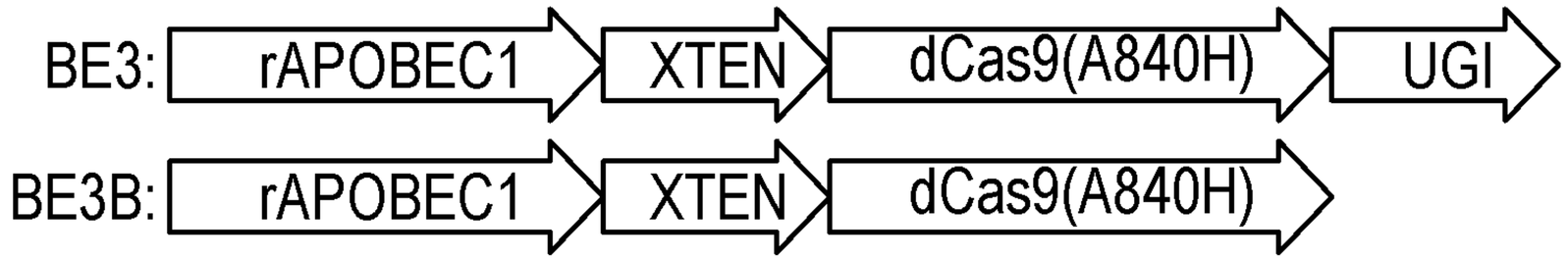
FIGURE 90 (CONTINUED)

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	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	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	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%	

(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%	
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	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	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%	

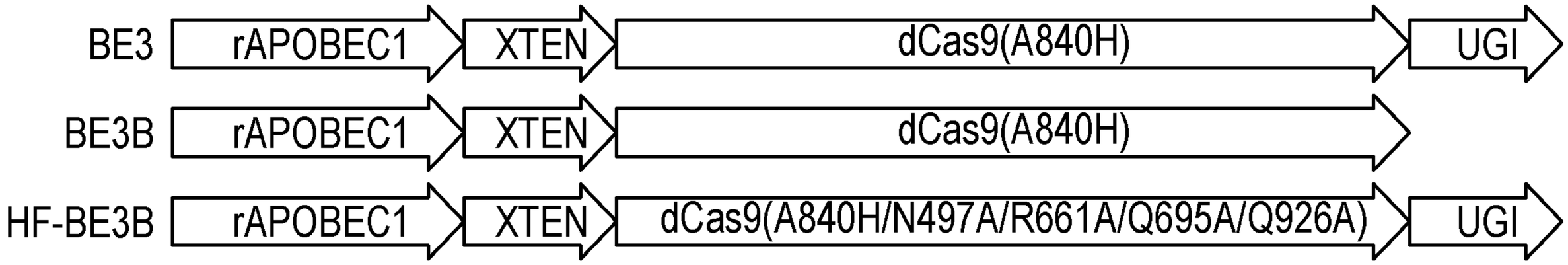
FIGURE 90



EMX1		C_3	C_6	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	
BE3B	A	4.9 ± 1.4	3.9 ± 1.1	0 ± 0	11.6 ± 2.6
	C	52.6 ± 12.1	61.9 ± 10.5	99.9 ± 0	
	G	12.3 ± 3.3	11.3 ± 3.1	0 ± 0	
	T	30.1 ± 7.3	22.7 ± 6.1	0 ± 0	

FANCF		C_6	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	
BE3B	A	2.9 ± 0.9	4.1 ± 1.4	2.8 ± 0.9	1.1 ± 0	20.5 ± 3.8
	C	67.3 ± 8.8	79.3 ± 5.8	79.5 ± 5.2	92 ± 1.9	
	G	2 ± 0.5	0.7 ± 0.3	0.9 ± 0.2	0.5 ± 0.1	
	T	27.7 ± 7.3	15.6 ± 4	16.5 ± 4	6.1 ± 1.3	

FIGURE 91



HEK3		C_6	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	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	7.7 ± 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		C_6	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	
BE3B	A	0 ± 0	10.6 ± 2.6	0.3 ± 0	0 ± 0	7.6 ± 0.7
	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)

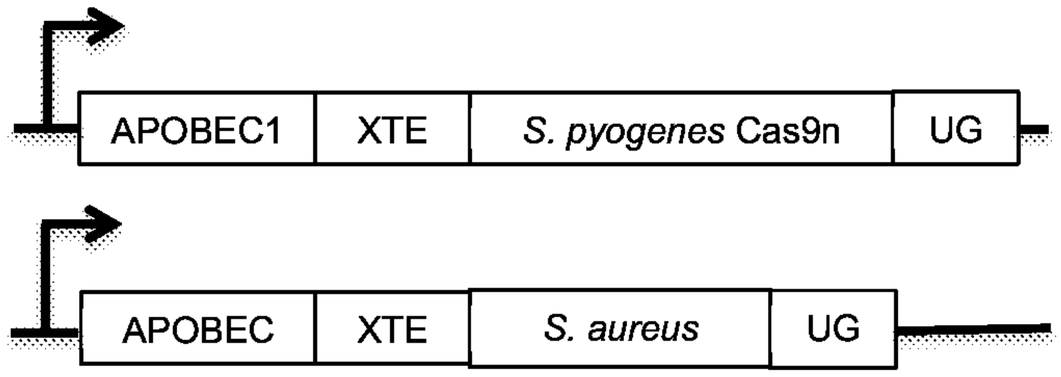


FIGURE 92A

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

FIGURE 92B

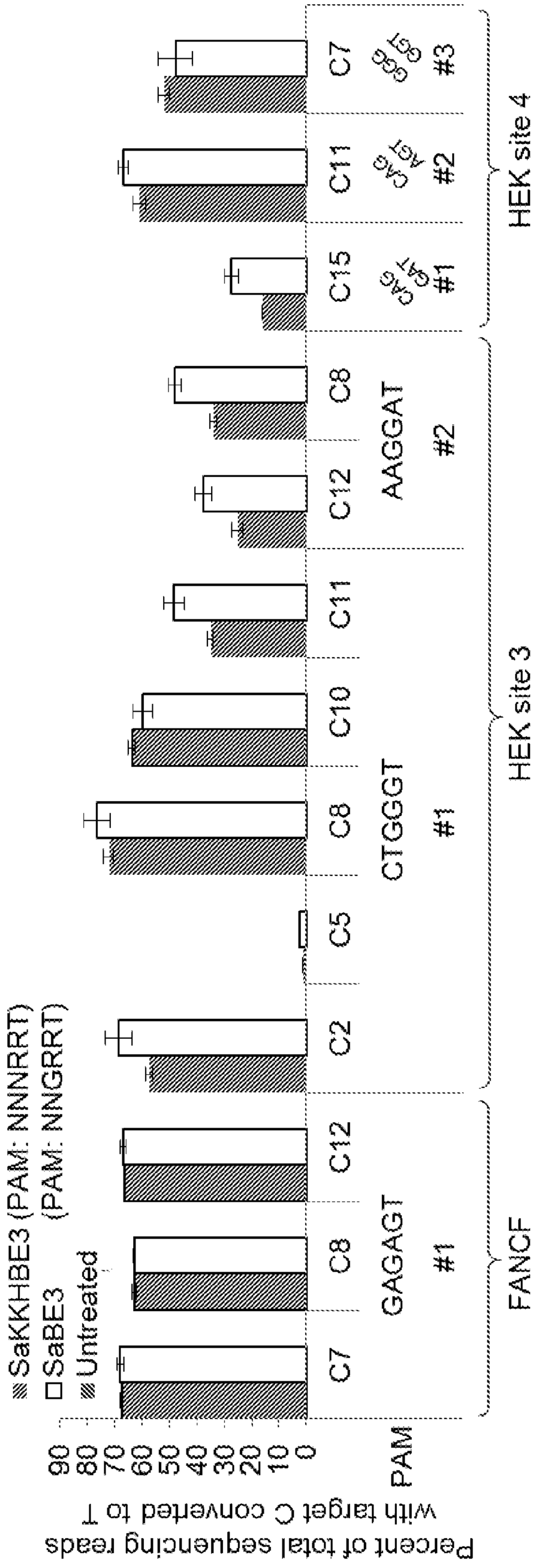

SaKKHBE3 (PAM: NNNRRT)
SaBE3 (PAM: NNGRRT)
Untreated
Percent of total sequencing reads with target C converted to T
PAM
90
80
70
60
50
40
30
20
10
0
FANCF
GAGAGT
#1
C7
C8
C12
C2
HEK site 4
CTGGGT
#1
C5
C8
C10
HEK site 3
AAGGAT
#2
C11
C12
C8
C10
HEK site 4
CAGGAT
#2
C11
C7
GGGGGT
#3
C15
CAGGAT
#1

FIGURE 92C

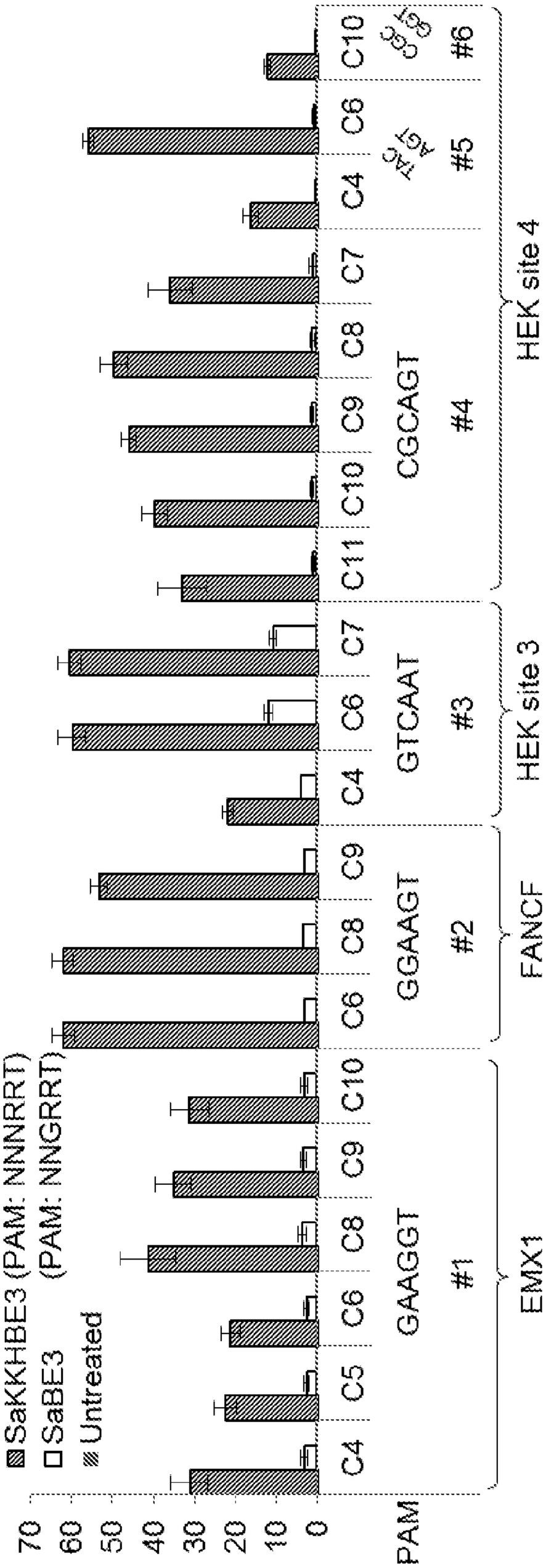

SaKKHBE3 (PAM: NNNRRT)
SaBE3 (PAM: NNGRRT)
Untreated
Percent of total sequencing reads with target C converted to T
PAM
C4
C5
C6
C8
C9
C10
GAAGGT
#1
EMX1
C4
C6
C7
C8
C9
C10
C11
GTCAAT
CGCAGT
#3
#4
HEK site 3
HEK site 4
C6
C8
C9
C10
GGAAGT
#2
FANCF
C4
C6
TAC AGT
#5
C7
C8
C9
C10
CGC CGT
#6
HEK site 4

FIGURE 92D

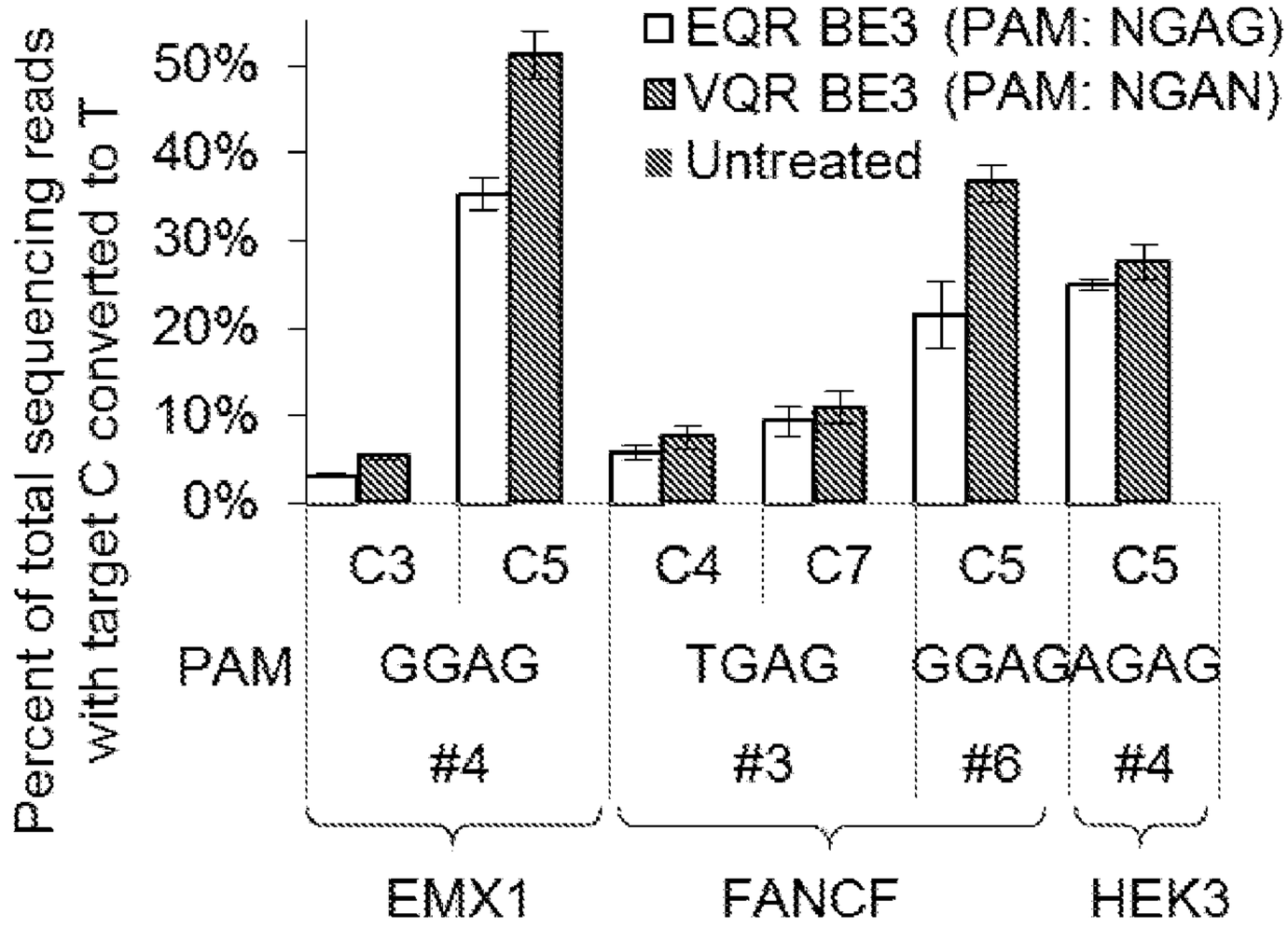


FIGURE 92E

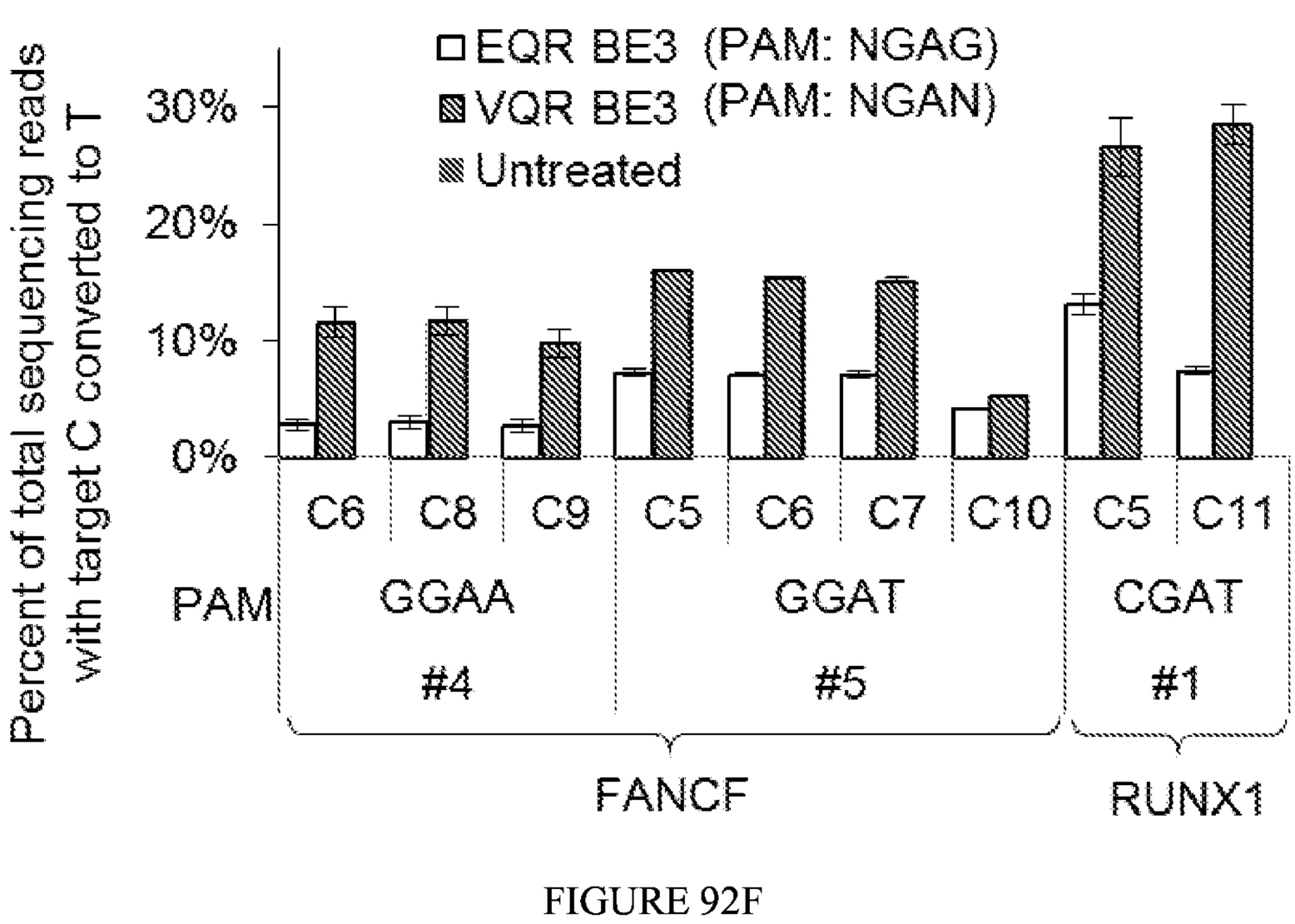


FIGURE 92F

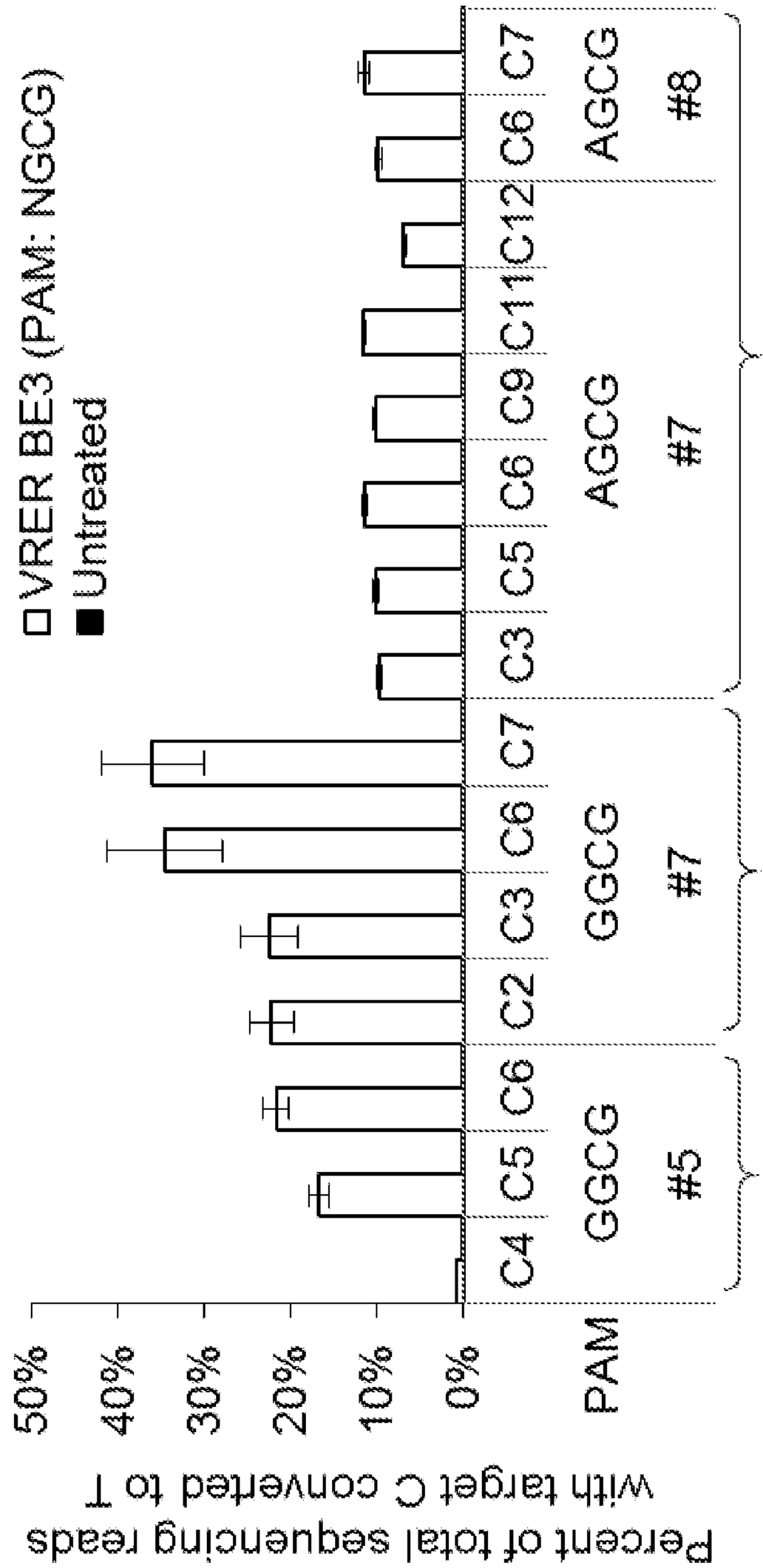

Percent of total sequencing reads with target C converted to T
50%
40%
30%
20%
10%
0%
PAM
HEK3
HEK4
FANCF
#5
#7
#7
#8
GGCG
AGCG
AGCG
AGCG
C4 C5 C6
C2 C3 C6
C3 C6 C7
C3 C5 C6 C9 C11 C12 C6 C7
Untreated
VRER BE3 (PAM: NGCG)

FIGURE 92G

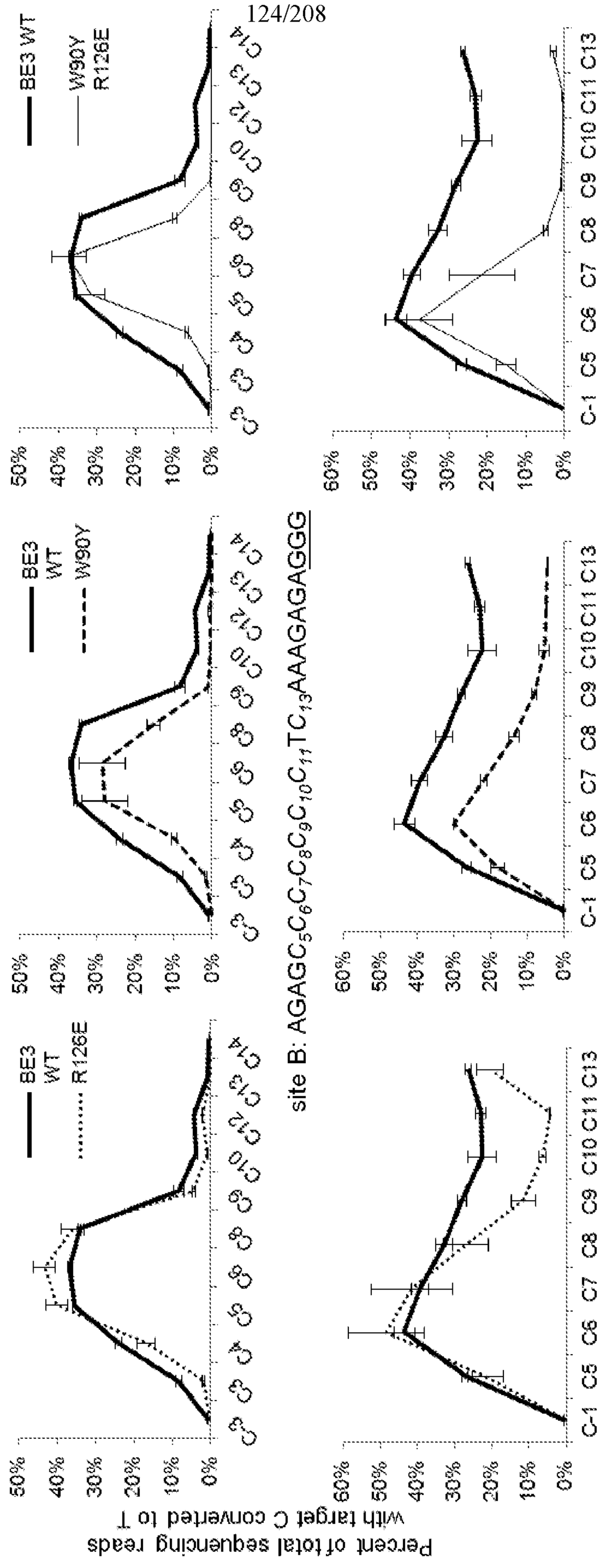
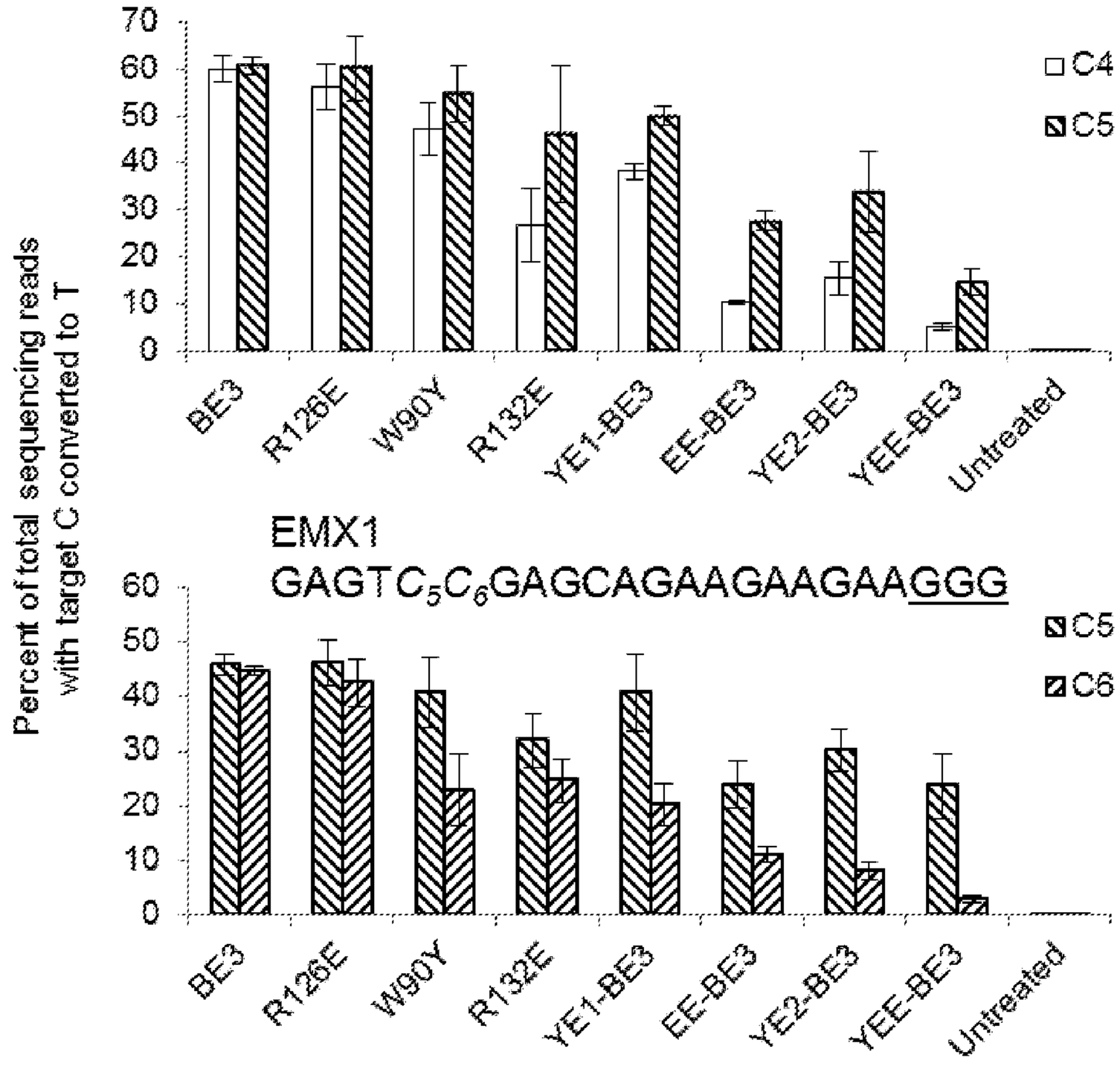

site A: TGC3C4C5C6TC8C9C10TC12C13C14TGGCCCAGG
site B: AGAGC5C6C7C8C9C10C11TC13AAAGAGGGG
BE3 WT
W90Y
R126E
BE3
WT
W90Y
R126E
Percent of total sequencing reads with target C converted to T
50%
40%
30%
20%
10%
0%
60%
C-1 C3 C4 C5 C6 C7 C8 C9 C10 C11 C13
C-1 C5 C6 C7 C8 C9 C10 C11 C13

FIGURE 93A


HEK site 3
GGCC4C5AGACTGAGCACGTGATGG
C4
C5
Percent of total sequencing reads with target C converted to T
70
60
50
40
30
20
10
0
BE3
R126E
W90Y
R132E
YE1-BE3
EE-BE3
YE2-BE3
YEE-BE3
Untreated
EMX1
GAGTC5C6GAGCAGAAGAAGAAGGG
C5
C6
60
50
40
30
20
10
0
BE3
R126E
W90Y
R132E
YE1-BE3
EE-BE3
YE2-BE3
YEE-BE3
Untreated

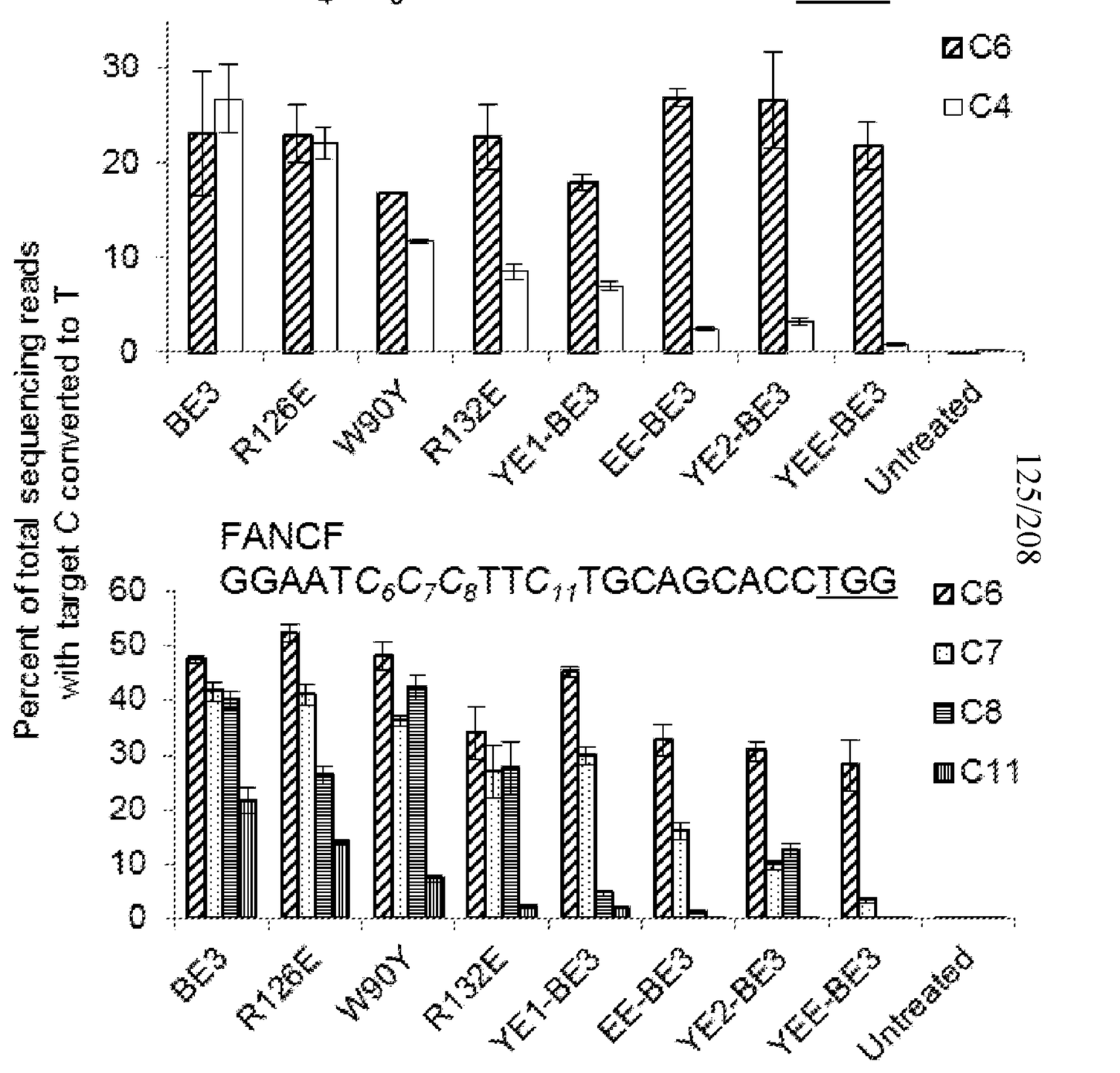

HEK site 2
GAAC4AC6AAAGCATAGACTGCGGG
C6
C4
Percent of total sequencing reads with target C converted to T
30
20
10
0
BE3
R126E
W90Y
R132E
YE1-BE3
EE-BE3
YE2-BE3
YEE-BE3
Untreated
FANCF
GGAATC6C7C8TTC11TGCAGCACCTGG
C6
C7
C8
C11
60
50
40
30
20
10
0
BE3
R126E
W90Y
R132E
YE1-BE3
EE-BE3
YE2-BE3
YEE-BE3
Untreated

FIGURE 93B

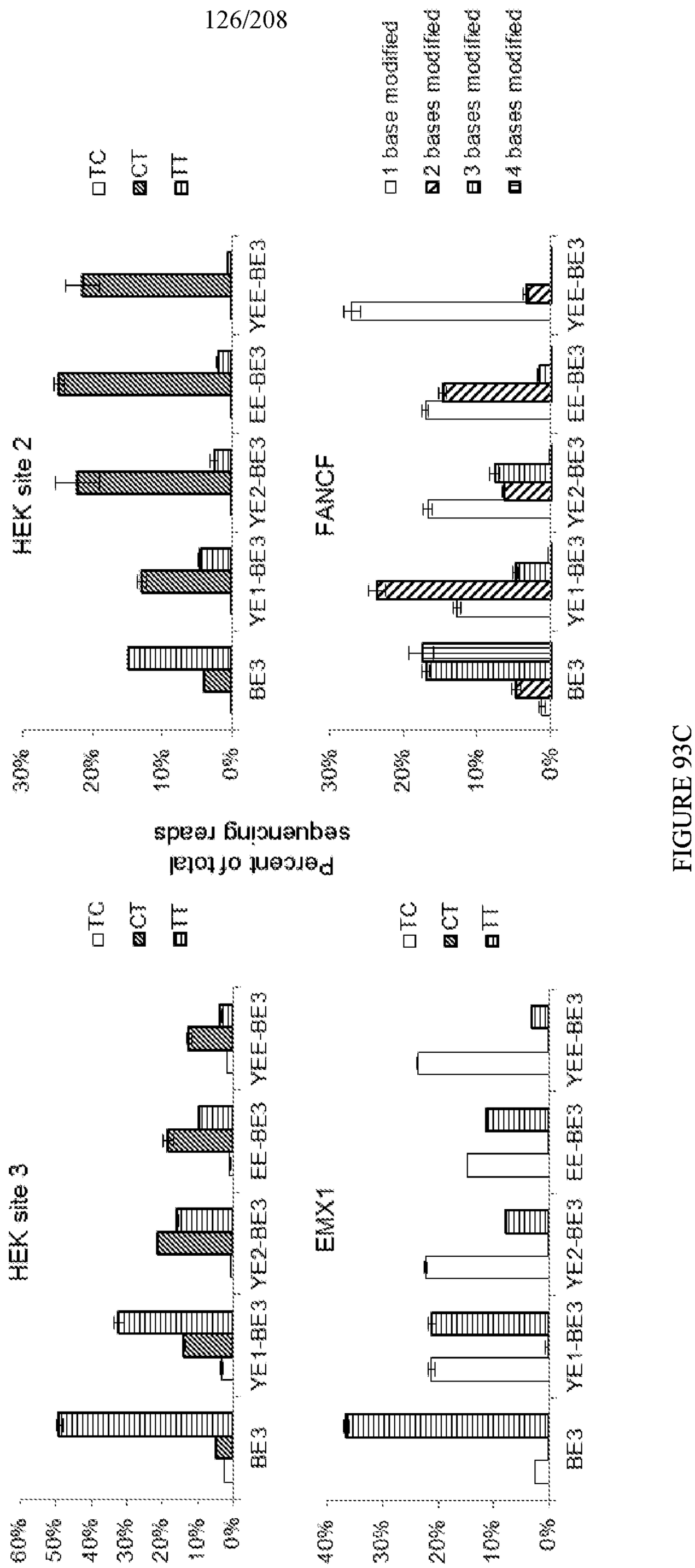

HEK site 2
FANCF
HEK site 3
EMX1
Percent of total sequencing reads
30%
20%
10%
0%
60%
50%
40%
BE3
YE1-BE3
YE2-BE3
EE-BE3
YEE-BE3
TC
CT
TT
1 base modified
2 bases modified
3 bases modified
4 bases modified

FIGURE 93C

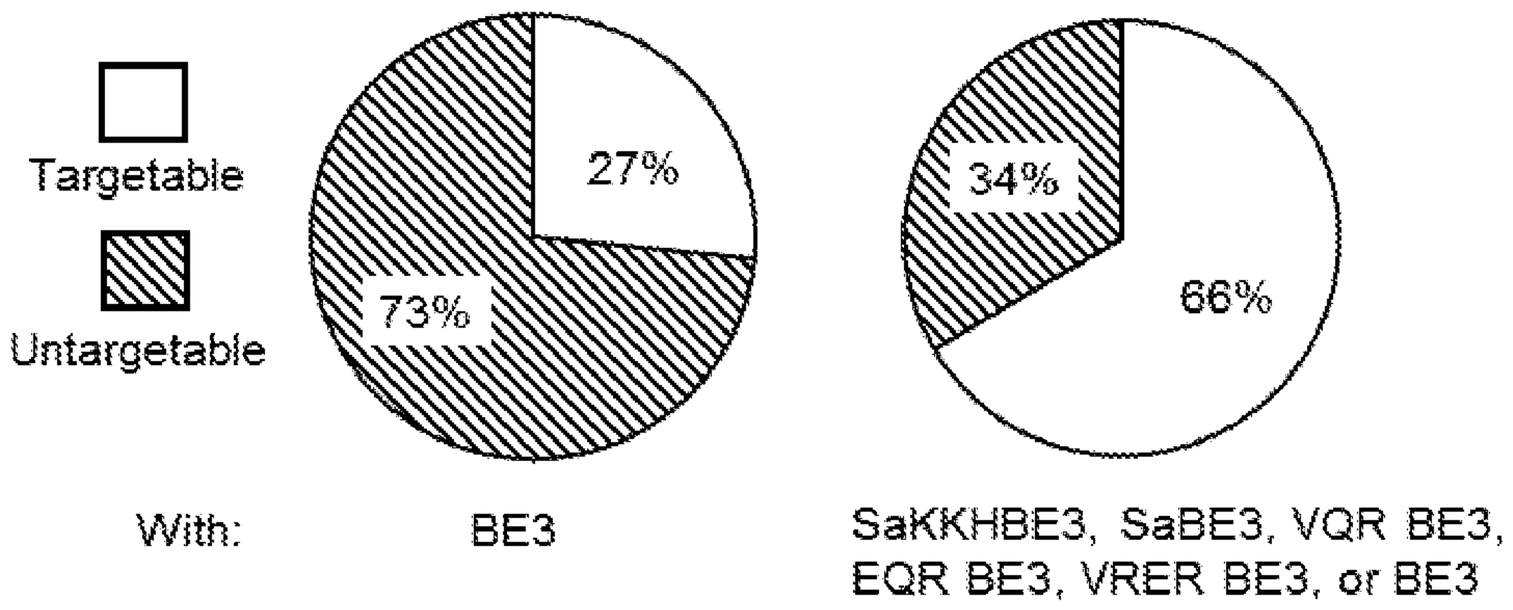


FIGURE 94A

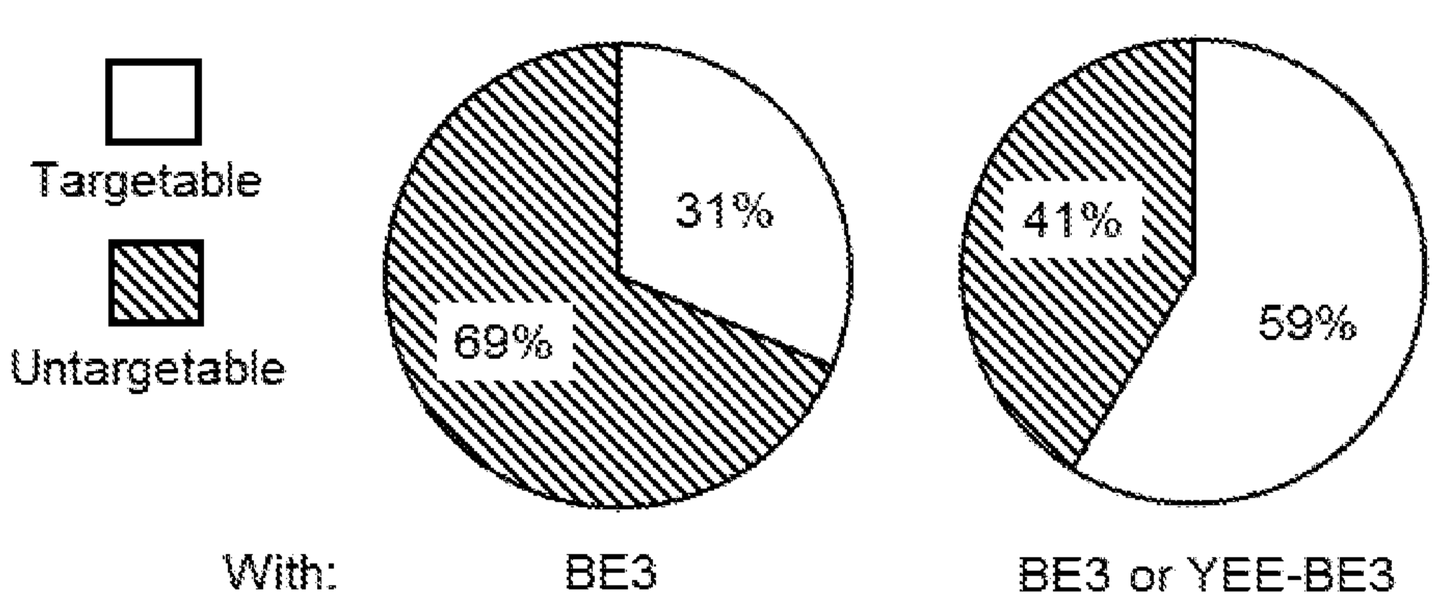


FIGURE 94B

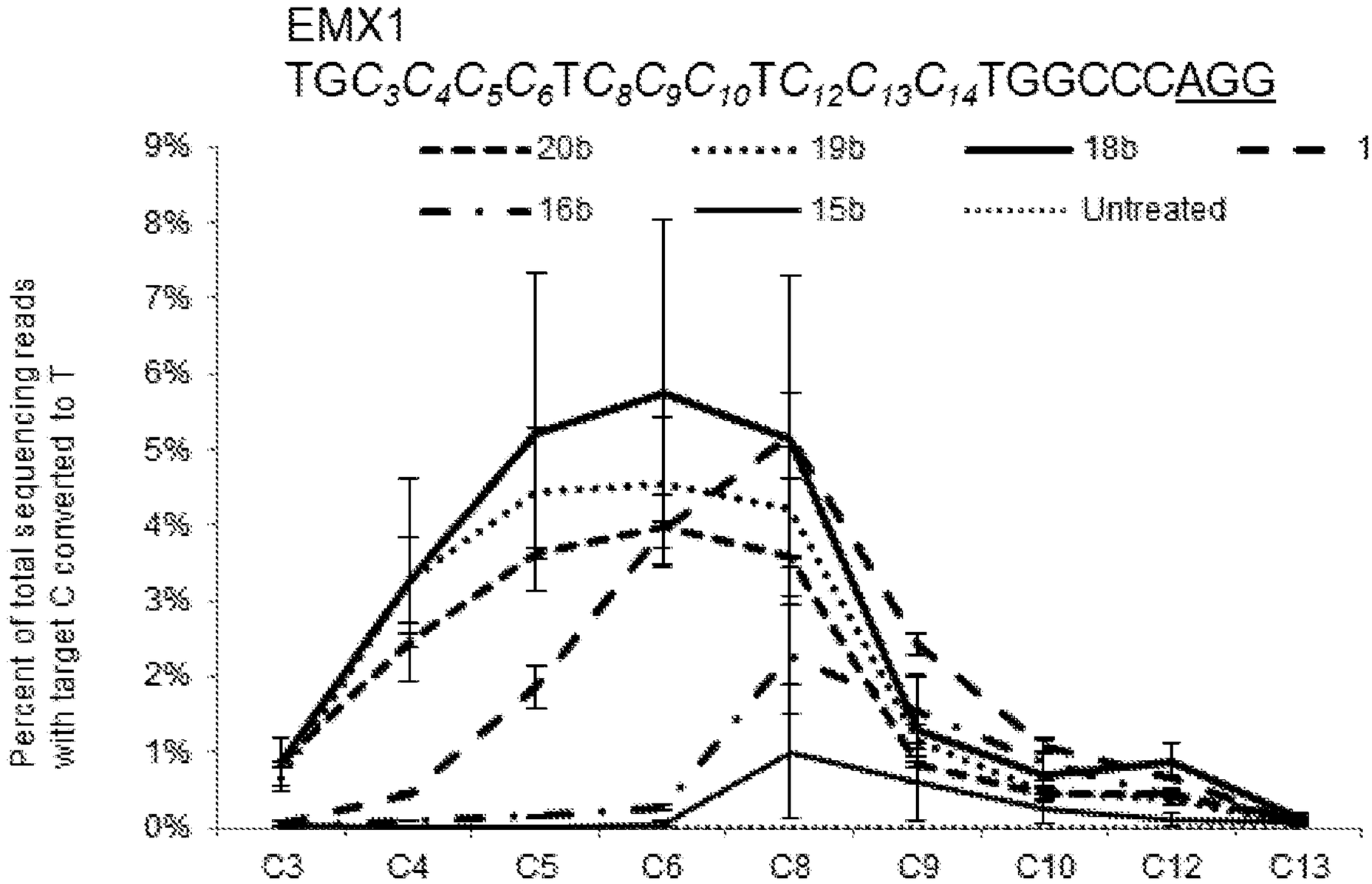

EMX1
TGC3C4C5C6TC8C9C10TC12C13C14TGGCCCAGG
20b
19b
18b
17b
16b
15b
Untreated
Percent of total sequencing reads with target C converted to T
9%
8%
7%
6%
5%
4%
3%
2%
1%
0%
C3
C4
C5
C6
C8
C9
C10
C12
C13

FIGURE 95A

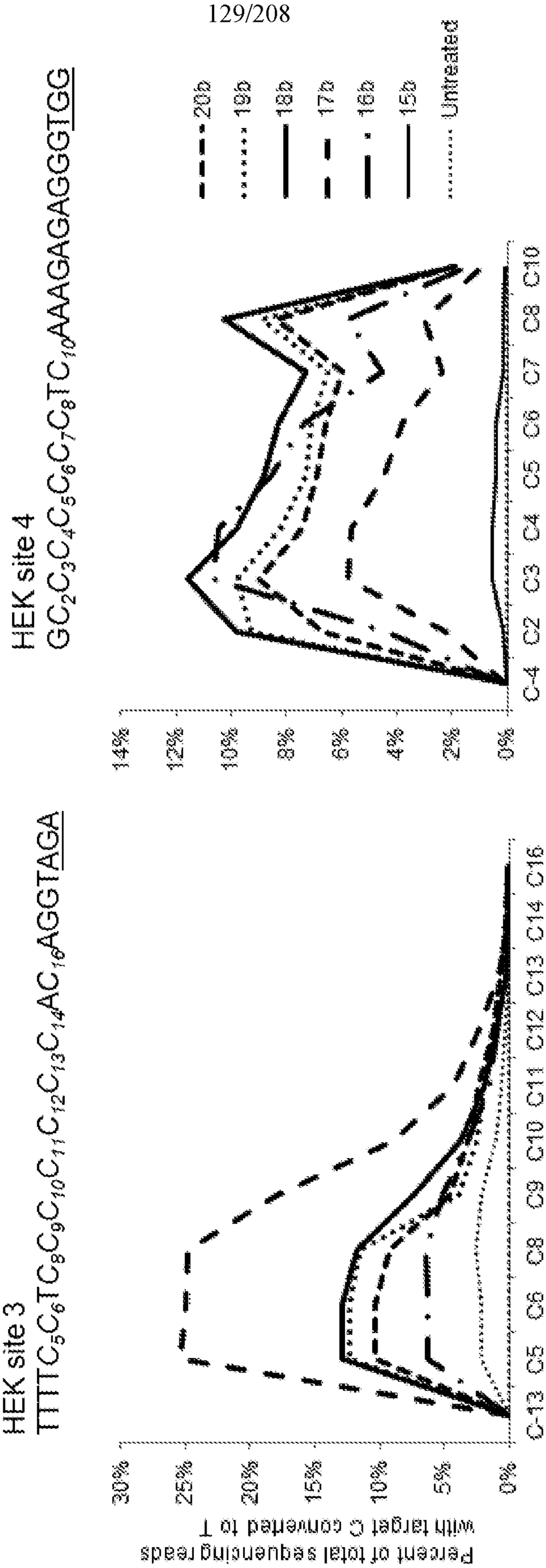

HEK site 4
GC2C3C4C5C6C7C8TC10AAAGAGGTGG
20b
19b
18b
17b
16b
15b
Untreated
14%
12%
10%
8%
6%
4%
2%
0%
C-4 C2 C3 C4 C5 C6 C7 C8 C10
HEK site 3
TTTTC5C6TC8C9C10C11C12C13C14AC16AGGTAGA
C-13 C5 C6 C8 C9 C10 C11 C12 C13 C14 C16
30%
25%
20%
15%
10%
5%
0%
Percent of total sequencing reads
with target C converted to T

FIGURE 95B

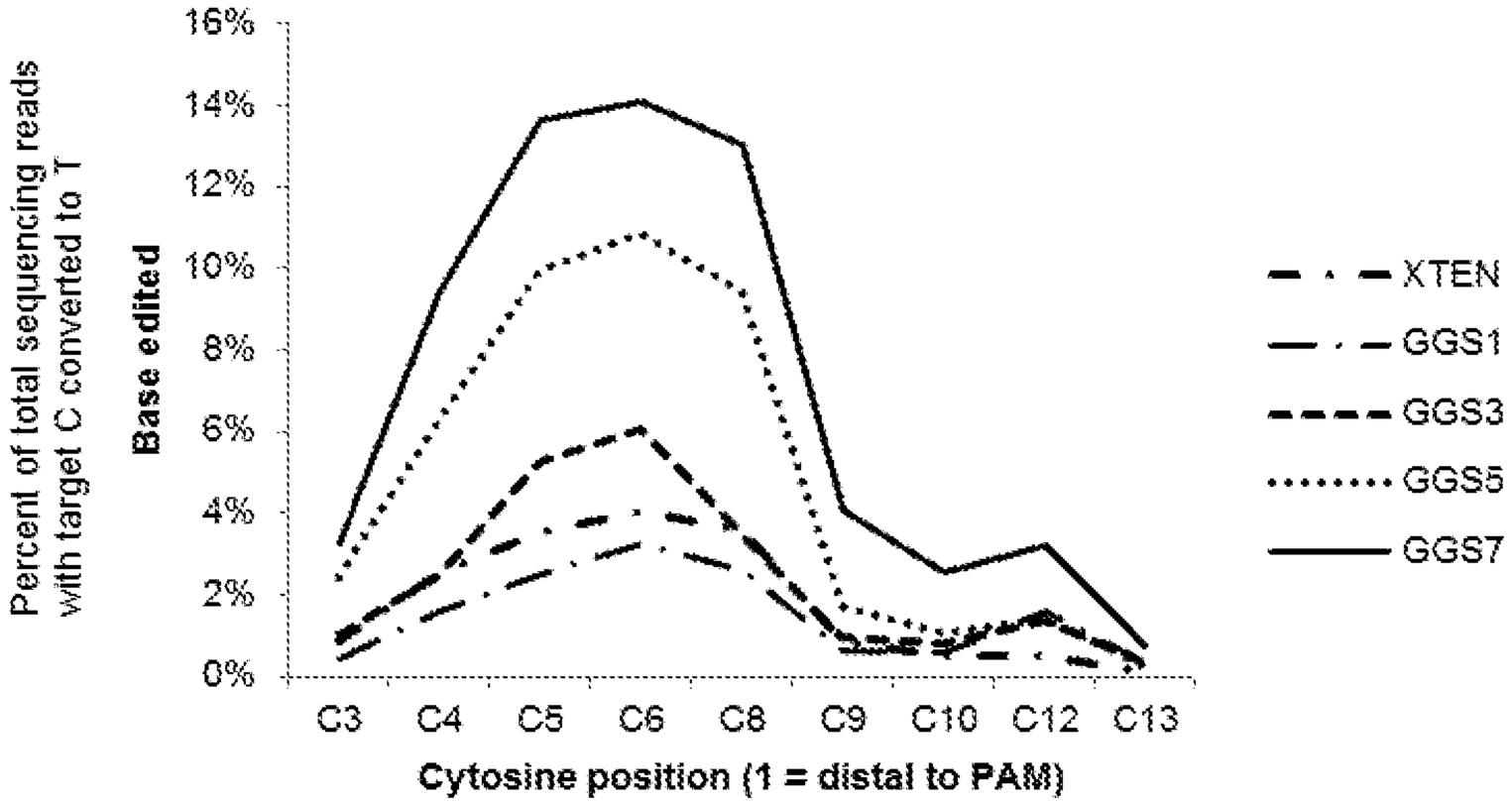


FIGURE 96

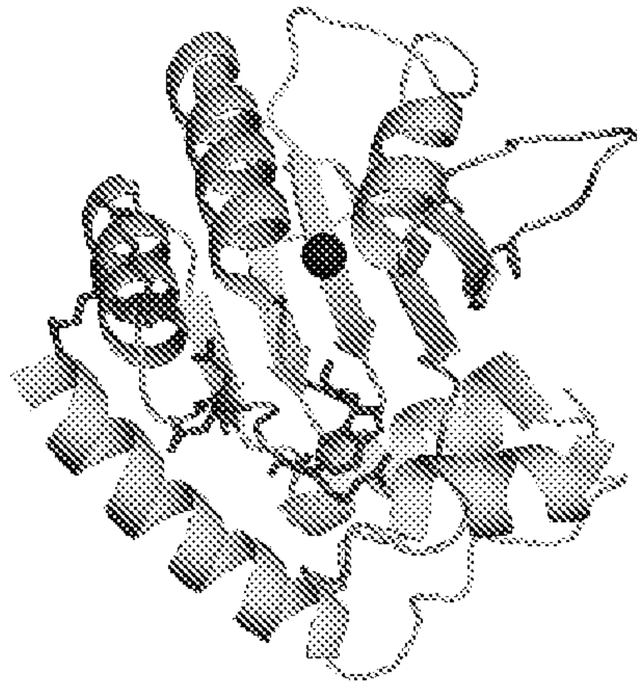


FIGURE 97A

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

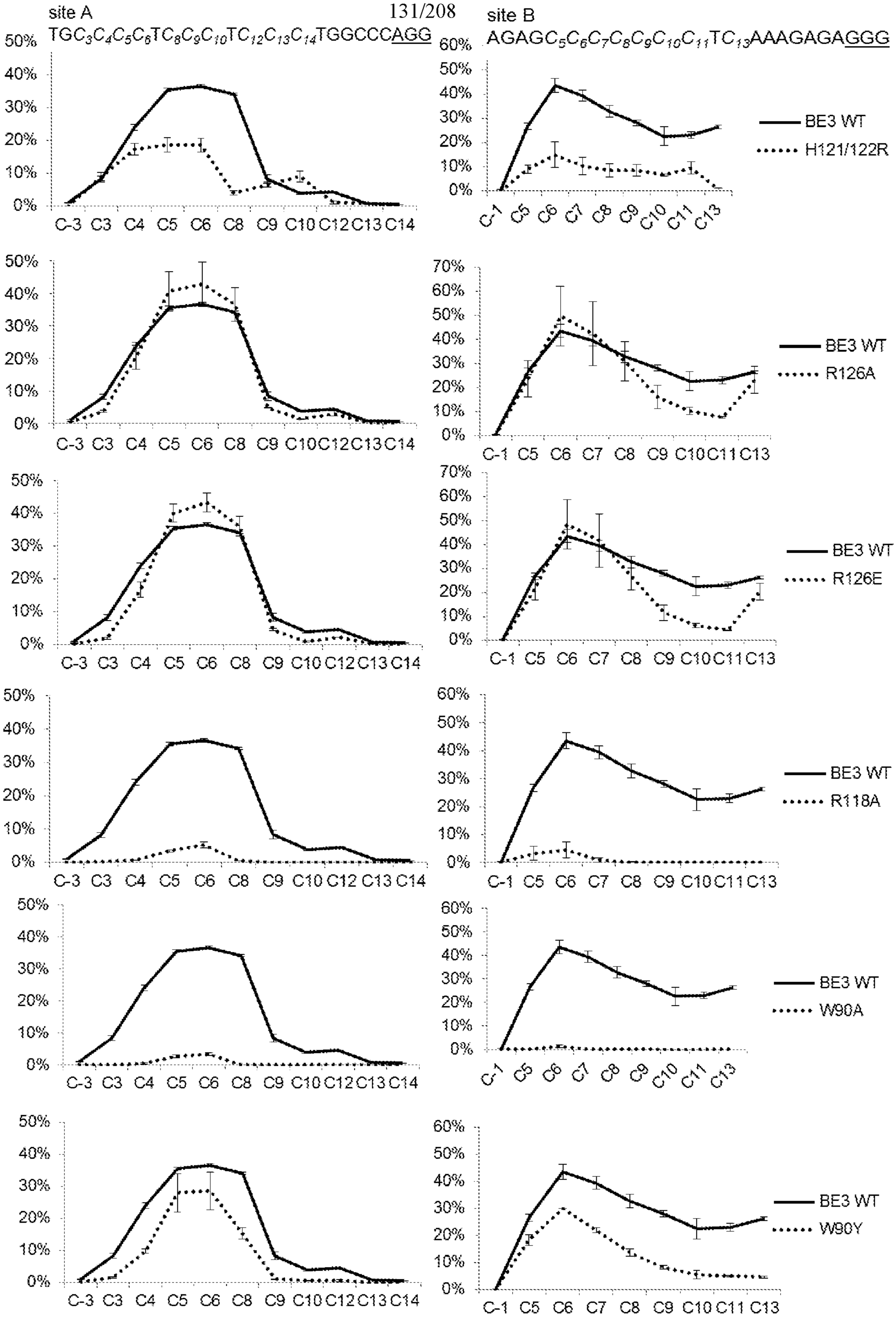
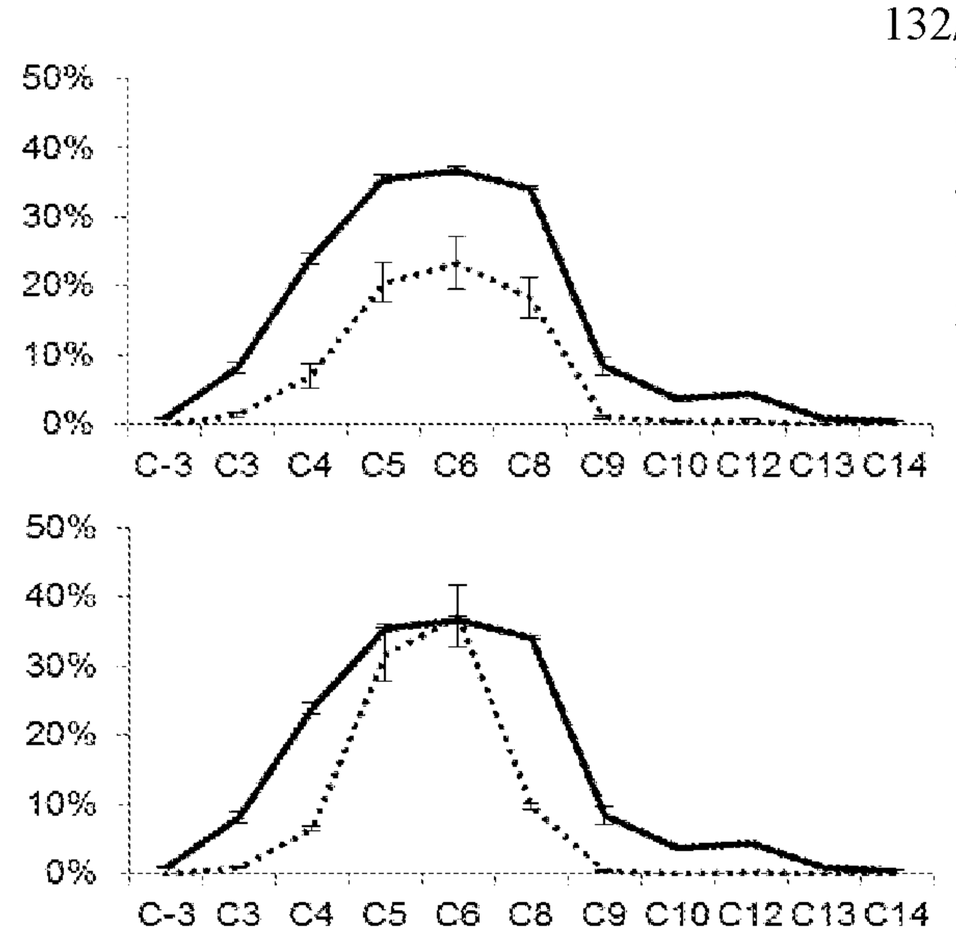
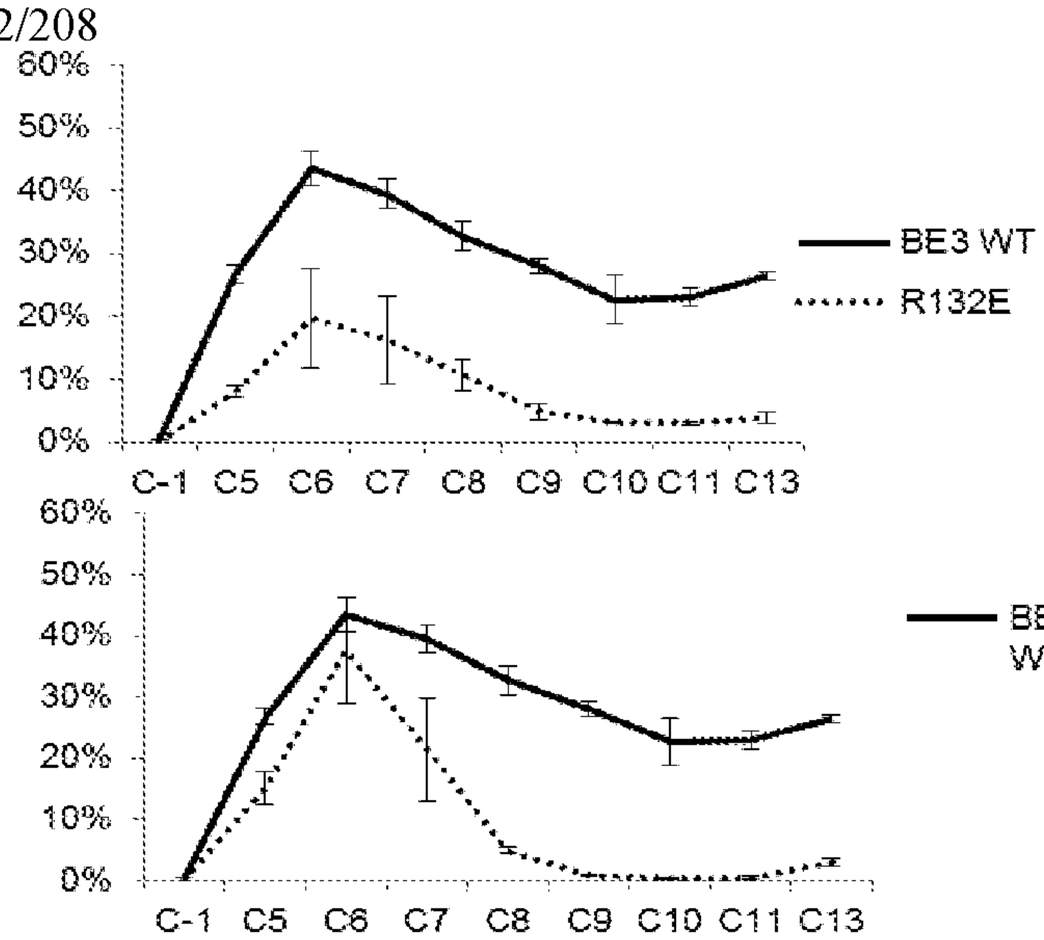
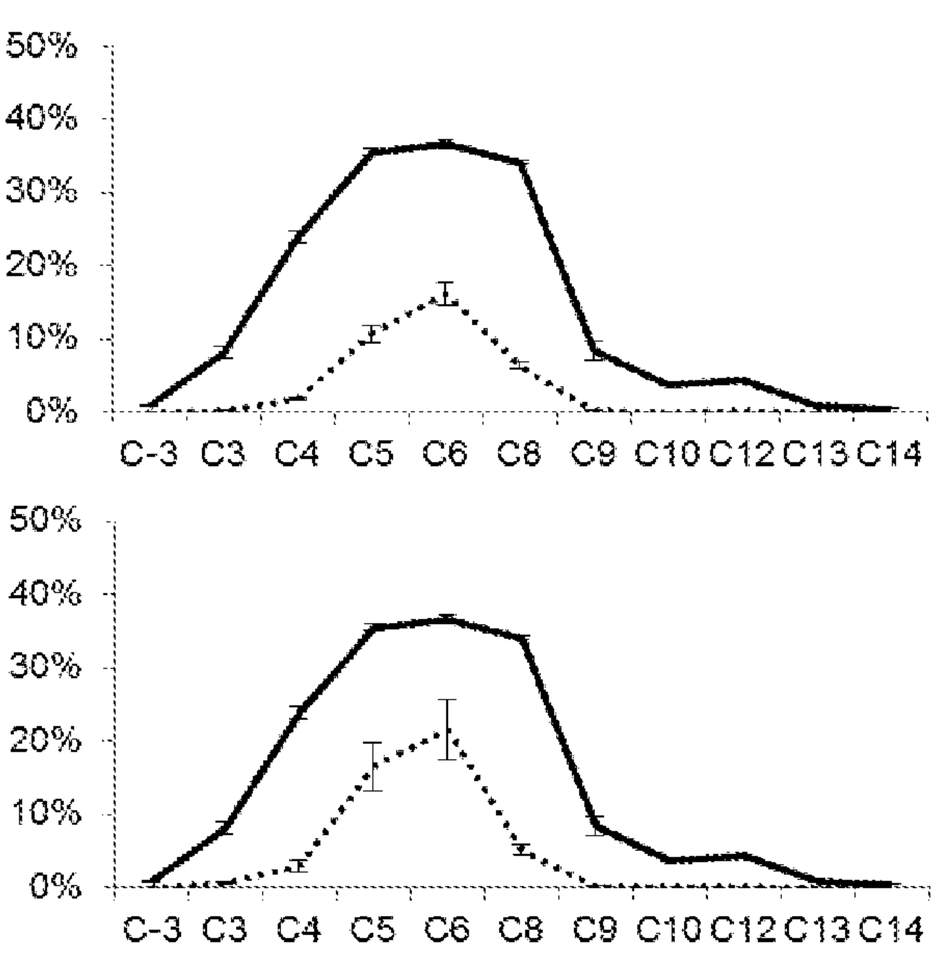
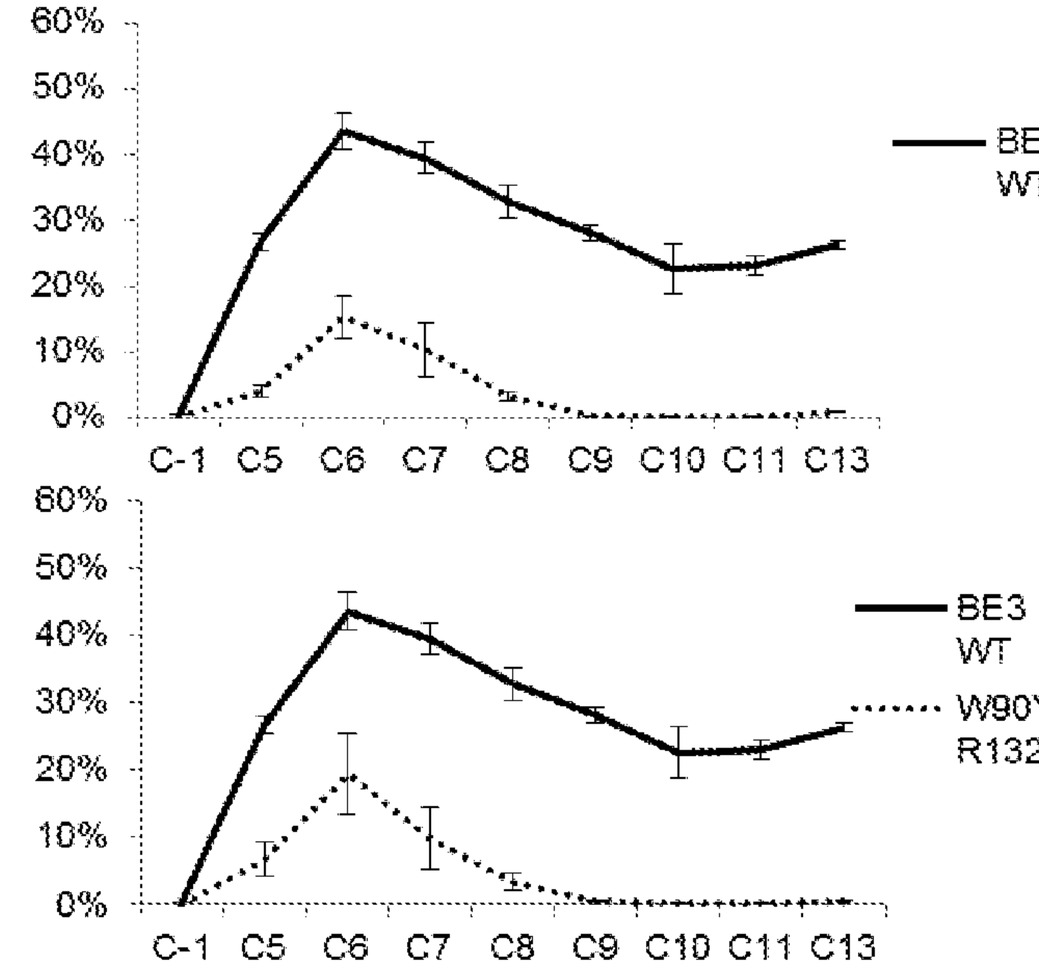

site A
TGC3C4C5C6TC8C9C10TC12C13C14TGGCCCAGG
site B
AGAGC5C6C7C8C9C10C11TC13AAAGAGAGGG
BE3 WT
H121/122R
R126A
R126E
R118A
W90A
W90Y
C-3 C3 C4 C5 C6 C8 C9 C10 C12 C13 C14
C-1 C5 C6 C7 C8 C9 C10 C11 C13

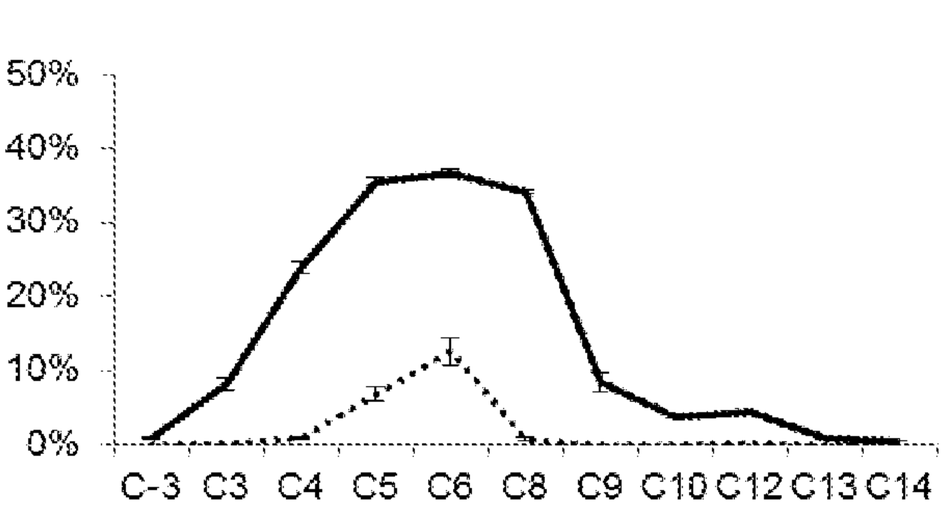
FIGURE 97C

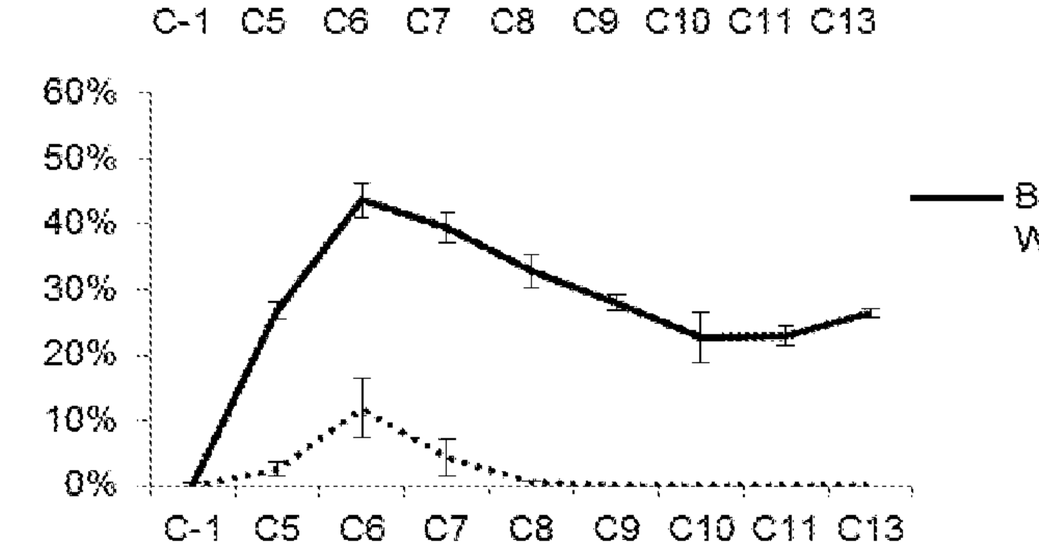












Editing window width

	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)

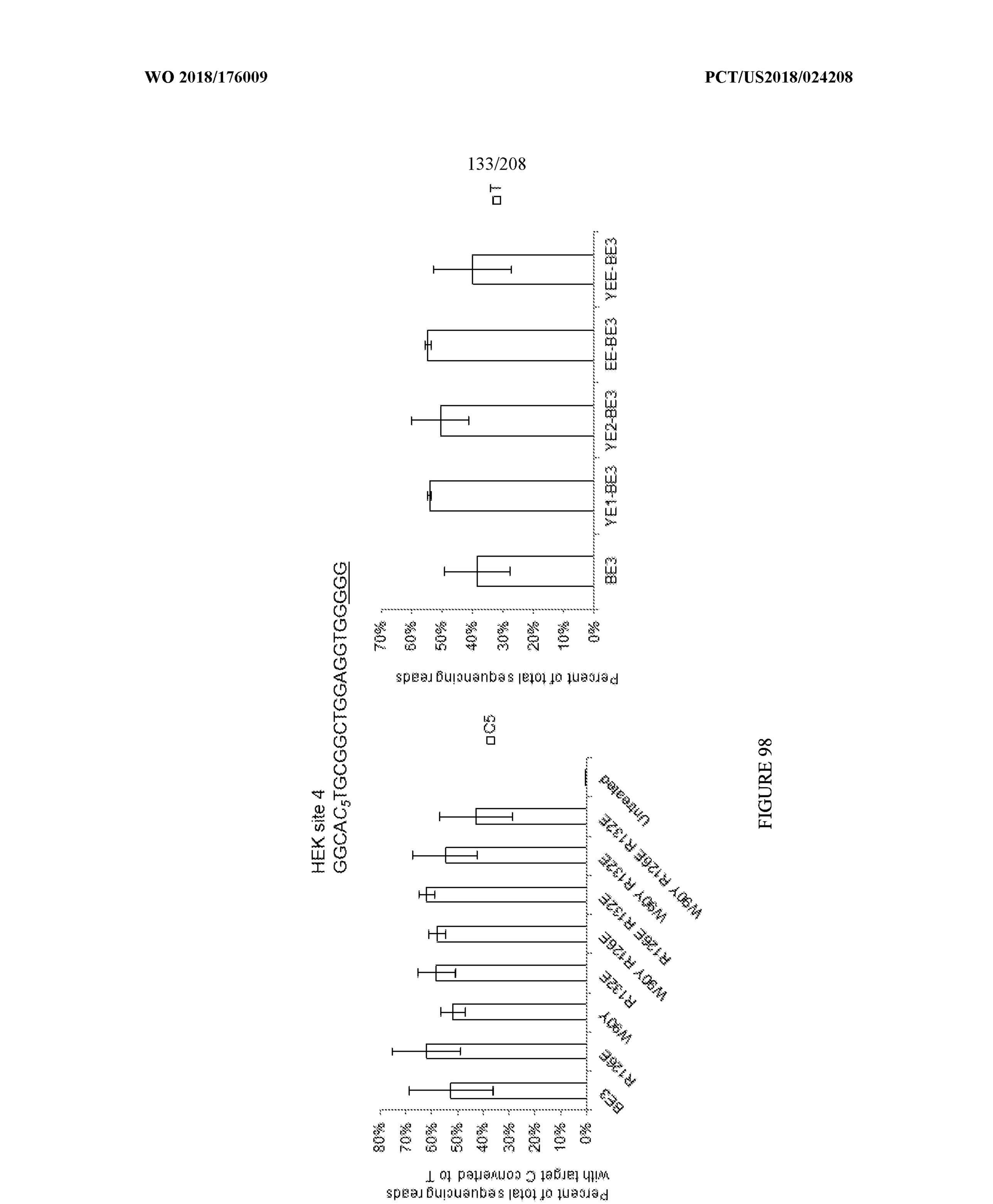

HEK site 4
GGCAC5TGCGGCTGAGGTGGGGG
C5
Untreated
W90Y R126E R132E
W90Y R132E
R126E R132E
W90Y R126E
R132E
W90Y
R126E
BE3
Percent of total sequencing reads with target C converted to T
0%
10%
20%
30%
40%
50%
60%
70%
80%
BE3
YE1-BE3
YE2-BE3
EE-BE3
YEE-BE3
Percent of total sequencing reads
0%
10%
20%
30%
40%
50%
60%
70%

FIGURE 98

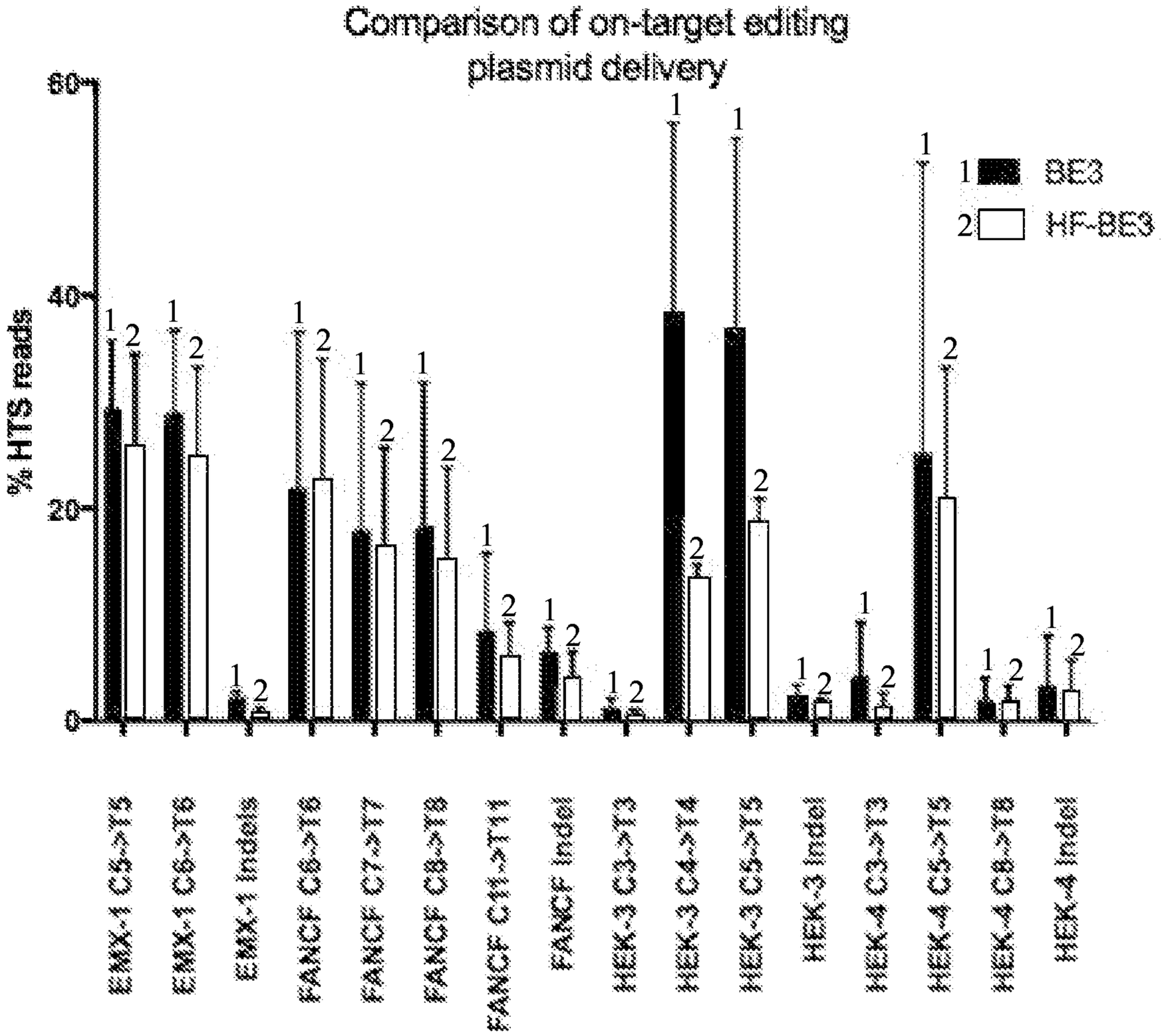

Comparison of on-target editing plasmid delivery
% HTS reads
0
20
40
60
1 BE3
2 HF-BE3
EMX-1 C5->T5
EMX-1 C6->T6
EMX-1 Indels
FANCF C6->T6
FANCF C7->T7
FANCF C8->T8
FANCF C11->T11
FANCF Indels
HEK-3 C3->T3
HEK-3 C4->T4
HEK-3 C5->T5
HEK-3 Indels
HEK-4 C3->T3
HEK-4 C5->T5
HEK-4 C8->T8
HEK-4 Indels

FIGURE 99

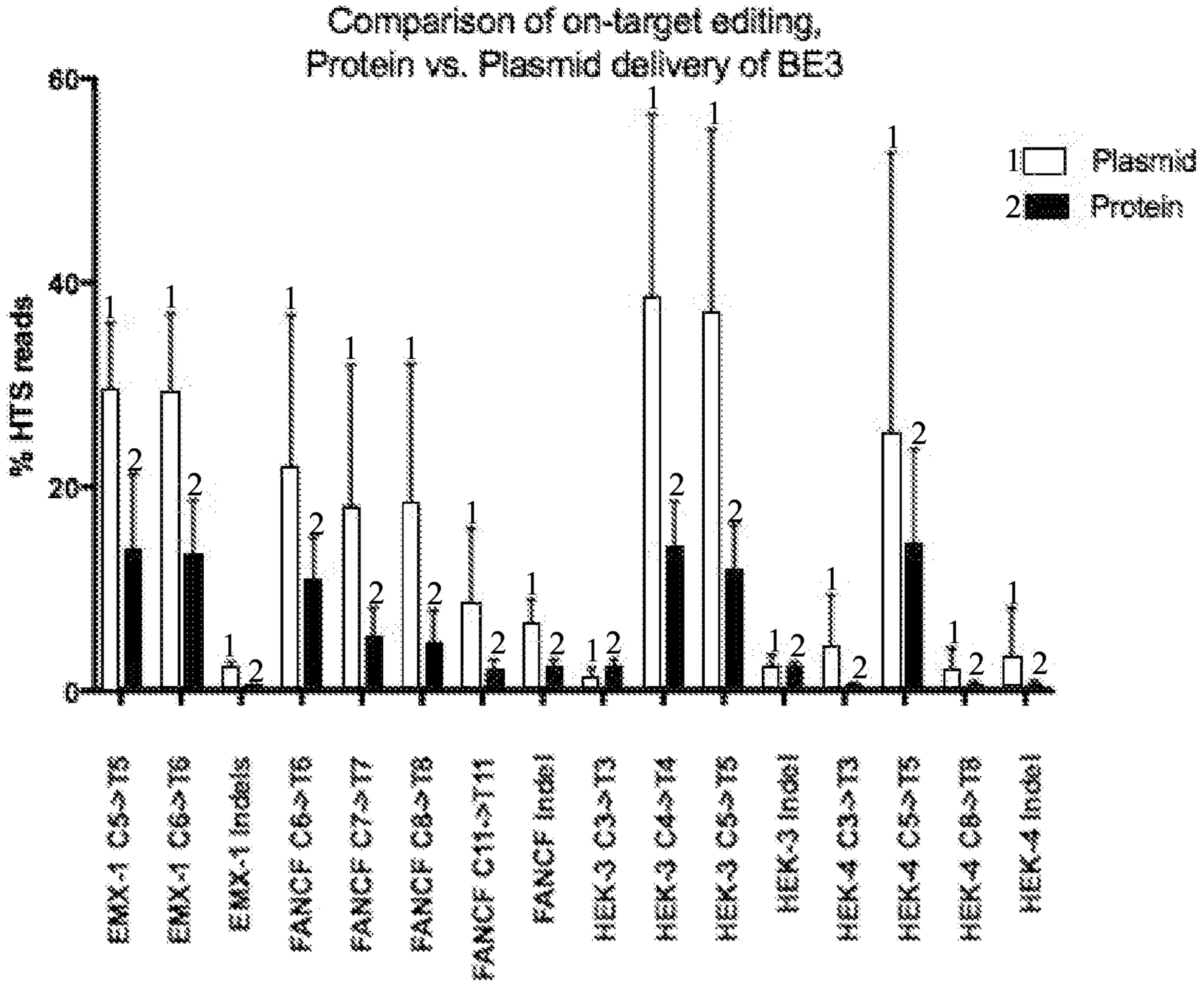

Comparison of on-target editing,
Protein vs. Plasmid delivery of BE3
% HTS reads
0
20
40
60
1 Plasmid
2 Protein
EMX-1 C5->T5
EMX-1 C6->T6
EMX-1 Indels
FANCF C6->T6
FANCF C7->T7
FANCF C8->T8
FANCF C11->T11
FANCF Indel
HEK-3 C3->T3
HEK-3 C4->T4
HEK-3 C5->T5
HEK-3 Indel
HEK-4 C3->T3
HEK-4 C5->T5
HEK-4 C8->T8
HEK-4 Indel

FIGURE 100

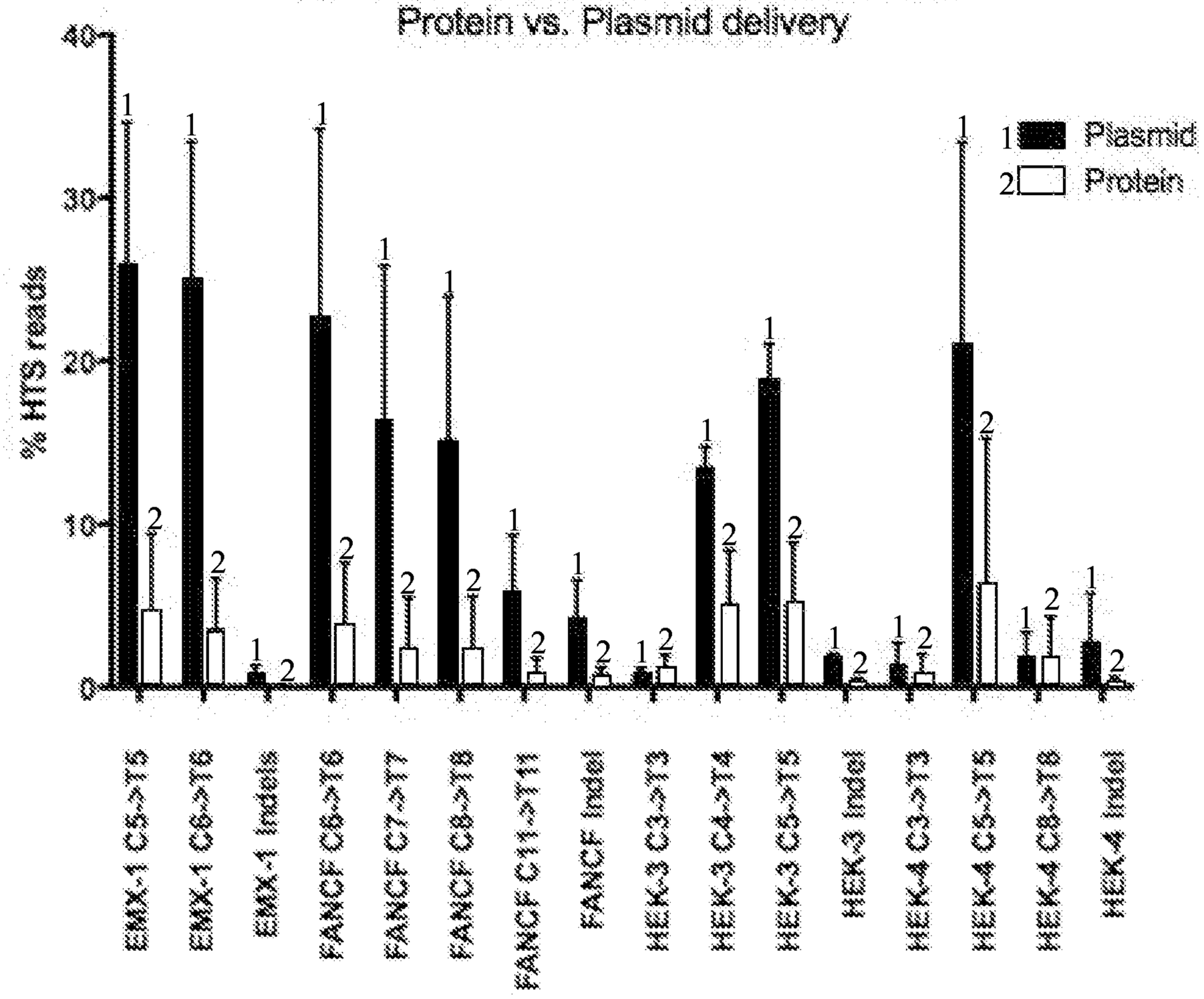

Comparison of on-target editing, HF-BE3
Protein vs. Plasmid delivery
% HTS reads
0
10
20
30
40
1 Plasmid
2 Protein
EMX-1 C5->T5
EMX-1 C6->T6
EMX-1 Indels
FANCF C6->T6
FANCF C7->T7
FANCF C8->T8
FANCF C11->T11
FANCF Indel
HEK-3 C3->T3
HEK-3 C4->T4
HEK-3 C5->T5
HEK-3 Indel
HEK-4 C3->T3
HEK-4 C5->T5
HEK-4 C8->T8
HEK-4 Indel

FIGURE 101

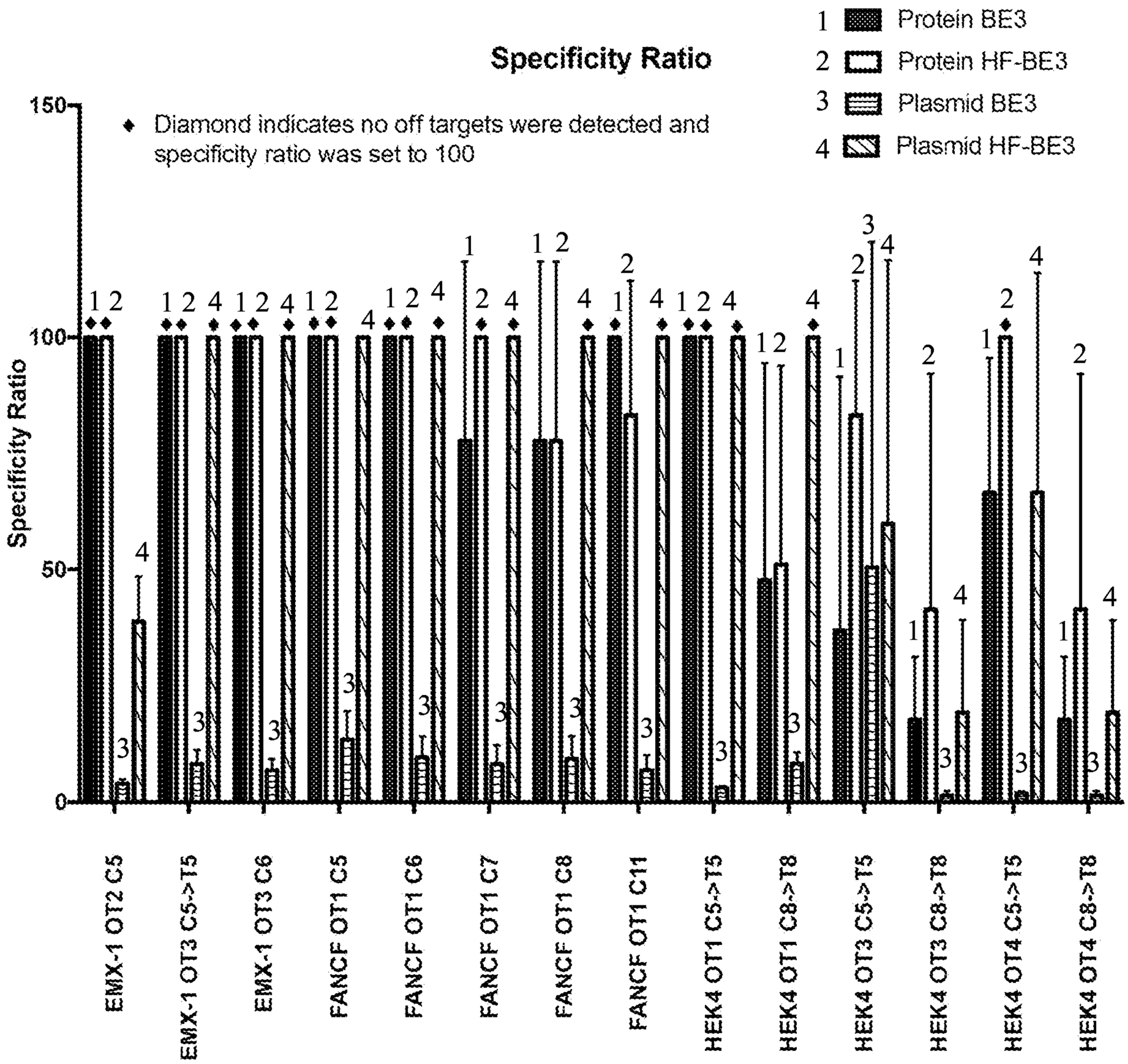

Specificity Ratio
◆ Diamond indicates no off targets were detected and specificity ratio was set to 100
1 Protein BE3
2 Protein HF-BE3
3 Plasmid BE3
4 Plasmid HF-BE3
Specificity Ratio
150
100
50
0
EMX-1 OT2 C5
EMX-1 OT3 C5->T5
EMX-1 OT3 C6
FANCF OT1 C5
FANCF OT1 C6
FANCF OT1 C7
FANCF OT1 C8
FANCF OT1 C11
HEK4 OT1 C5->T5
HEK4 OT1 C8->T8
HEK4 OT3 C5->T5
HEK4 OT3 C8->T8
HEK4 OT4 C5->T5
HEK4 OT4 C8->T8

FIGURE 102

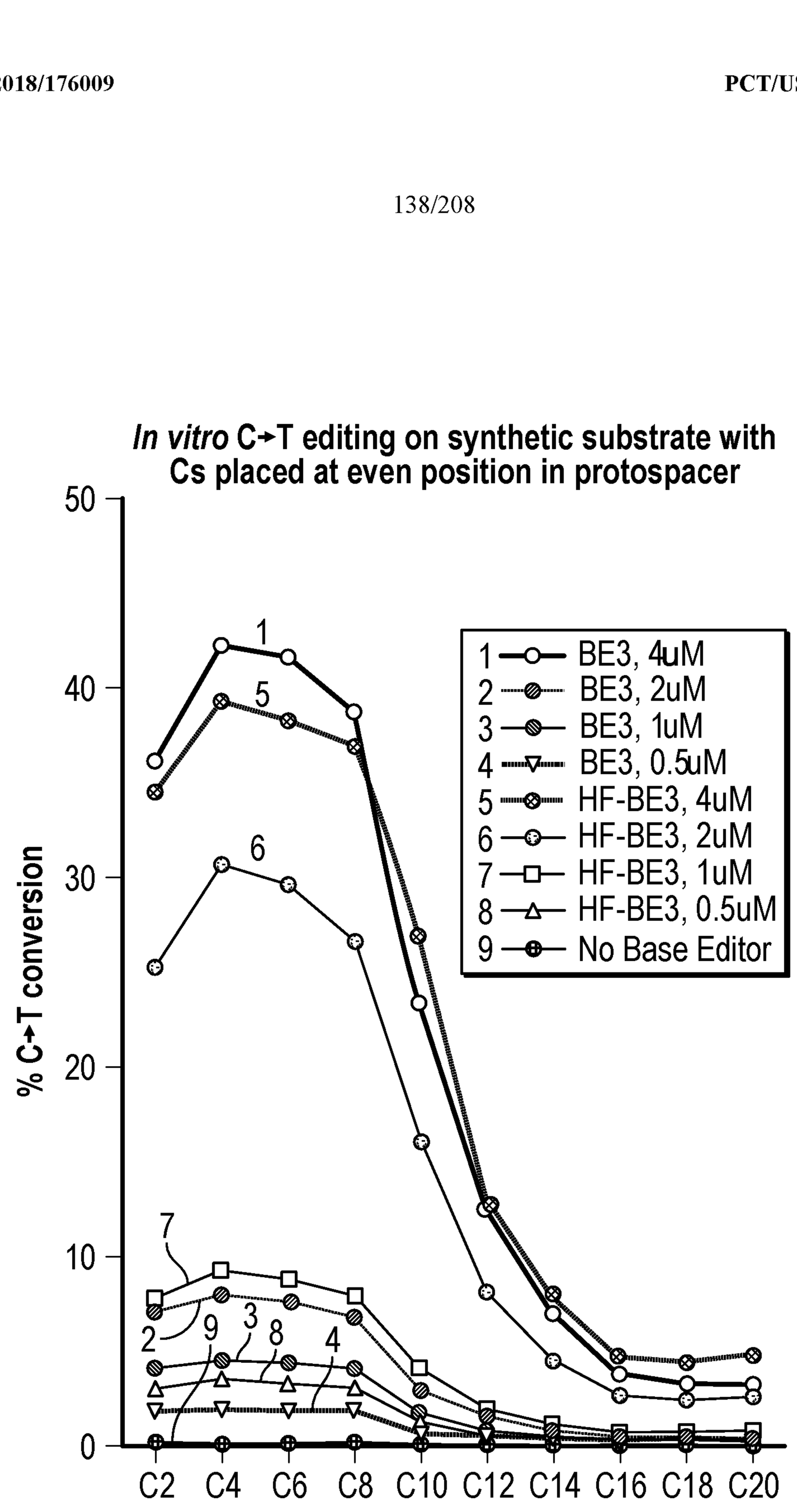

In vitro C→T editing on synthetic substrate with Cs placed at even position in protospacer
% C→T conversion
50
40
30
20
10
0
C2 C4 C6 C8 C10 C12 C14 C16 C18 C20
Position in protospacer
1 BE3, 4uM
2 BE3, 2uM
3 BE3, 1uM
4 BE3, 0.5uM
5 HF-BE3, 4uM
6 HF-BE3, 2uM
7 HF-BE3, 1uM
8 HF-BE3, 0.5uM
9 No Base Editor

FIGURE 103

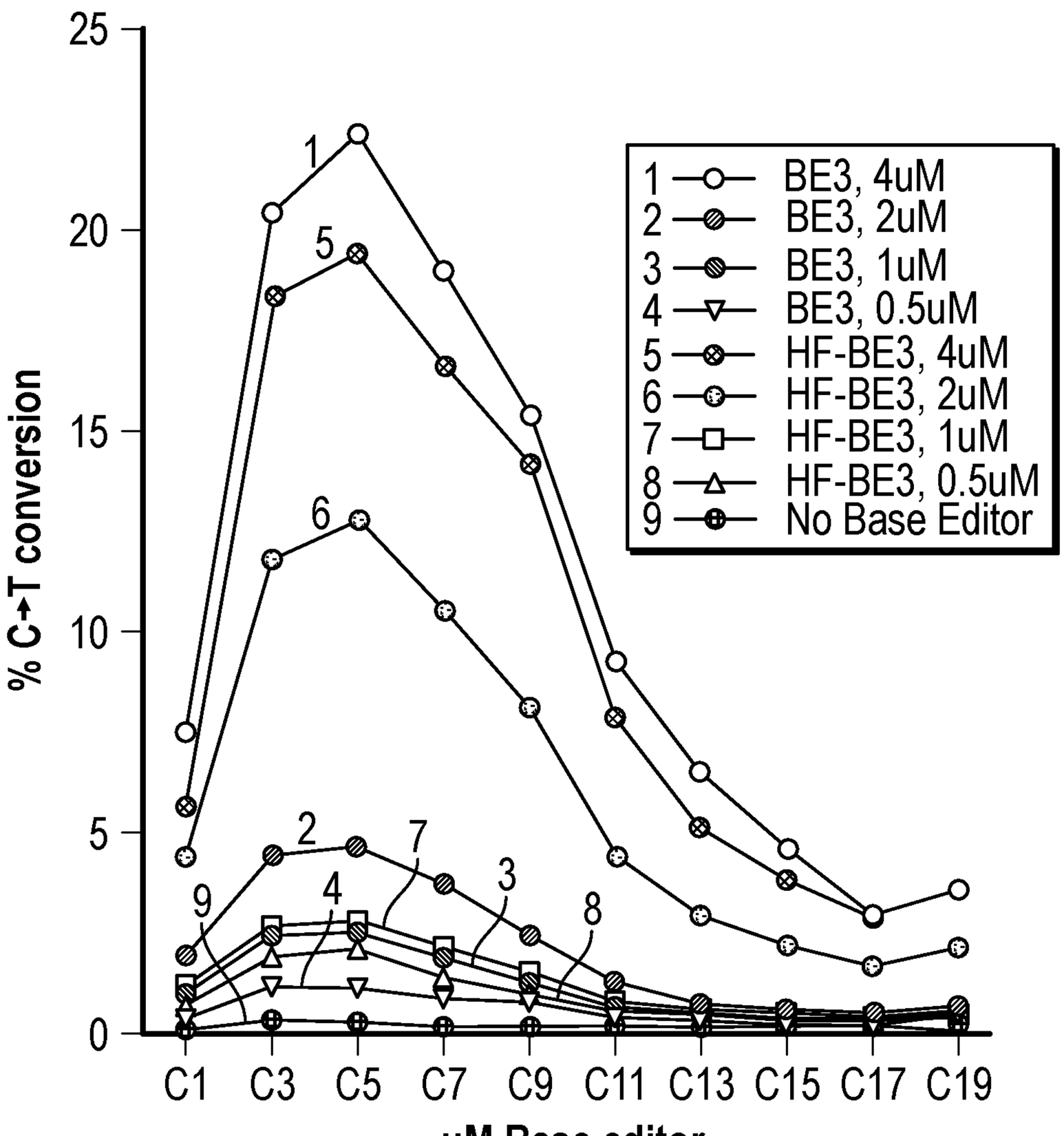

In vitro C→T editing on synthetic substrate with Cs placed at odd positions in protospacer
% C→T conversion
25
20
15
10
5
0
1
2
3
4
5
6
7
8
9
1 BE3, 4uM
2 BE3, 2uM
3 BE3, 1uM
4 BE3, 0.5uM
5 HF-BE3, 4uM
6 HF-BE3, 2uM
7 HF-BE3, 1uM
8 HF-BE3, 0.5uM
9 No Base Editor
C1 C3 C5 C7 C9 C11 C13 C15 C17 C19
uM Base editor

FIGURE 104

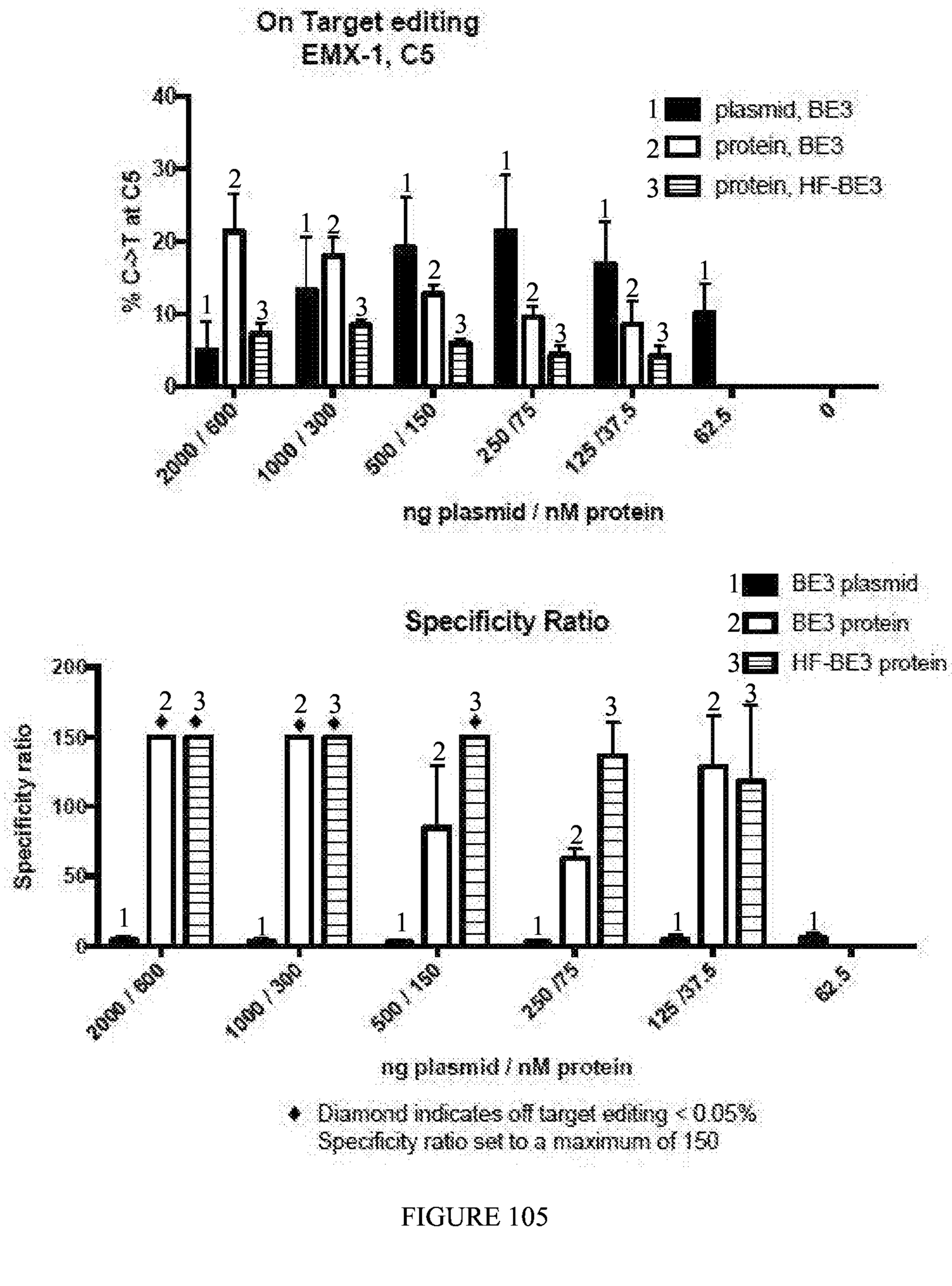
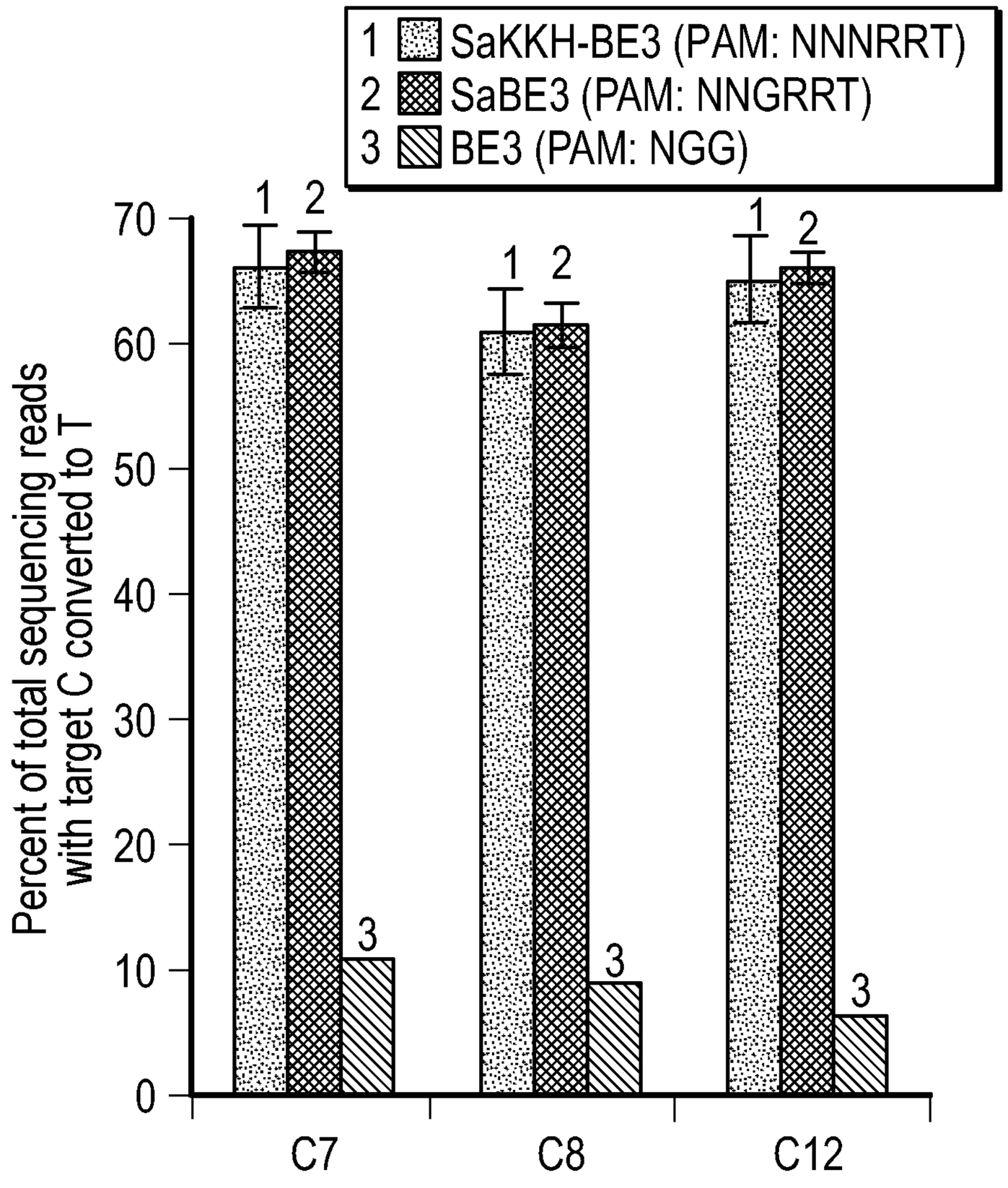

On Target editing
EMX-1, C5
% C>T at C5
40
30
20
10
0
1 plasmid, BE3
2 protein, BE3
3 protein, HF-BE3
2000 / 600
1000 / 300
500 / 150
250 /75
125 /37.5
62.5
0
ng plasmid / nM protein
Specificity Ratio
1 BE3 plasmid
2 BE3 protein
3 HF-BE3 protein
Specificity ratio
200
150
100
50
0
2000 / 600
1000 / 300
500 / 150
250 /75
125 /37.5
62.5
ng plasmid / nM protein
♦ Diamond indicates off target editing < 0.05%
Specificity ratio set to a maximum of 150

FIGURE 105

FANCF
GATGTTC$_7$C$_8$AATC$_{12}$AGTACGCAGAGAGT



HEK site 3
CTTC$_4$TC$_6$C$_7$AGCCCTGGCCTGGGTCAAT

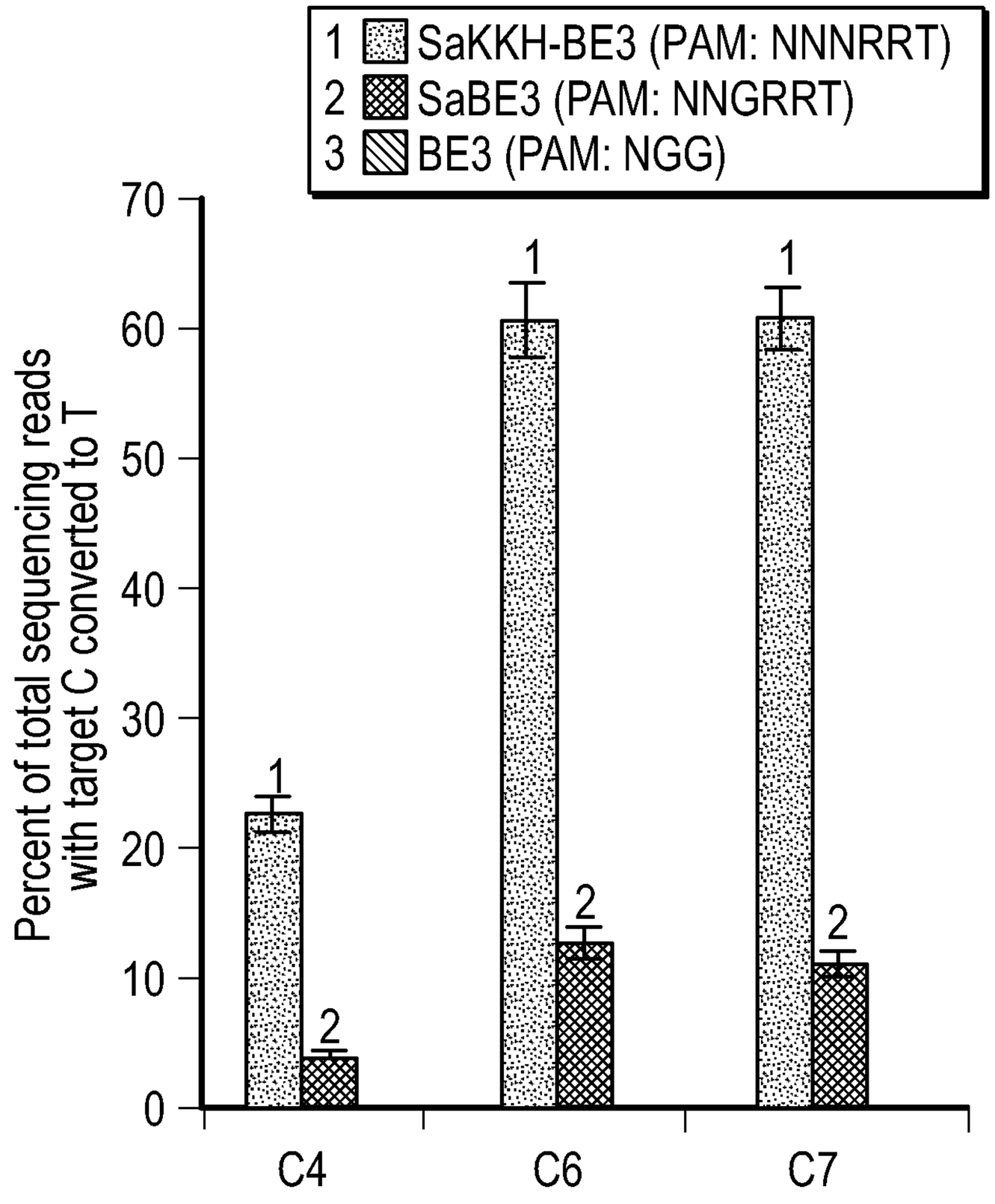


FIGURE 106A

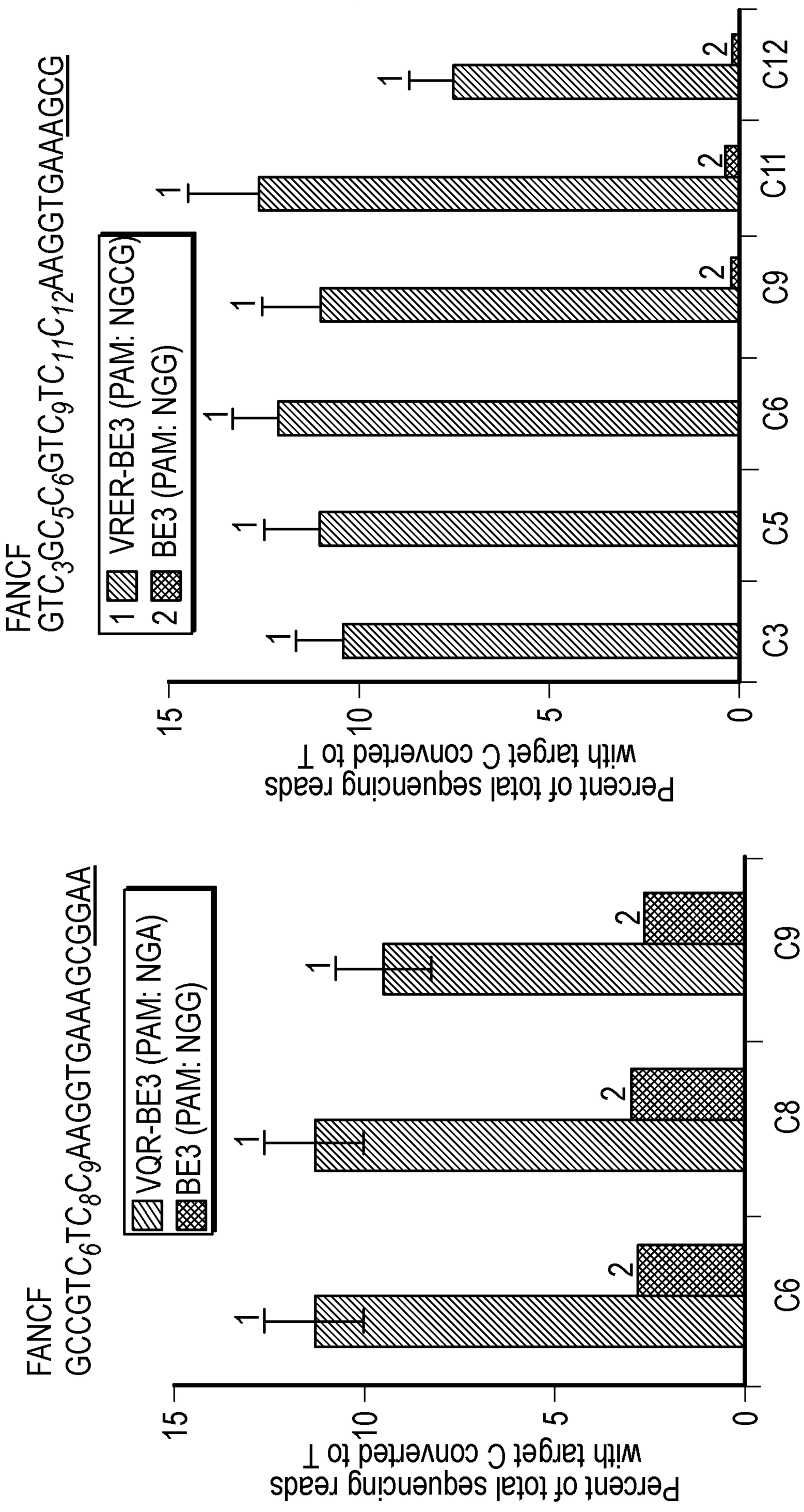

FANCF
GTC3GC5C6GTC9TC11C12AAGGTGAAAGCGG
1 VRER-BE3 (PAM: NGCG)
2 BE3 (PAM: NGG)
Percent of total sequencing reads with target C converted to T
C3
C5
C6
C9
C11
C12
FANCF
GTCGTC6TC8C9AAGGTGAAAGCGGAA
VQR-BE3 (PAM: NGA)
BE3 (PAM: NGG)
C6
C8
C9
FANCF
GCCGTC6TC8C9AAGGTGAAAGCGGAA
VQR-BE3 (PAM: NGA)
BE3 (PAM: NGG)
C6
C8
C9

FIGURE 106B

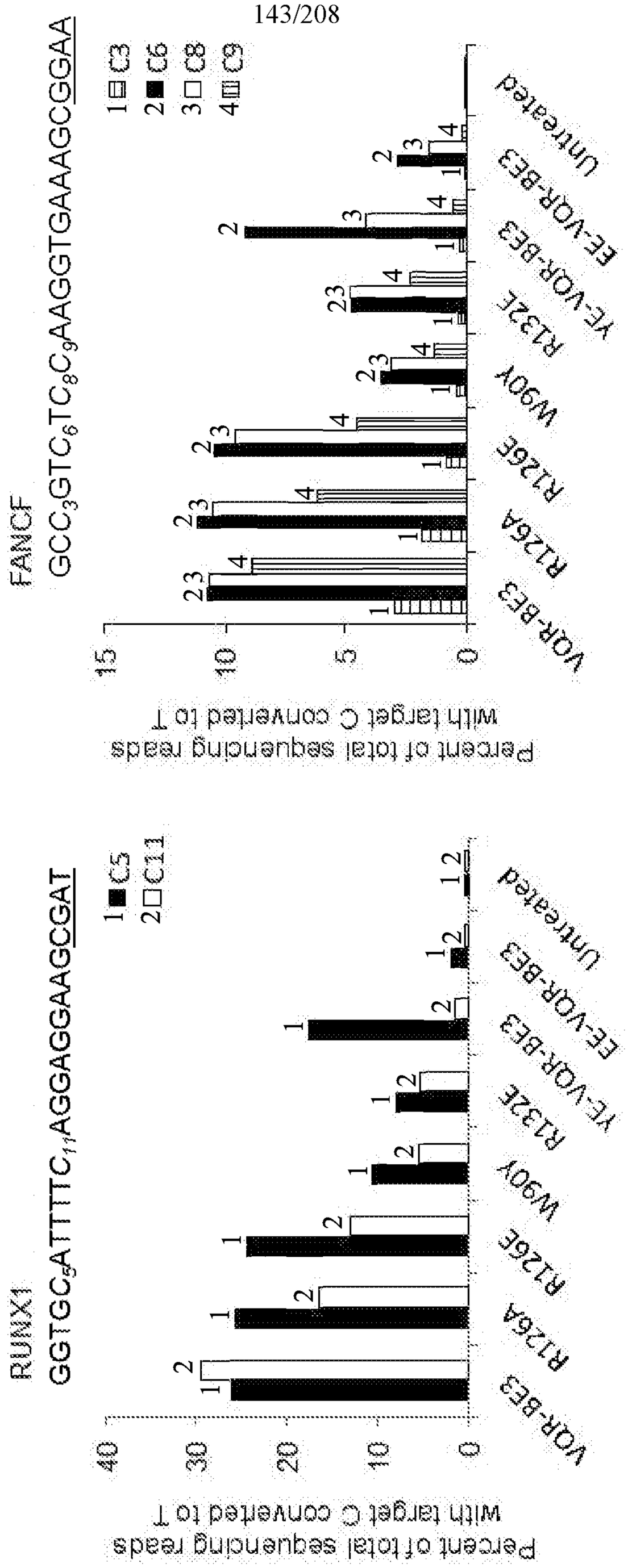

FANCF
GCC3GTC6TC8C9AAGGTGAAAGCGGAA
1 C3
2 C6
3 C8
4 C9
Percent of total sequencing reads with target C converted to T
0
5
10
15
VQR-BE3
R126A
R126E
W90Y
R132E
YE-VQR-BE3
EE-VQR-BE3
Untreated
RUNX1
GGTGC5ATTTTC11AGGAGGAAGCGAT
1 C5
2 C11
Percent of total sequencing reads with target C converted to T
0
10
20
30
40
VQR-BE3
R126A
R126E
W90Y
R132E
YE-VQR-BE3
EE-VQR-BE3
Untreated

FIGURE 107A

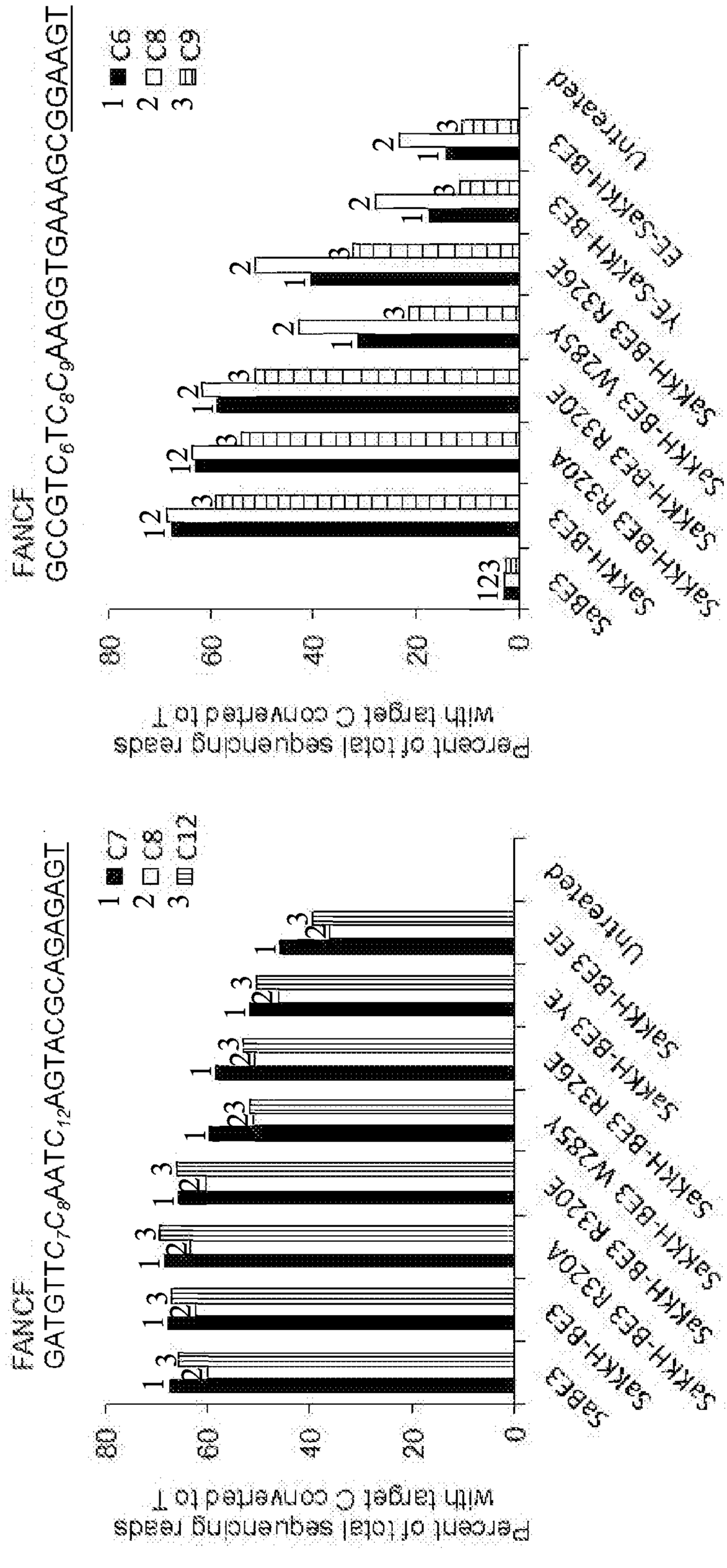

FANCF
GCCGTC6TC8C9AAGGTGAAAG
1 C6
2 C8
3 C9
Untreated
EE-SaKKH-BE3
YE-SaKKH-BE3 R326E
SaKKH-BE3 W285Y
SaKKH-BE3 R320E
SaKKH-BE3 R320A
SaKKH-BE3
SaBE3
With target C converted to T
Percent of total sequencing reads
FANCF
GATGTTC7C8AATC12AGTACGCAGAGT
1 C7
2 C8
3 C12
Untreated
SaKKH-BE3 EE
SaKKH-BE3 YE
SaKKH-BE3 R326E
SaKKH-BE3 W285Y
SaKKH-BE3 R320E
SaKKH-BE3 R320A
SaKKH-BE3
SaBE3
With target C converted to T
Percent of total sequencing reads

FIGURE 107B

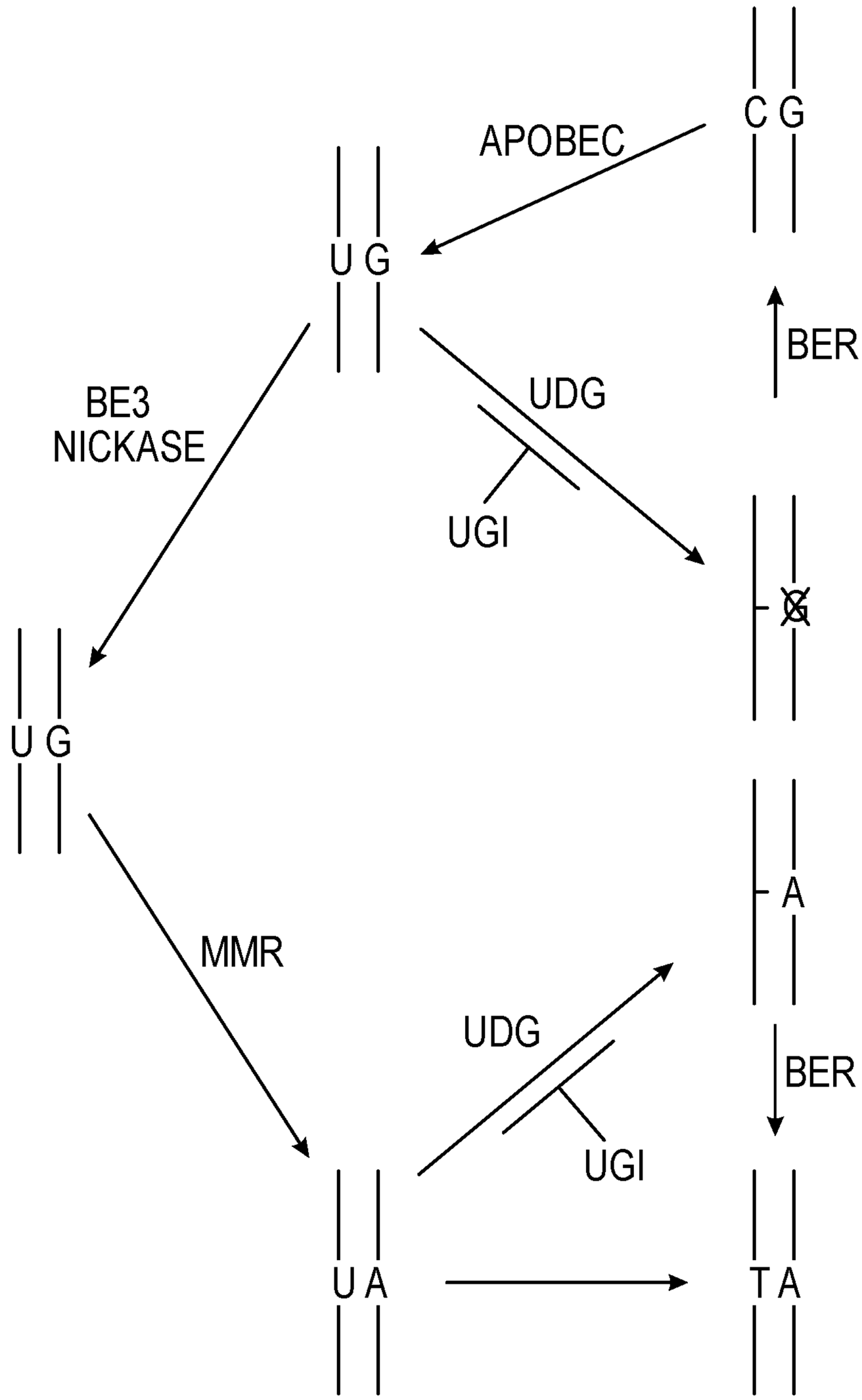


FIGURE 108

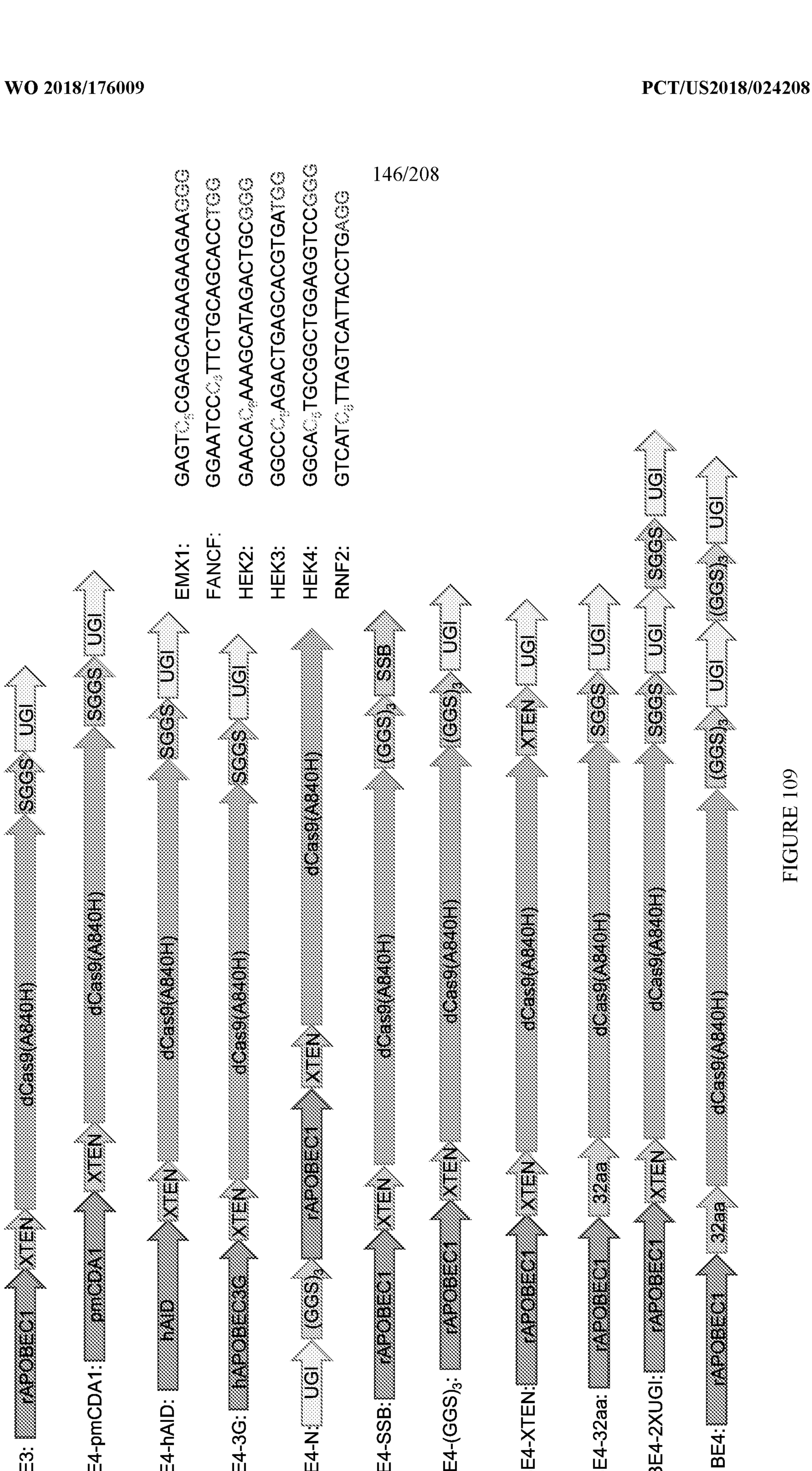

EMX1: GAGTC_8CGAGCAGAAGAAGAAGGG
FANCF: GGAATCC_8TTCTGCAGCACCTGG
HEK2: GAACAC_8AAAGCATAGACTGCGGG
HEK3: GGCCC_8AGACTGAGCACGTGATGG
HEK4: GGCAC_8TGCGGCTGGAGGTCCGGG
RNF2: GTCATC_8TTAGTCATTACCTGAGG
BE3: rAPOBEC1 XTEN dCas9(A840H) SGGS UGI
BE4-pmCDA1: pmCDA1 XTEN dCas9(A840H) SGGS UGI
BE4-hAID: hAID XTEN dCas9(A840H) SGGS UGI
BE4-3G: hAPOBEC3G XTEN dCas9(A840H) SGGS UGI
BE4-N: UGI $(GGS)_3$ rAPOBEC1 XTEN dCas9(A840H) SSB $(GGS)_3$
BE4-SSB: rAPOBEC1 XTEN dCas9(A840H) $(GGS)_3$ UGI
BE4-$(GGS)_3$: rAPOBEC1 XTEN dCas9(A840H) SGGS UGI
BE4-XTEN: rAPOBEC1 XTEN dCas9(A840H) XTEN UGI
BE4-32aa: rAPOBEC1 32aa dCas9(A840H) SGGS UGI
BE4-2XUGI: rAPOBEC1 XTEN dCas9(A840H) SGGS UGI SGGS UGI
BE4: rAPOBEC1 32aa dCas9(A840H) $(GGS)_3$ UGI $(GGS)_3$ UGI

FIGURE 109

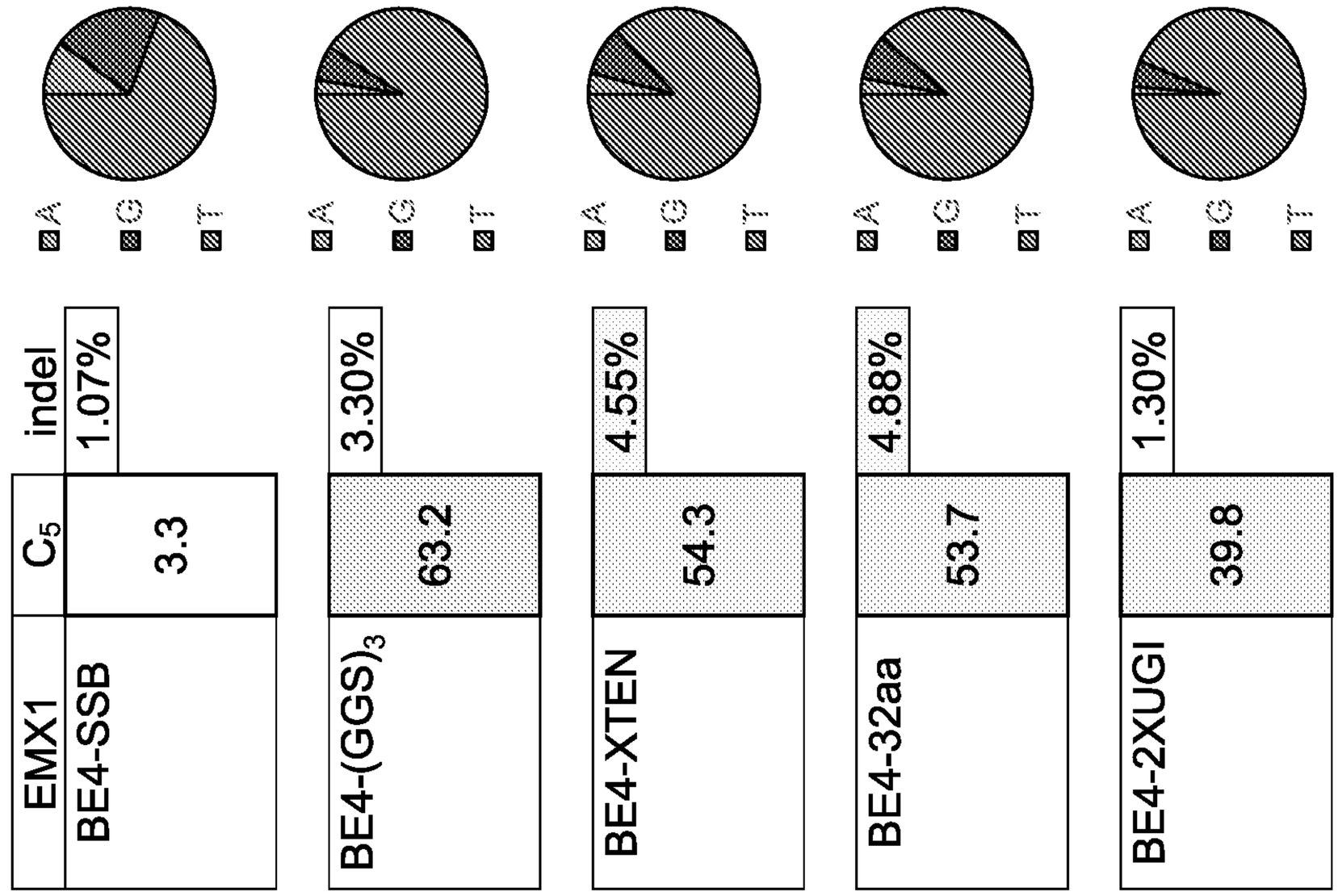
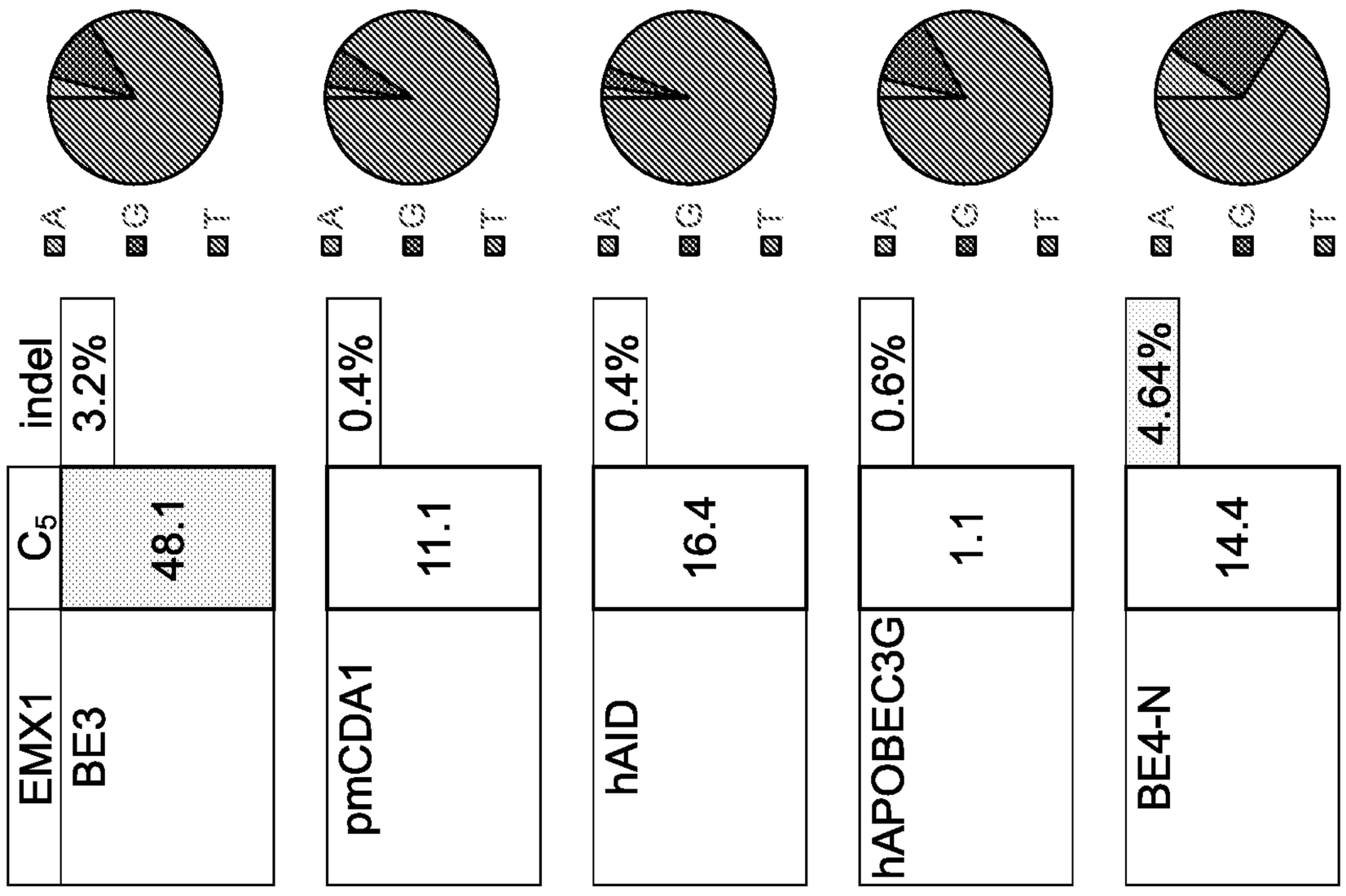

EMX1
BE4-SSB
C_5
3.3
indel
1.07%
BE4-(GGS)$_3$
63.2
3.30%
BE4-XTEN
54.3
4.55%
BE4-32aa
53.7
4.88%
BE4-2XUGI
39.8
1.30%
A
G
T

FIGURE 110


EMX1
BE3
C_5
48.1
indel
3.2%
pmCDA1
11.1
0.4%
hAID
16.4
0.4%
hAPOBEC3G
1.1
0.6%
BE4-N
14.4
4.64%
A
G
T

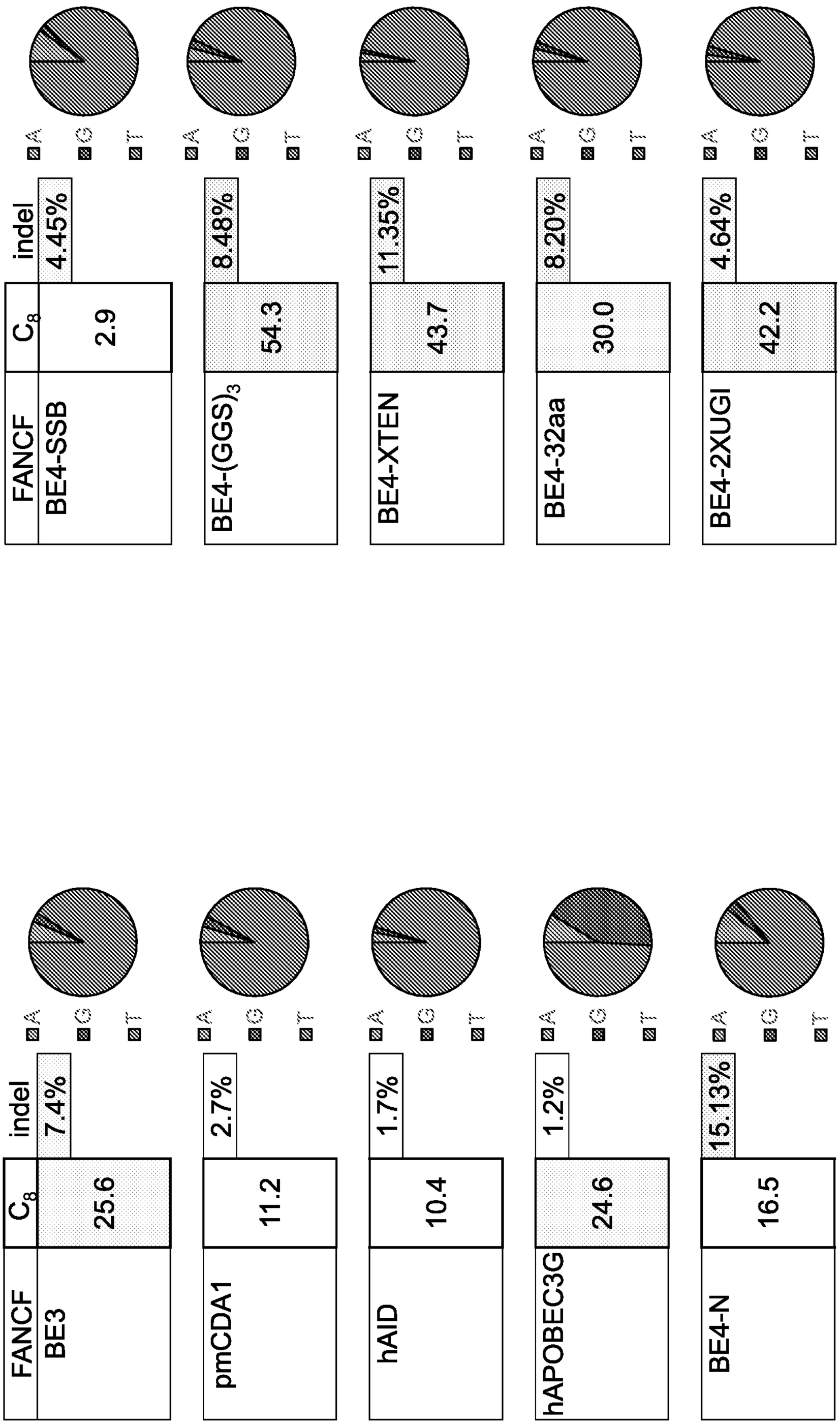
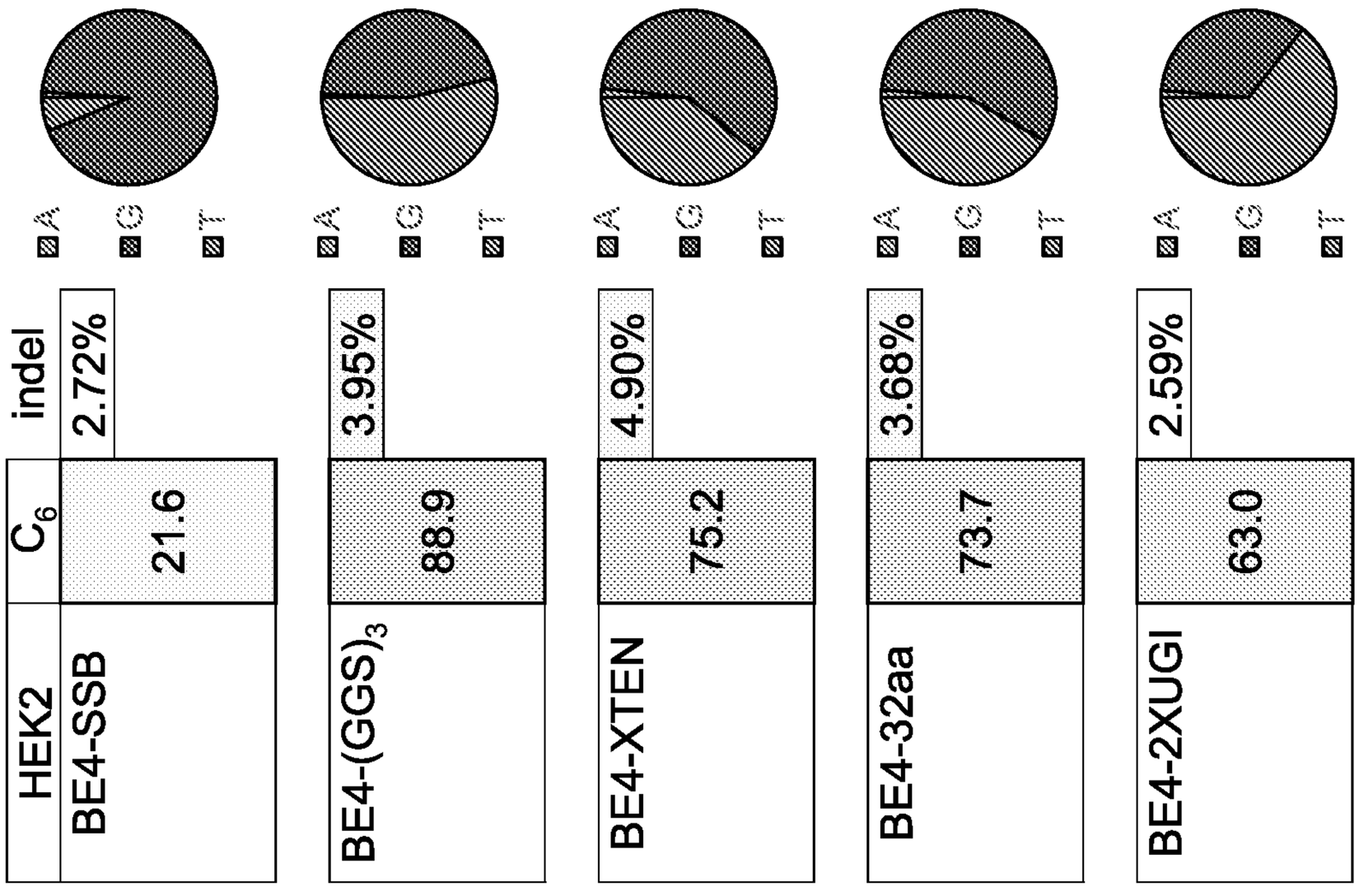

A
G
T
indel
4.45%
FANCF
BE4-SSB
C_8
2.9
8.48%
BE4-(GGS)$_3$
54.3
11.35%
BE4-XTEN
43.7
8.20%
BE4-32aa
30.0
4.64%
BE4-2XUGI
42.2
7.4%
BE3
25.6
2.7%
pmCDA1
11.2
1.7%
hAID
10.4
1.2%
hAPOBEC3G
24.6
15.13%
BE4-N
16.5

FIGURE 111


HEK2
BE4-SSB
C6
21.6
indel
2.72%
BE4-(GGS)3
88.9
3.95%
BE4-XTEN
75.2
4.90%
BE4-32aa
73.7
3.68%
BE4-2XUGI
63.0
2.59%
A
G
T

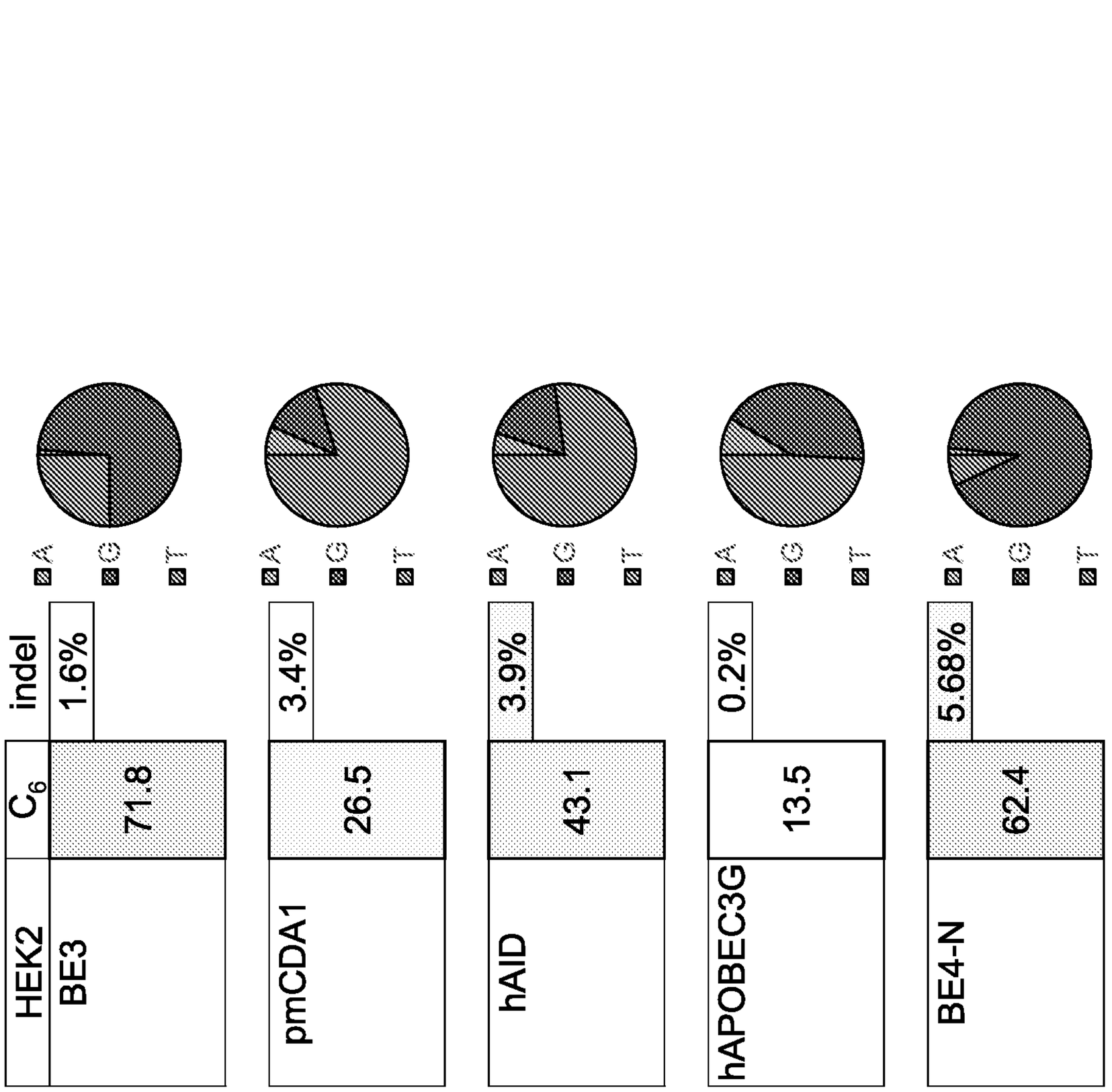

HEK2
BE3
C6
71.8
indel
1.6%
pmCDA1
26.5
3.4%
hAID
43.1
3.9%
hAPOBEC3G
13.5
0.2%
BE4-N
62.4
5.68%
A
G
T

FIGURE 112

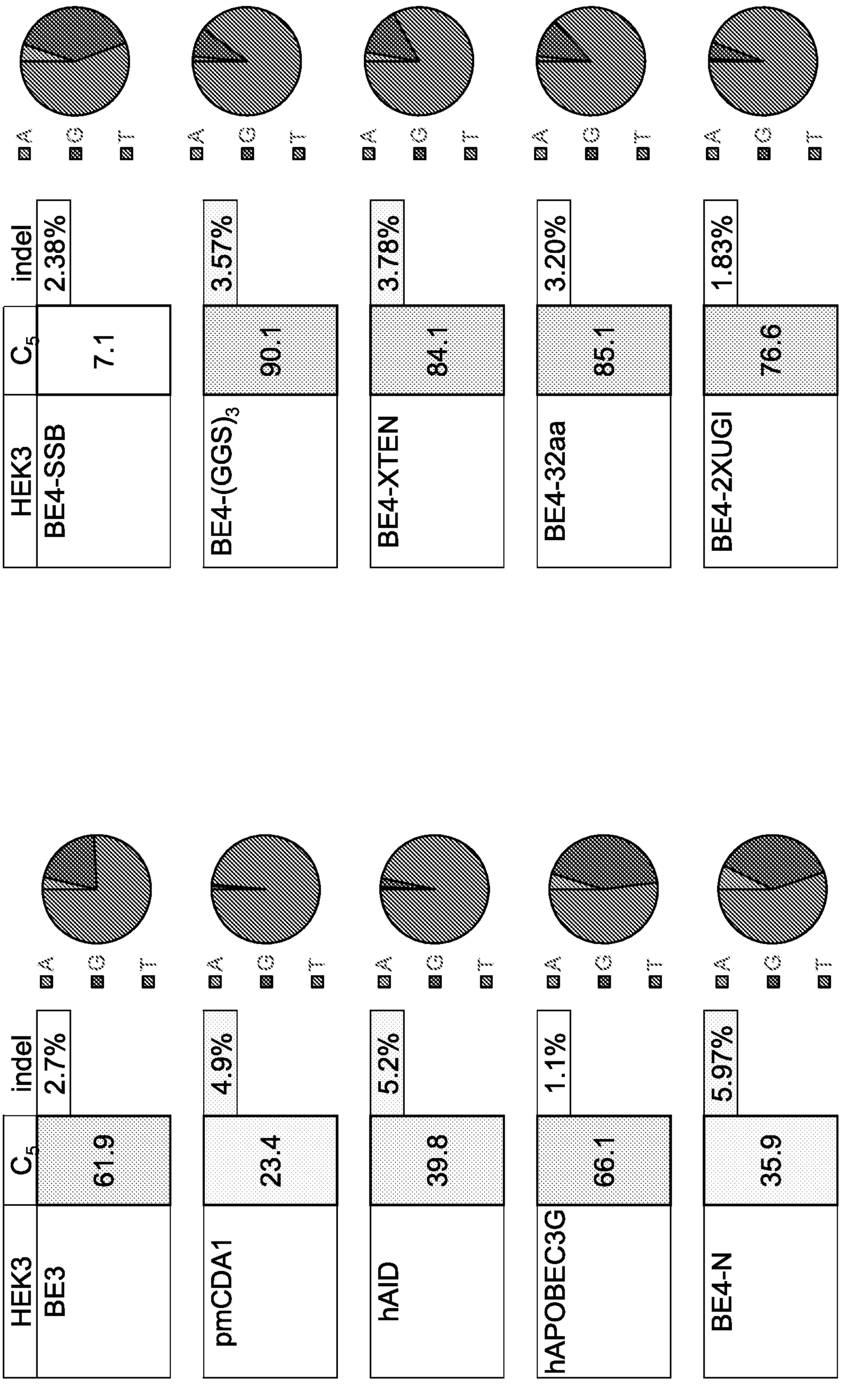

HEK3
BE4-SSB
C_5
7.1
indel
2.38%
A
G
T
BE4-(GGS)$_3$
90.1
3.57%
BE4-XTEN
84.1
3.78%
BE4-32aa
85.1
3.20%
BE4-2XUGI
76.6
1.83%
BE3
61.9
2.7%
pmCDA1
23.4
4.9%
hAID
39.8
5.2%
hAPOBEC3G
66.1
1.1%
BE4-N
35.9
5.97%

FIGURE 113

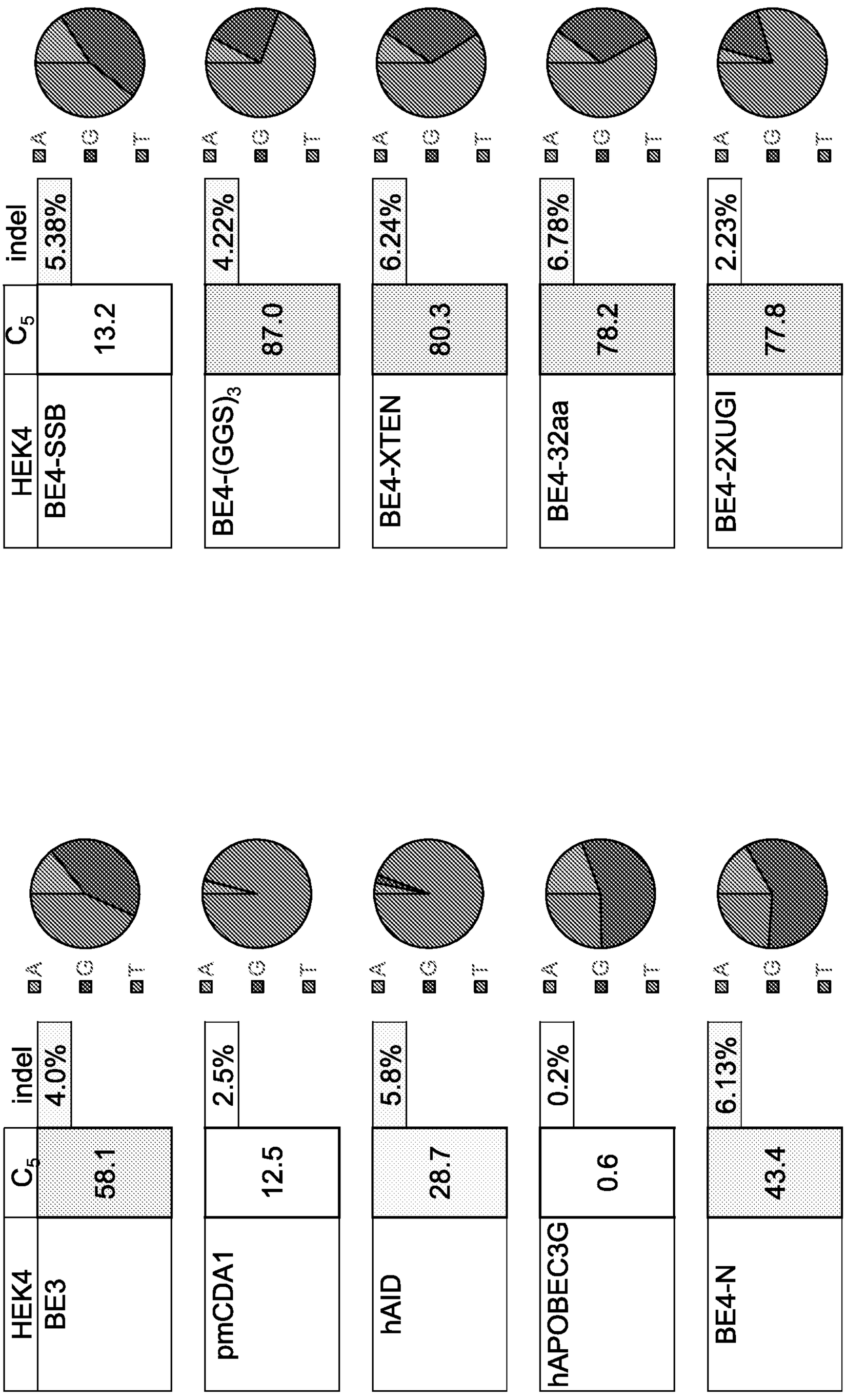
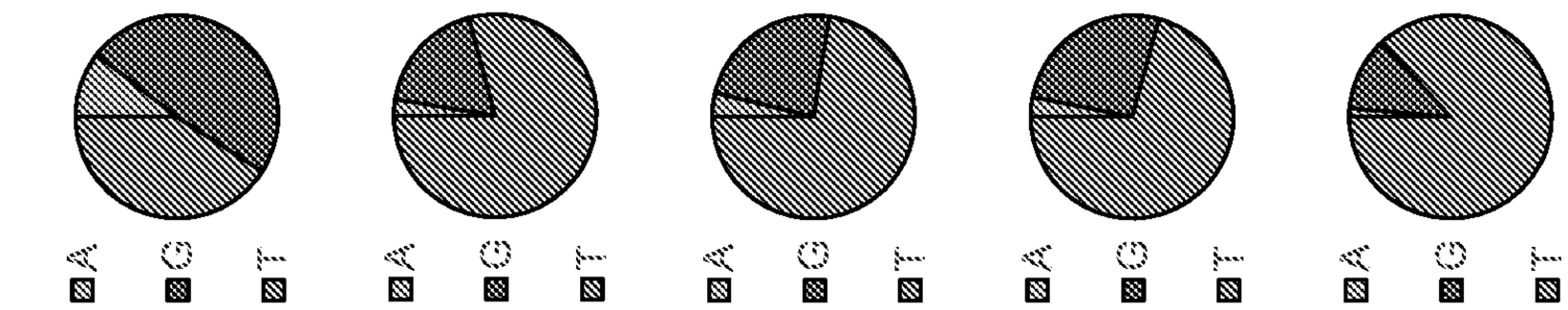

HEK4
BE4-SSB
C5
13.2
indel
5.38%
BE4-(GGS)3
87.0
4.22%
BE4-XTEN
80.3
6.24%
BE4-32aa
78.2
6.78%
BE4-2XUGI
77.8
2.23%
A
G
T
HEK4
BE3
C5
58.1
indel
4.0%
pmCDA1
12.5
2.5%
hAID
28.7
5.8%
hAPOBEC3G
0.6
0.2%
BE4-N
43.4
6.13%

FIGURE 114


A
G
T

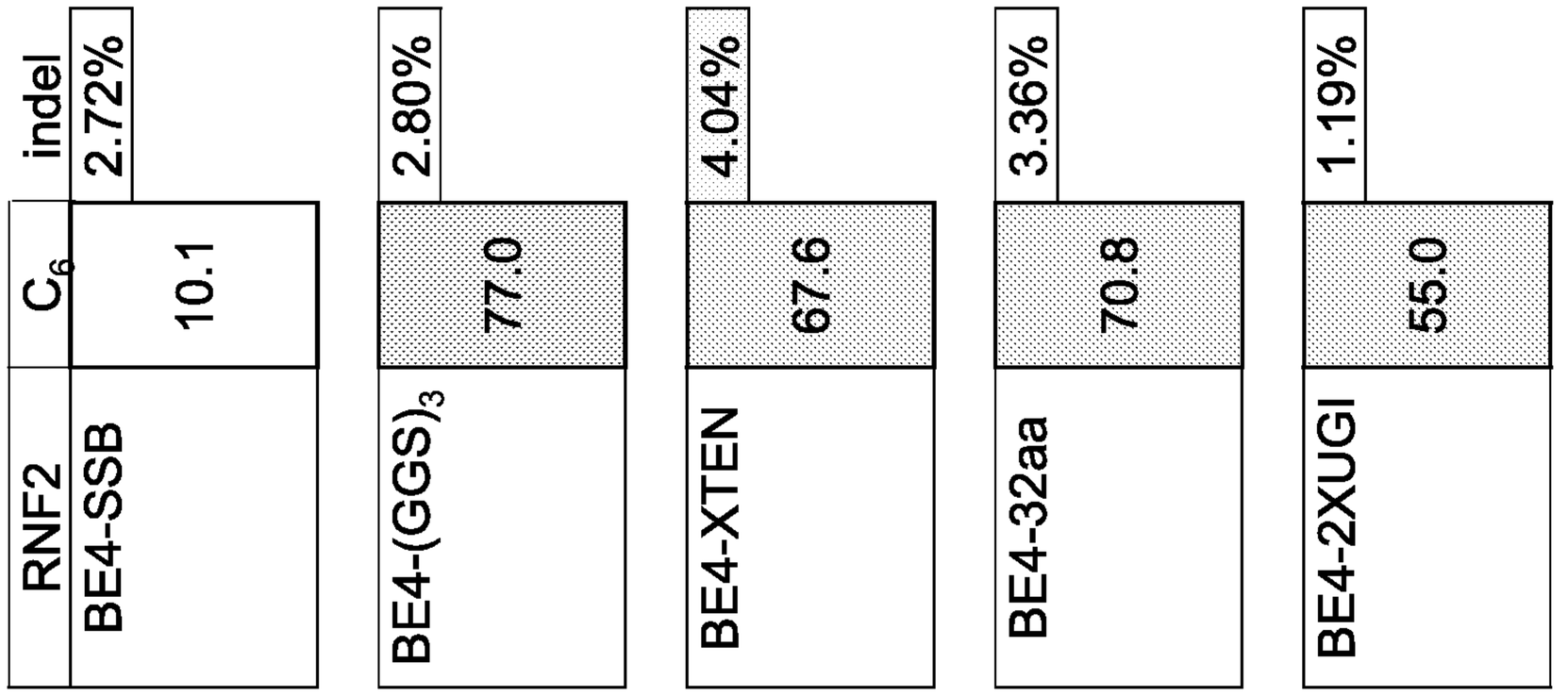
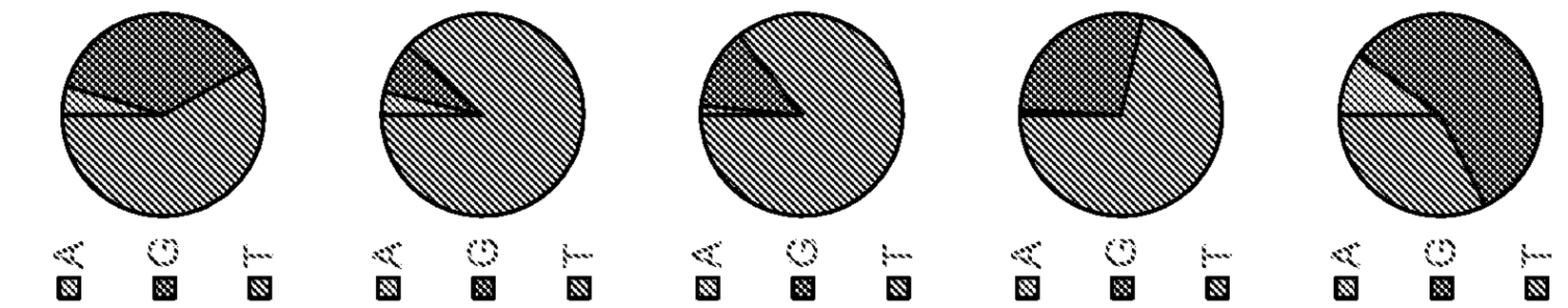
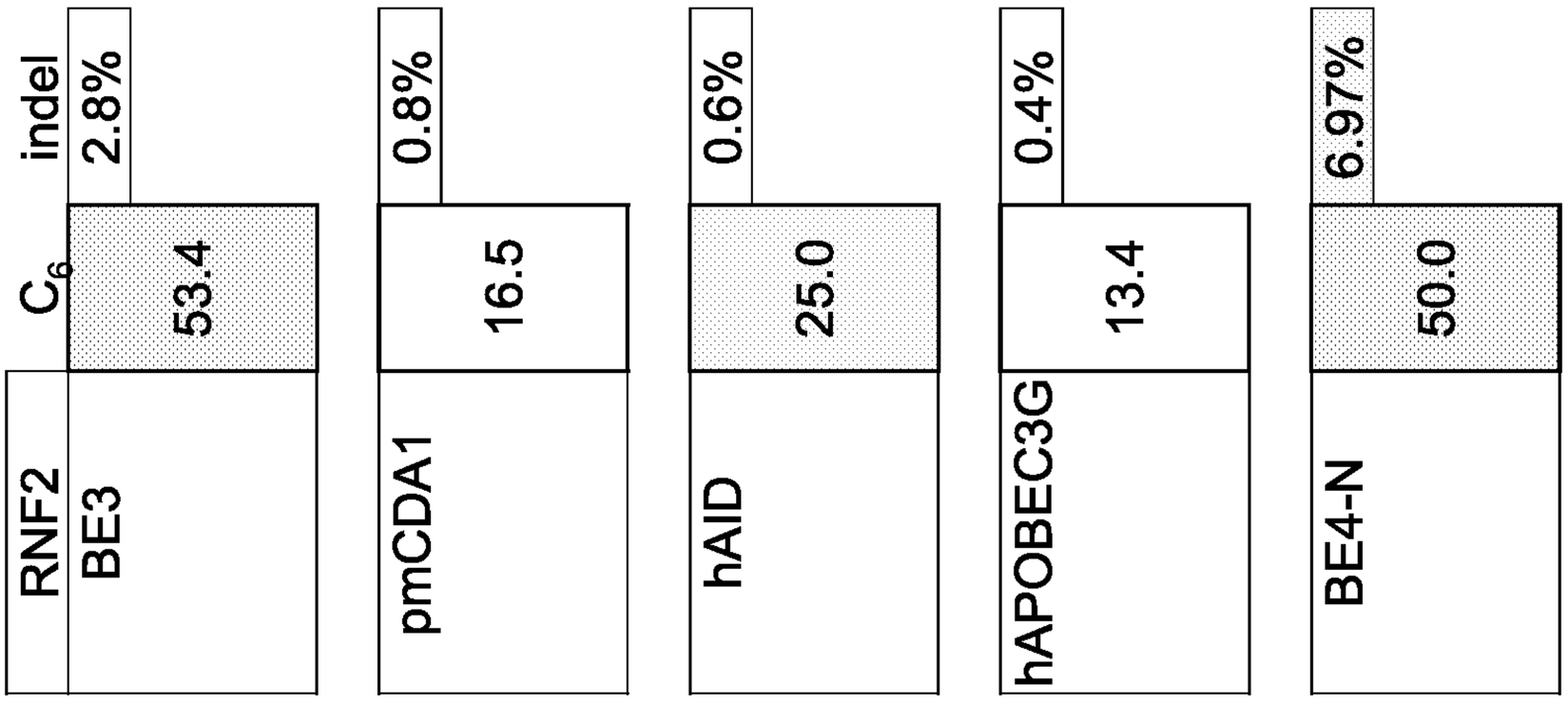
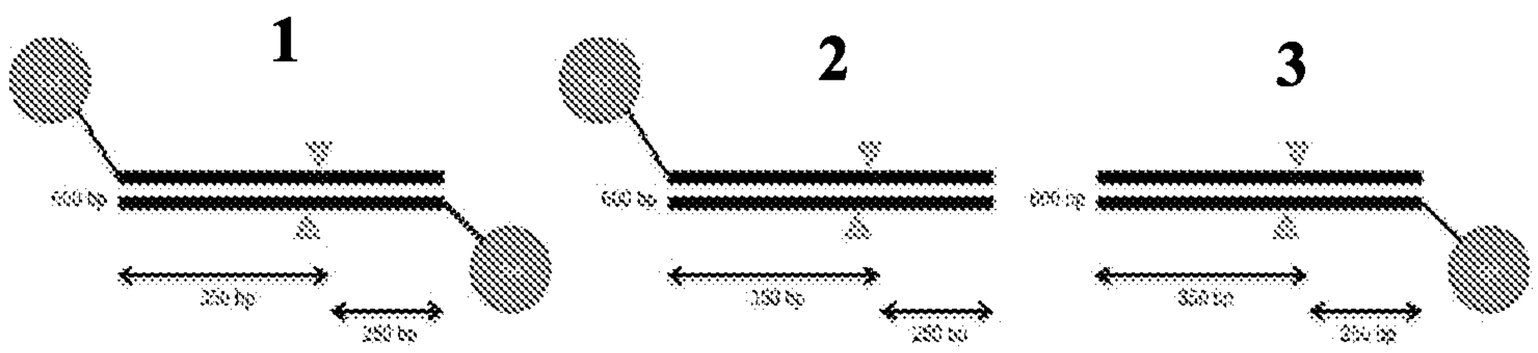

RNF2
BE4-SSB
C6
10.1
indel
2.72%
BE4-(GGS)3
77.0
2.80%
BE4-XTEN
67.6
4.04%
BE4-32aa
70.8
3.36%
BE4-2XUGI
55.0
1.19%

FIGURE 115


A
G
T


RNF2
BE3
C6
53.4
indel
2.8%
pmCDA1
16.5
0.8%
hAID
25.0
0.6%
hAPOBEC3G
13.4
0.4%
BE4-N
50.0
6.97%



Top strand: non-target strand; Bottom strand: target strand

FIGURE 116

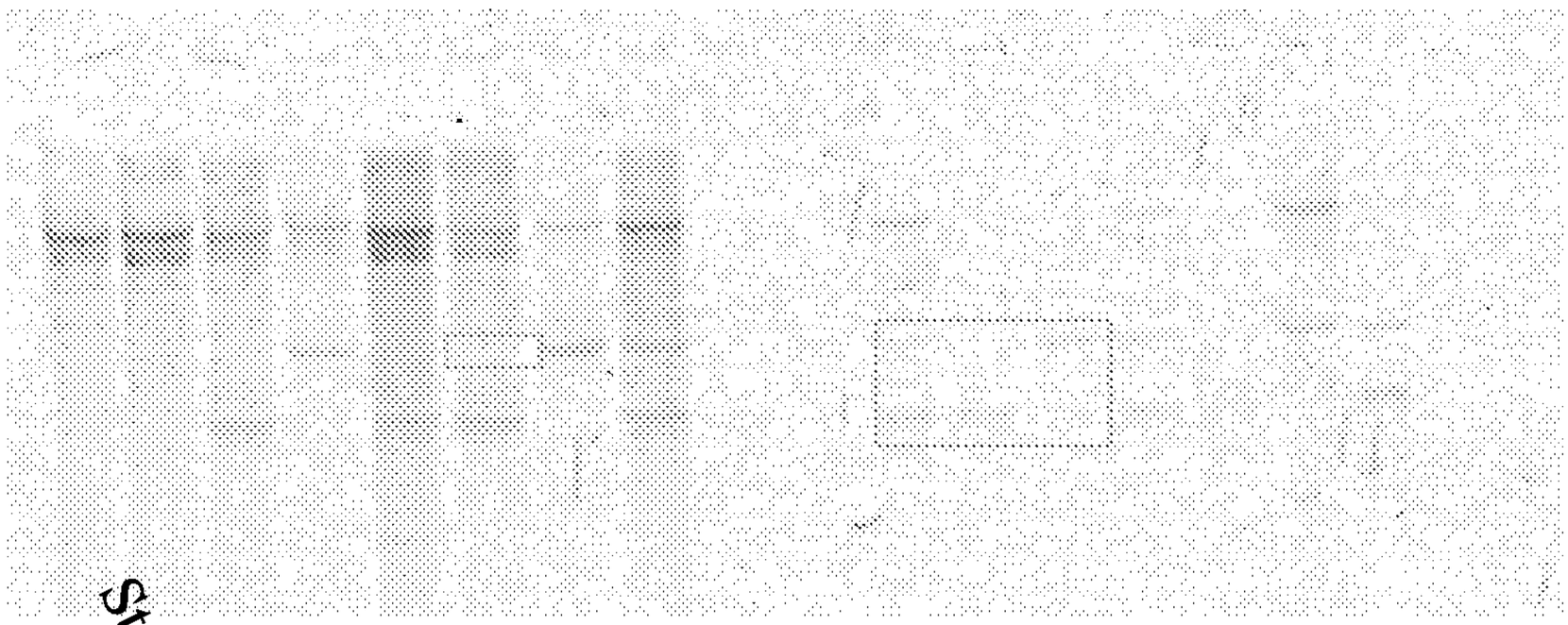


FIGURE 117

PAM

FANCF1	TTTC	G1	C2	G3	G4	G7	C10	C11	C15	G17	C20	C22
BG		0.01005	0.03022	0.01083	0.00933	0.00502	0.01872	0.02014	0.03740	0.00504	0.01938	0.02099
AsCpf1		0.00895	0.02769	0.07439	0.00672	0.06495	0.02395	0.01795	0.02691	0.01570	0.02257	0.02406
APOBEC-AsCpf1(R912A)-UGI		0.00883	0.02606	0.01430	0.00539	0.00490	0.28513	0.28158	0.04373	0.01425	0.02795	0.01631
APOBEC-AsCpf1(R1225A)-UGI		0.00796	0.03754	0.01131	0.00749	0.01124	0.02769	0.02908	0.03946	0.02016	0.01732	0.01651

FANCF2	TTTC	C1	G2	G3	C4	C7	G8	G10	C11	G12	G13	C15	C16	G17	C18
BG		0.02628	0.01963	0.02346	0.00318	0.00798	0.00844	0.00850	0.08758	0.05168	0.00637	0.00499	0.07694	0.01382	0.01805
AsCpf1		0.03489	0.03325	0.05248	0.00392	0.00722	0.02484	0.00791	0.06139	0.10805	0.01851	0.02139	0.10988	0.00927	0.00992
APOBEC-AsCpf1(R912A)-UGI		0.02440	0.02677	0.00699	0.00481	0.19389	0.01115	0.00534	0.11463	0.01660	0.00427	0.00722	0.10175	0.01119	0.01065
APOBEC-AsCpf1(R1225A)-UGI		0.02855	0.04216	0.00322	0.00479	0.00587	0.01004	0.00585	0.06534	0.00586	0.00638	0.00444	0.07056	0.00797	0.01061

HEK3-3	TTTC	C3	C6	C8	C9	C12	C13	C14	C18	C19
BG		0.00807	0.00726	0.01448	0.01538	0.01084	0.01281	0.00729	0.01540	0.00634
AsCpf1		0.01118	0.00670	0.01994	0.00892	0.01334	0.01342	0.01797	0.01118	0.03351
APOBEC-AsCpf1(R912A)-UGI		0.00647	0.02264	0.44917	0.30191	0.03754	0.12192	0.01513	0.01291	0.00754
APOBEC-AsCpf1(R1225A)-UGI		0.00770	0.00769	0.10243	0.07236	0.01202	0.00770	0.00551	0.01865	0.00548

PAM

HEK3-4	G23	C20	G18	G16	C15	C13	G12	G10	G7	G6	C5	G1	GAAA
BG	0.00638	0.01001	0.03459	0.01008	0.01008	0.01285	0.01284	0.00548	0.01458	0.02557	0.01089	0.00636	
AsCpf1	0.00968	0.00862	0.02466	0.01984	0.03343	0.02600	0.00865	0.00617	0.01718	0.02216	0.01232	0.00488	
APOBEC-AsCpf1(R912A)-UGI	0.00323	0.01185	0.03012	0.00759	0.01735	0.01734	0.04550	0.35878	0.00862	0.02266	0.00542	0.00644	
APOBEC-AsCpf1(R1225A)-UGI	0.01142	0.01045	0.03044	0.01435	0.01626	0.02104	0.01051	0.01238	0.01045	0.03428	0.01810	0.00473	

BG –background; R912A – B E 3 ; R1225A –self-defeating BE (nicks non-target strand)

FIGURE 118

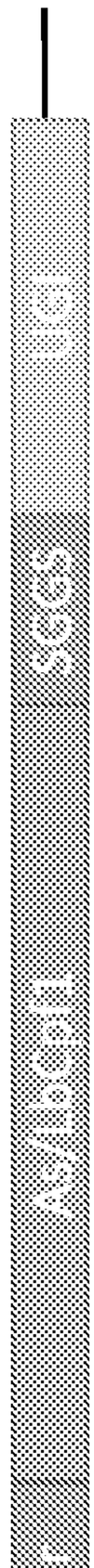


FIGURE 119

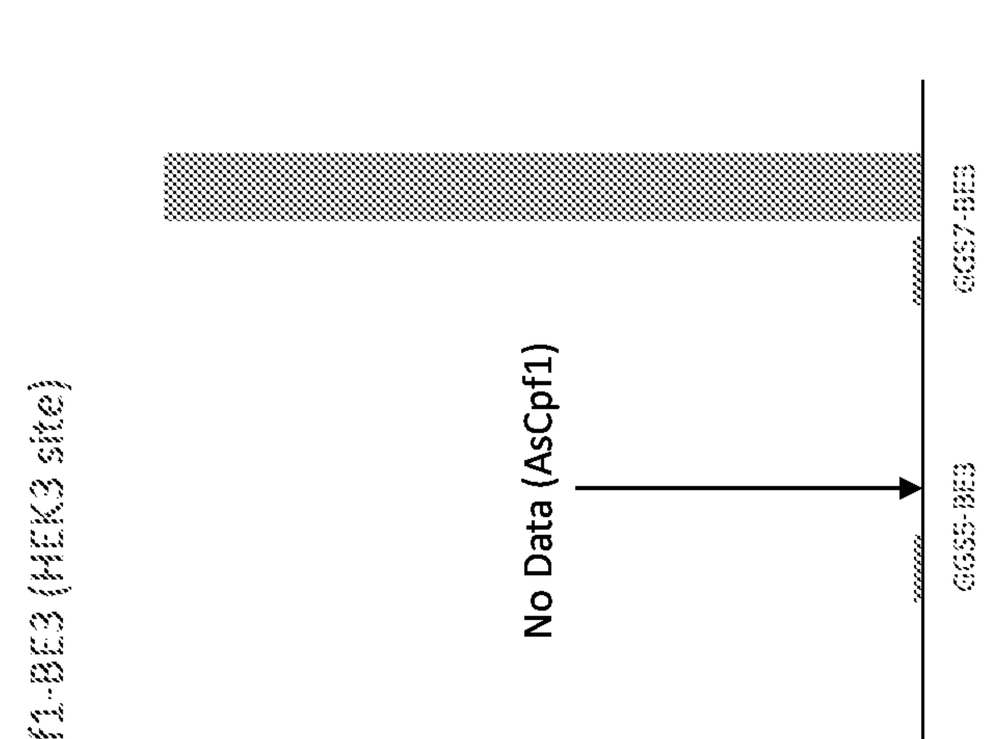


FIGURE 120

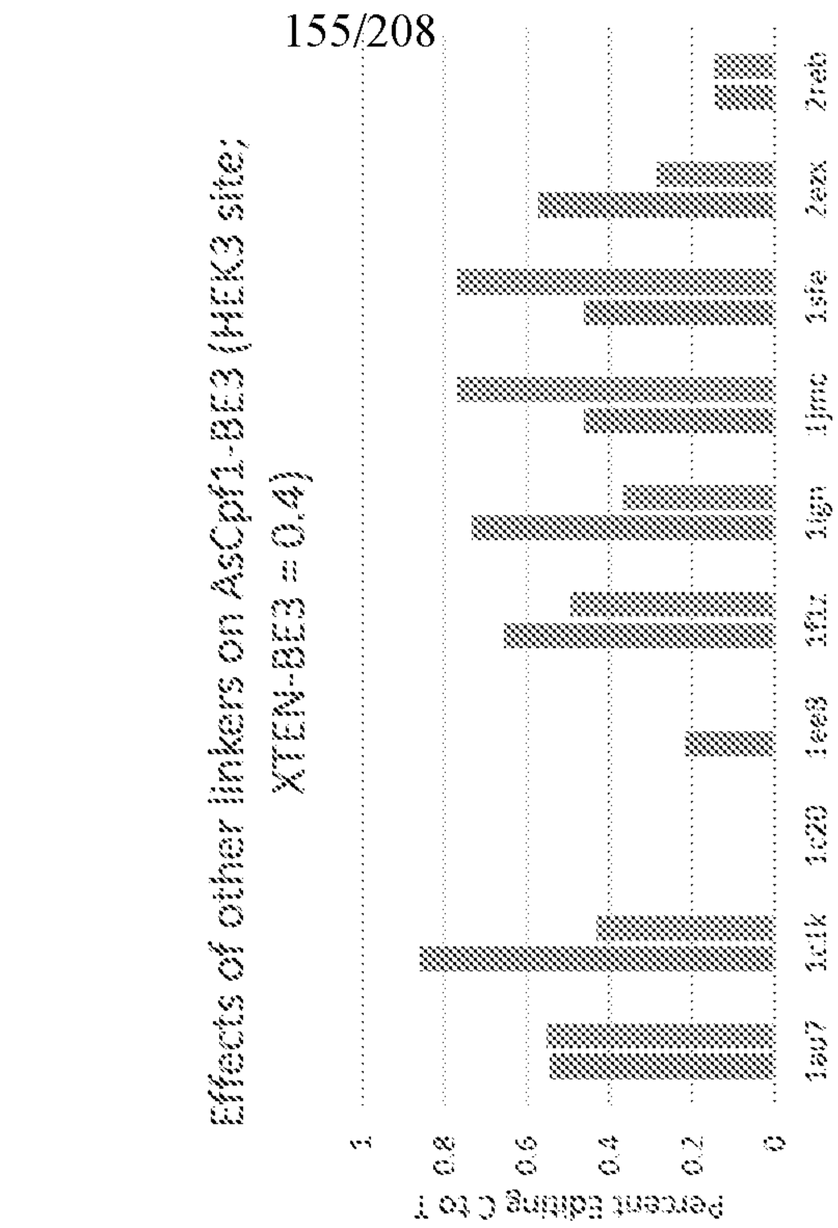


FIGURE 121

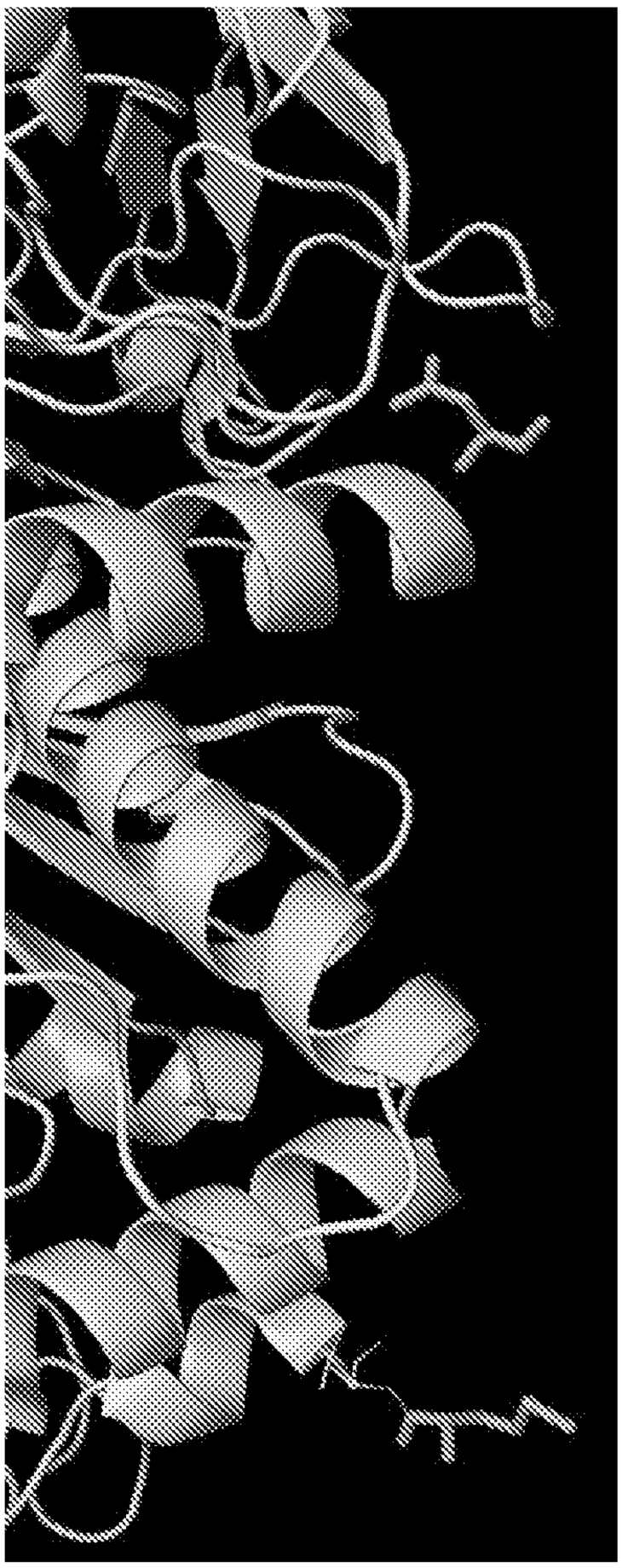


FIGURE 122



FIGURE 123



FIGURE 124

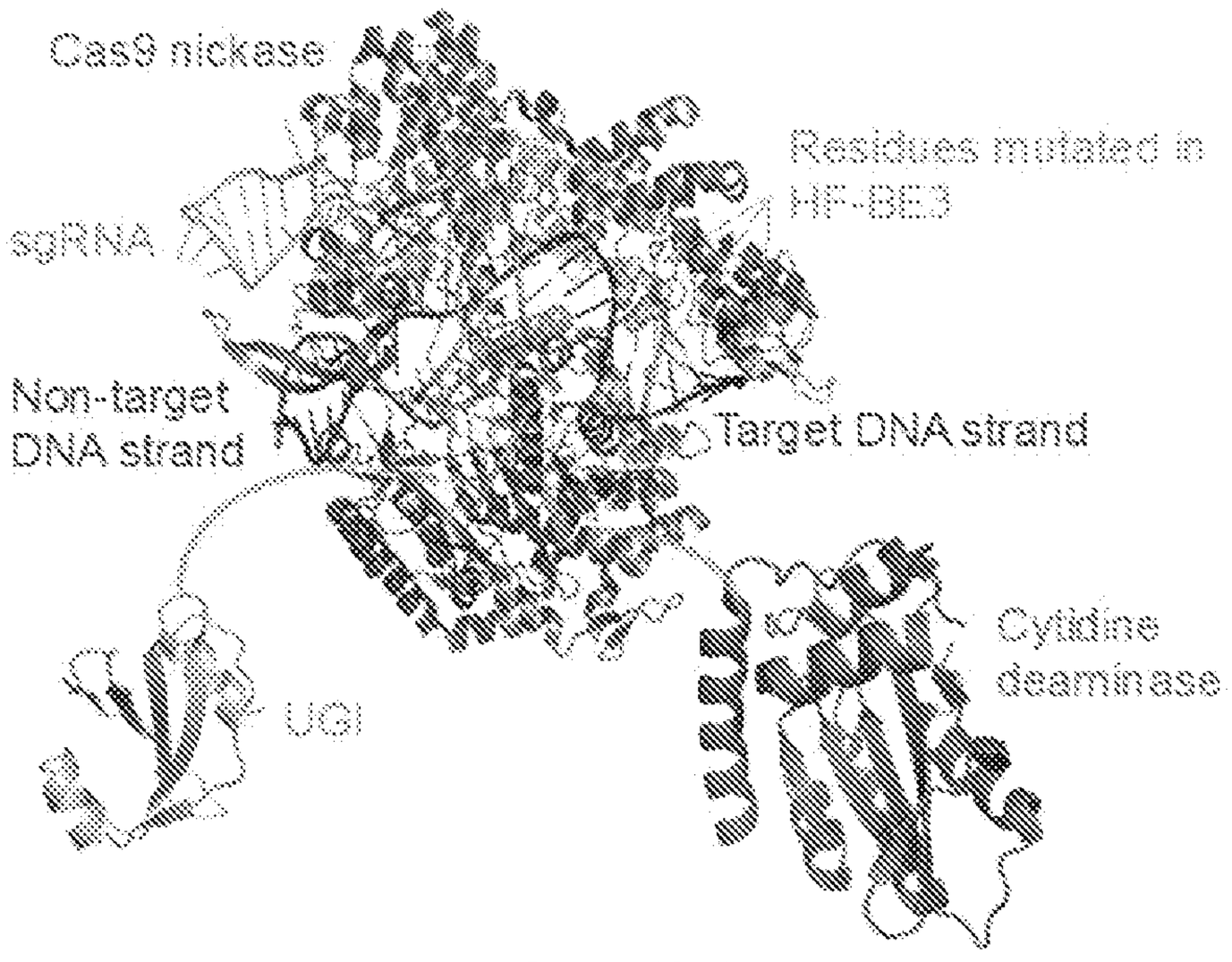


FIGURE 125A

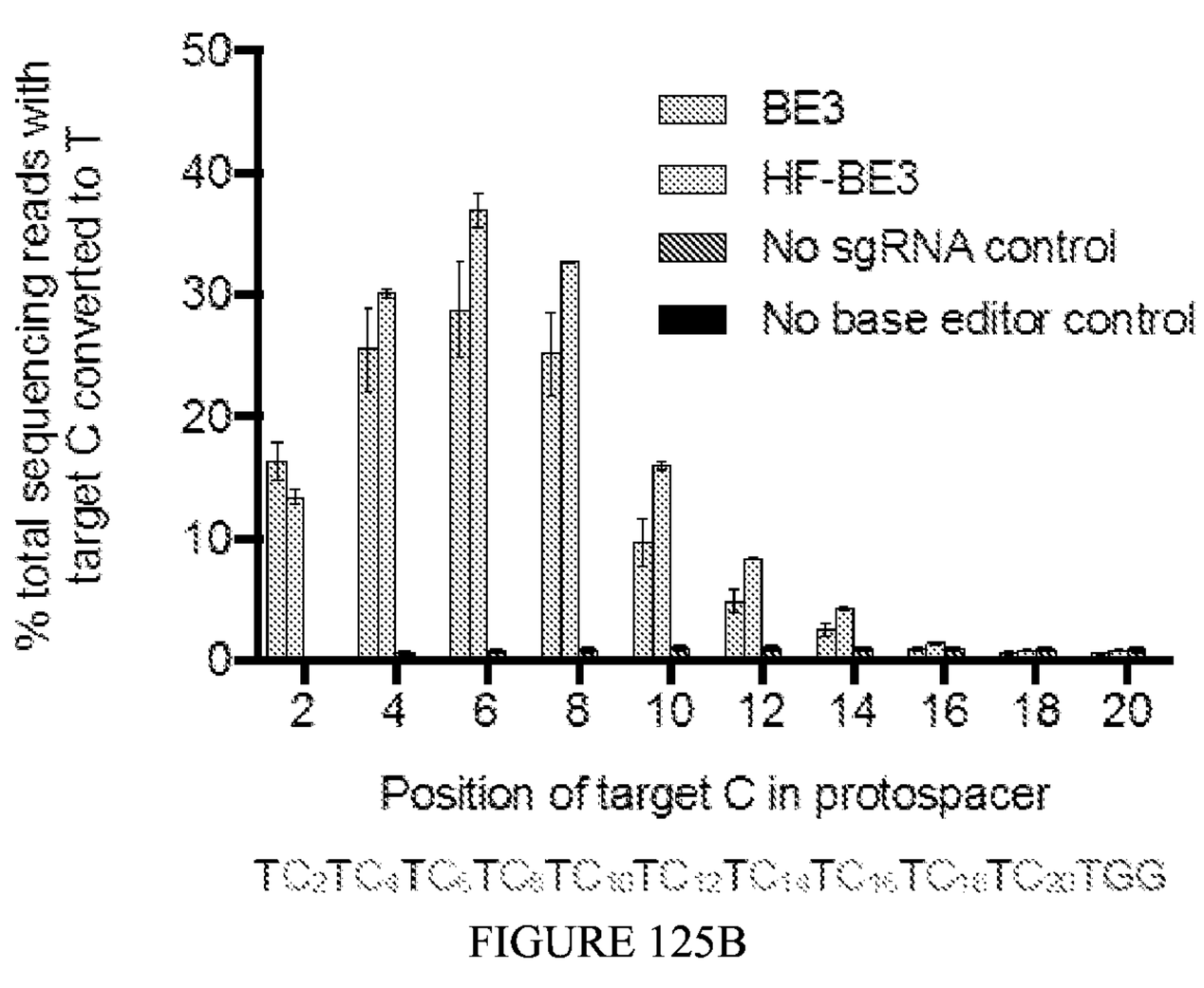


FIGURE 125B

Protein	Cas9	BE3	HF-BE3	BE3	HF-BE3	BE3	HF-BE3
E Coli cell type	Rosetta	Rosetta	Rosetta	BL21 Star	BL21 Star	Rosetta pLysS	Rosetta pLysS

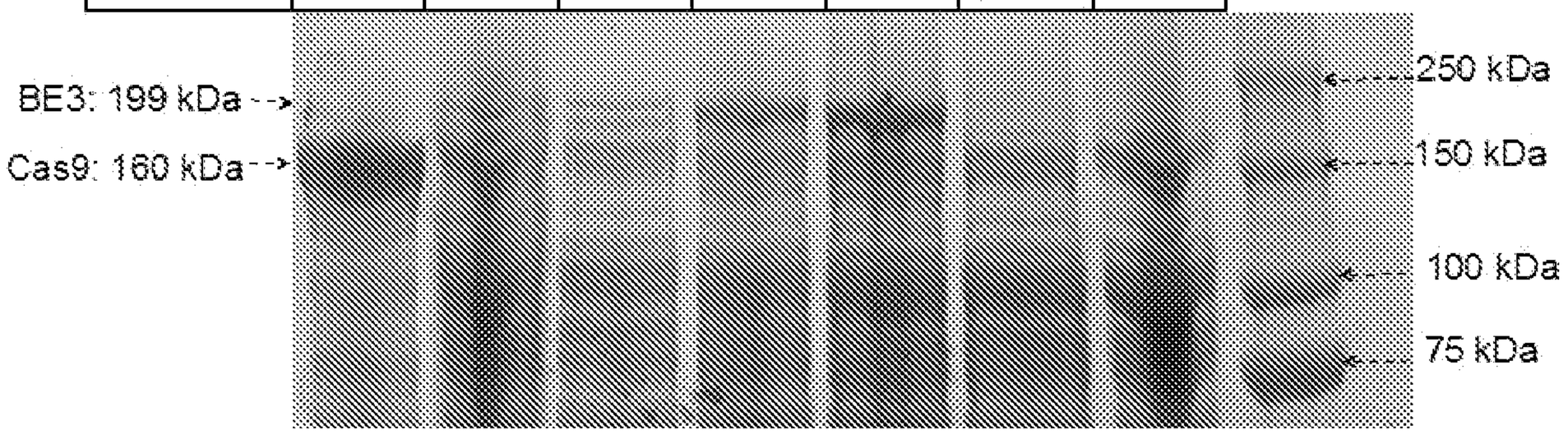


FIGURE 126A

Protein	HF-BE3	BE3	HF-BE3	BE3	HF-BE3	BE3	Cas9	Cas9
His-tag	N-term	N-term	C-term	C-term	C-term	C-term	N-term	N-term
Induction OD_{600}	0.7	0.7	0.4	0.7	0.7	0.4	0.4	0.4
Purification method	Nickel resin + FPLC	Nickel resin + FPLC	Nickel resin + FPLC	Nickel resin + FPLC	Nickel resin + FPLC	Nickel resin + FPLC	Nickel resin	Nickel resin + FPLC

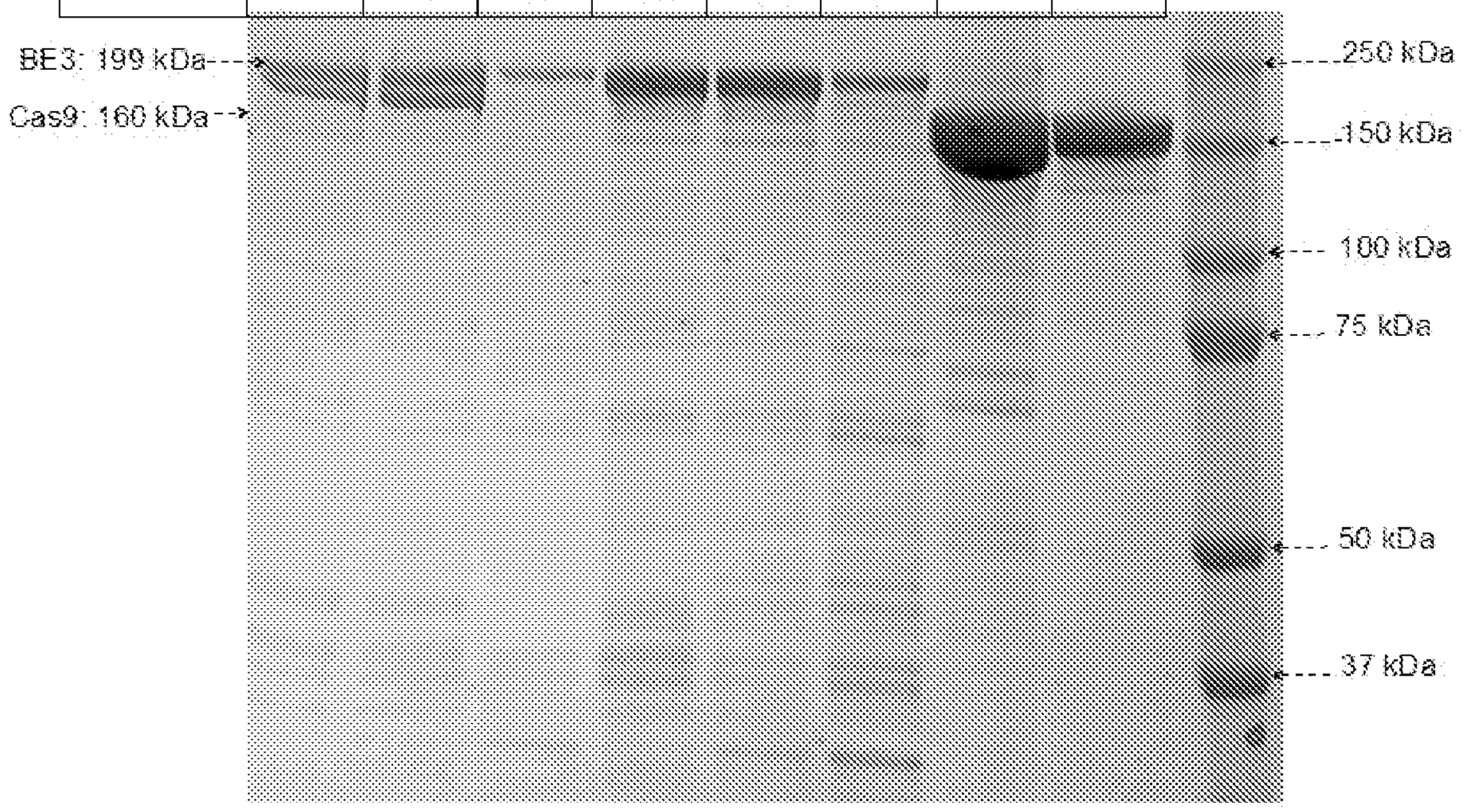


FIGURE 126B

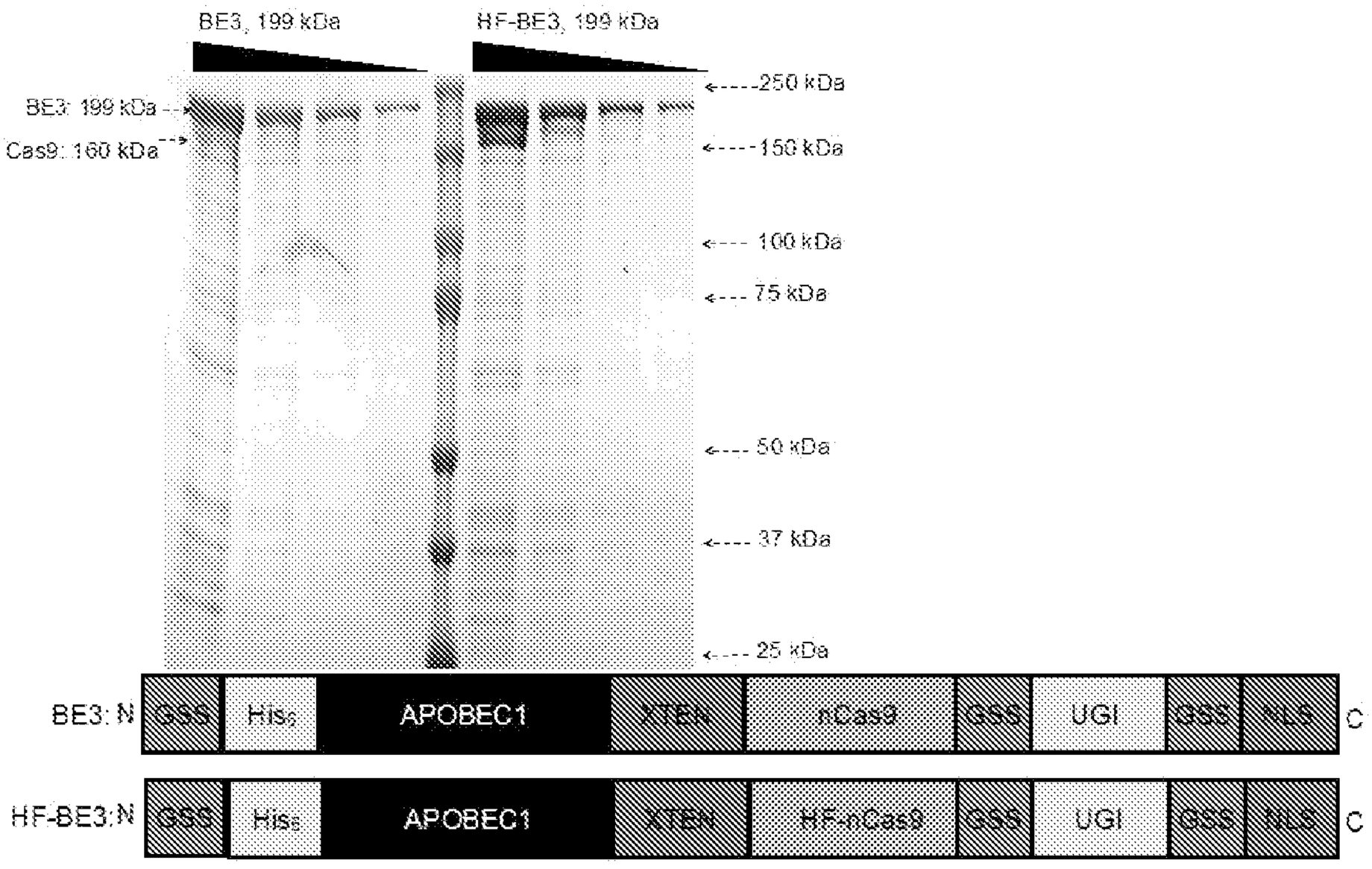
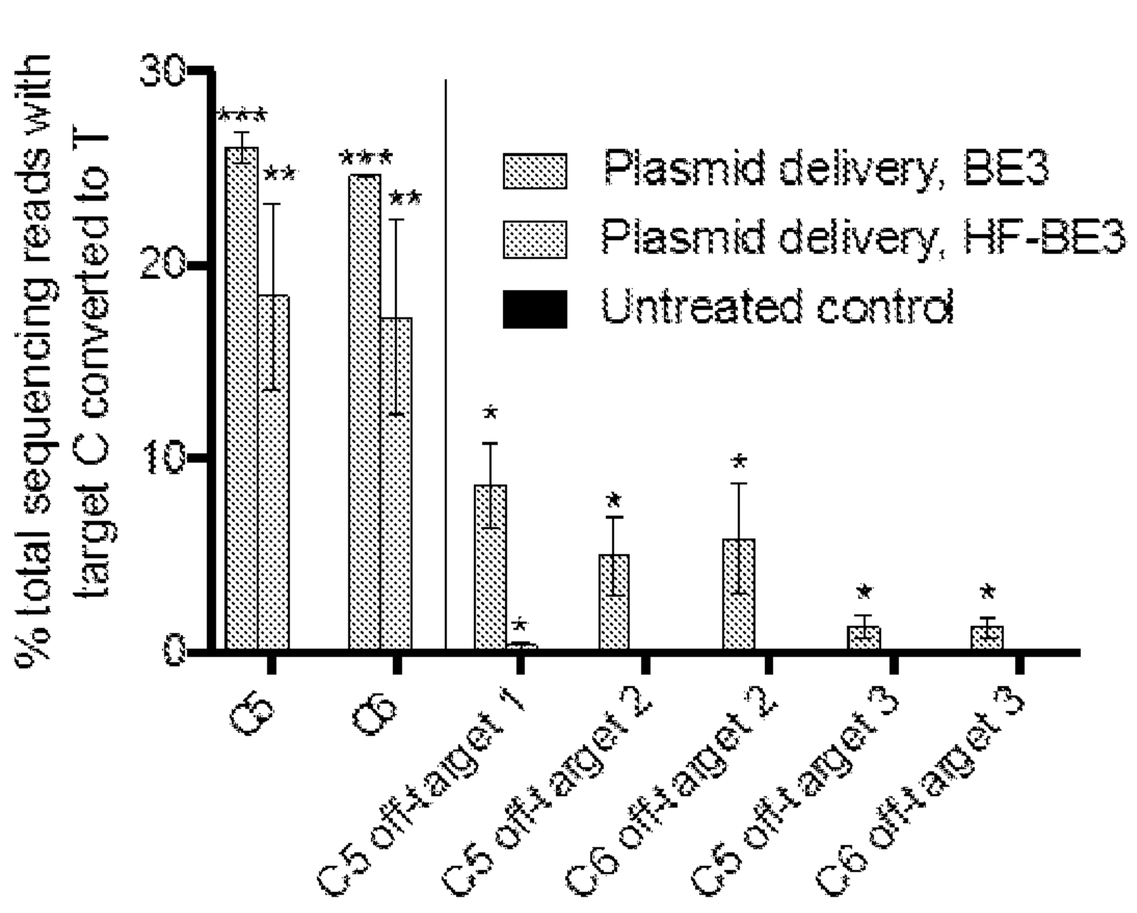


FIGURE 126C



EMX1 on-target : GAGTC$_5$C$_6$GAGCAGAAGAAGAAGGG

EMX1 off-target 1: GAGTC$_5$TAAGCAGAAGAAGAAGAG

EMX1 off-target 2: GAGGC$_5$C$_6$GAGCAGAAGAAAAGACGG

EMX1 off-target 3: GAGTC$_5$C$_6$TAGCAGGAGAAGAAGAG

FIGURE 127A

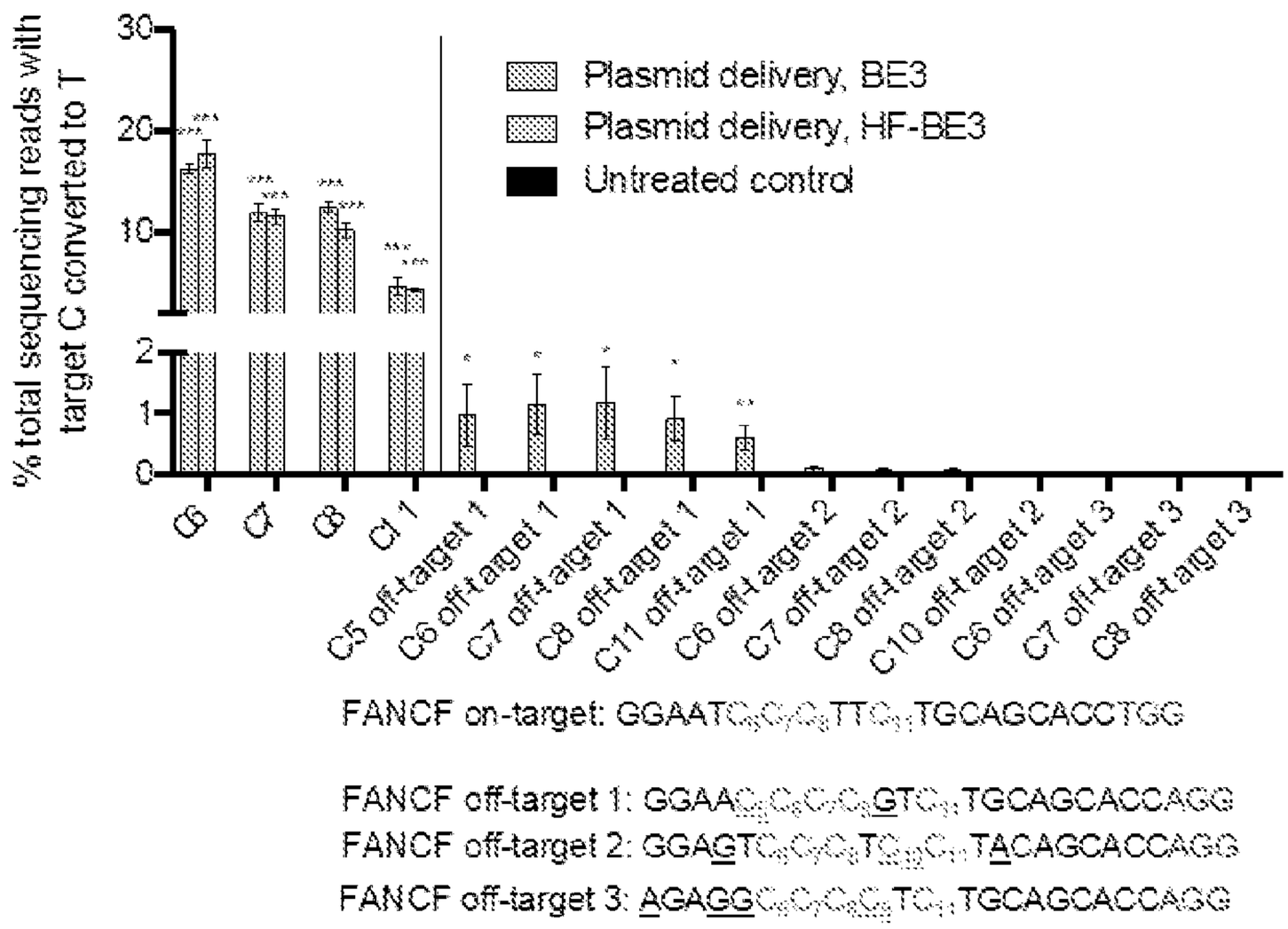


FIGURE 127B

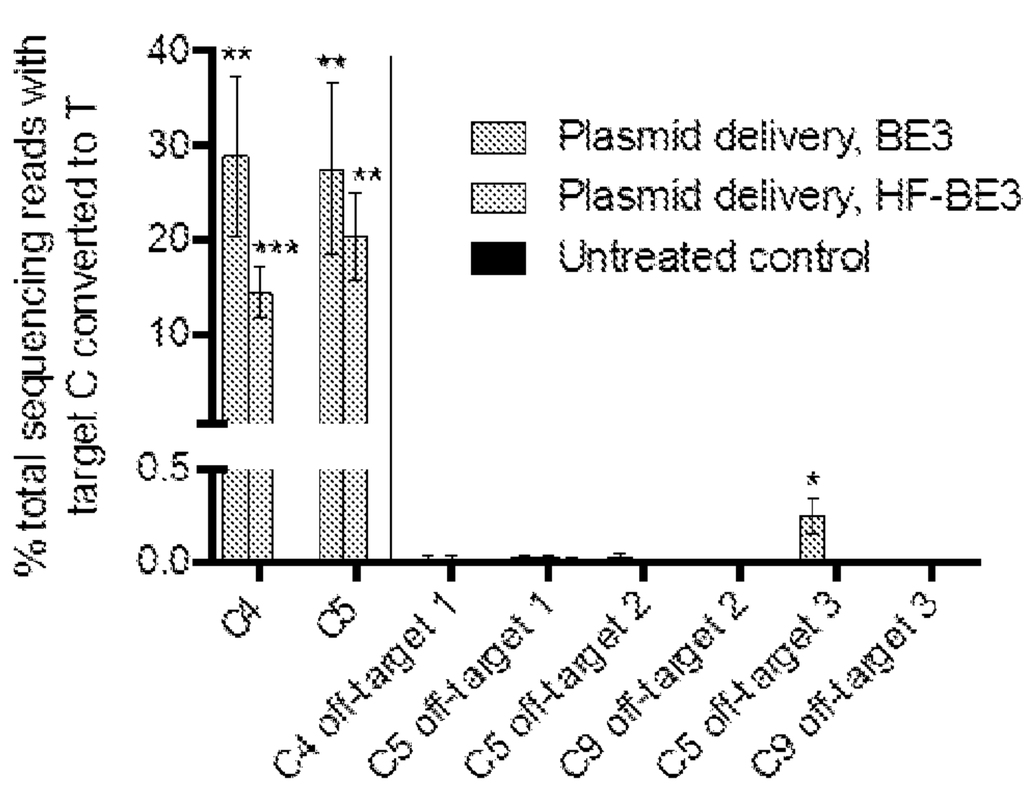


FIGURE 127C

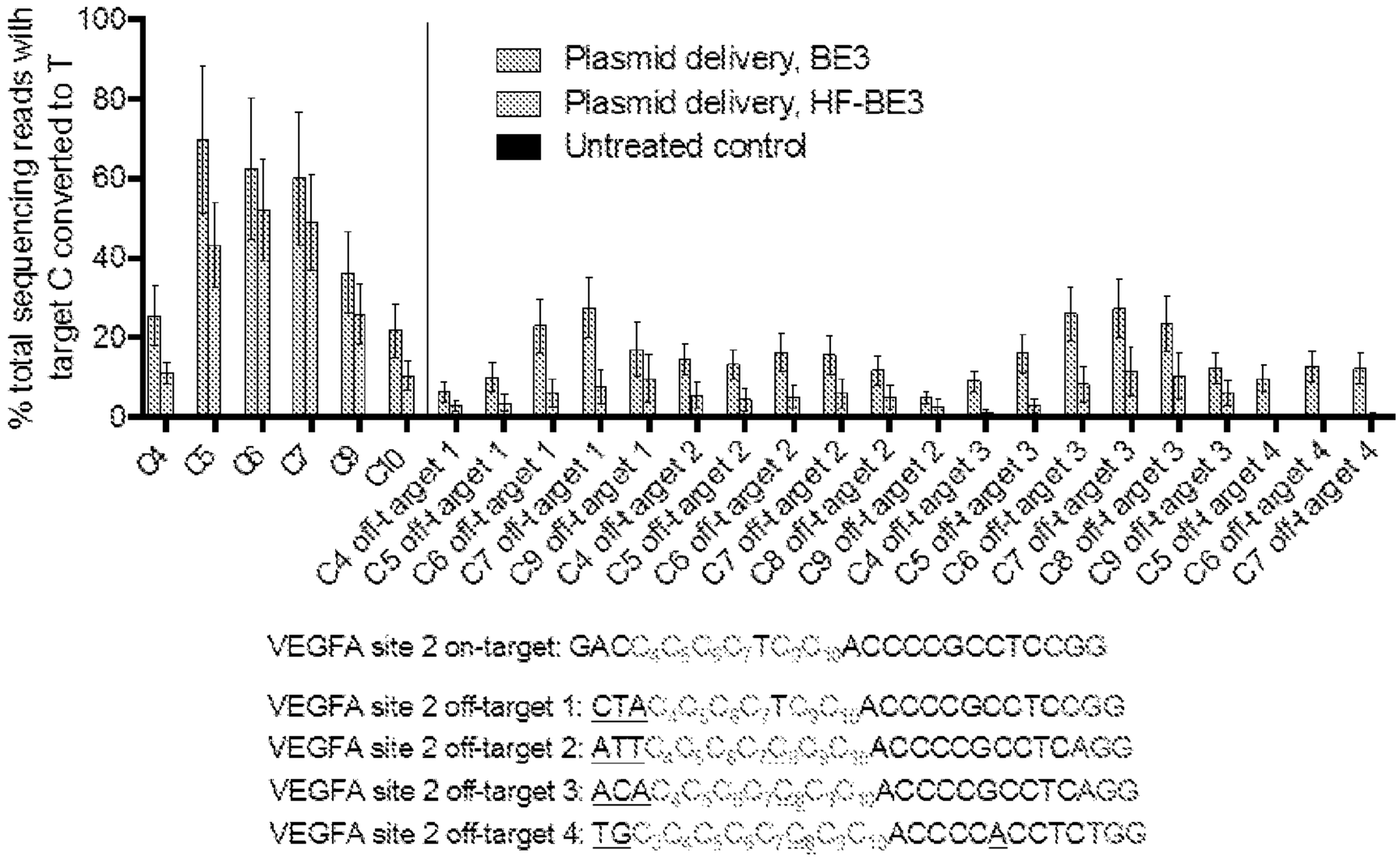


FIGURE 127D

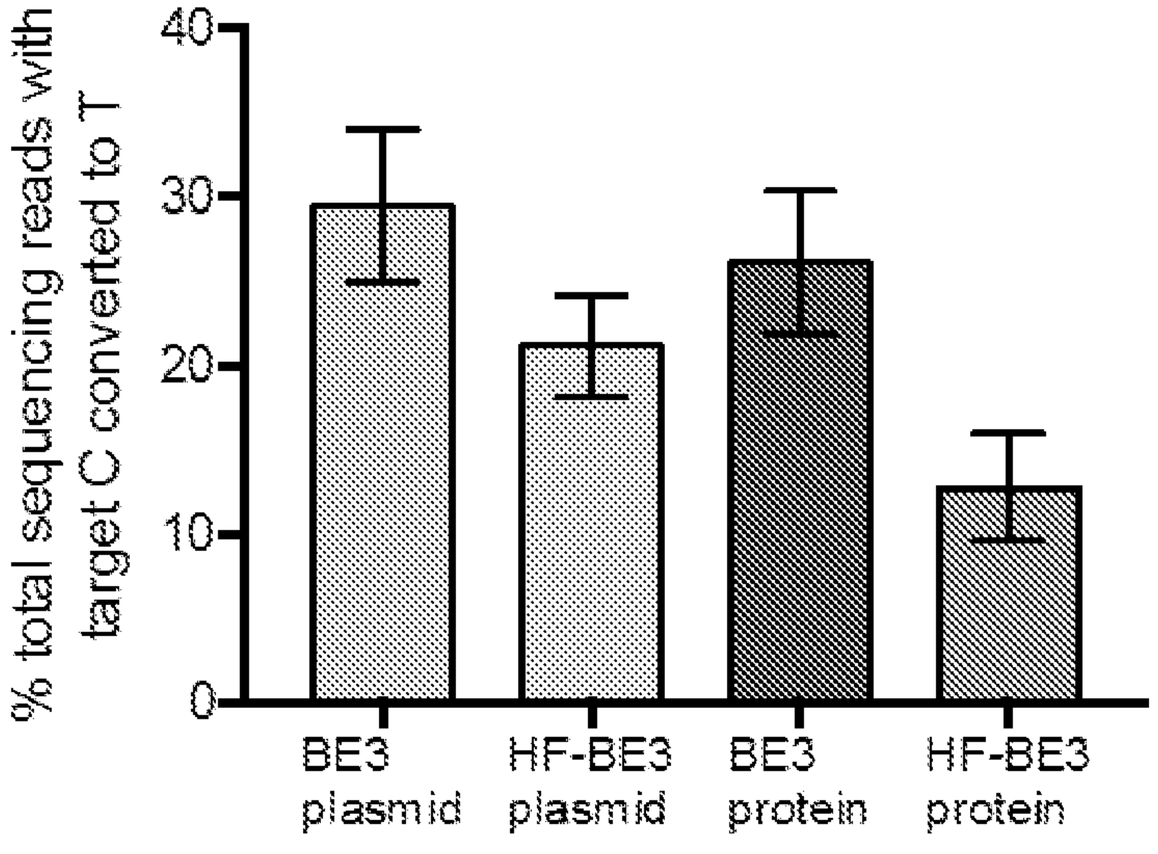
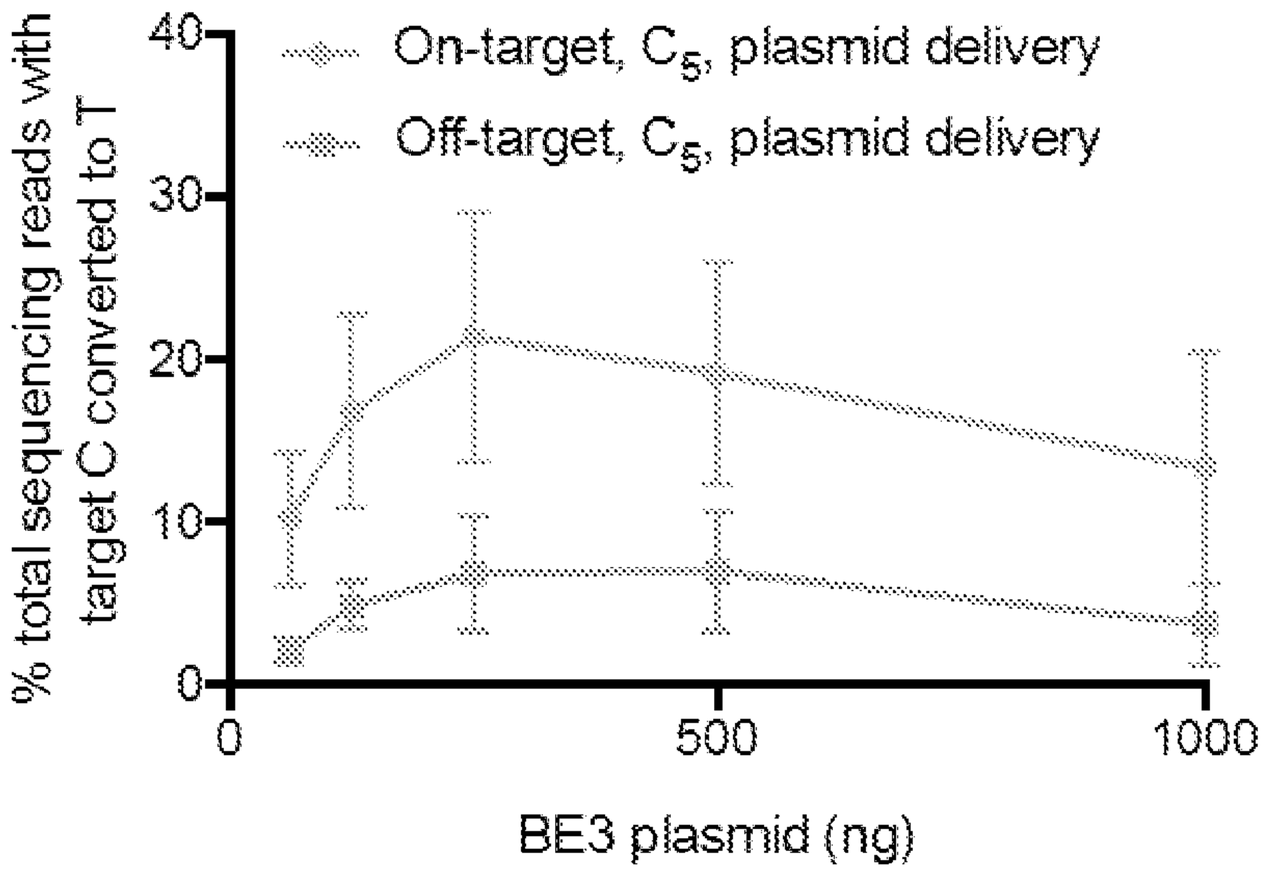


FIGURE 128A



EMX1: GAGTC5C6GAGCAGAAGAAGAAGGG

EMX1 off target 1: GAGTC5TAAGCAGAAGAAGAAGAG

FIGURE 128B

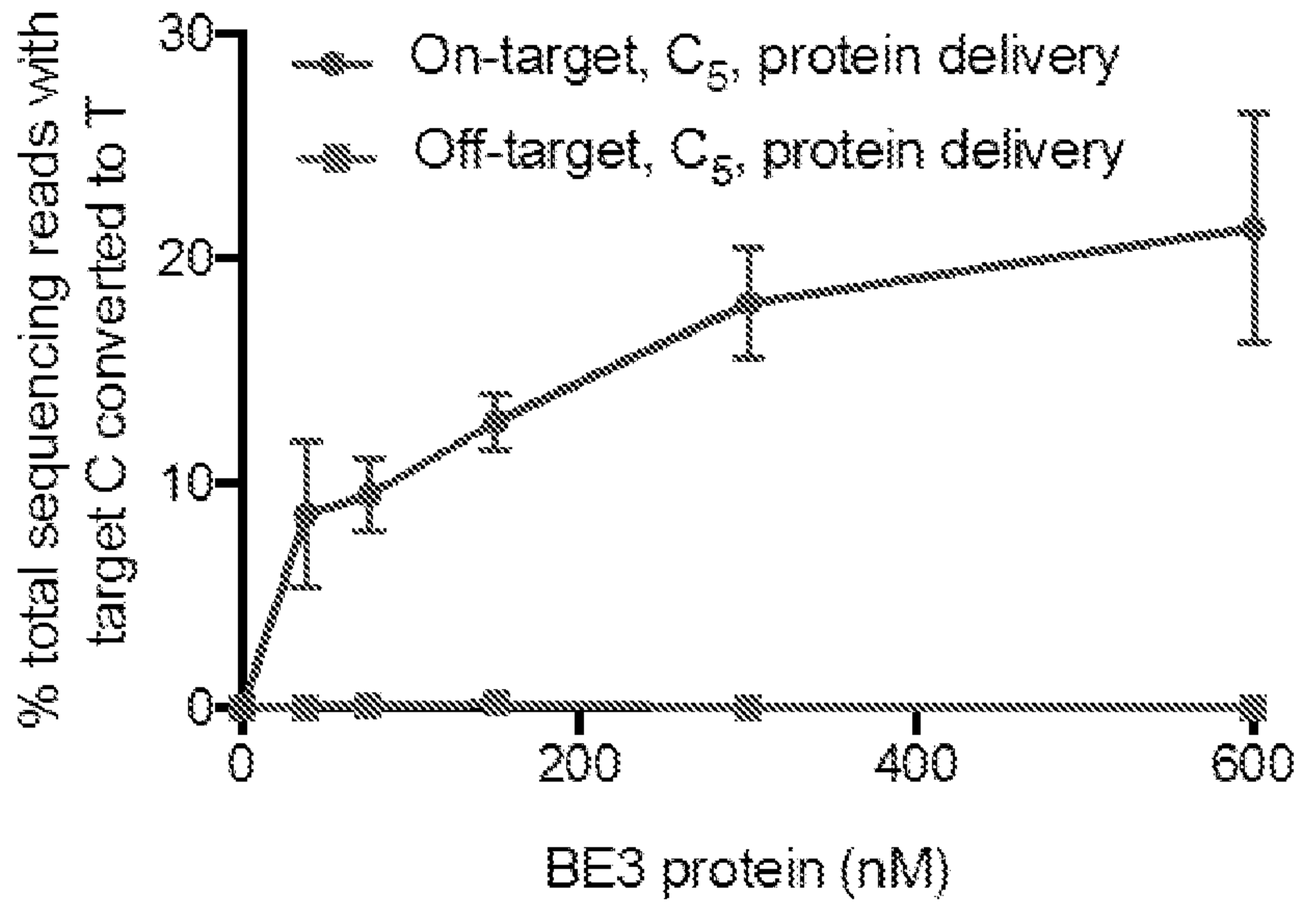


FIGURE 128C

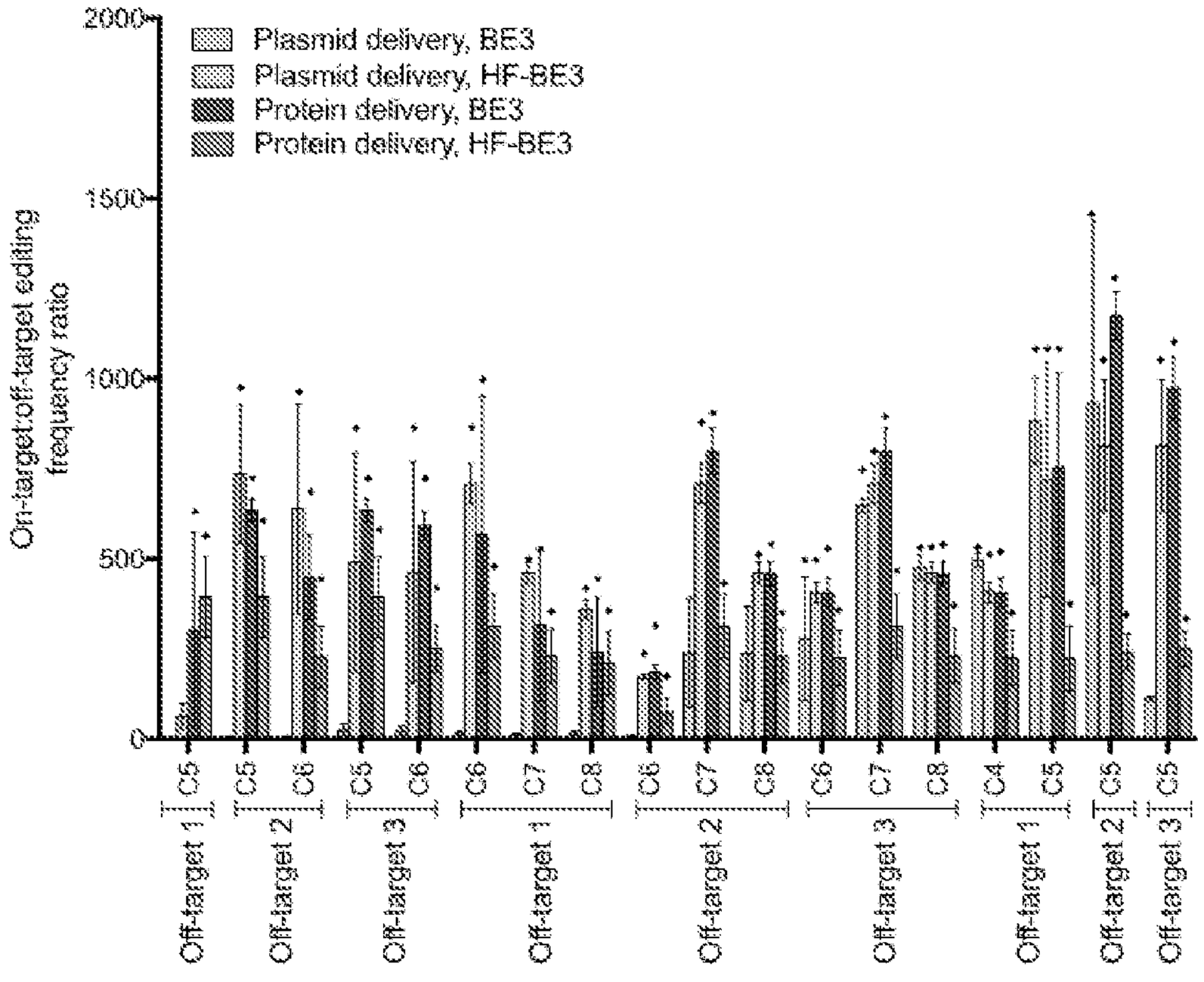


FIGURE 129A

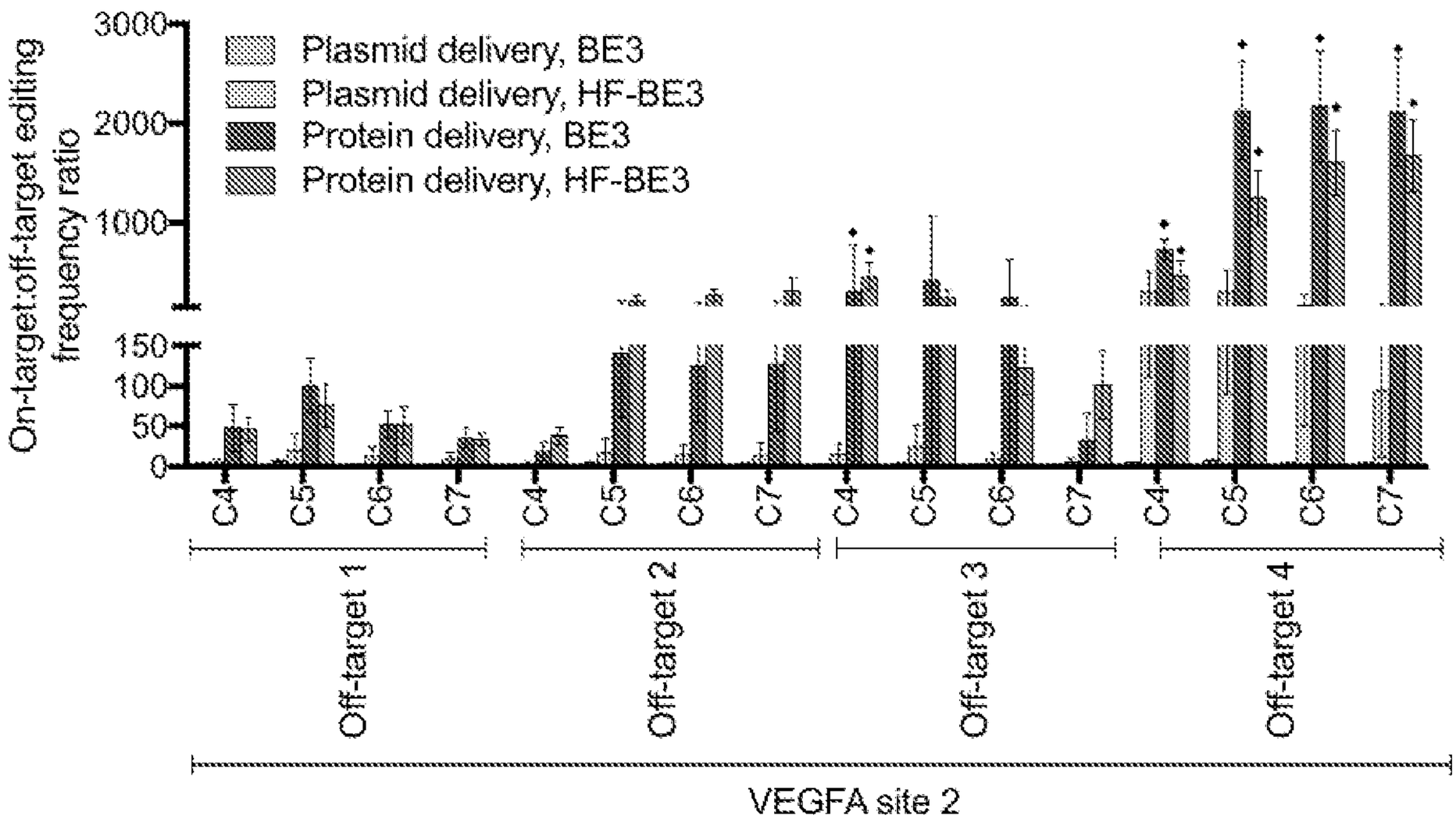
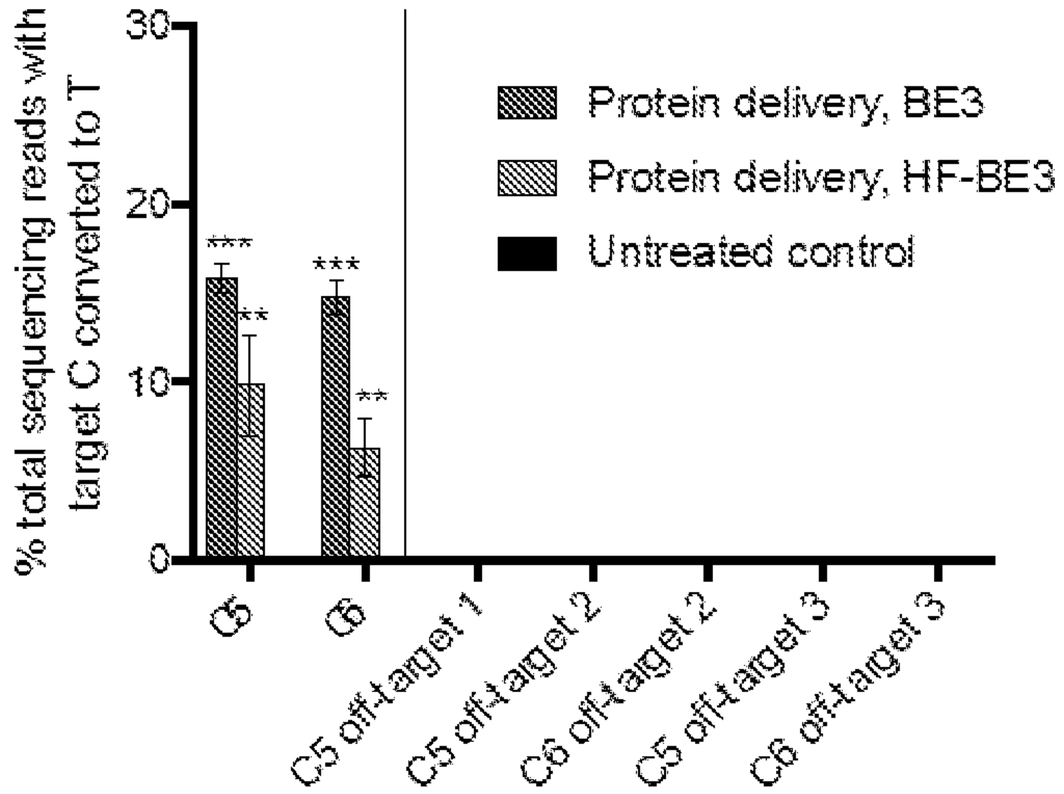


FIGURE 129B



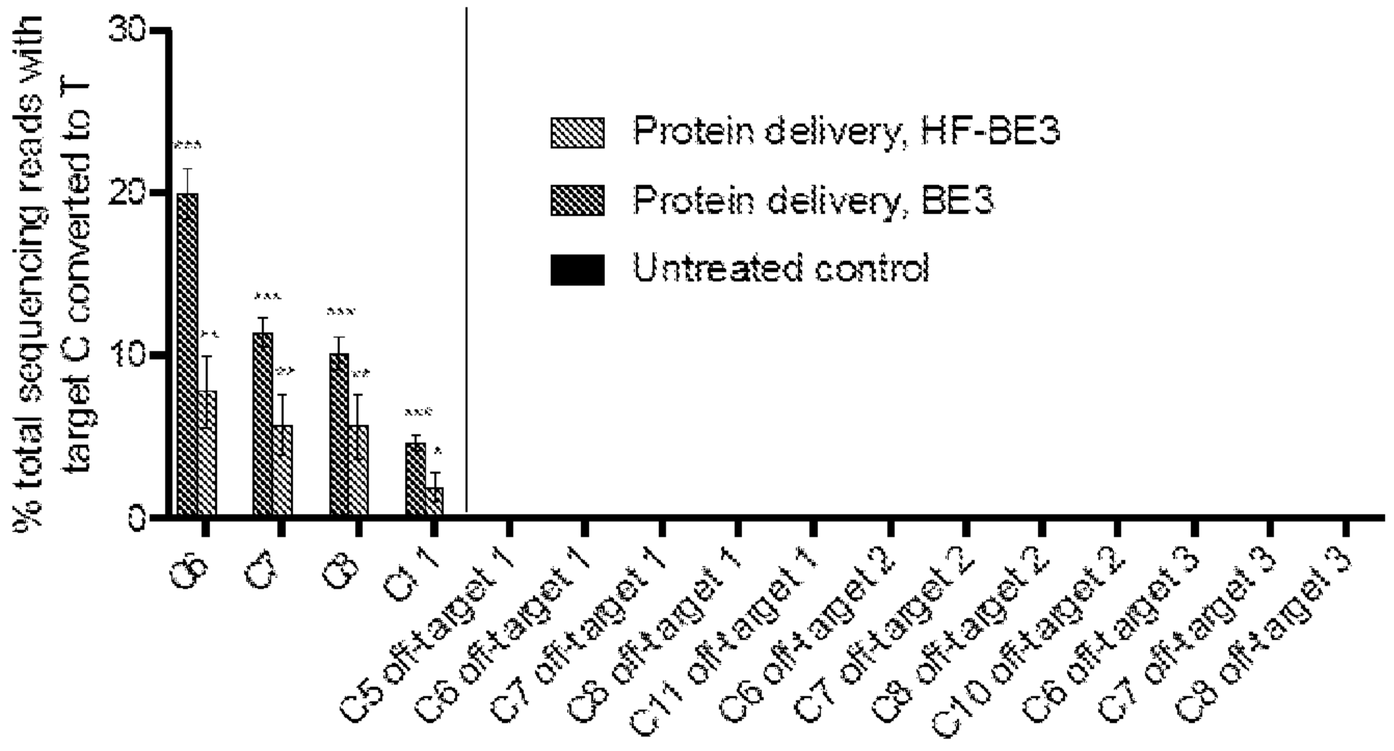
EMX1 on-target : GAGTC$_5$C$_6$GAGCAGAAGAAGAAGGG

EMX1 off-target 1: GAGTC$_5$TAAGCAGAAGAAGAAGAG

EMX1 off-target 2: GAGGC$_5$C$_6$GAGCAGAAGAAAGACGG

EMX1 off-target 3: GAGTC$_5$C$_6$TAGCAGGAGAAGAAGAG

FIGURE 130A



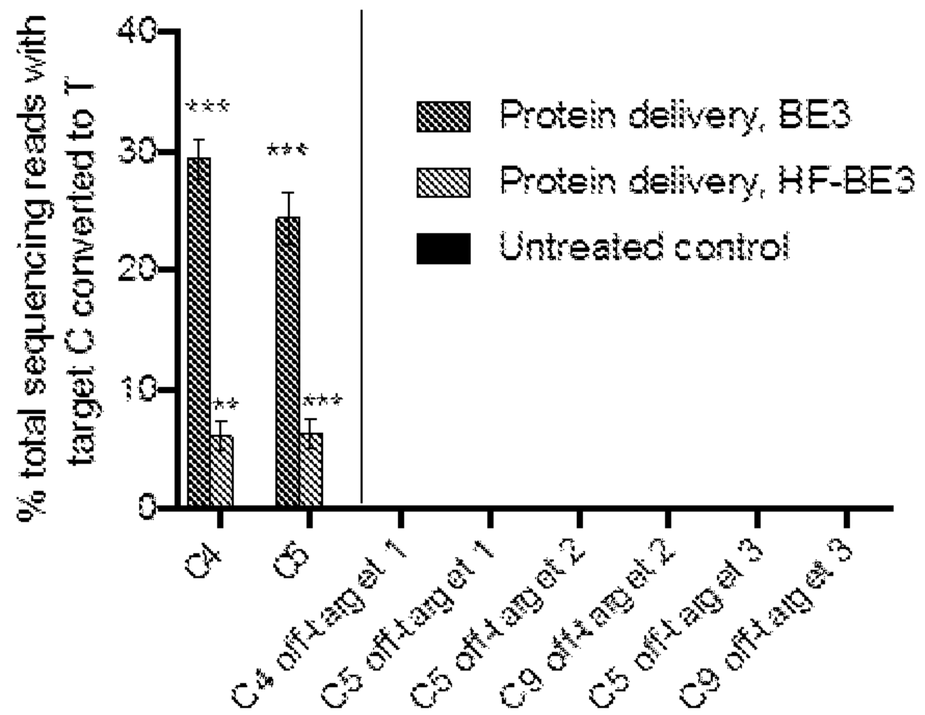
FANCF on-target: GGAATC$_8$C$_9$C$_8$TTC$_{11}$TGCAGCACCTGG

FANCF off-target 1: GGAAC$_8$C$_8$C$_7$C$_6$GTC$_{11}$TGCAGCACCAGG

FANCF off-target 2: GGAGTC$_8$C$_7$C$_8$TC$_{10}$C$_{11}$TACAGCACCAGG

FANCF off-target 3: AGAGGC$_8$C$_7$C$_8$C$_{10}$TC$_{11}$TGCAGCACCAGG

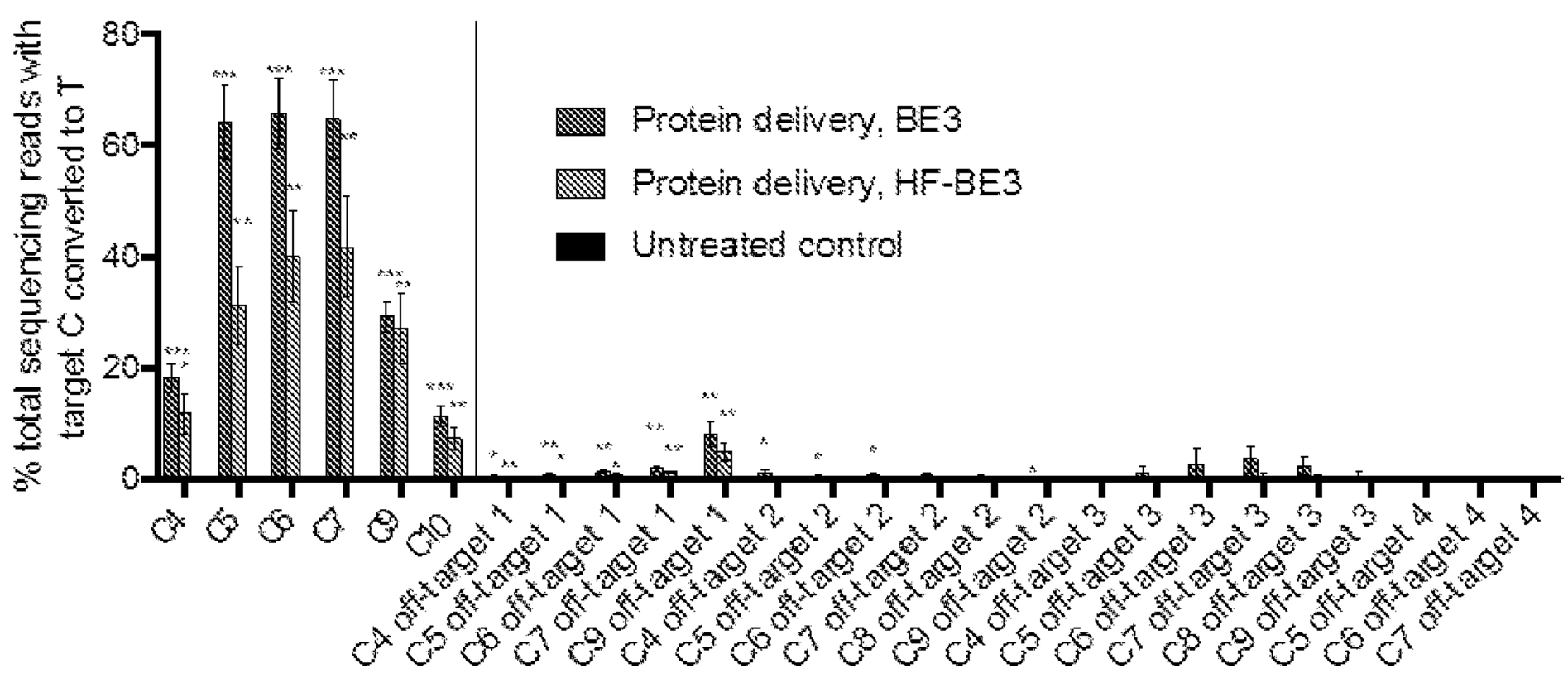
FIGURE 130B



HEK293 site 3 on-target: GCCC$_{4}$C$_{5}$AGACTGAGCACGTGATGG

HEK293 site 3 off-target 1: CACC$_{4}$C$_{5}$AGACTGAGCACGTGCTGG
HEK293 site 3 off-target 2: GACAC$_{5}$AGACTGGGCACGTGAGGG
HEK293 site 3 off-target 3: AGCTC$_{5}$AGACTGAGCAAGTGAGGG

FIGURE 130C



VEGFA site 2 on-target: GACC$_{4}$C$_{5}$C$_{6}$C$_{7}$TC$_{9}$C$_{10}$ACCCCGCCTCCGG

VEGFA site 2 off-target 1: CTAC$_{4}$C$_{5}$C$_{6}$C$_{7}$TC$_{9}$C$_{10}$ACCCCGCCTCCGG
VEGFA site 2 off-target 2: ATTC$_{4}$C$_{5}$C$_{6}$C$_{7}$C$_{8}$C$_{9}$C$_{10}$ACCCCGCCTCAGG
VEGFA site 2 off-target 3: ACAC$_{4}$C$_{5}$C$_{6}$C$_{7}$C$_{8}$C$_{9}$C$_{10}$ACCCCGCCTCAGG
VEGFA site 2 off-target 4: TGC$_{4}$C$_{5}$C$_{6}$C$_{7}$C$_{8}$C$_{9}$C$_{10}$ACCCCACCTCTGG

FIGURE 130D

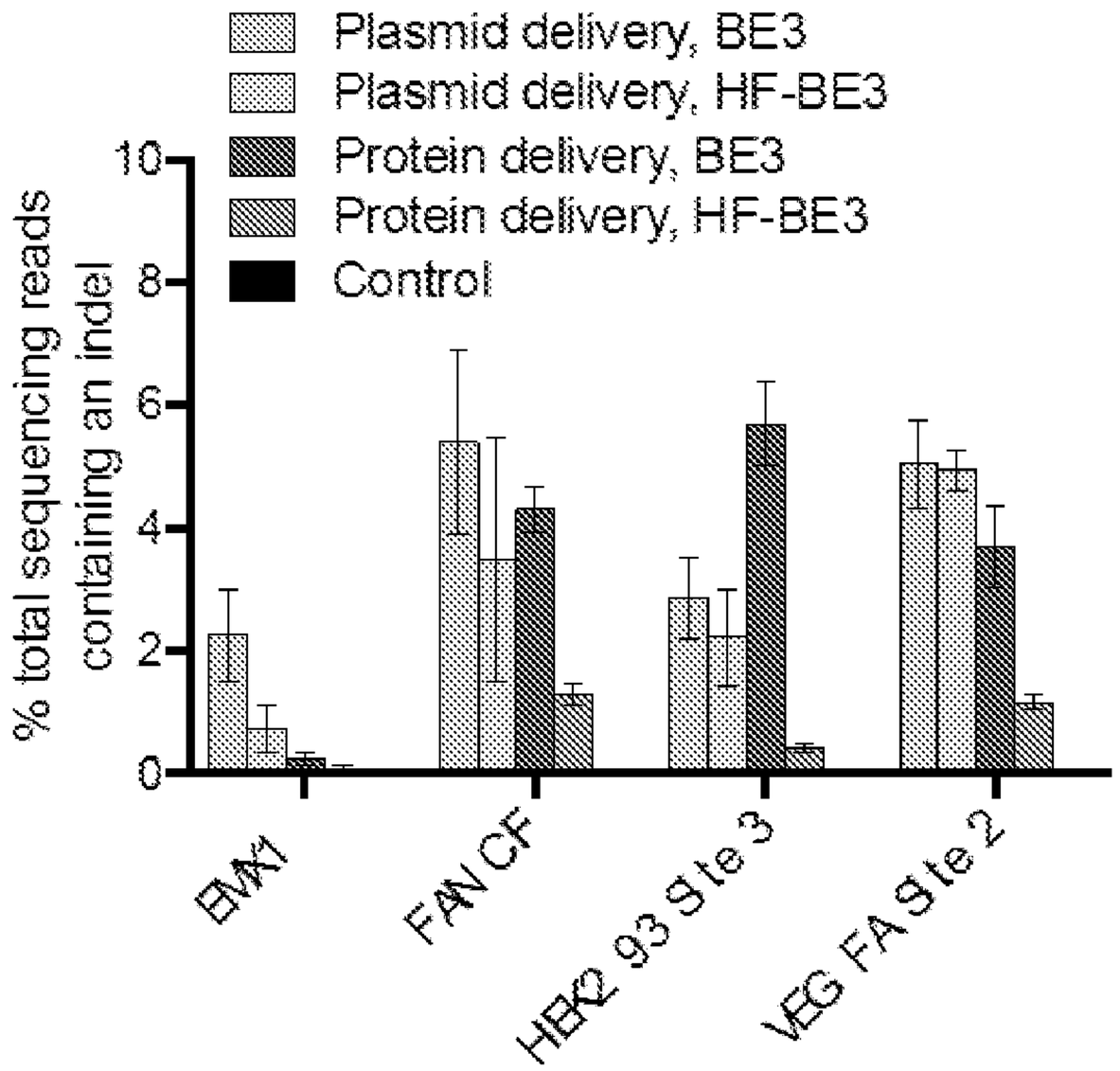


FIGURE 131A

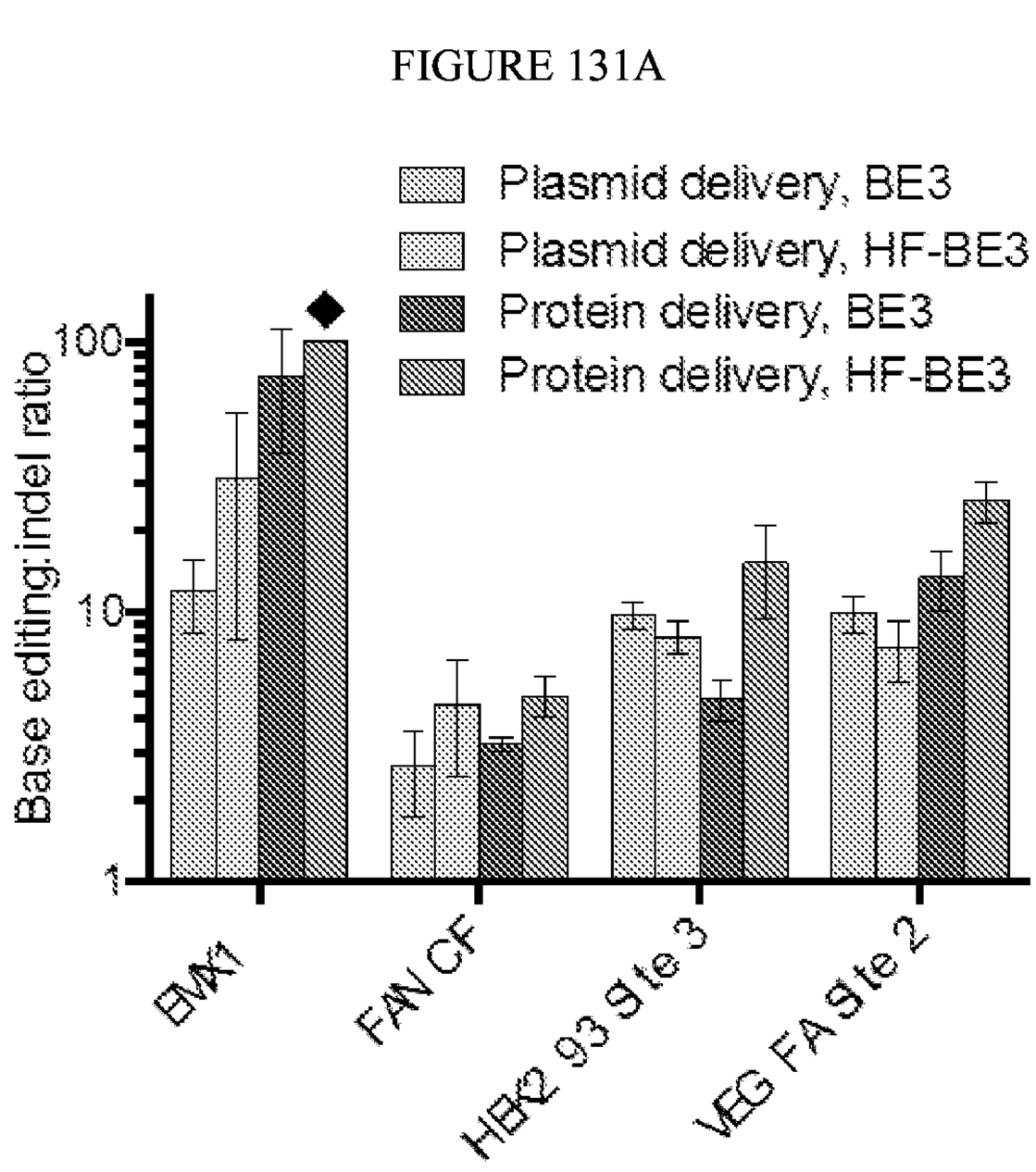


FIGURE 131B

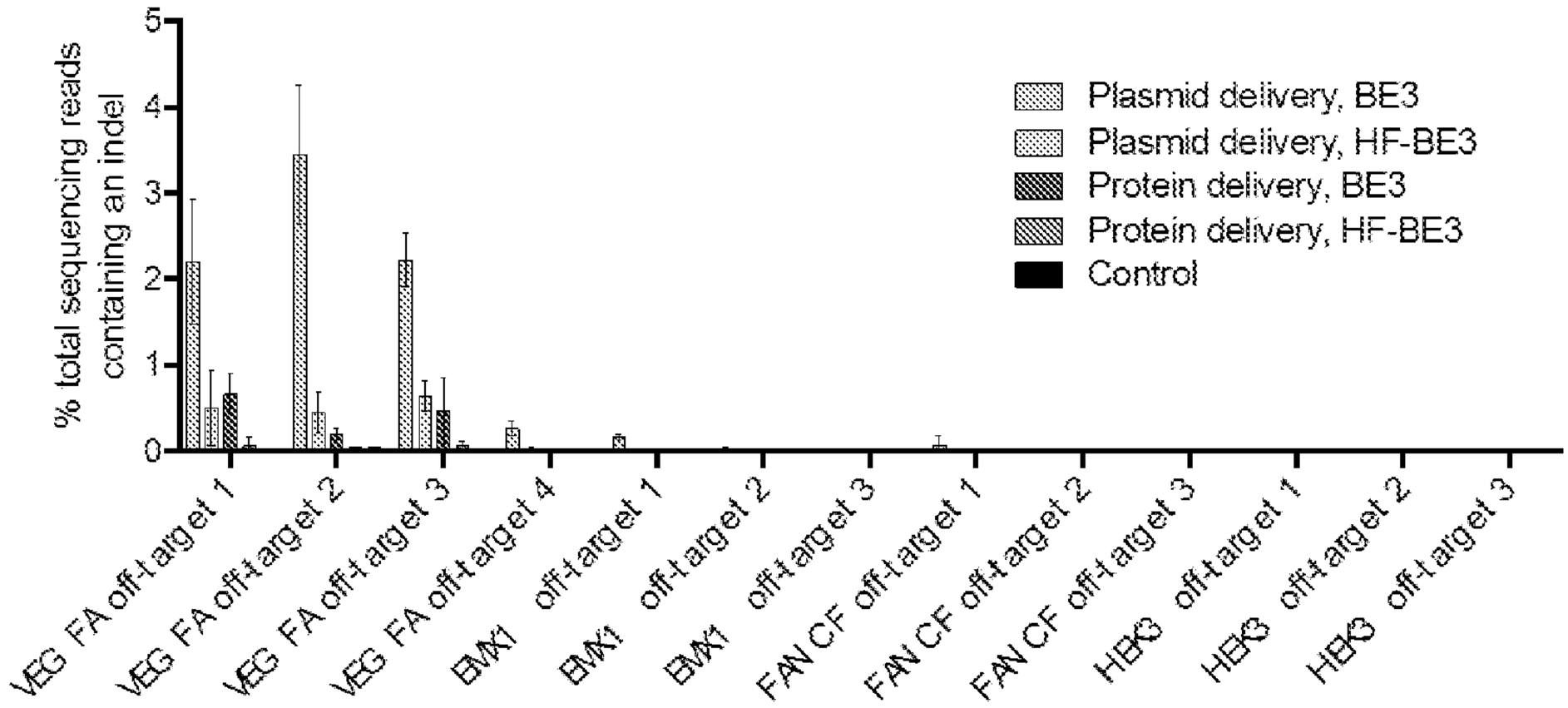
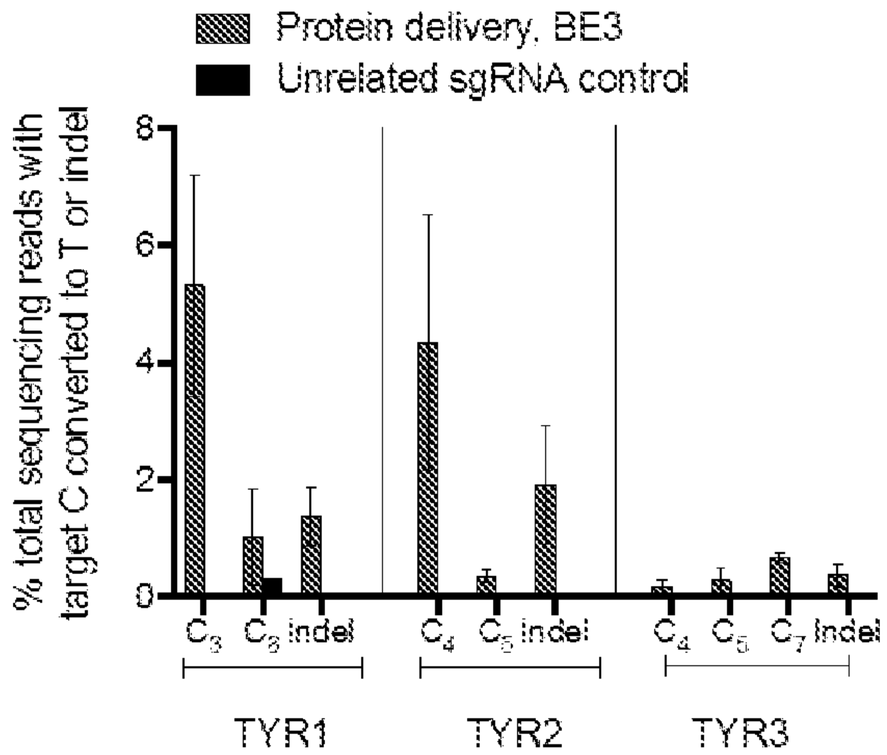


FIGURE 131C



TYR1: GTC$_3$AGGTC$_8$GAGGGTTCTGTCAGG

TYR2: CTTC$_4$C$_5$AGGATGAGAACACAGAGG

TYR3: CAAC$_4$C$_5$AC$_7$TGCTCAAAGATGCTGG

FIGURE 132A

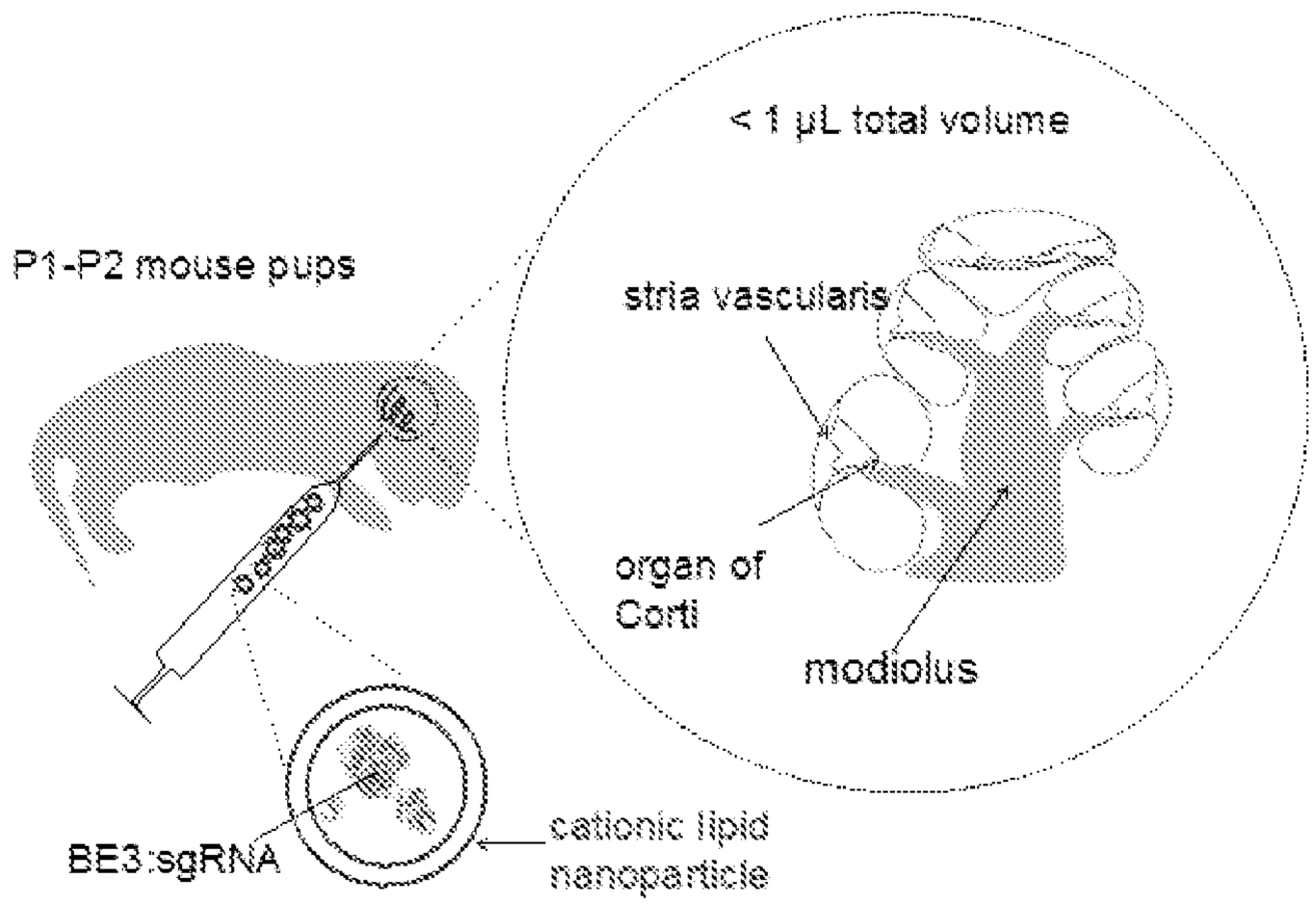
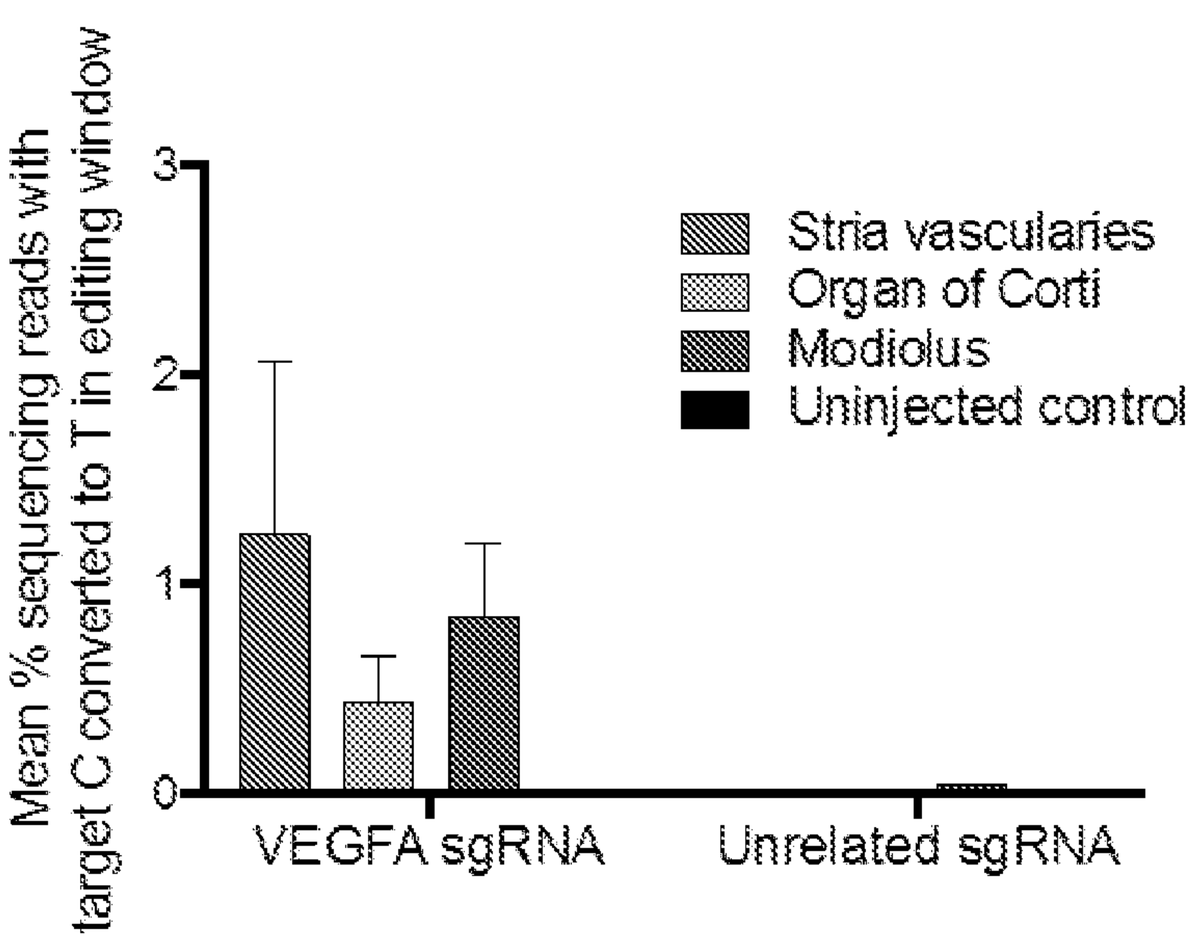


FIGURE 132B



VEGFA site 2: GAC$C_4C_5C_6C_7TC_9C_{10}$ACCCCGCCTCCGG

FIGURE 132C

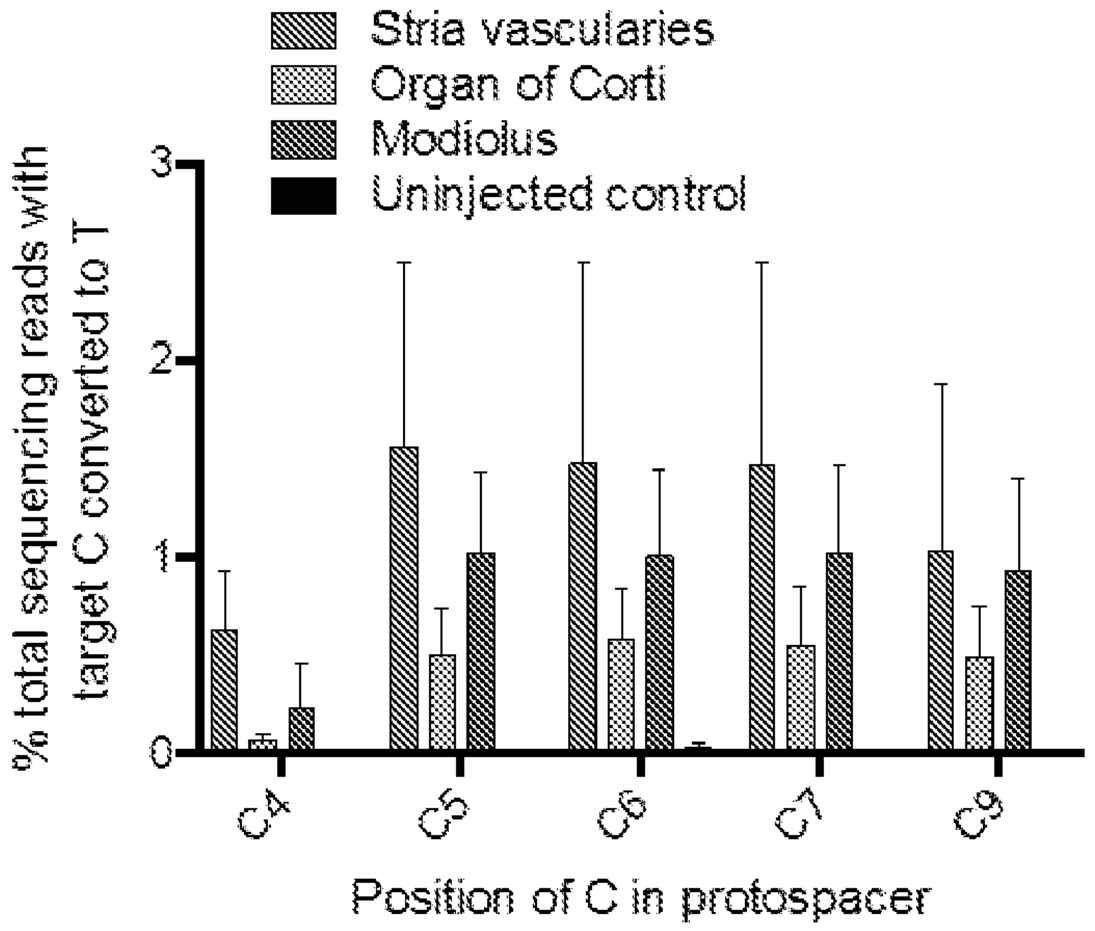


FIGURE 132D

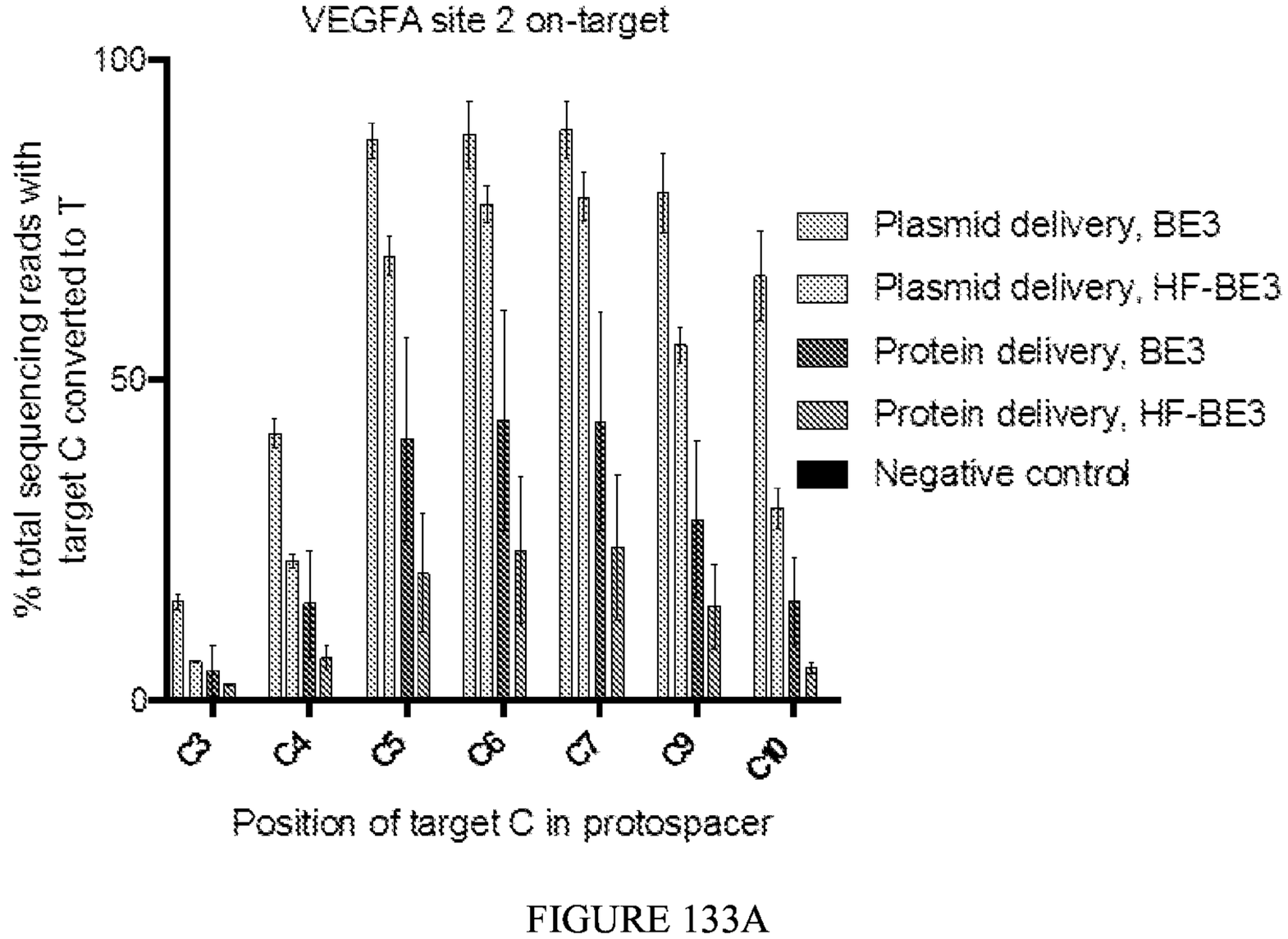


FIGURE 133A

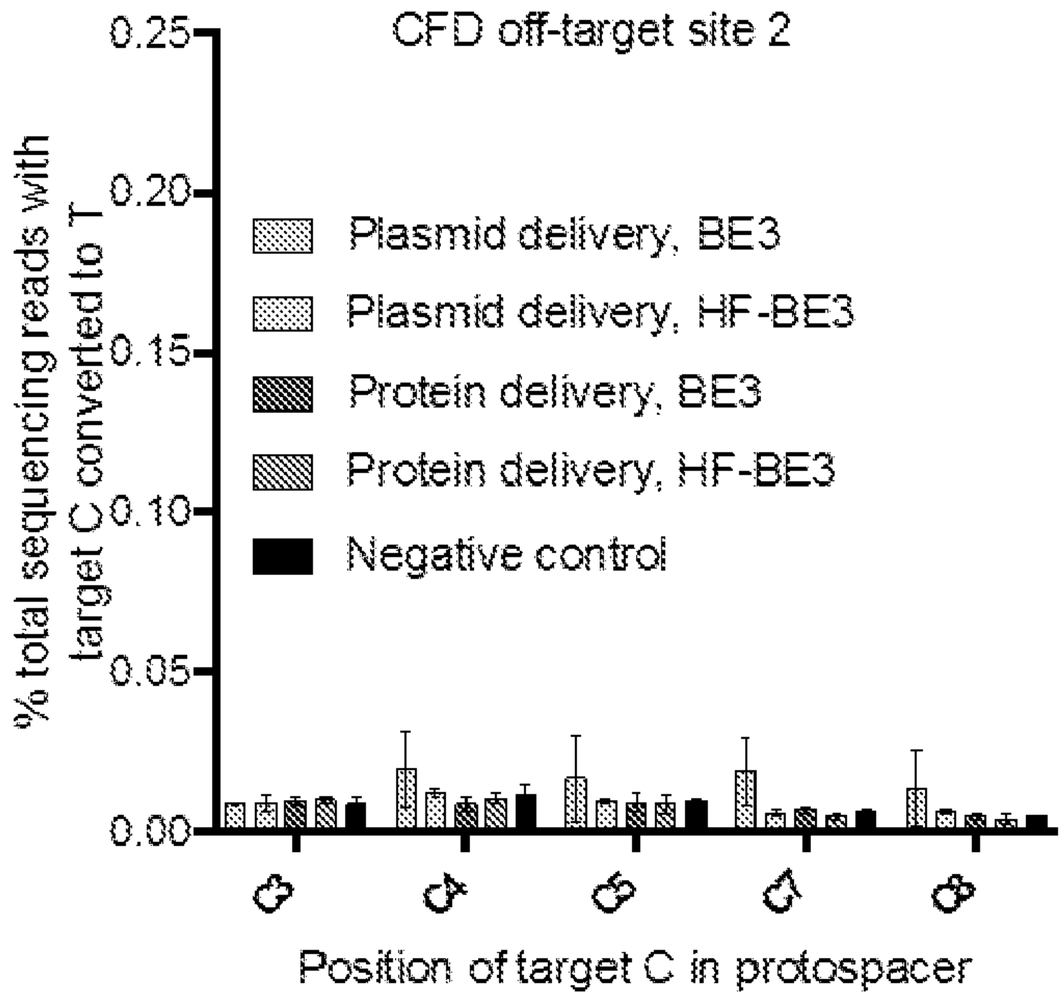


FIGURE 133B

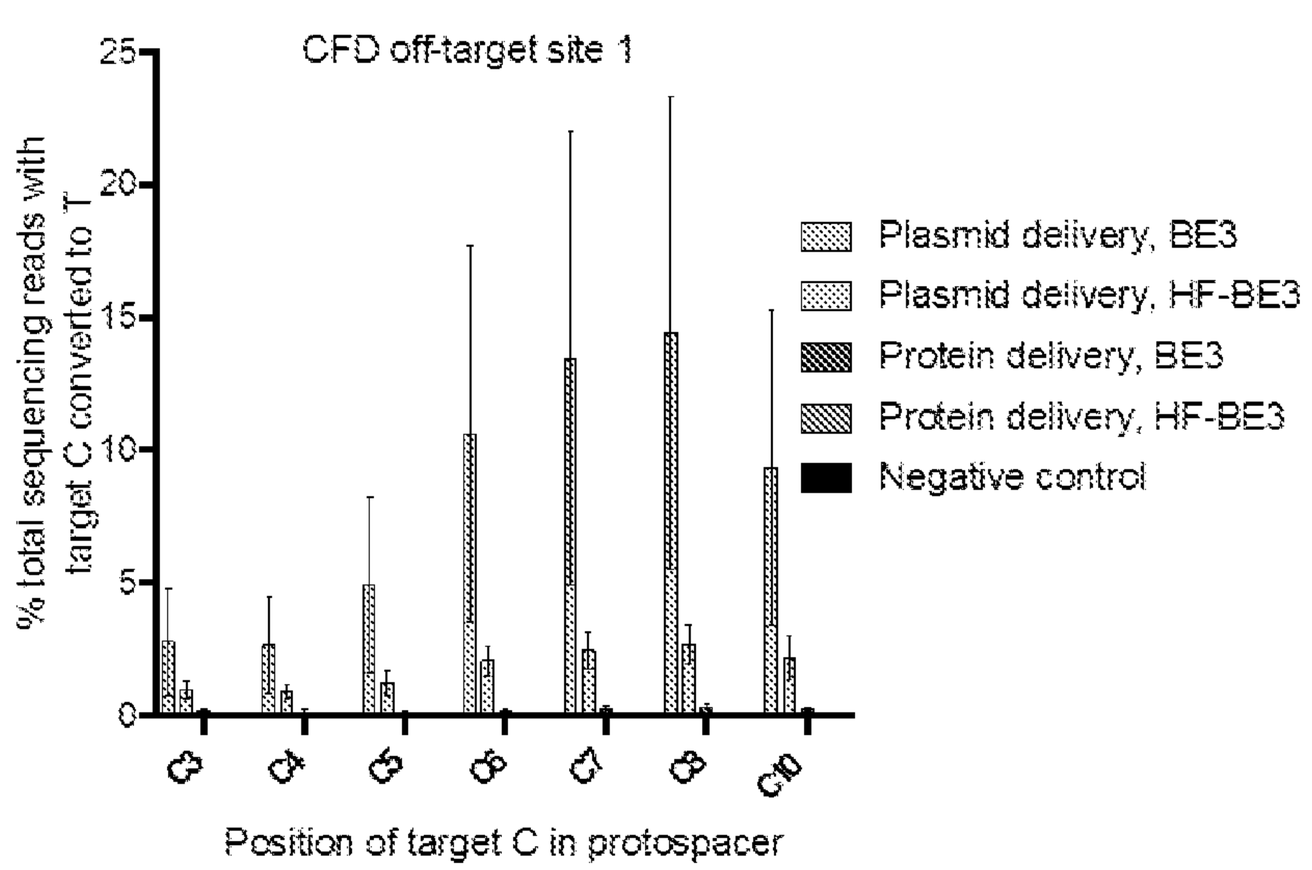


FIGURE 133C

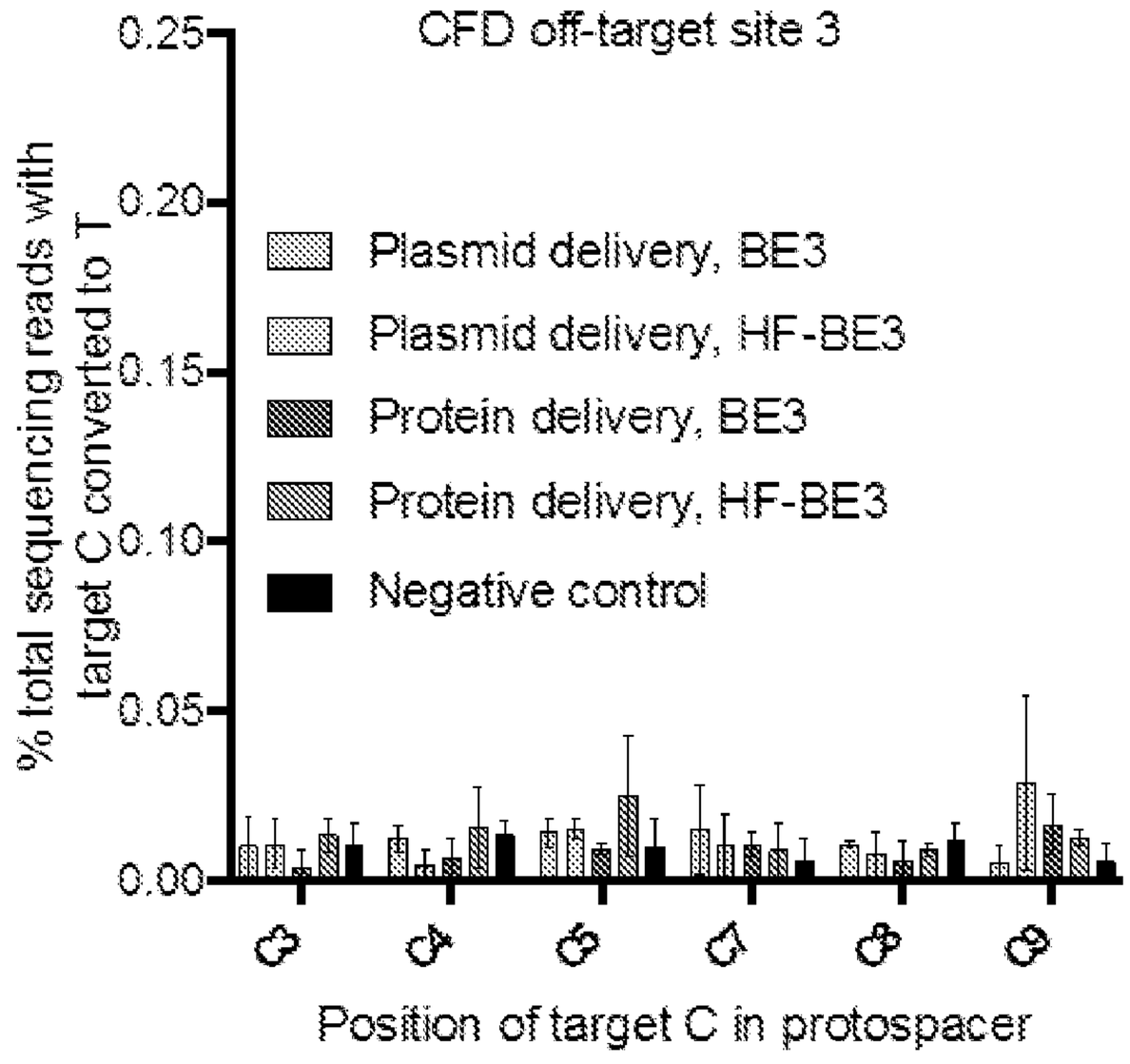


FIGURE 133D

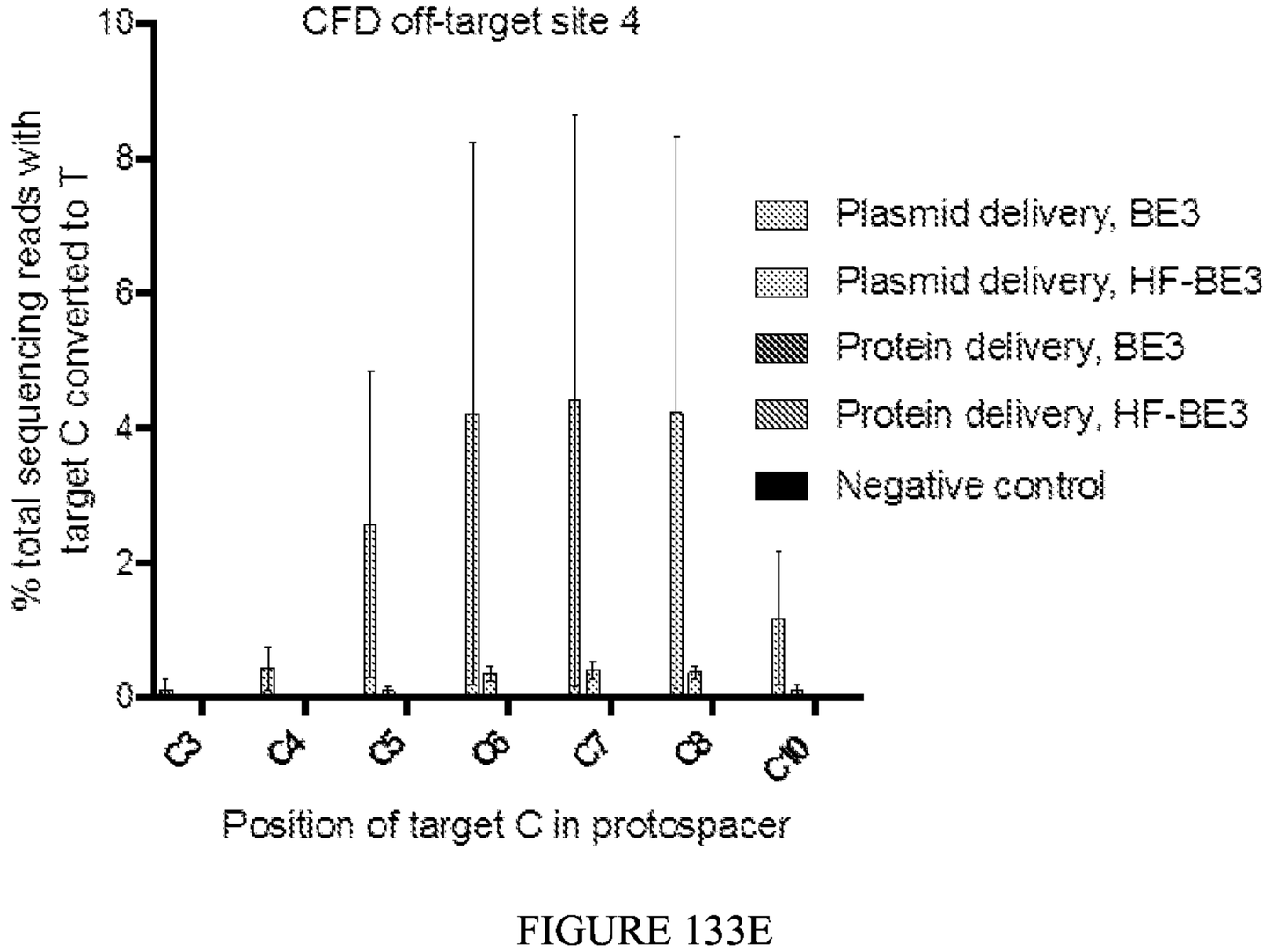


FIGURE 133E

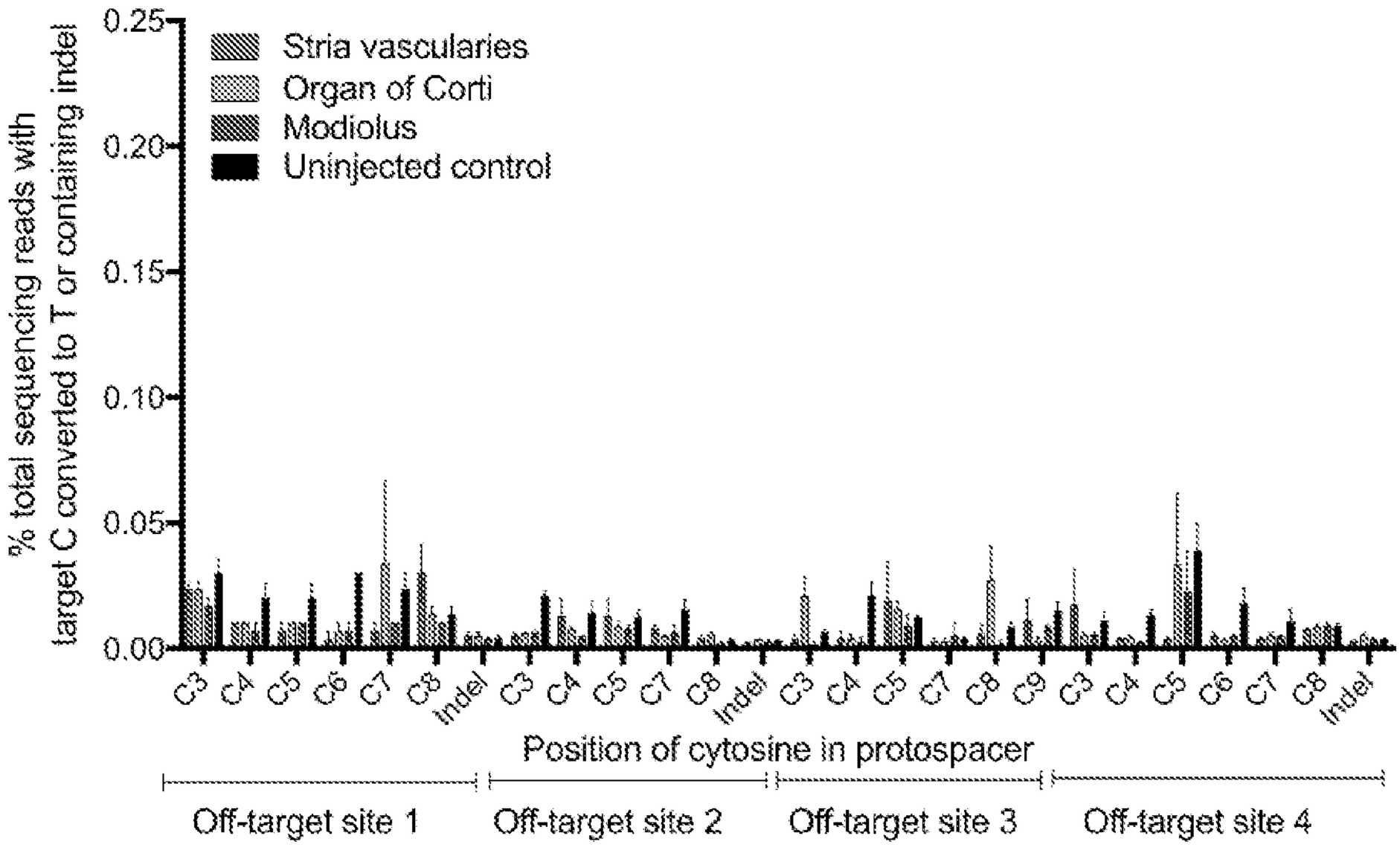


FIGURE 134A

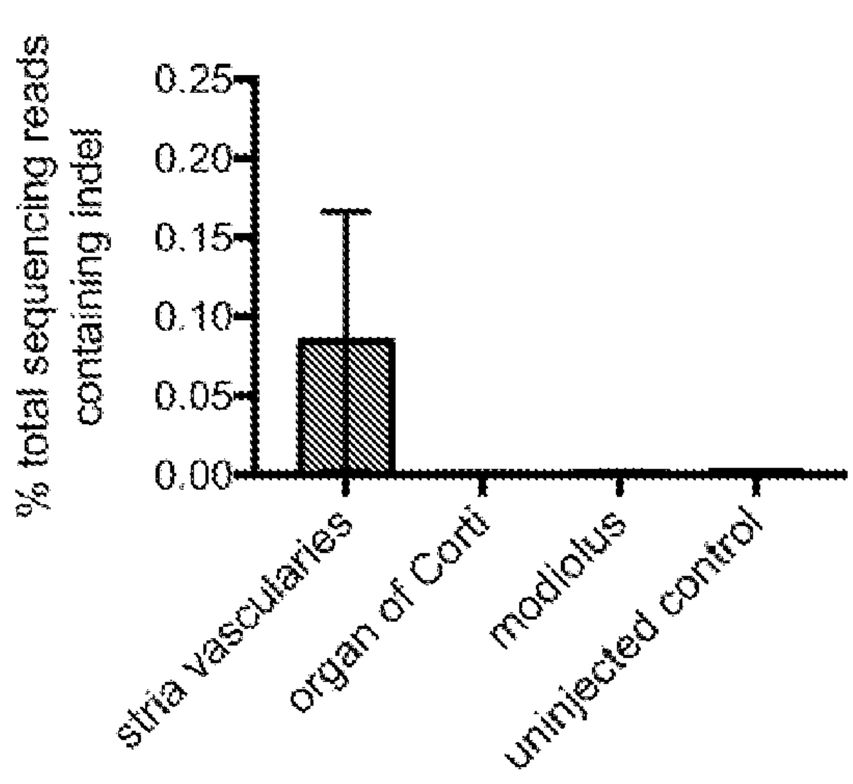


FIGURE 134B

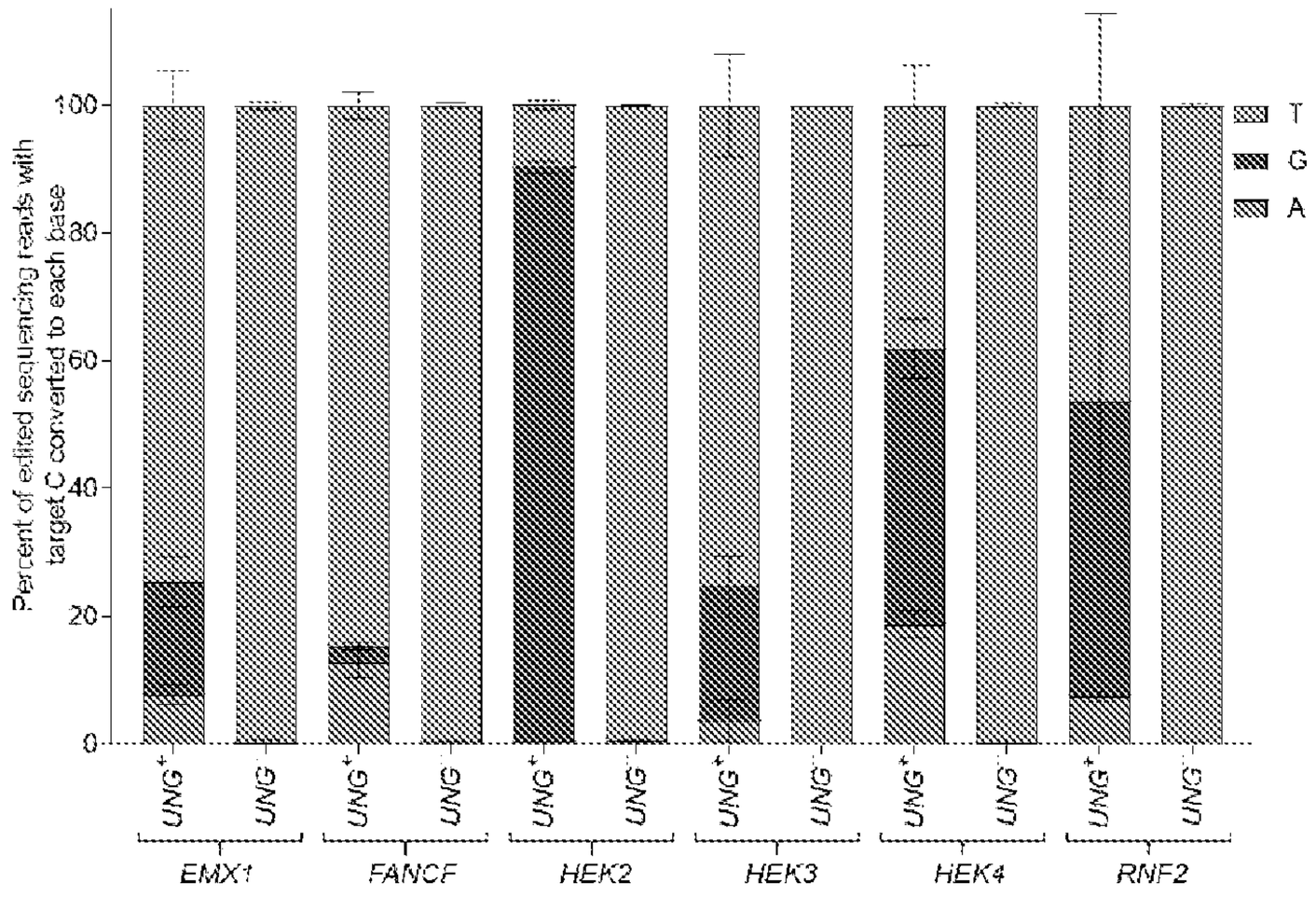


FIGURE 135A

EMX1: GAGTC$_9$CGAGCAGAAGAAGAAGGG

FANCF: GGAATCC$_9$CTTCTGCAGCACCTGG

HEK2: GAACAC$_9$AAAGCATAGACTGCGGG

HEK3: GGCCC$_9$AGACTGAGCACGTGATGG

HEK4: GGCAC$_9$TGCGGCTGGAGGTCCGGG

RNF2: GTCATC$_9$TTAGTCATTACCTGAGG

FIGURE 135B

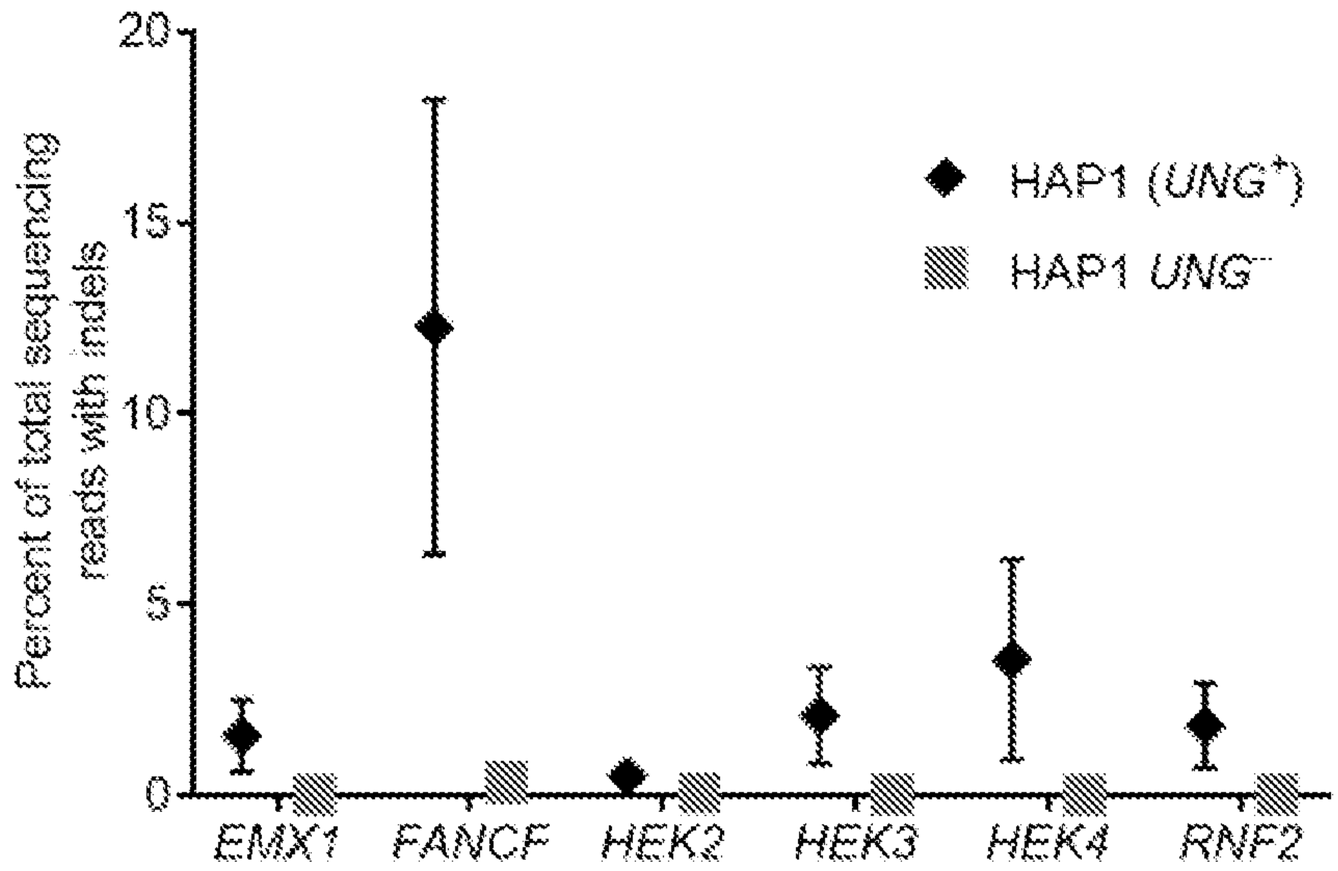


FIGURE 135C

HEK4		G	G	C_2	A	C_5	T	G	C_8	G	G	C	T	G	G	A	G	G	T	G	G	G	G	G
untreated	A	0.0	0.1	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	100.0	0.0	100.0	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	0.0	0.1	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.0
	G	99.9	99.9	0.0	0.0	0.0	0.0	100.0	0.0	100.0	100.0	0.0	0.0	100.0	100.0	0.0	100.0	100.0	0.4	99.9	99.9	100.0	99.9	99.9
	T	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	0.0	99.5	0.1	0.0	0.0	0.0	0.0
BE3	A	0.1	0.0	0.1	99.9	8.4	0.1	0.0	0.1	0.0	0.1	0.0	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	99.0	0.0	41.9	0.0	0.0	99.3	0.0	0.0	99.8	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	99.9	99.9	0.0	0.0	24.5	0.0	100.0	0.0	100.0	99.9	0.0	0.0	100.0	100.0	0.1	100.0	100.0	0.0	100.0	100.0	100.0	100.0	100.0
	T	0.0	0.0	0.9	0.0	25.2	99.9	0.0	0.5	0.0	0.0	0.2	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0
AID-BE3	A	0.3	0.4	0.3	100.0	0.9	0.0	0.0	0.9	0.0	0.0	0.1	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	31.5	0.0	71.3	0.0	0.0	80.7	0.0	0.0	97.9	0.1	0.0	0.0	0.2	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0
	G	99.7	99.6	0.1	0.0	0.7	0.0	100.0	0.1	100.0	100.0	0.0	0.0	99.3	100.0	0.0	100.0	100.0	0.2	99.9	100.0	100.0	100.0	99.9
	T	0.0	0.0	18.0	0.0	27.1	100.0	0.0	18.3	0.0	0.0	2.0	99.9	0.0	0.0	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.1

FIGURE 136A

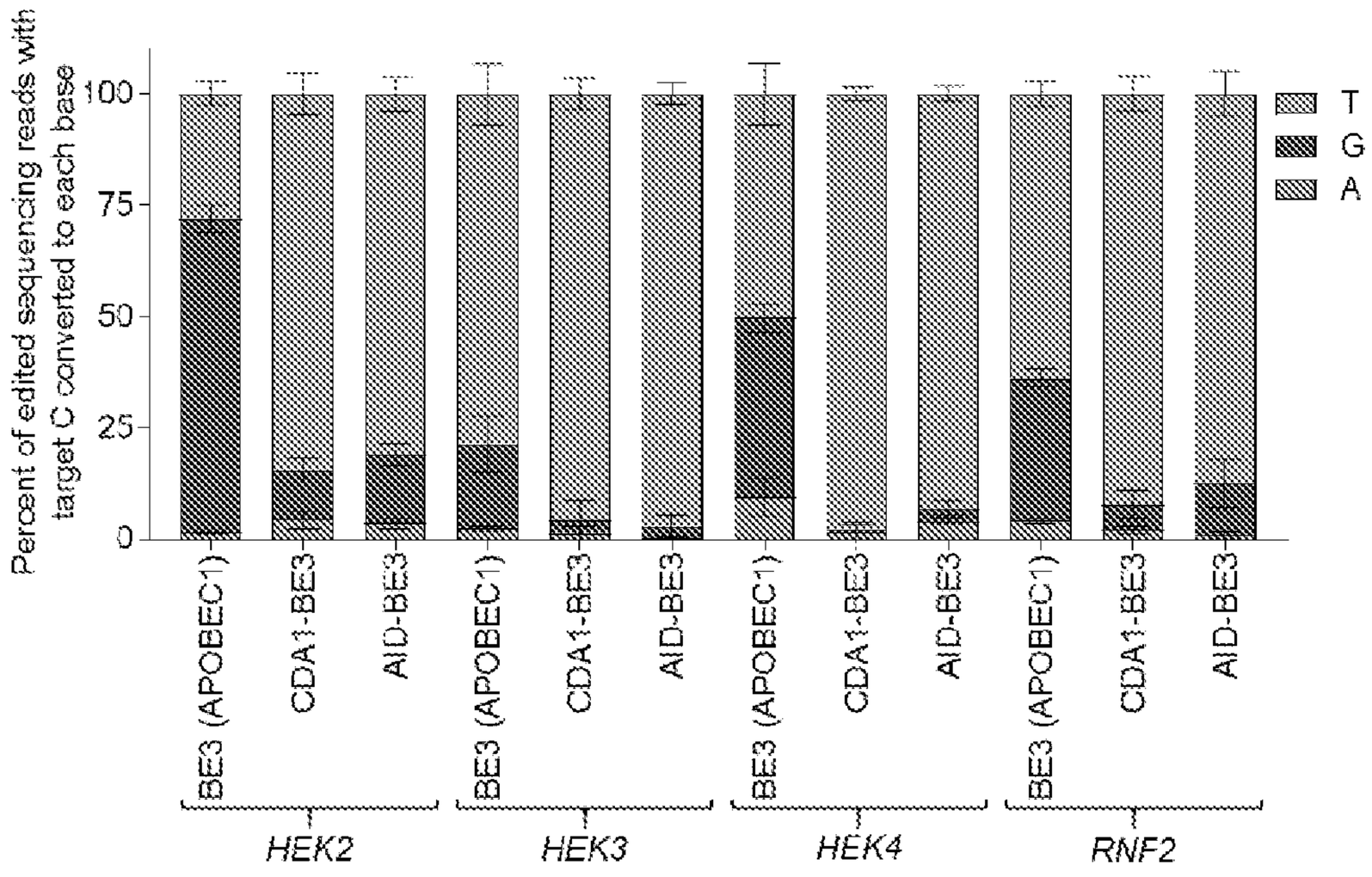


FIGURE 136B

HEK2: GAACAC$_g$AAAGCATAGACTGCGGG

HEK3: GGCCC$_g$AGACTGAGCACGTGATGG

HEK4: GGCAC$_g$TGCGGCTGGAGGTCCGGG

RNF2: GTCATC$_g$TTAGTCATTACCTGAGG

FIGURE 136C

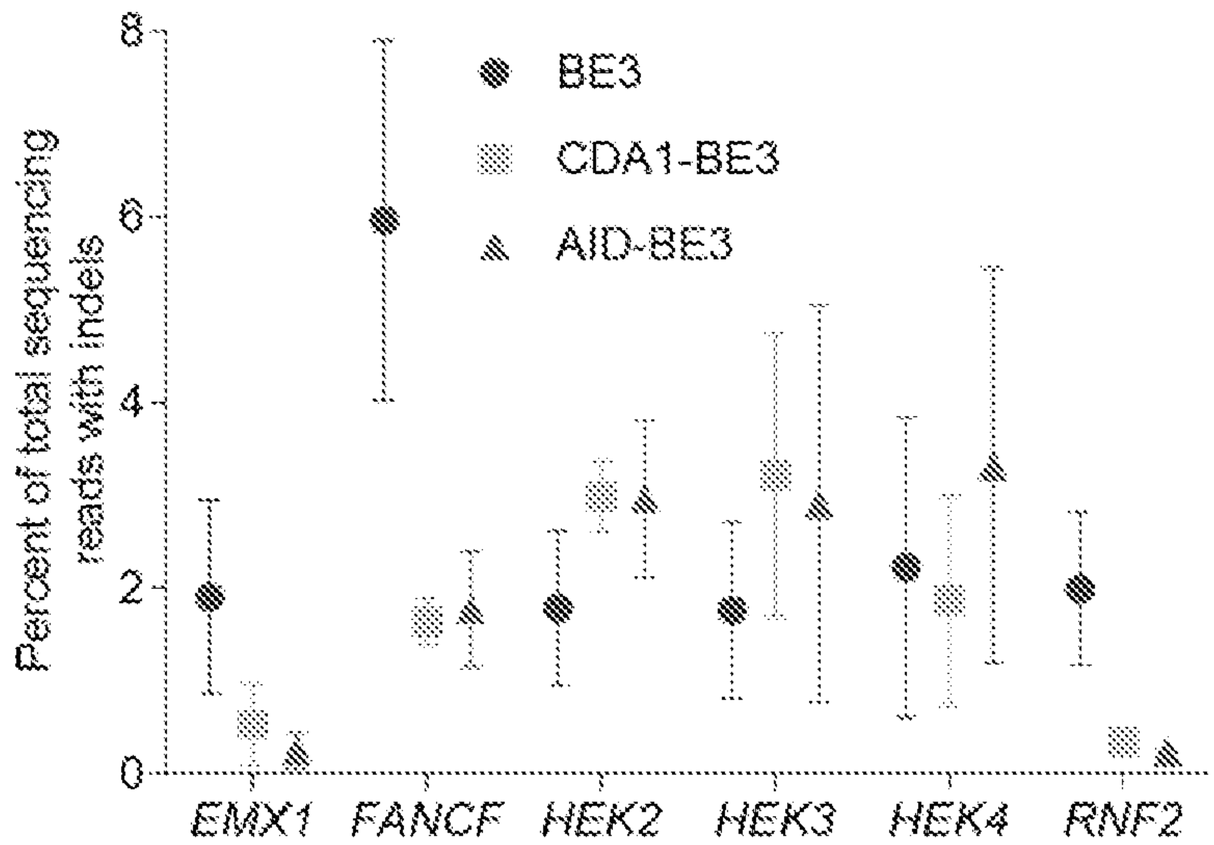


FIGURE 136D

HEK2: GAAC$_4$AC$_8$AAAGCATAGACTGCGGG

HEK3: GGCC$_4$C$_5$AGACTGAGCACGTGATGG

HEK4: GGCAC$_5$TGCGGCTGGAGGTCCGGG

RNF2: GTC$_3$ATC$_8$TTAGTCATTACCTGAGG

FIGURE 137A

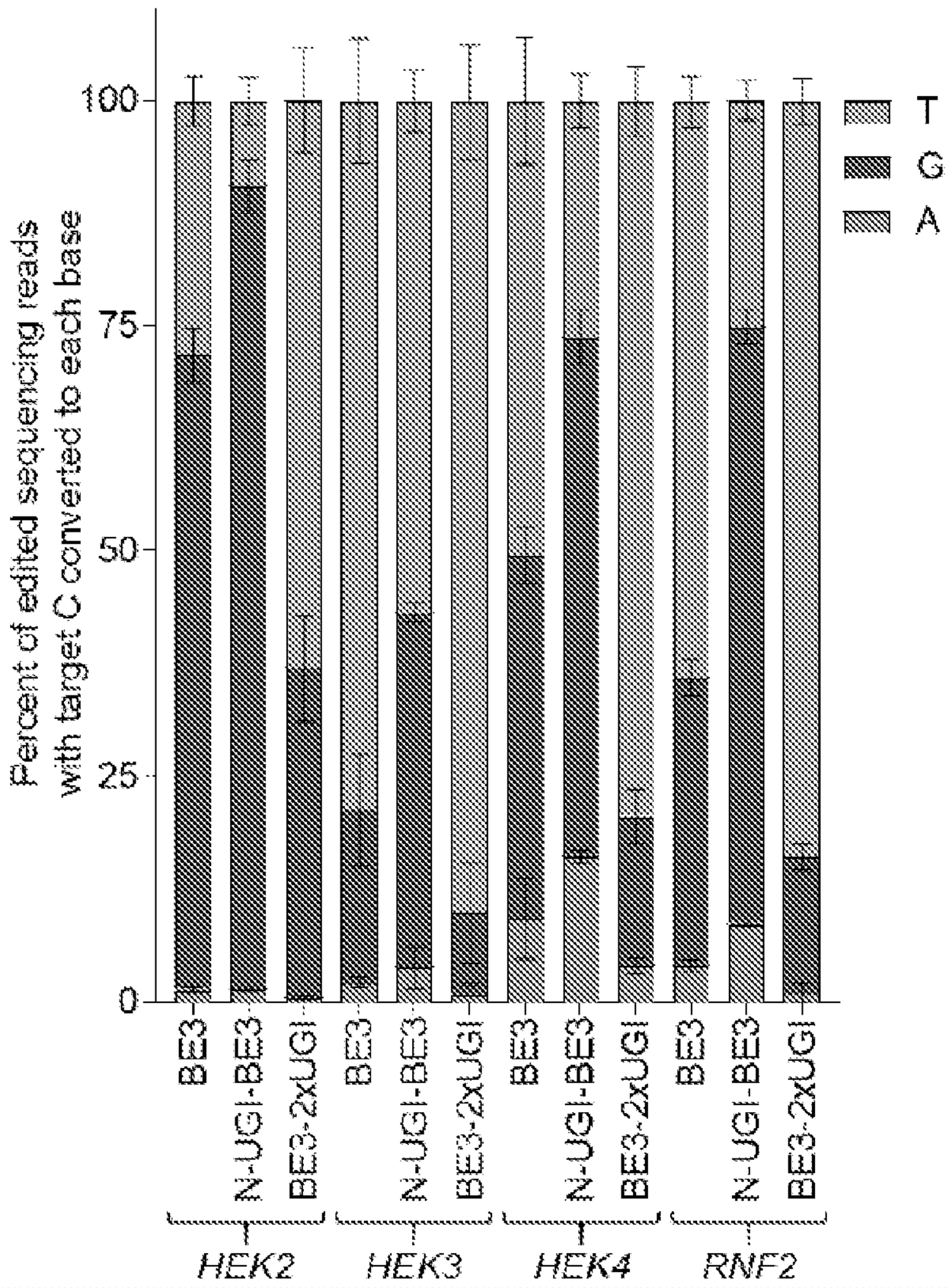


FIGURE 137B

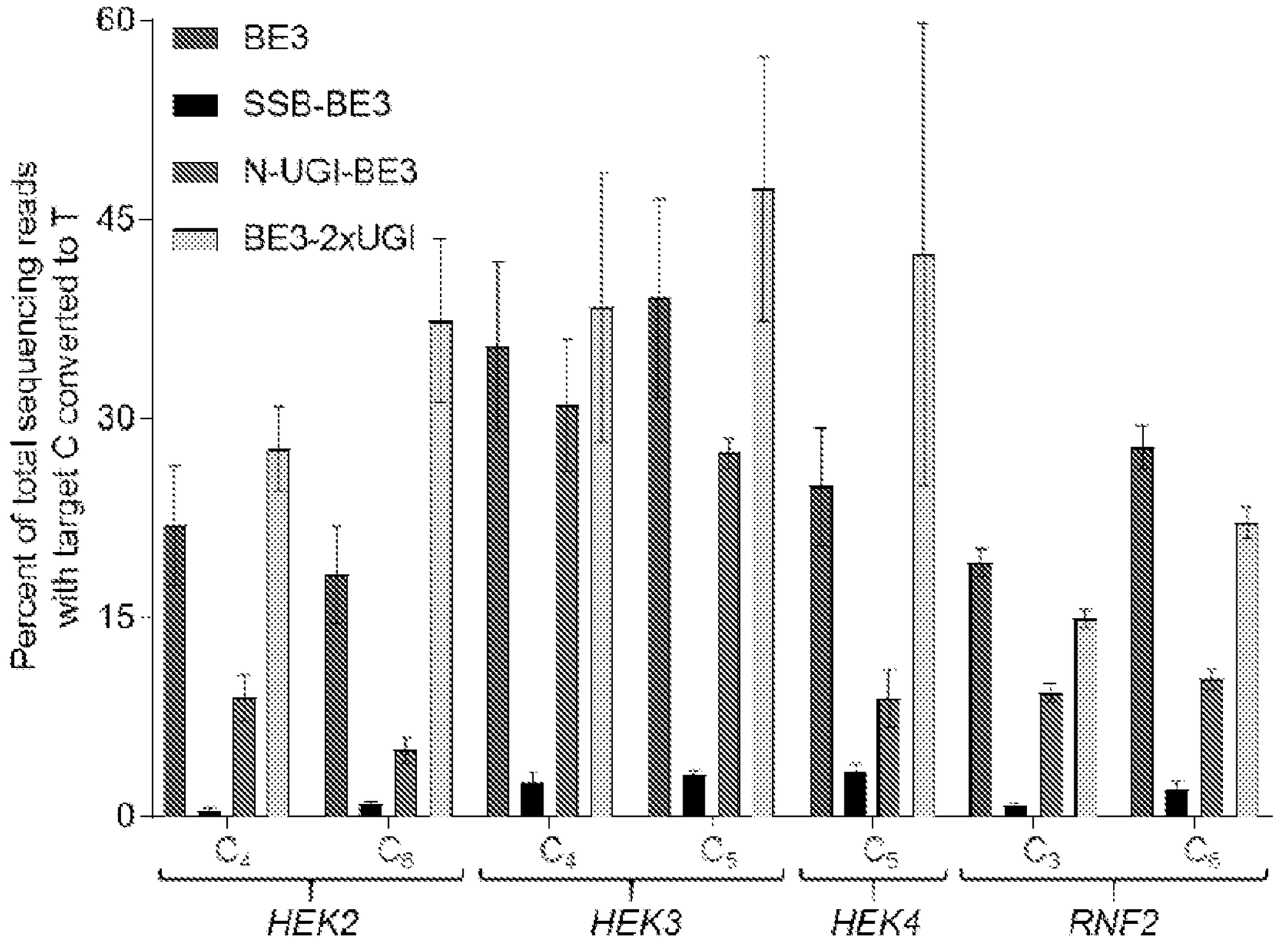

BE3
SSB-BE3
N-UGI-BE3
BE3-2xUGI
Percent of total sequencing reads with target C converted to T
60
45
30
15
0
C4
C8
C4
C5
C5
C3
C8
HEK2
HEK3
HEK4
RNF2

FIGURE 137C



FIGURE 138A

HEK2: GAAC$_9$AC$_{13}$AAAGCATAGACTGCGGG

HEK3: GGCC$_9$C$_{13}$AGACTGAGCACGTGATGG

HEK4: GGCAC$_9$TGCGGCTGGAGGTCCGGG

RNF2: GTC$_9$ATC$_{13}$TTAGTCATTACCTGAGG

FIGURE 138B

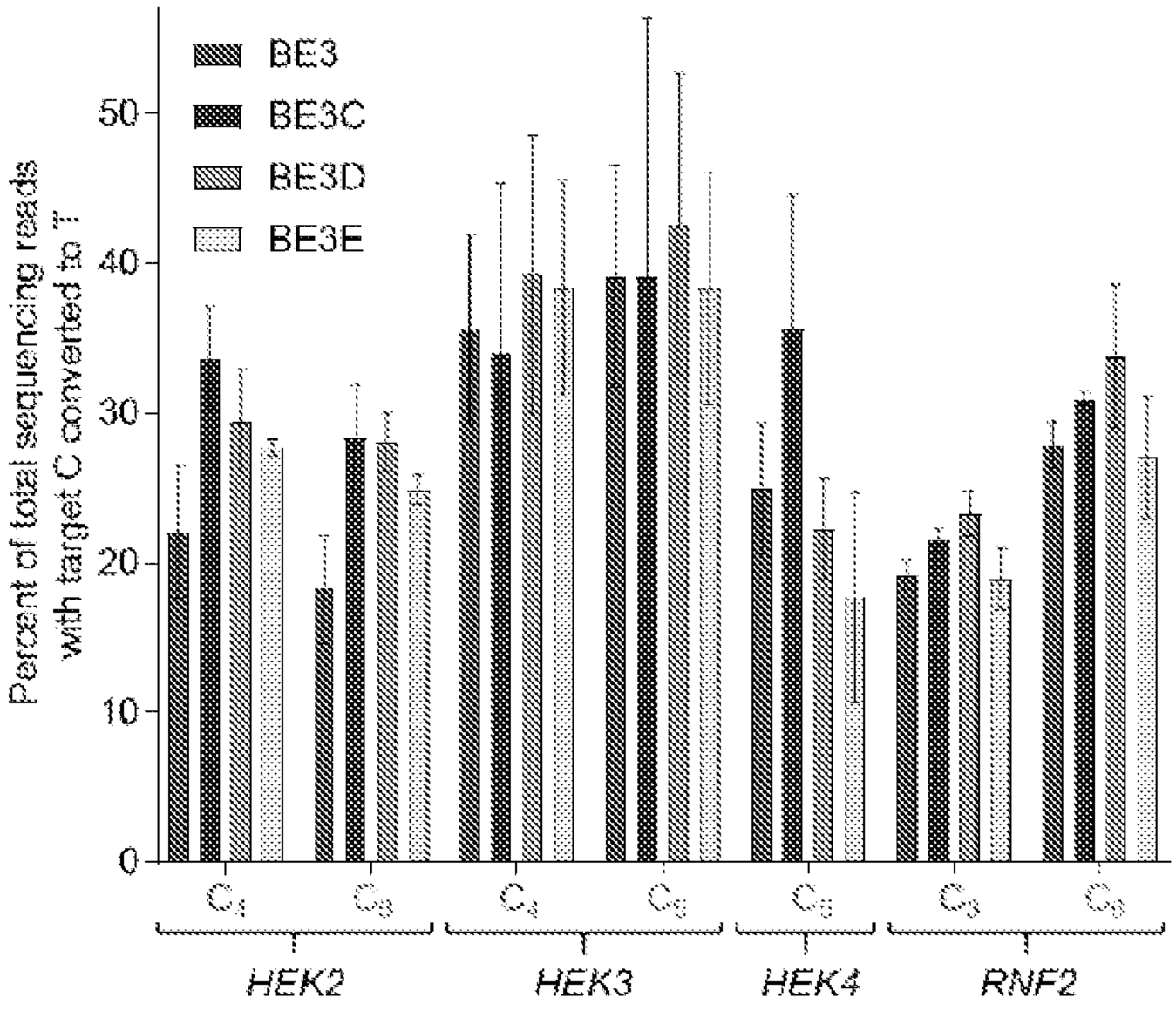


FIGURE 138C

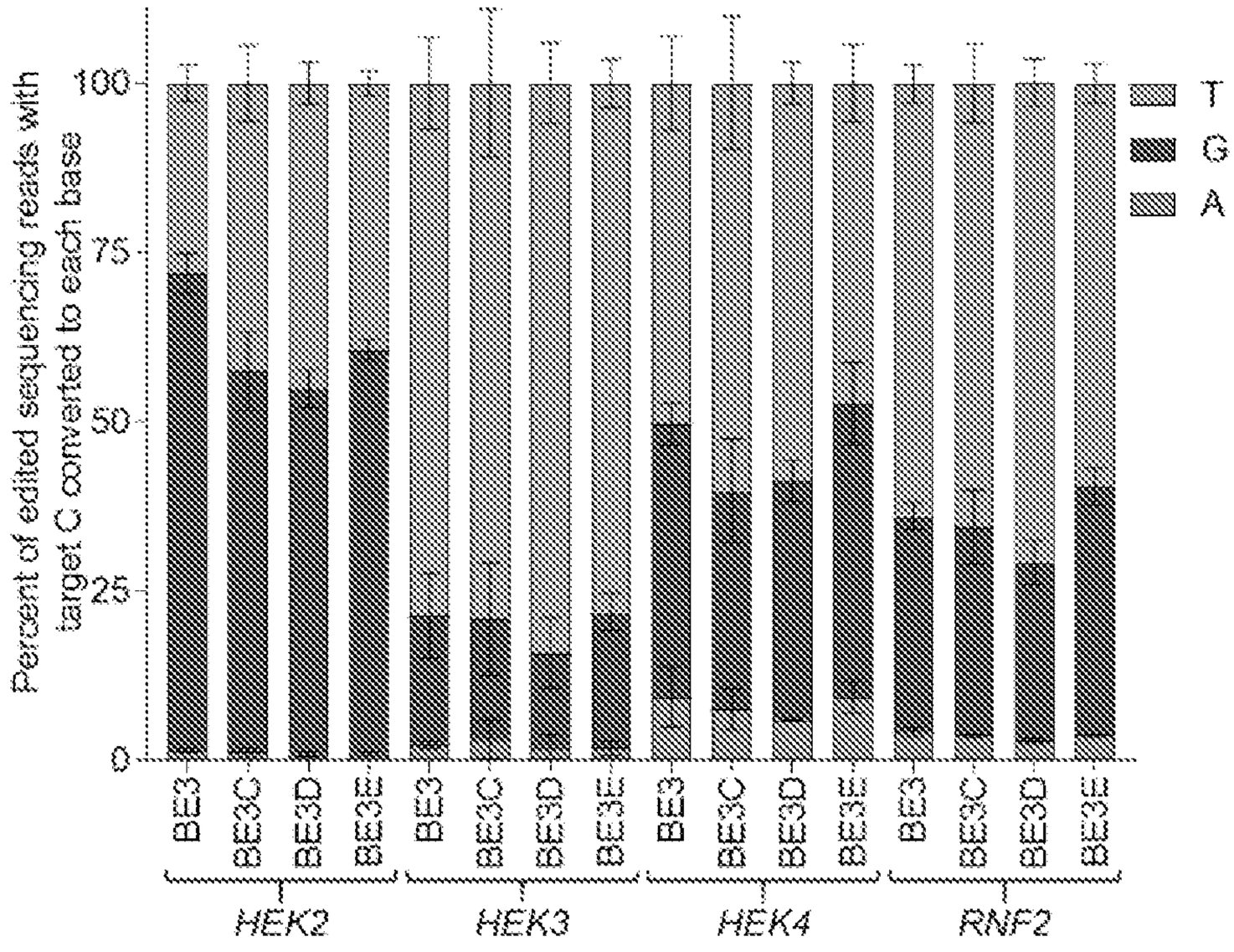

Percent of edited sequencing reads with target C converted to each base
0
25
50
75
100
T
G
A
BE3
BE3C
BE3D
BE3E
HEK2
HEK3
HEK4
RNF2

FIGURE 138D

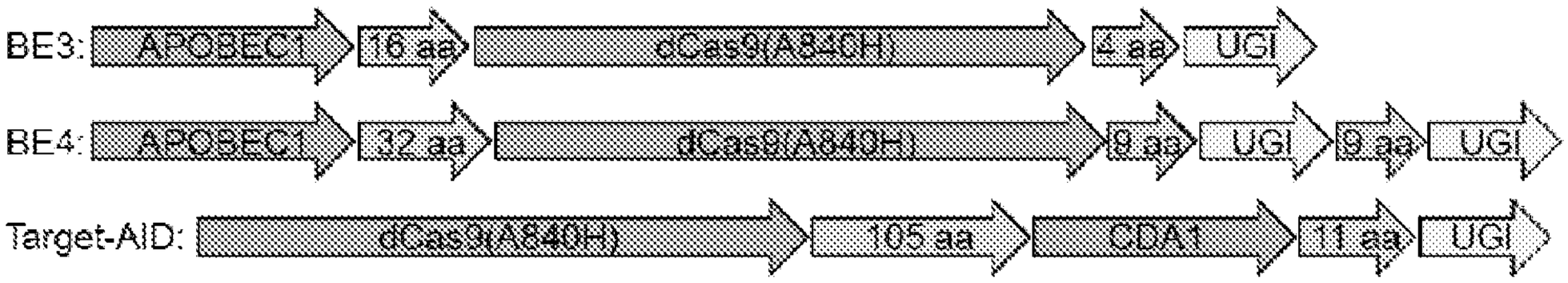


FIGURE 139A

EMX1: GAGTC$_5$C$_6$GAGCAGAAGAAGAAGGG

FANCF: GGAATC$_6$C$_7$C$_8$TTCTGCAGCACCTGG

HEK2: GAAC$_4$AC$_6$AAAGCATAGACTGCGGG

HEK3: GGCC$_4$C$_5$AGACTGAGCACGTGATGG

HEK4: GGCAC$_5$TGCGGCTGGAGGTCCGGG

RNF2: GTC$_3$ATC$_6$TTAGTCATTACCTGAGG

FIGURE 139B

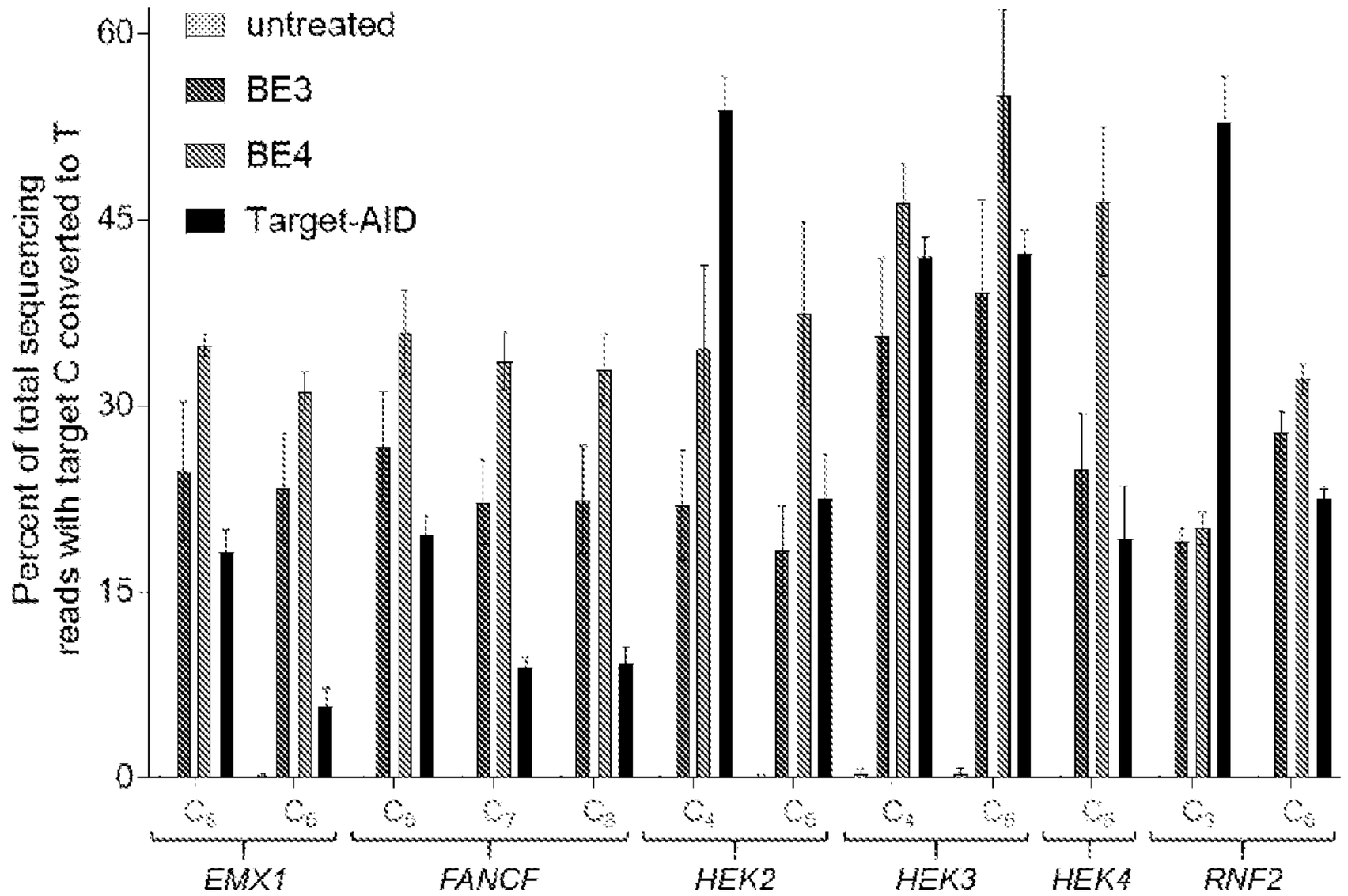


FIGURE 139C

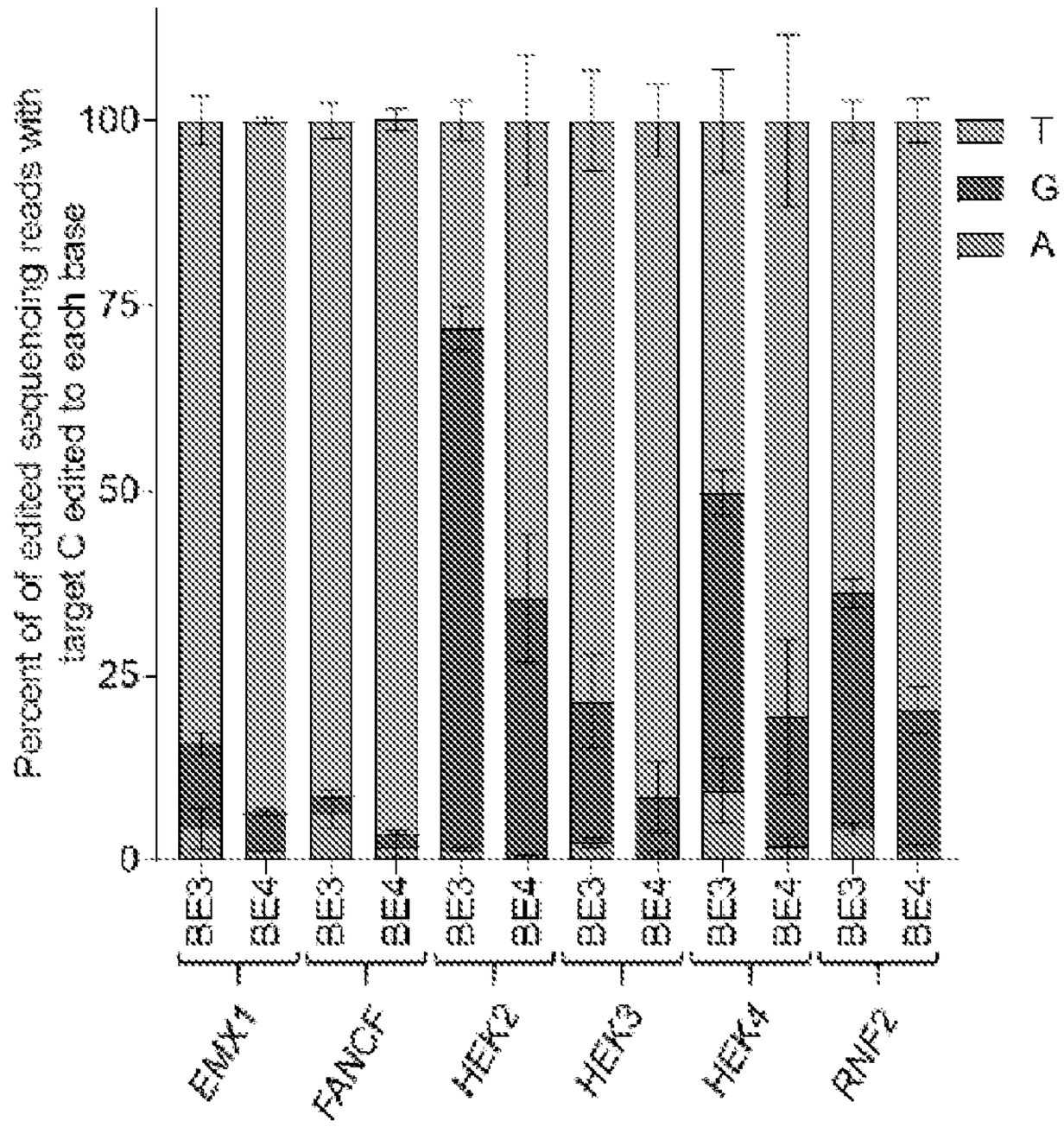

Percent of of edited sequencing reads with target C edited to each base
100
75
50
25
0
T
G
A
BE3
BE4
EMX1
FANCF
HEK2
HEK3
HEK4
RNF2

FIGURE 139D

EMX1: GAGTC$_5$C$_6$GAGCAGAAGAAGAAGGG

FANCF: GGAATC$_5$C$_7$C$_8$TTCTGCAGCACCTGG

HEK2: GAAC$_5$AC$_8$AAAGCATAGACTGCGGG

HEK3: GGC$_3$C$_4$C$_5$AGACTGAGCACGTGATGG

HEK4: GGC$_3$AC$_5$TGC$_8$GGCTGGAGGTCCGGG

RNF2: GTC$_3$ATC$_8$TTAGTCATTACCTGAGG

FIGURE 140A

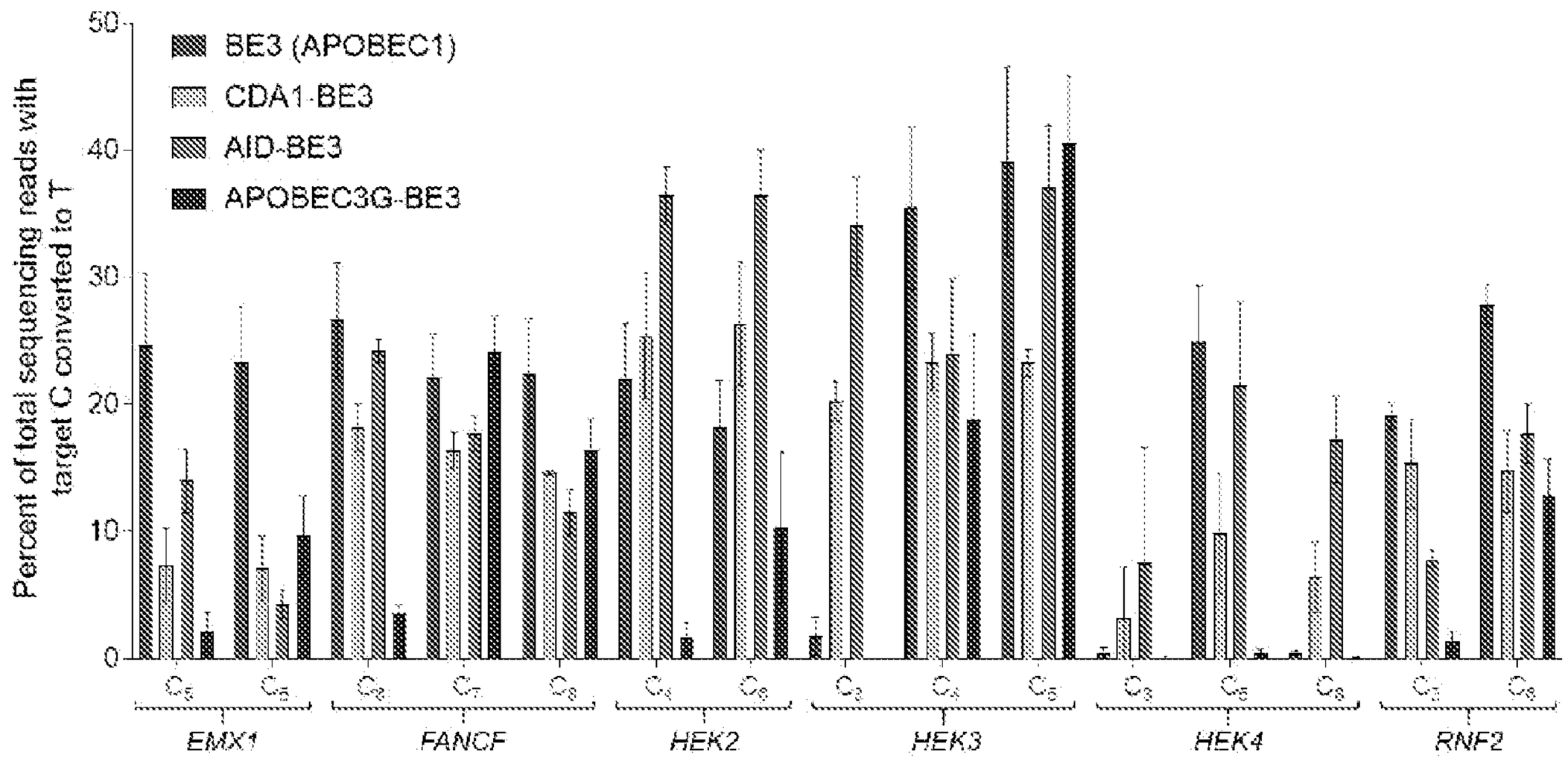


FIGURE 140B

HEK2 protospacer sequence	Percent of cleanly edited reads with given sequence		
	BE3	CDA1-BE3	AID-BE3
GAAT$_4$AT$_8$AAAGCATAGACTGCGGG	77 ± 1	88 ± 2	92 ± 2
GAAC$_4$AT$_8$AAAGCATAGACTGCGGG	23 ± 1	5 ± 1	4 ± 1
GAAT$_4$AC$_8$AAAGCATAGACTGCGGG	0 ± 0	7 ± 2	4 ± 2

FIGURE 140C

EMX1: GAGTC$_8$C$_9$GAGCAGAAGAAGAAGGG

FANCF: GGAATC$_8$C$_7$C$_8$TTCTGCAGCACCTGG

HEK2: GAAC$_6$AC$_8$AAAGCATAGACTGCGGG

HEK3: GGCC$_4$C$_5$AGACTGAGCACGTGATGG

HEK4: GGCAC$_5$TGCGGCTGGAGGTCCGGG

RNF2: GTC$_5$ATC$_8$TTAGTCATTACCTGAGG

FIGURE 141A

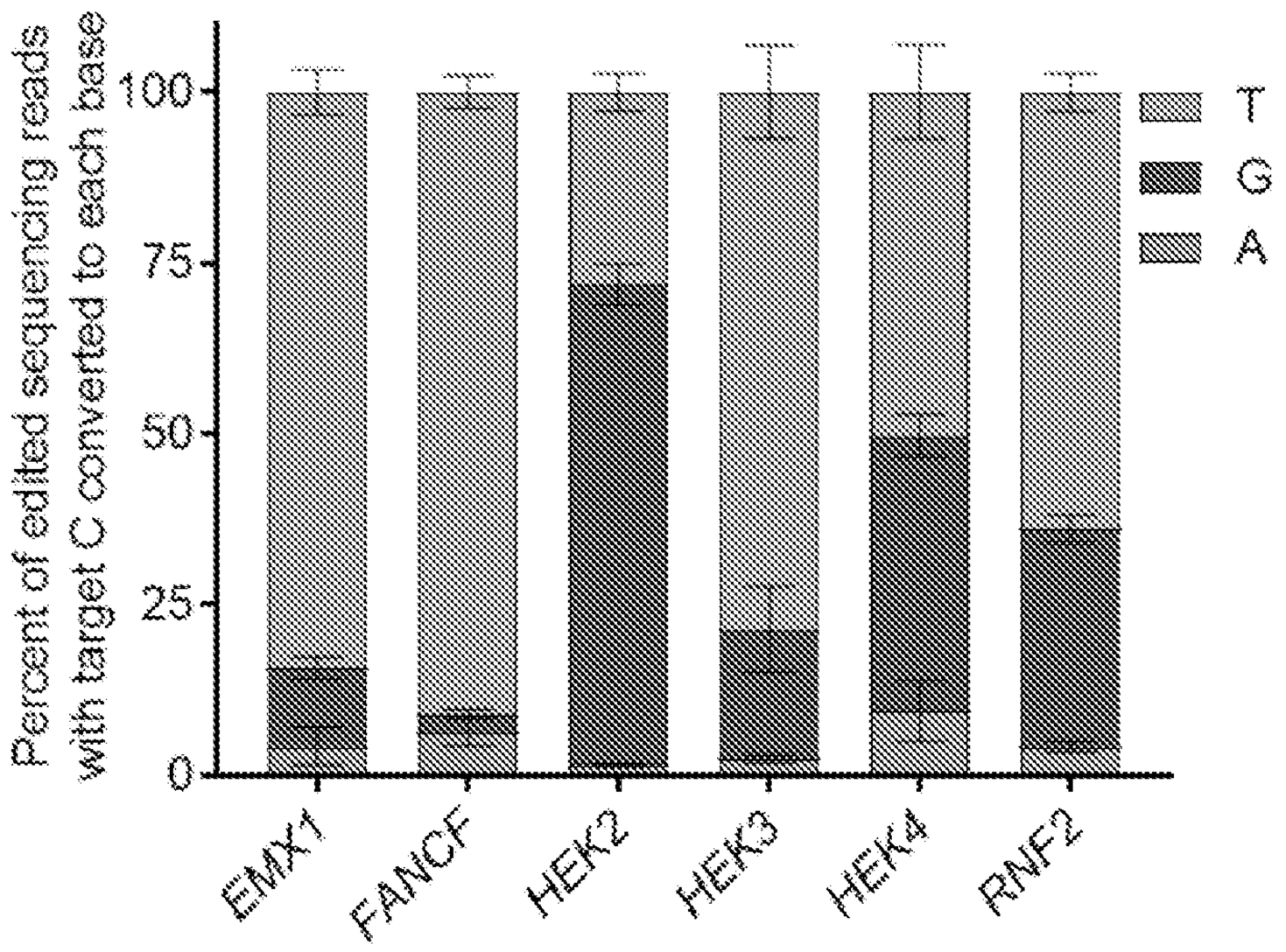


FIGURE 141B

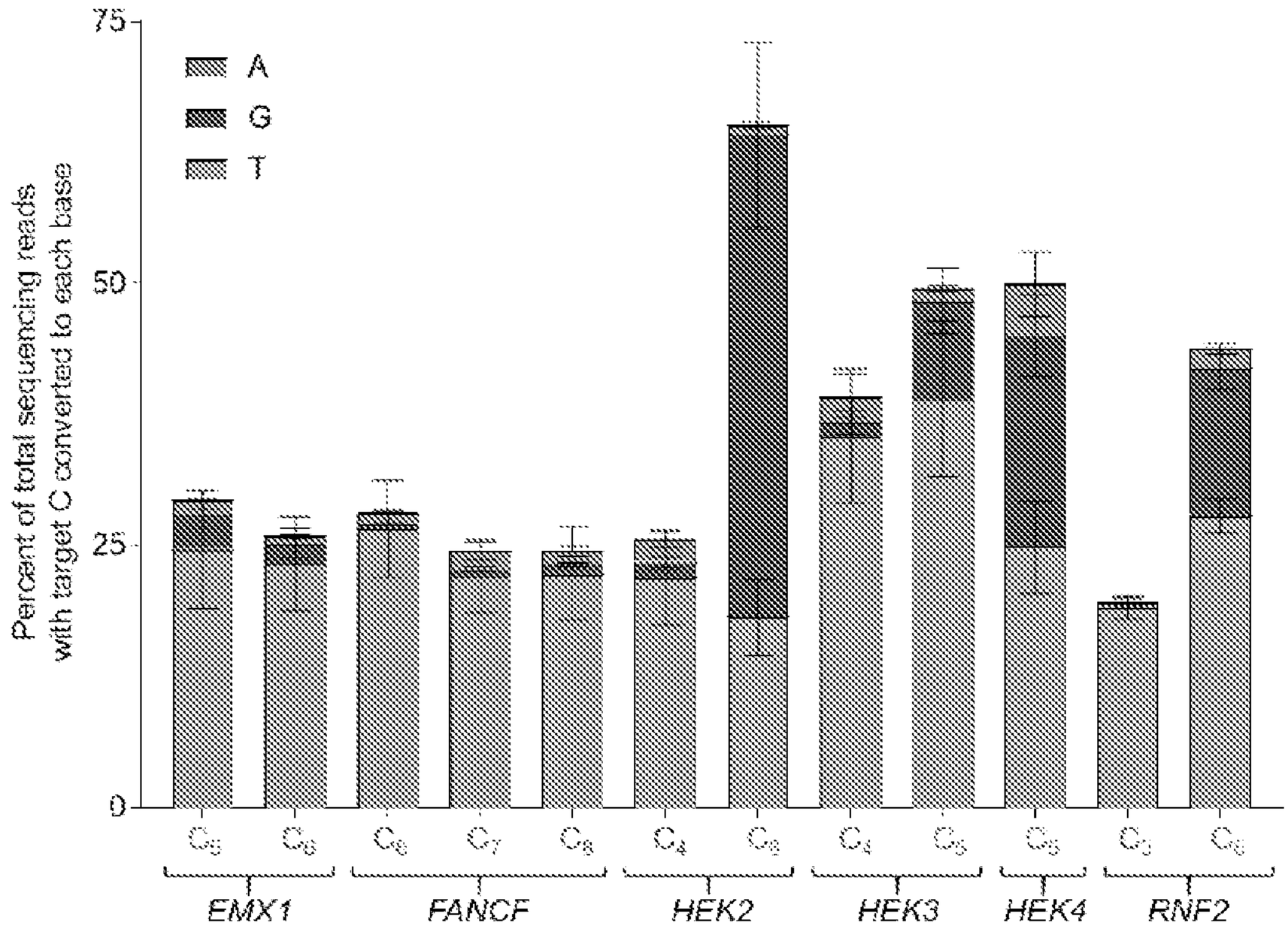

75
50
25
0
A
G
T
Percent of total sequencing reads with target C converted to each base
C5
C6
C8
C7
C8
C4
C3
C4
C5
C5
C3
C6
EMX1
FANCF
HEK2
HEK3
HEK4
RNF2

FIGURE 141C

HEK2: GAAC$_4$AC$_6$AAAGCATAGACTGCGGG

HEK3: GGCC$_4$C$_6$AGACTGAGCACGTGATGG

HEK4: GGCAC$_5$TGCGGCTGGAGGTCCGGG

RNF2: GTC$_3$ATC$_6$TTAGTCATTACCTGAGG

FIGURE 142A

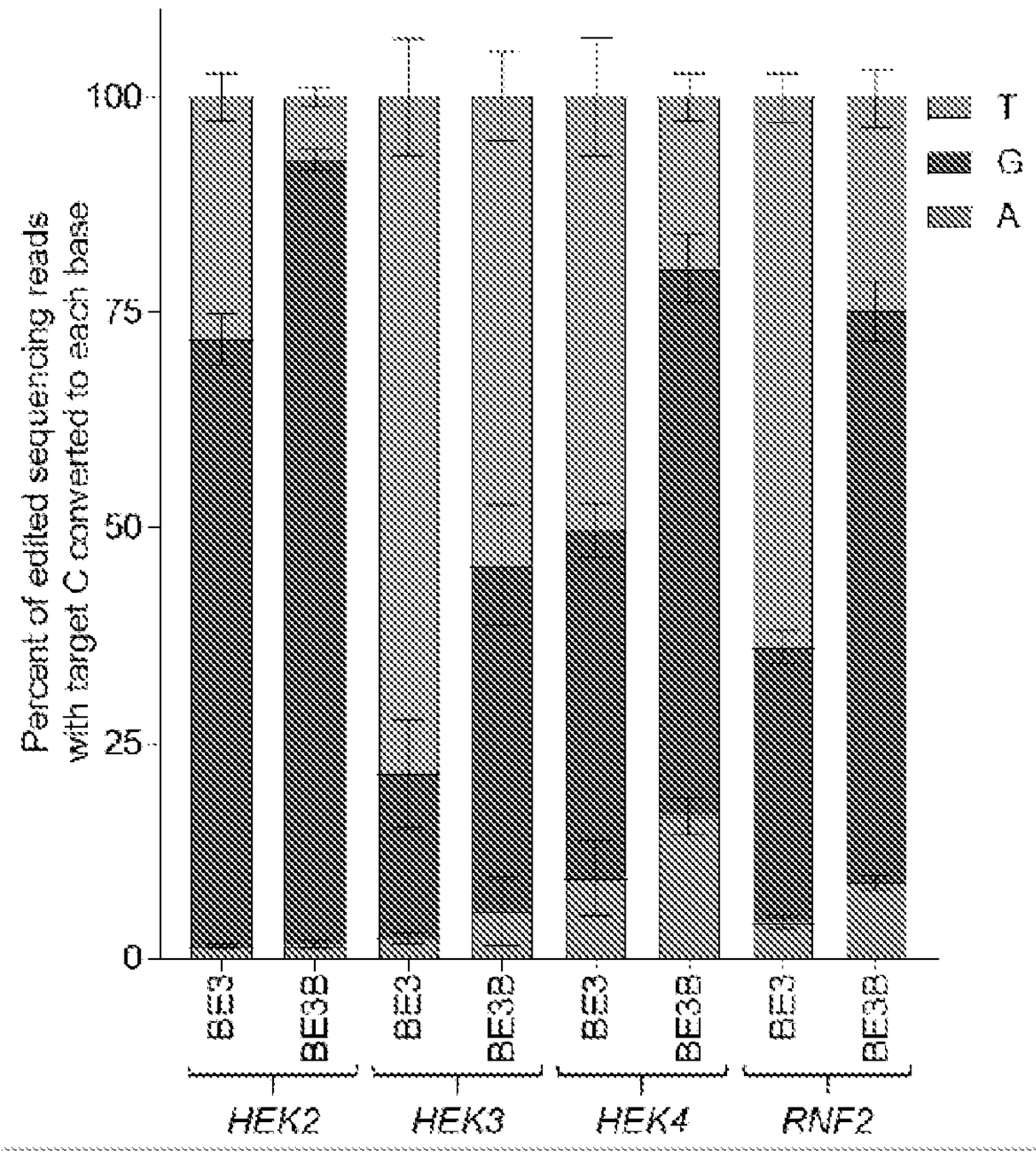


FIGURE 142B

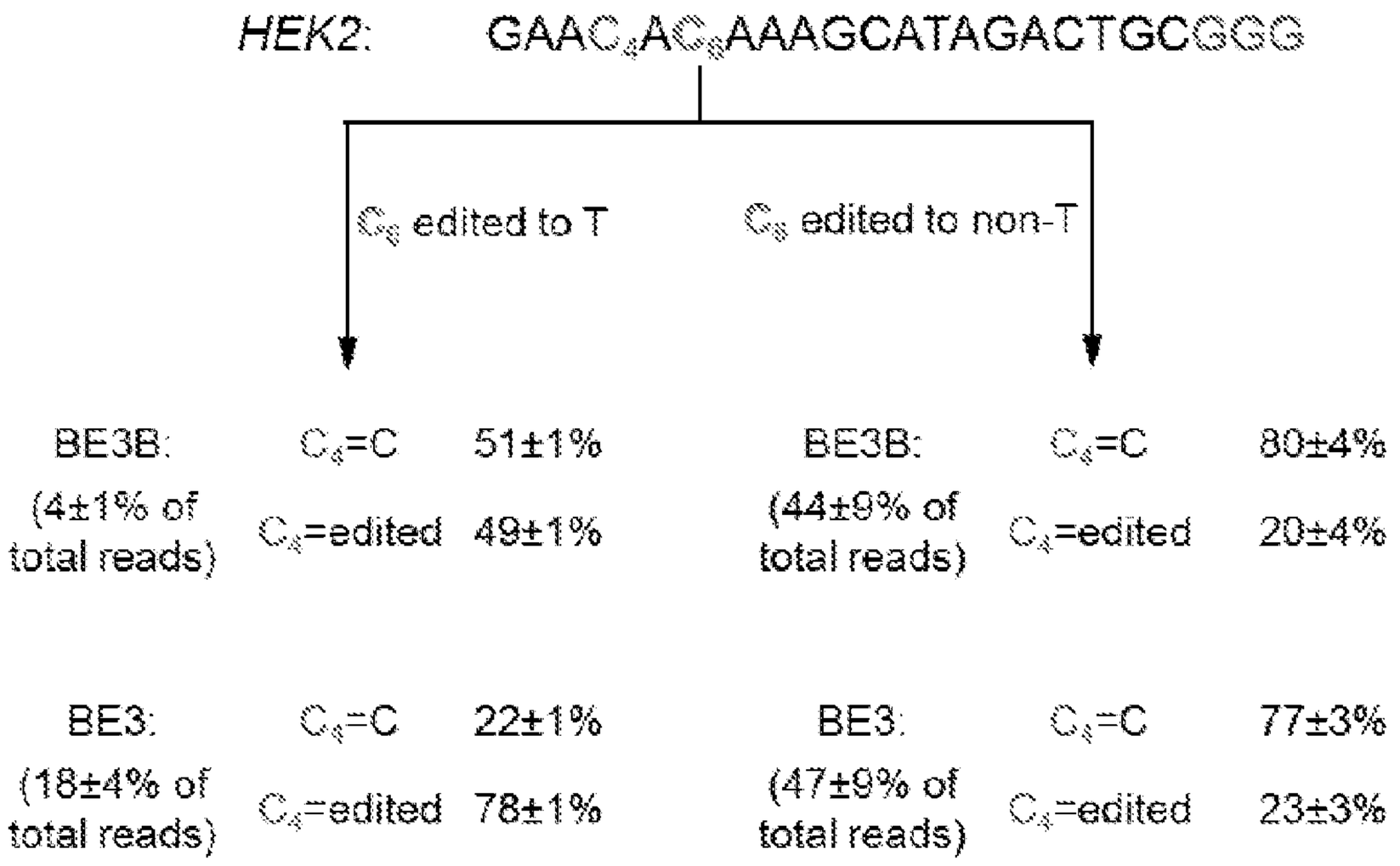


FIGURE 142C

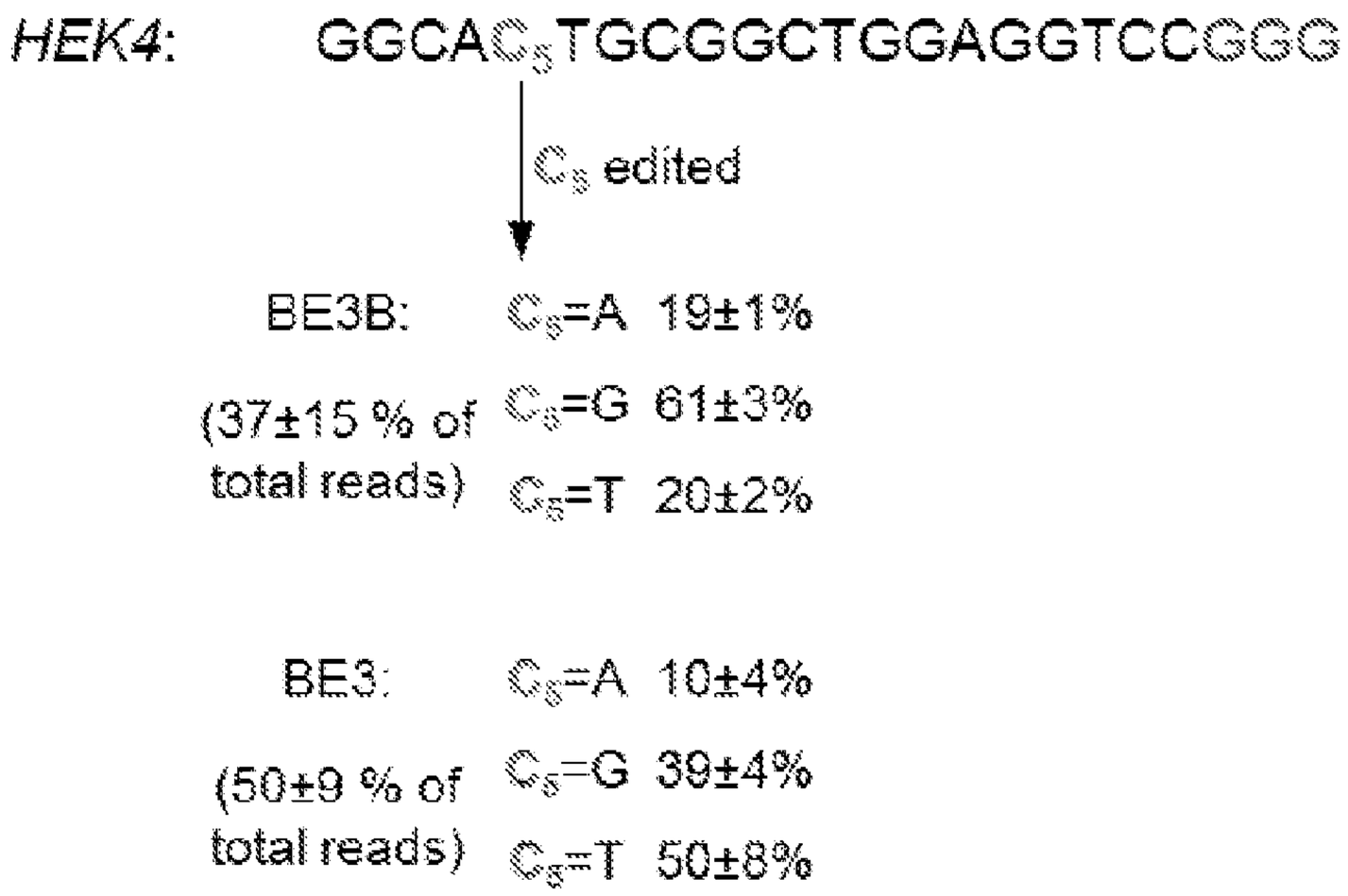
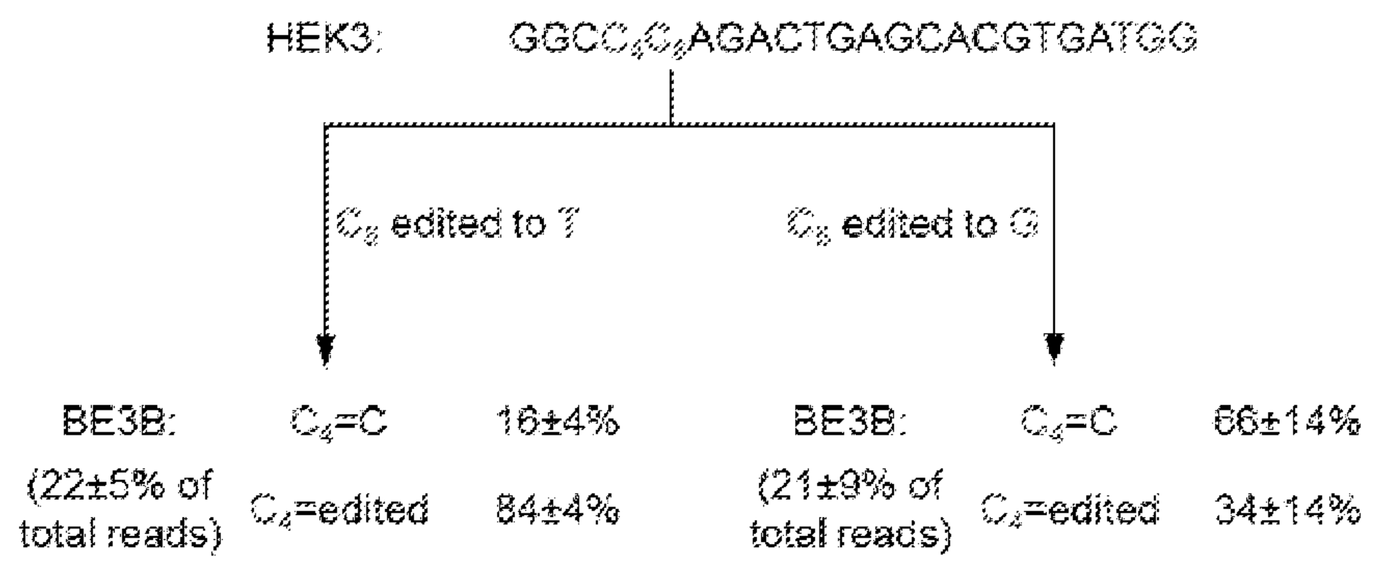


FIGURE 142D


HEK3: GGCC4C3AGACTGAGCACGTGATGG
C4 edited to T
C3 edited to G
BE3B: C4=C 16±4%
(22±5% of total reads) C4=edited 84±4%
BE3B: C3=C 66±14%
(21±9% of total reads) C3=edited 34±14%
BE3: C4=C 13±8%
(41±12% of total reads) C4=edited 87±8%
BE3: C3=C 81±21%
(9±2% of total reads) C3=edited 19±21%


RNF2: GTC3ATC6TTAGTCATTACCTGAGG
C6 edited to T
C3 edited to G
BE3B: C6=C 53±3%
(10±1% of total reads) C6=edited 47±3%
BE3B: C3=C 85±2%
(30±8% of total reads) C3=edited 15±2%
BE3: C6=C 37±3%
(28±2% of total reads) C6=edited 63±3%
BE3: C3=C 88±1%
(16±2% of total reads) C3=edited 12±1%

FIGURE 143

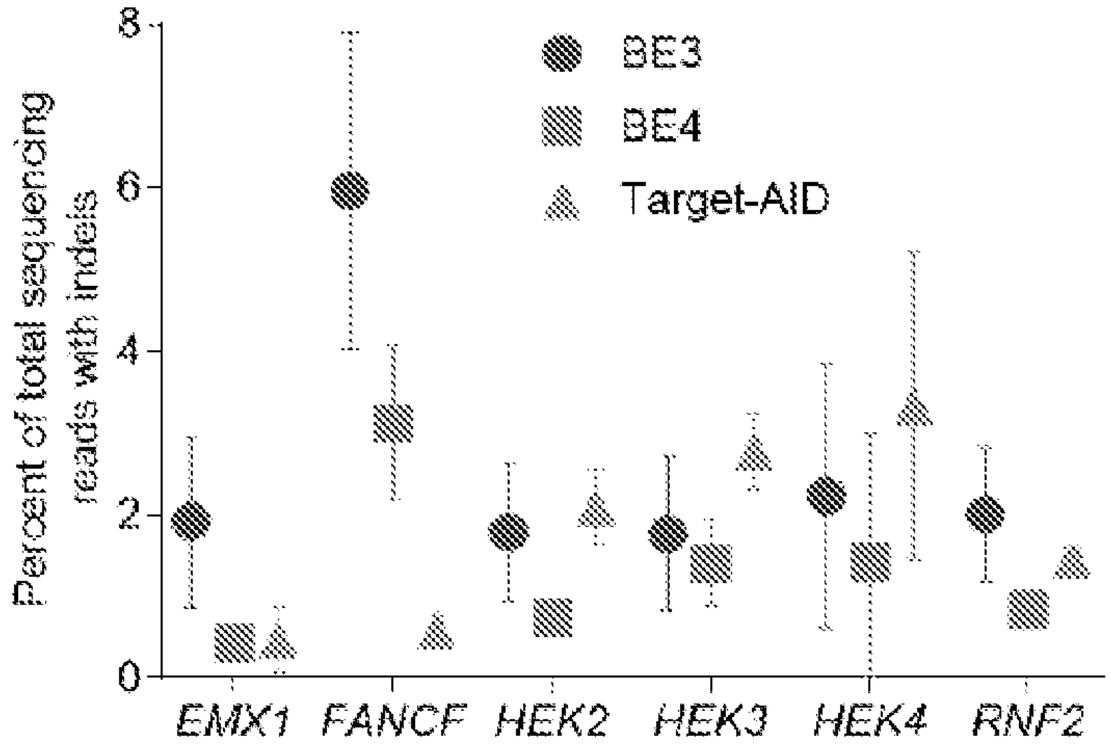


FIGURE 144A

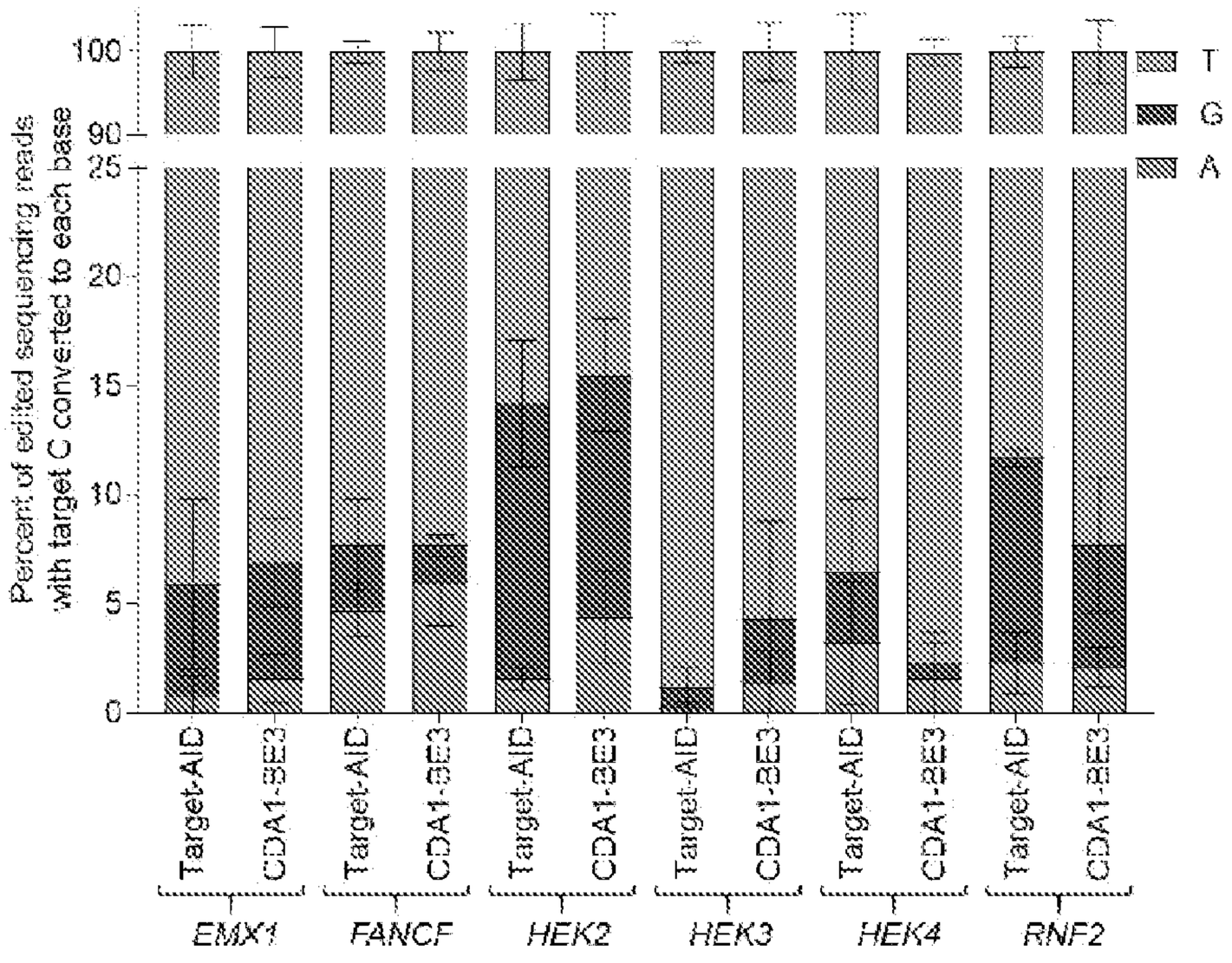


FIGURE 144B

EMX1: GAGTC$_5$CGAGCAGAAGAAGAAGGG

FANCF: GGAATCC$_7$CTTCTGCAGCACCTGG

HEK2: GAACAC$_5$AAAGCATAGACTGCGGG

HEK3: GGCCC$_5$AGACTGAGCACGTGATGG

HEK4: GGCAC$_5$TGCGGCTGGAGGTCCGGG

RNF2: GTCATC$_5$TTAGTCATTACCTGAGG

FIGURE 144C

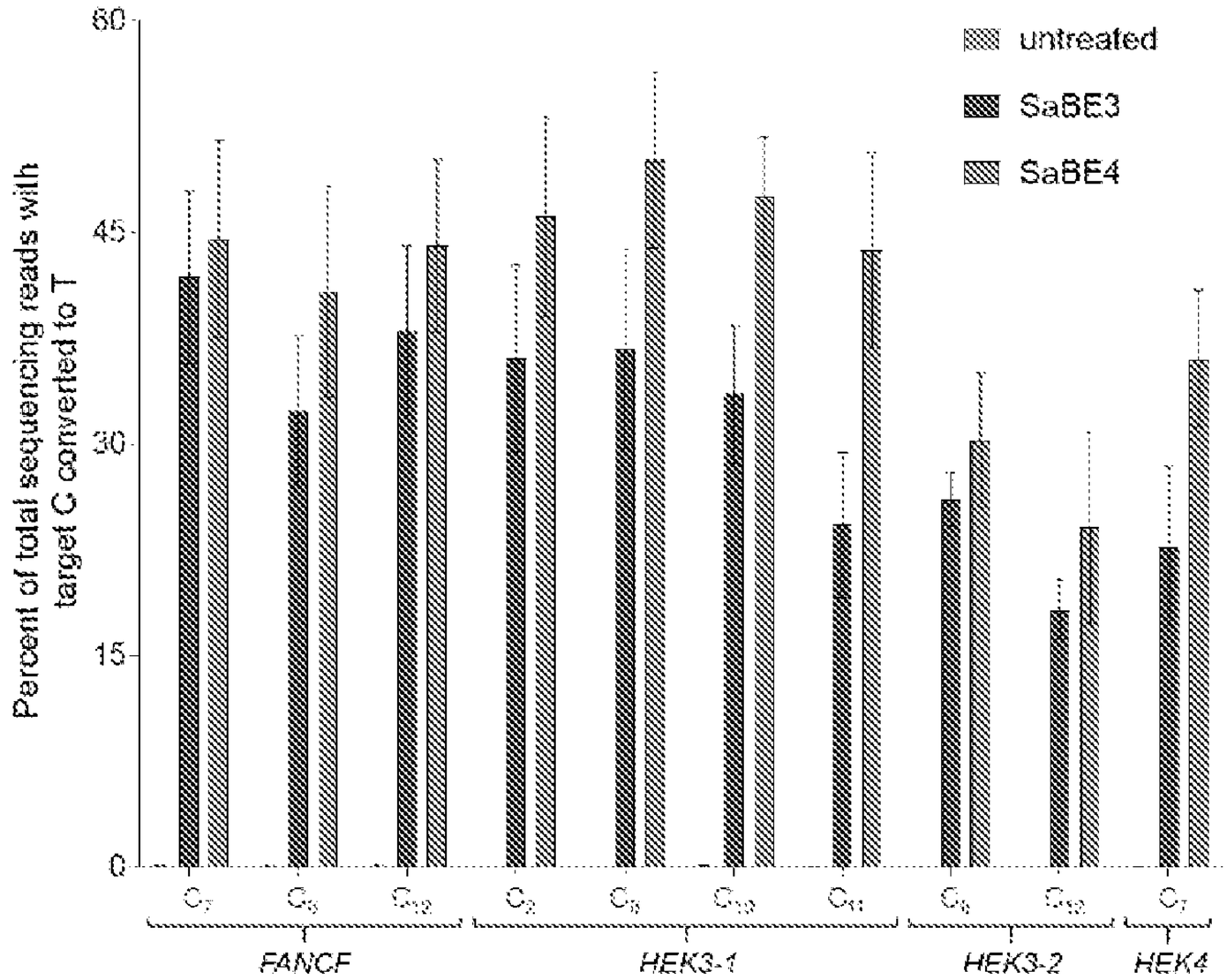


FIGURE 145A

FANCF: GATGTTC$_7$C$_8$AATC$_{12}$AGTACGCAGAGAGT

HEK3-1: TC$_2$TGCTTC$_6$TC$_{10}$C$_{11}$AGCCCTGGCCTGGGT

HEK3-2: ACGTGCTC$_6$AGTC$_{12}$TGGGCCCCAAGGAT

HEK4: GTGGCAC$_7$TGCGGCTGGAGGTGGGGGT

FIGURE 145B

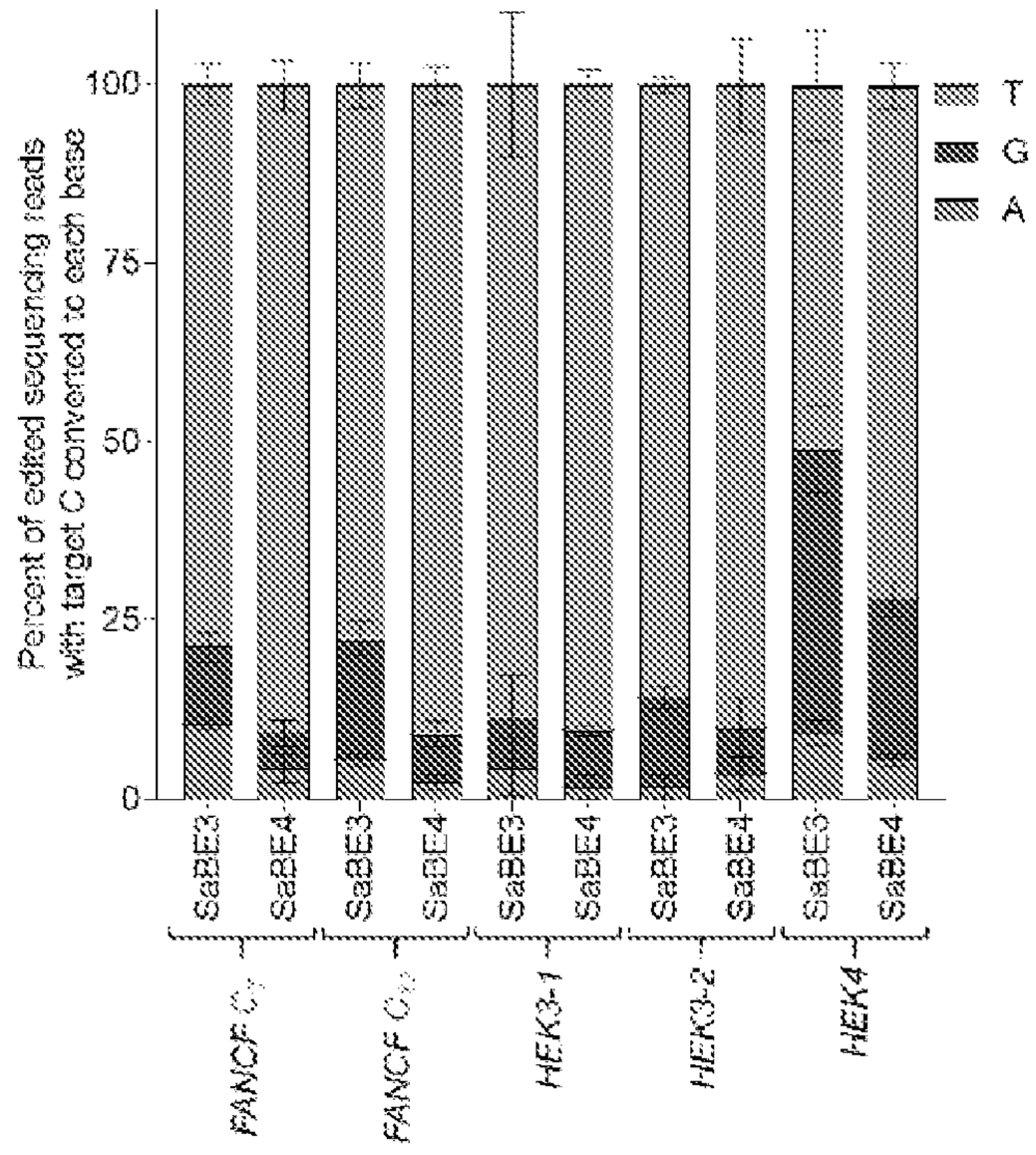


FIGURE 145C

EMX1		G	A	G	T	C$_5$	C$_6$	G	A	G	C$_{10}$	A	G	A	A	G	A	A	G	A	A	G	C	G
untreated	A	0.0	99.9	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	99.9	100.0	0.0	100.0	100.0	0.0	99.9	99.9	0.0	0.0	0.0
	C	0.0	0.0	0.0	0.0	99.9	100.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.0	0.0	0.0
	G	100.0	0.1	100.0	0.0	0.0	0.0	100.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	99.9	100.0	100.0
	T	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	0.0	0.0	0.1	0.0	0.0
BE3	A	0.0	100.0	0.0	0.0	2.0	0.8	0.0	99.5	0.0	0.0	100.0	0.0	100.0	100.0	0.0	100.0	100.0	0.0	100.0	100.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	0.0	72.6	76.2	0.0	0.5	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
	G	100.0	0.0	100.0	0.0	3.0	1.1	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	100.0	100.0	100.0
	T	0.0	0.0	0.0	100.0	22.3	21.9	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
CDA1-BE3	A	0.1	100.0	0.0	0.0	0.2	0.0	0.1	99.9	0.0	0.0	100.0	0.0	100.0	100.0	0.0	100.0	100.0	0.0	100.0	100.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	0.0	91.5	92.8	0.0	0.0	0.0	98.6	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
	G	99.9	0.0	99.9	0.0	0.4	0.1	99.8	0.0	99.9	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	100.0	100.0
	T	0.0	0.0	0.0	100.0	7.9	7.1	0.0	0.0	0.0	1.4	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
AID-BE3	A	0.0	100.0	0.2	0.0	0.2	0.1	0.3	100.0	0.0	0.1	100.0	0.0	100.0	100.0	0.0	100.0	100.0	0.0	100.0	100.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	0.0	85.8	95.2	0.0	0.0	0.3	94.5	0.0	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	99.9	0.0	99.8	0.0	0.7	0.0	99.7	0.0	99.6	0.3	0.0	99.7	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	100.0	99.9
	T	0.0	0.0	0.0	100.0	13.4	4.6	0.0	0.0	0.0	5.1	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
APOBEC3G-BE3	A	0.0	100.0	0.0	0.0	0.0	0.7	0.0	100.0	0.0	0.0	100.0	0.0	100.0	100.0	0.0	100.0	100.0	0.0	100.0	100.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	0.0	98.9	98.0	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	0.0	0.0	0.0	0.0
	G	100.0	0.0	100.0	0.0	0.2	2.3	99.9	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	100.0	100.0	100.0
	T	0.0	0.0	0.0	100.0	1.0	8.9	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

FIGURE 146

FANCF		G	G	A	A	T	C$_6$	C$_7$	C$_8$	T	T	C$_{11}$	T	G	C	A	G	C	A	C	C	T	G	G
untreated	A	0.1	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	100.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	0.0	0.0	100.0	100.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	100.0	100.0	0.0	0.0	0.0
	G	99.9	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	100.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0
	T	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0
BE3	A	0.0	0.1	100.0	100.0	0.0	1.0	1.4	1.4	0.0	0.0	0.2	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	0.0	0.0	70.7	75.0	74.4	0.0	0.0	84.8	0.0	0.0	99.9	0.0	0.0	100.0	0.0	100.0	99.9	0.0	0.0	0.0
	G	100.0	99.9	0.0	0.0	0.0	0.4	0.8	0.9	0.0	0.0	0.1	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	99.9	100.0
	T	0.0	0.0	0.0	0.0	100.0	28.0	22.9	23.4	100.0	100.0	10.9	100.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.1	100.0	0.0	0.0
CDA1-BE3	A	0.1	0.1	100.0	100.0	0.0	0.3	0.6	0.3	0.0	0.0	0.0	0.0	0.1	0.0	100.0	0.1	0.0	100.0	0.0	0.0	0.0	0.1	0.1
	C	0.0	0.0	0.0	0.0	0.0	82.4	83.5	84.7	0.0	0.0	97.3	0.0	0.0	99.6	0.0	0.0	99.8	0.0	100.0	100.0	0.0	0.0	0.0
	G	99.9	99.9	0.0	0.0	0.0	0.1	0.3	0.2	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	99.9	99.9
	T	0.0	0.0	0.0	0.0	100.0	17.2	15.6	14.7	99.9	100.0	2.6	100.0	0.0	0.3	0.0	0.0	0.2	0.0	0.0	0.0	100.0	0.0	0.0
AID-BE3	A	0.0	0.0	99.9	99.9	0.1	0.2	0.6	0.3	0.0	0.0	0.0	0.0	0.1	0.0	99.9	0.1	0.1	100.0	0.0	0.0	0.0	0.1	0.1
	C	0.0	0.0	0.0	0.0	0.0	73.8	80.3	86.6	0.0	0.0	96.7	0.0	0.0	98.8	0.0	0.0	97.0	0.0	99.9	100.0	0.0	0.0	0.0
	G	99.9	99.9	0.0	0.0	0.0	0.8	0.5	0.4	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	99.9	99.9
	T	0.0	0.0	0.0	0.0	99.9	25.2	18.6	12.7	100.0	100.0	3.2	100.0	0.0	1.2	0.0	0.0	2.9	0.0	0.1	0.0	100.0	0.0	0.0
APOBEC3G-BE3	A	0.0	0.0	100.0	100.0	0.0	0.0	2.9	1.7	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.1	0.0	100.0	0.0	0.0	0.0	0.0	0.1
	C	0.0	0.0	0.0	0.0	0.0	96.1	68.3	68.3	0.0	0.0	99.8	0.0	0.0	99.9	0.0	0.0	100.0	0.0	100.0	100.0	0.0	0.0	0.0
	G	100.0	99.9	0.0	0.0	0.0	0.3	1.6	10.8	0.0	0.0	0.0	0.0	100.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	100.0	99.9
	T	0.0	0.0	0.0	0.0	100.0	3.6	27.2	19.2	100.0	100.0	0.1	100.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0

FIGURE 147

HEK2		G	A	A	C	A	C	A	A	A	G	C	A	T	A	G	A	C	T	G	C	C	C	G
untreated	A	0.0	100.0	100.0	0.0	100.0	0.0	100.0	100.0	100.0	0.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	100.0	0.0	99.9	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	99.9	0.0	0.0	0.0
	G	100.0	0.0	0.0	0.0	0.0	0.1	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	99.9	100.0	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	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.1	0.0	0.0	0.0
BE3	A	0.1	100.0	100.0	1.3	99.9	0.7	100.0	100.0	100.0	0.0	0.0	100.0	0.0	100.0	0.0	100.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	80.5	0.0	48.5	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	99.7	0.0	0.0	100.0	0.0	0.0	0.0
	G	99.9	0.0	0.0	0.9	0.1	36.0	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	100.0	99.9	100.0
	T	0.0	0.0	0.0	17.2	0.0	14.8	0.0	0.0	0.0	0.0	0.1	0.0	100.0	0.0	0.0	0.0	0.2	100.0	0.0	0.0	0.0	0.0	0.0
CDA1-BE3	A	0.0	99.9	99.9	9.6	99.9	1.8	100.0	100.0	100.0	0.0	0.2	100.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	70.3	0.0	73.5	0.0	0.0	0.0	0.0	90.7	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	99.9	0.0	0.0	0.0
	G	100.0	0.0	0.1	0.3	0.1	3.5	0.0	0.0	0.0	100.0	0.3	0.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	100.0	100.0	100.0
	T	0.0	0.0	0.0	19.8	0.0	21.2	0.0	0.0	0.0	0.0	8.8	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.1	0.0	0.0	0.0
AID-BE3	A	0.0	99.9	99.9	6.9	99.9	1.2	100.0	100.0	100.0	0.0	0.2	100.0	0.0	100.0	0.0	100.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	54.5	0.0	52.4	0.0	0.0	0.0	0.0	83.8	0.0	0.0	0.0	0.0	0.0	99.7	0.0	0.0	99.8	0.0	0.0	0.0
	G	99.9	0.0	0.1	0.7	0.1	6.1	0.0	0.0	0.0	99.9	0.6	0.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	100.0	100.0	100.0
	T	0.1	0.1	0.0	37.9	0.0	40.3	0.0	0.0	0.0	0.1	15.5	0.0	100.0	0.0	0.0	0.0	0.2	99.9	0.0	0.2	0.0	0.0	0.0
APOBEC3G-BE3	A	0.0	100.0	100.0	0.1	100.0	0.1	100.0	100.0	100.0	0.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	97.8	0.0	80.3	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	99.9	0.0	0.0	0.0
	G	100.0	0.0	0.0	0.1	0.0	5.9	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	100.0	100.0	100.0
	T	0.0	0.0	0.0	2.0	0.0	13.7	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	0.1	0.0	0.0	0.0

FIGURE 148

HEK3		G	G	C	C	C	A	G	A	C	T	G	A	G	C	A	C	G	T	G	A	T	G	G
untreated	A	0.0	0.1	0.0	0.0	0.0	99.9	0.0	100.0	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.1
	C	0.0	0.0	100.0	99.9	99.9	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	0.0	0.1	0.0	0.0	0.0
	G	100.0	99.9	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	99.9	0.0	99.9	0.0	0.0	0.0	99.9	0.0	100.0	0.0	0.0	100.0	99.9
	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	0.0	100.0	0.0	0.0	100.0	0.0	0.0
BE3	A	0.0	0.0	0.0	0.8	1.1	100.0	0.0	100.0	0.4	0.0	0.0	100.0	0.2	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	98.6	67.4	58.1	0.0	0.0	0.0	98.3	0.0	0.0	0.0	0.0	100.0	0.0	99.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	100.0	100.0	0.0	0.4	8.9	0.0	100.0	0.0	0.6	0.0	100.0	0.0	99.8	0.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	99.9	100.0
	T	0.0	0.0	1.3	31.4	31.9	0.0	0.0	0.0	0.7	100.0	0.0	0.0	0.0	0.0	0.0	0.3	0.0	100.0	0.0	0.0	100.0	0.1	0.0
CDA1-BE3	A	0.1	0.0	0.8	0.6	0.0	100.0	0.0	99.9	0.4	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	0.0	0.0	99.9	0.0	0.1	0.1
	C	0.0	0.0	79.4	73.6	73.4	0.0	0.0	0.0	91.0	0.0	0.0	0.0	0.0	99.9	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	99.9	100.0	0.0	0.0	2.1	0.0	100.0	0.0	0.3	0.0	99.9	0.0	100.0	0.0	0.0	0.0	99.9	0.0	99.9	0.1	0.0	99.9	99.9
	T	0.1	0.0	19.8	25.9	24.4	0.0	0.0	0.0	8.3	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0
AID-BE3	A	0.1	0.3	1.0	0.7	0.3	99.9	0.0	100.0	1.6	0.0	0.0	100.0	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	63.9	75.4	60.2	0.0	0.0	0.0	86.6	0.0	0.0	0.0	0.0	98.9	0.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	99.8	99.7	0.1	0.4	1.0	0.0	100.0	0.0	1.2	0.0	100.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	100.0	99.9
	T	0.0	0.0	35.0	23.5	38.5	0.0	0.0	0.0	10.6	100.0	0.0	0.0	0.0	1.1	0.0	0.2	0.0	100.0	0.0	0.0	100.0	0.0	0.0
APOBEC3G-BE3	A	0.0	0.0	0.0	0.6	3.1	100.0	0.0	100.0	0.0	0.0	0.0	100.0	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	99.9	86.7	93.9	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	0.0	0.0	0.0	0.0	0.0
	G	100.0	99.9	0.0	1.4	28.6	0.0	100.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	100.0	100.0
	T	0.0	0.0	0.0	11.3	34.4	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0

FIGURE 149

HEK4		G	G	C_3	A	C_6	T	G	C_8	G	G	C	T	G	G	A	G	G	T	G	G	G	G	G
untreated	A	0.0	0.1	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	100.0	0.0	100.0	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	0.0	0.1	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.0
	G	99.9	99.9	0.0	0.0	0.0	0.0	100.0	0.0	100.0	100.0	0.0	0.0	100.0	100.0	0.0	100.0	100.0	0.4	99.9	99.9	100.0	99.9	99.9
	T	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	0.0	99.5	0.1	0.0	0.0	0.0	0.0
BE3	A	0.1	0.0	0.1	99.9	8.4	0.1	0.0	0.1	0.0	0.1	0.0	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	99.0	0.0	41.9	0.0	0.0	99.3	0.0	0.0	99.8	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	99.9	99.9	0.0	0.0	24.5	0.0	100.0	0.0	100.0	99.9	0.0	0.0	100.0	100.0	0.1	100.0	100.0	0.0	100.0	100.0	100.0	100.0	100.0
	T	0.0	0.0	0.9	0.0	25.2	99.9	0.0	0.5	0.0	0.0	0.2	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0
CDA1-BE3	A	0.2	0.1	0.5	100.0	0.5	0.0	0.0	0.2	0.0	0.0	0.1	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	91.3	0.0	87.5	0.0	0.0	93.4	0.0	0.0	97.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	99.8	99.9	0.3	0.0	0.0	0.0	100.0	0.0	100.0	100.0	0.0	0.0	100.0	100.0	0.0	100.0	100.0	0.0	100.0	100.0	100.0	100.0	100.0
	T	0.0	0.0	7.8	0.0	12.0	100.0	0.0	6.3	0.0	0.0	2.9	100.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0
AID-BE3	A	0.3	0.4	0.3	100.0	0.9	0.0	0.0	0.9	0.0	0.0	0.1	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	81.5	0.0	71.3	0.0	0.0	80.7	0.0	0.0	97.9	0.1	0.0	0.0	0.2	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0
	G	99.7	99.6	0.1	0.0	0.7	0.0	100.0	0.1	100.0	100.0	0.0	0.0	99.9	100.0	0.0	100.0	100.0	0.2	99.9	100.0	100.0	100.0	99.9
	T	0.0	0.0	18.0	0.0	27.1	100.0	0.0	18.3	0.0	0.0	2.0	99.9	0.0	0.0	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.1
APOBEC3G-BE3	A	0.1	0.0	0.0	99.9	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	99.9	0.0	99.4	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0
	G	99.9	99.9	0.0	0.0	0.4	0.0	99.9	0.0	100.0	99.9	0.0	0.0	99.9	100.0	0.1	100.0	99.9	0.0	99.9	100.0	100.0	100.0	99.9
	T	0.0	0.0	0.0	0.0	0.2	99.9	0.0	0.1	0.0	0.1	0.0	99.9	0.1	0.0	0.0	0.0	0.1	99.9	0.0	0.0	0.0	0.0	0.1

FIGURE 150

RNF2		G	T	C	A	T	C	T	T	A	G	T	C	G	T	T	A	C	C	T	G	A	C	C
untreated	A	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	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0
	C	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	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	0.0	0.0
	G	100.0	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	100.0	100.0
	T	0.0	100.0	0.1	0.0	100.0	0.0	100.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	100.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0
BE3	A	0.0	0.0	0.3	99.9	0.1	1.6	0.1	0.0	100.0	0.0	0.0	0.1	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0
	C	0.0	0.0	81.1	0.0	0.0	59.7	0.0	0.0	0.0	0.0	0.0	96.6	0.0	0.0	0.0	0.0	99.9	99.9	0.0	0.0	0.0	0.0	0.0
	G	99.9	0.0	0.0	0.0	0.0	12.6	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	0.0	99.9	100.0
	T	0.0	100.0	18.6	0.0	99.9	26.1	99.9	100.0	0.0	0.0	100.0	3.3	0.0	100.0	100.0	0.0	0.0	0.1	100.0	0.0	0.0	0.0	0.0
CDA1-BE3	A	0.0	0.0	0.3	100.0	0.0	0.3	0.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0
	C	0.0	0.0	86.1	0.0	0.0	67.9	0.0	0.0	0.0	0.0	0.0	99.1	0.0	0.0	0.0	0.0	99.9	99.9	0.0	0.0	0.0	0.0	0.0
	G	100.0	0.0	0.0	0.0	0.0	0.4	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	100.0	100.0
	T	0.0	100.0	11.6	0.0	100.0	11.5	100.0	100.0	0.0	0.0	100.0	0.9	0.0	100.0	100.0	0.0	0.1	0.1	100.0	0.0	0.0	0.0	0.0
AID-BE3	A	0.0	0.0	0.1	100.0	0.1	0.1	0.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0
	C	0.0	0.0	92.7	0.0	0.0	81.5	0.0	0.0	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	99.7	99.8	0.0	0.0	0.0	0.0	0.0
	G	100.0	0.0	0.0	0.0	0.0	3.2	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	99.9	0.0	99.9	100.0
	T	0.0	100.0	7.2	0.0	99.9	15.2	100.0	100.0	0.0	0.0	100.0	0.1	0.0	100.0	100.0	0.0	1.2	0.2	100.0	0.0	0.0	0.0	0.0
APOBEC3G-BE3	A	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	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0
	C	0.0	0.0	98.2	0.0	0.0	82.8	0.0	0.0	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	99.8	99.8	0.0	0.0	0.0	0.0	0.0
	G	100.0	0.0	0.0	0.0	0.0	3.4	0.0	0.0	0.0	99.9	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	100.0	100.0
	T	0.0	100.0	1.8	0.0	100.0	13.8	100.0	100.0	0.0	0.0	100.0	0.2	0.0	100.0	100.0	0.0	0.2	0.2	100.0	0.0	0.0	0.0	0.0

FIGURE 151

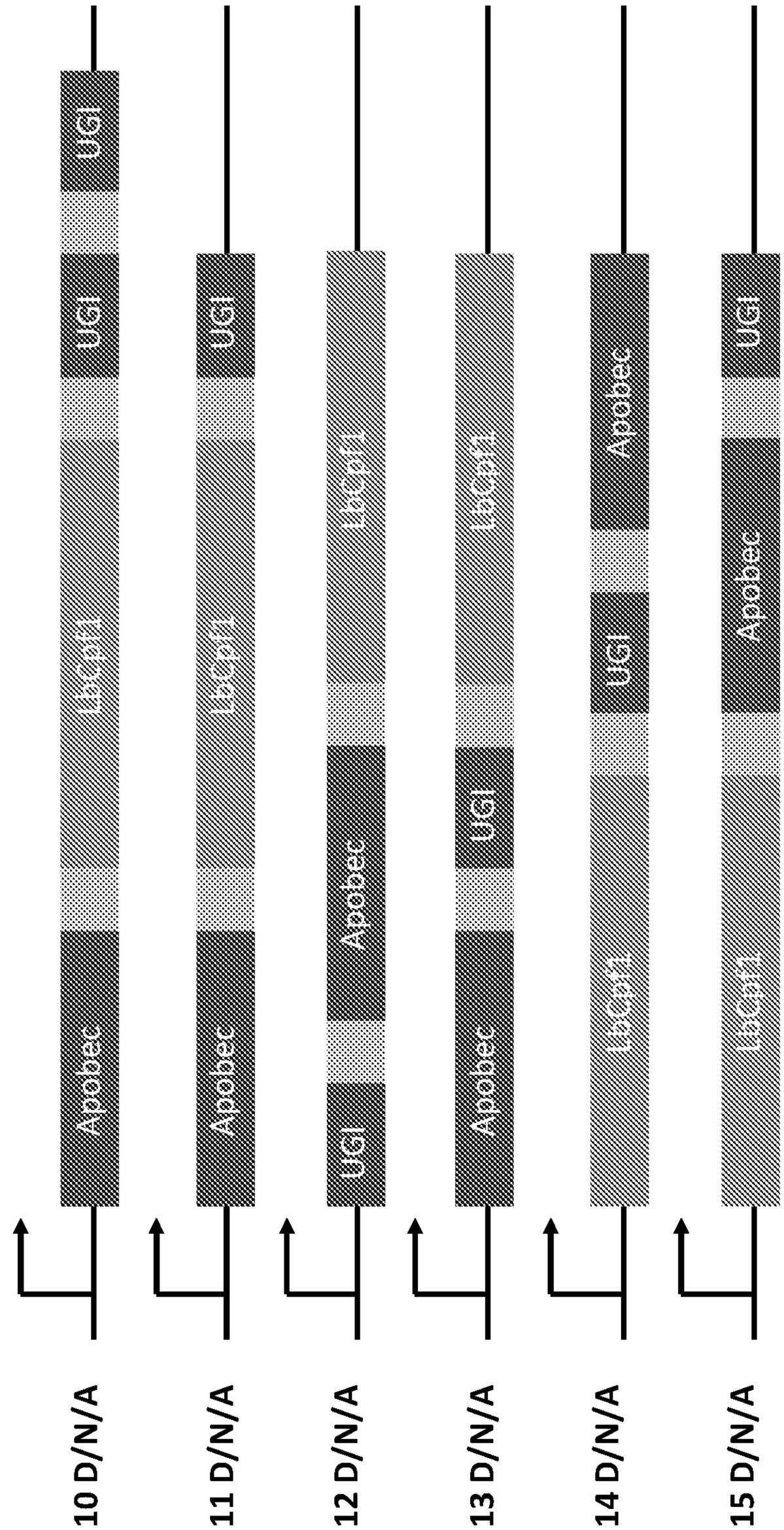


FIGURE 152

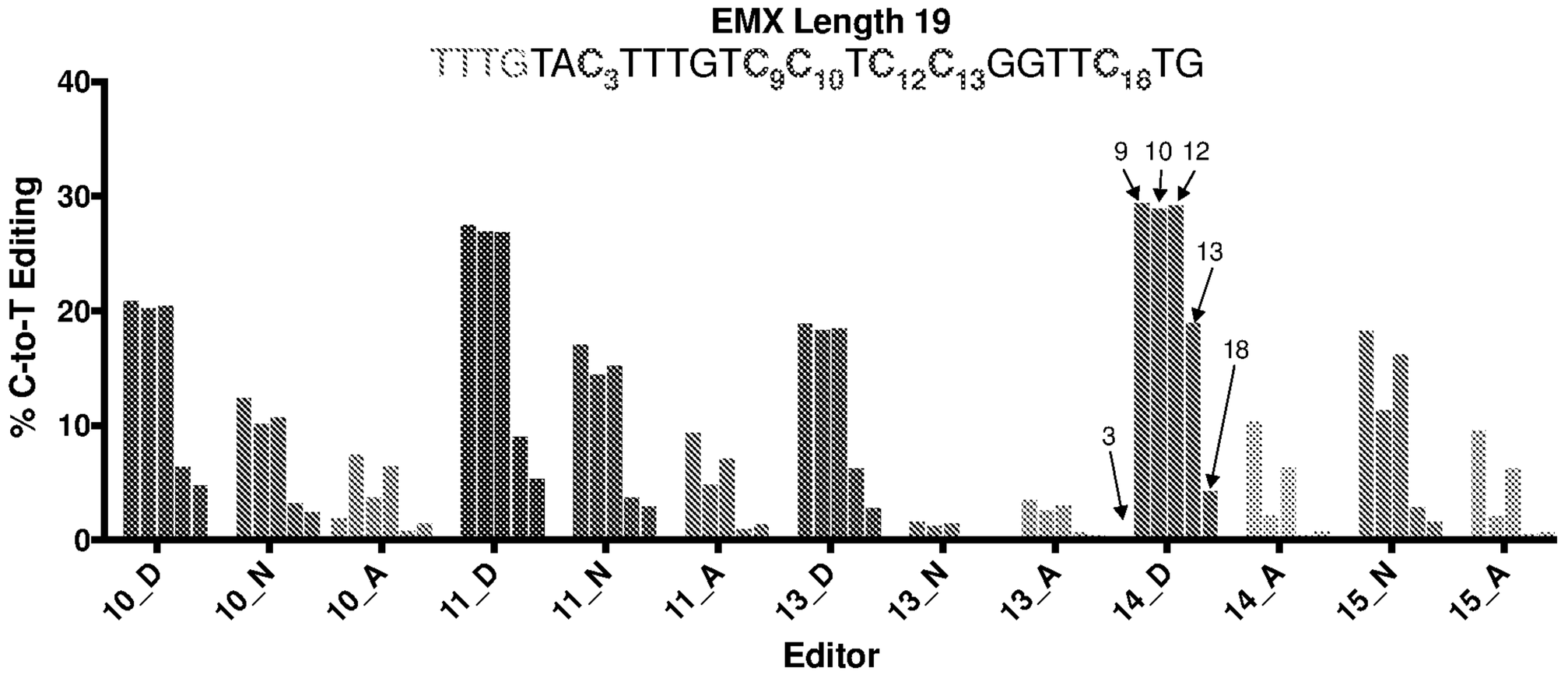


FIGURE 153

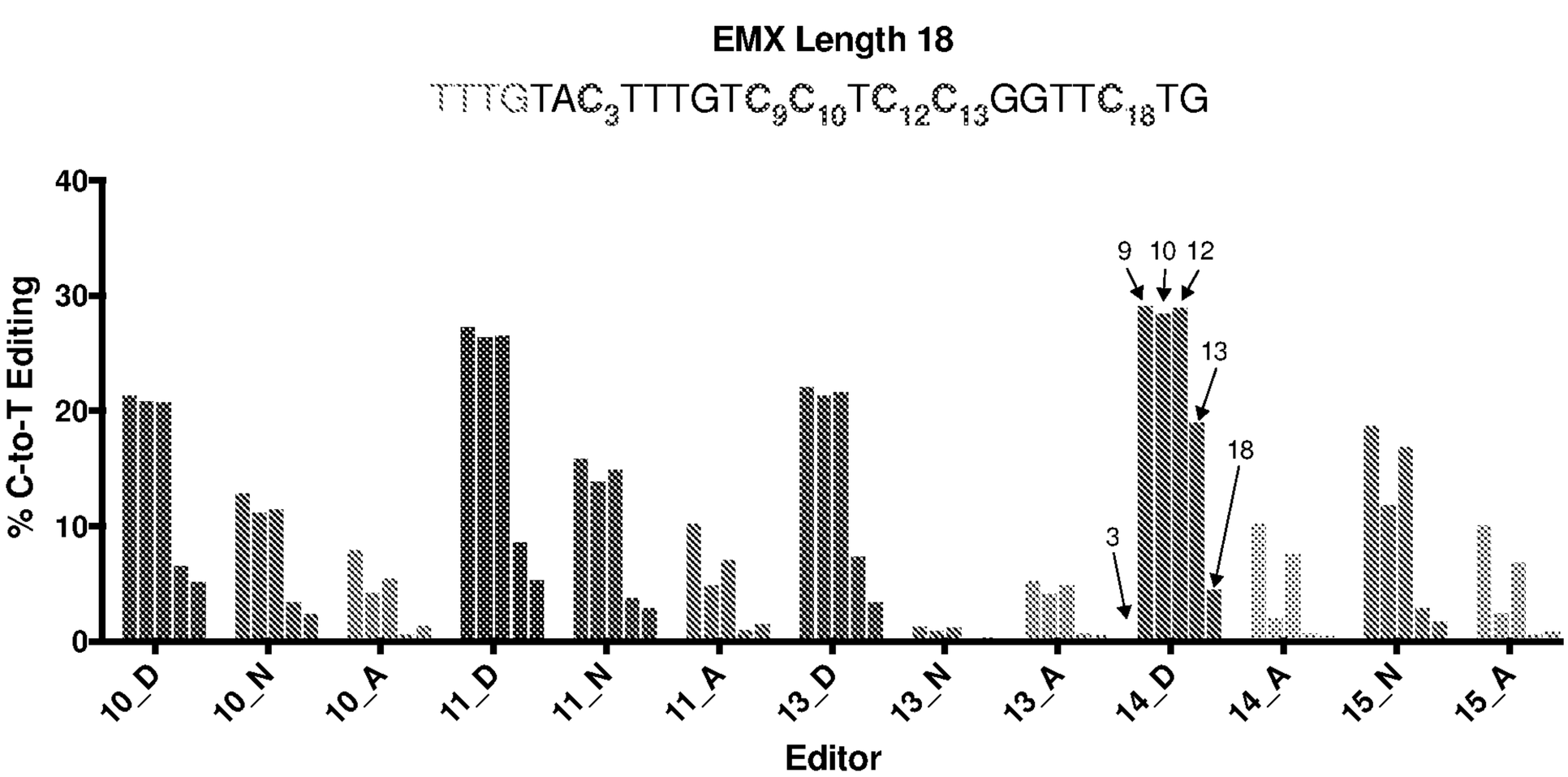


FIGURE 154

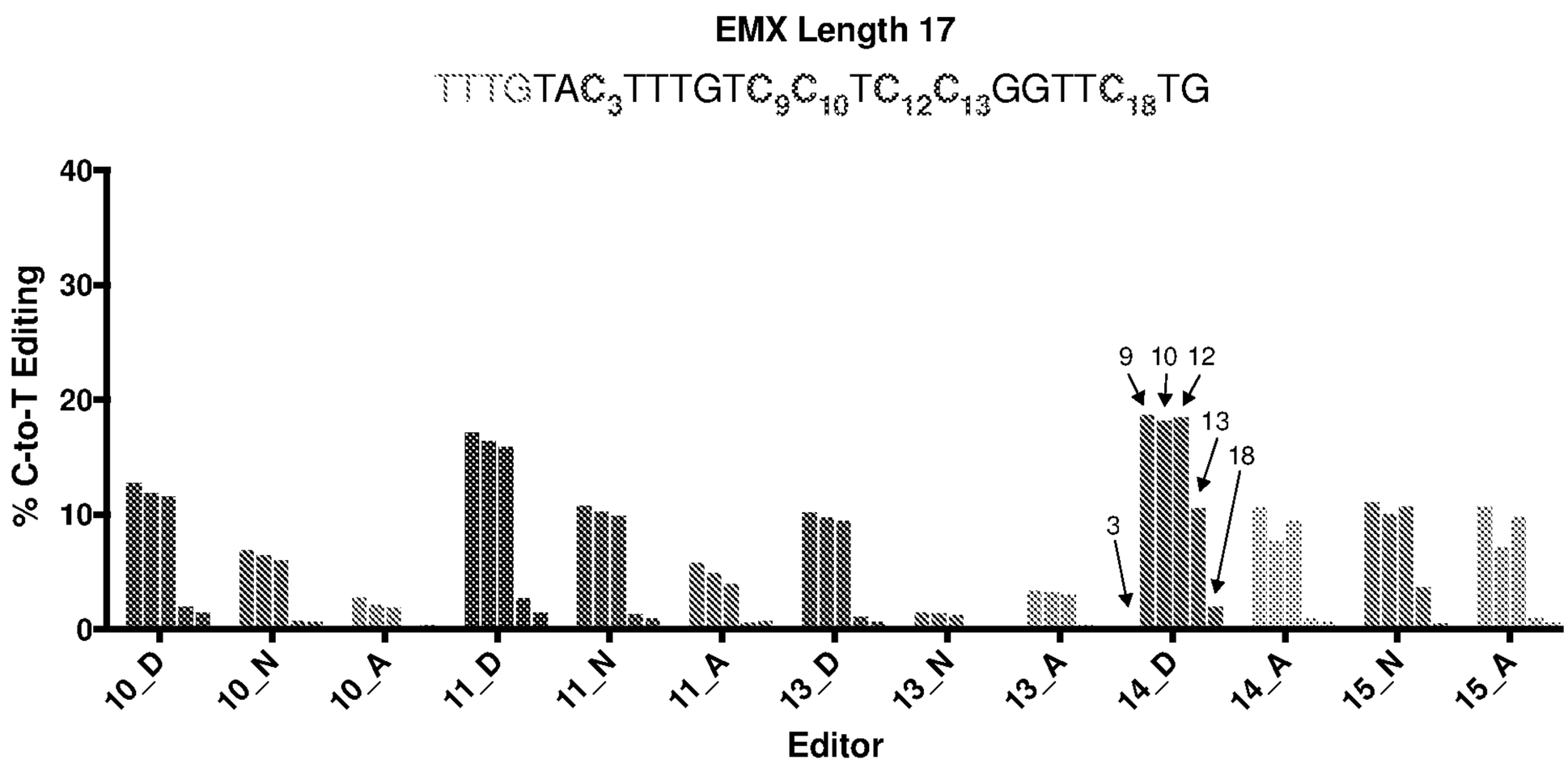
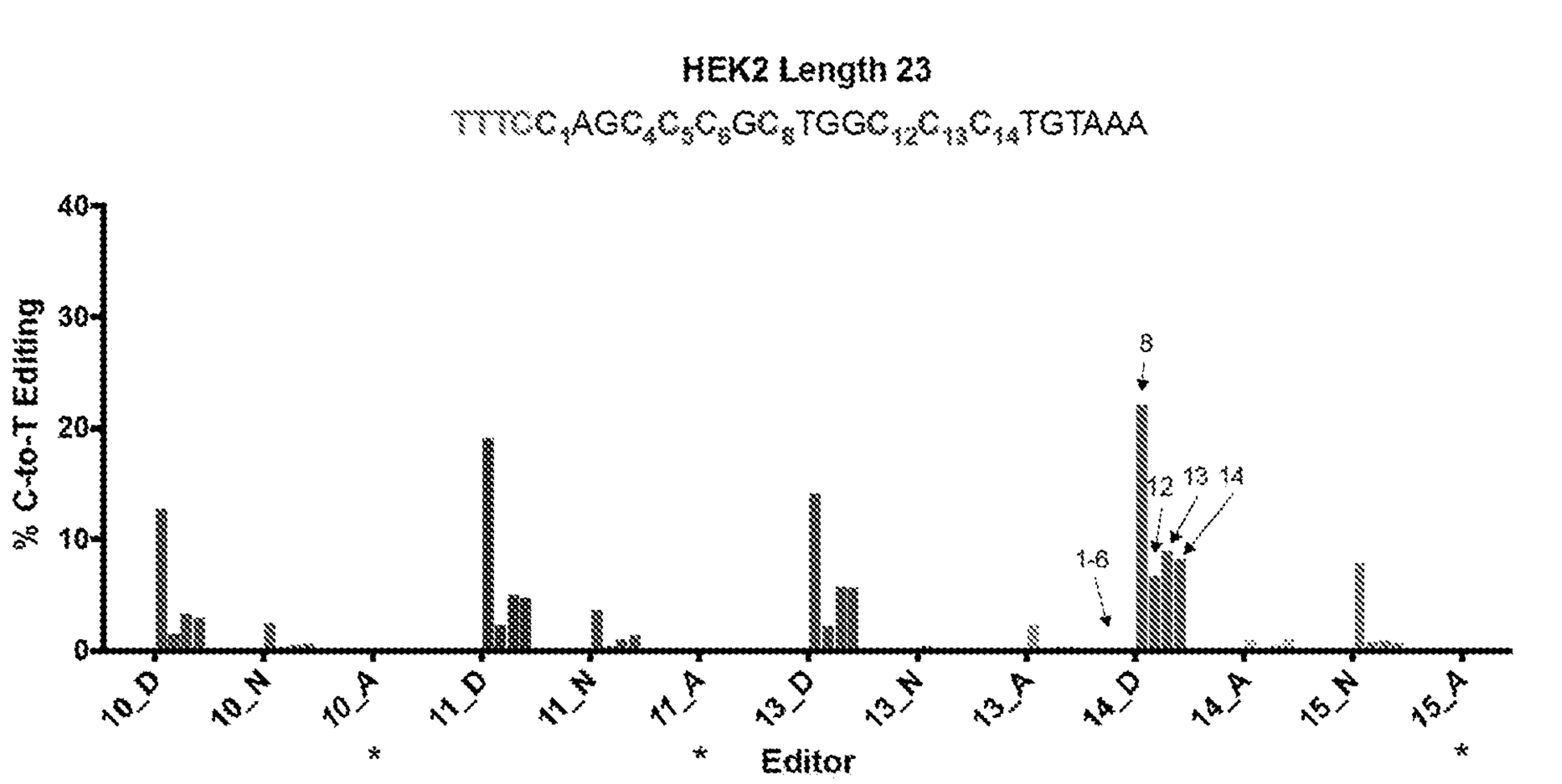


FIGURE 155



(*Data not obtained)

FIGURE 156

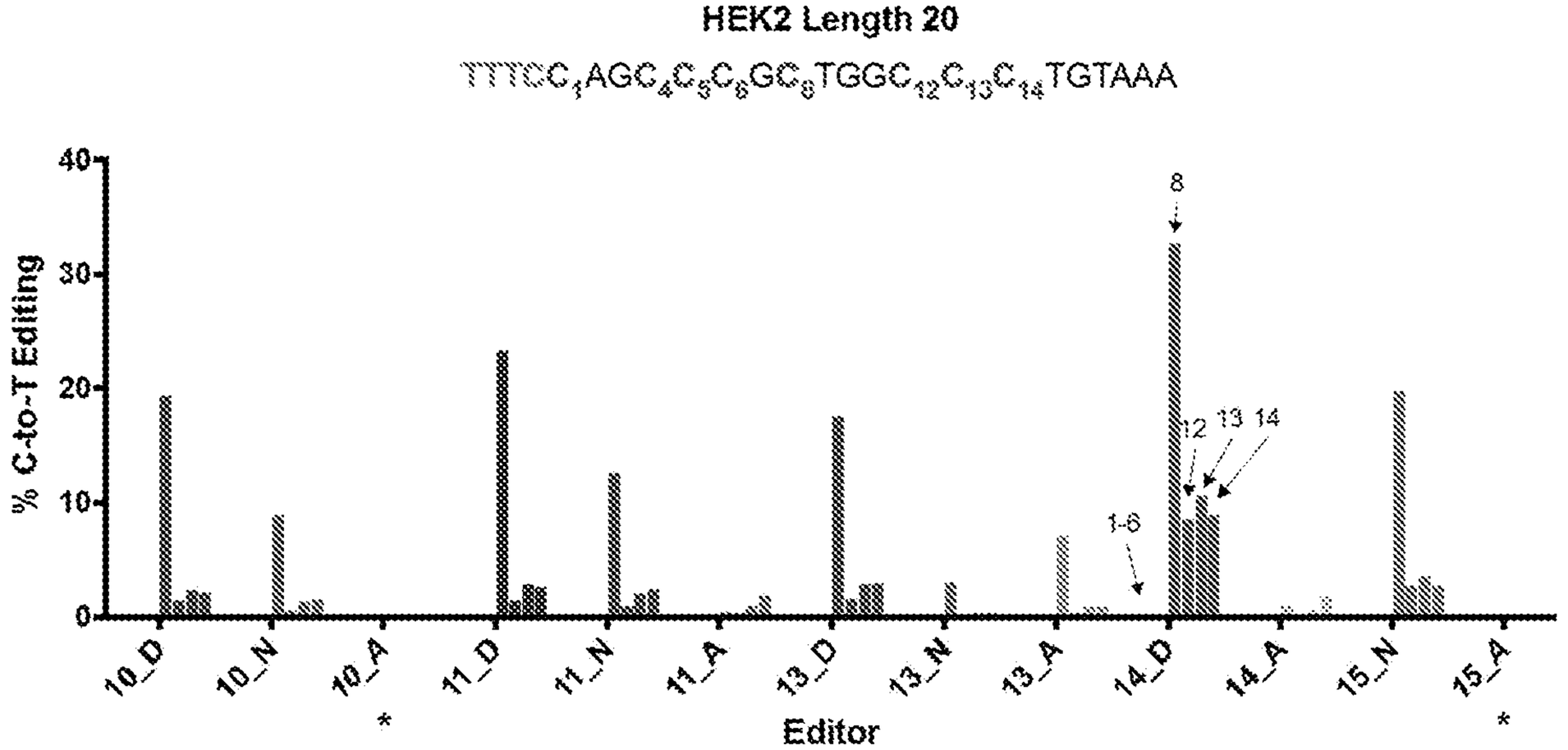
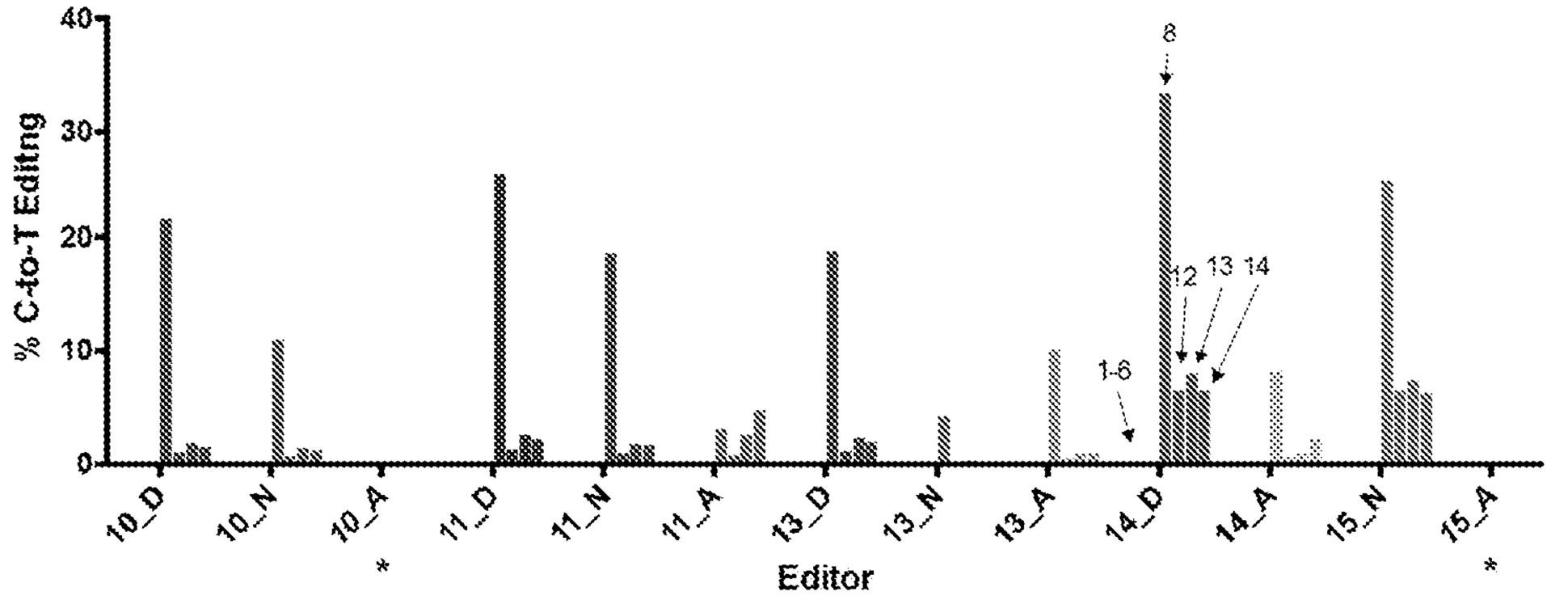

HEK2 Length 20
TTTCC1AGC4C5C6GC8TGGC12C13C14TGTAAA
% C-to-T Editing
40
30
20
10
0
8
12
13
14
1-6
10_D
10_N
10_A
11_D
11_N
11_A
13_D
13_N
13_A
14_D
14_A
15_N
15_A
*
*
Editor
(*Data not obtained)

FIGURE 157

HEK2 Length 19

TTTCC$_1$AGC$_4$C$_5$C$_6$GC$_8$TGGC$_{12}$C$_{13}$C$_{14}$TGTAA

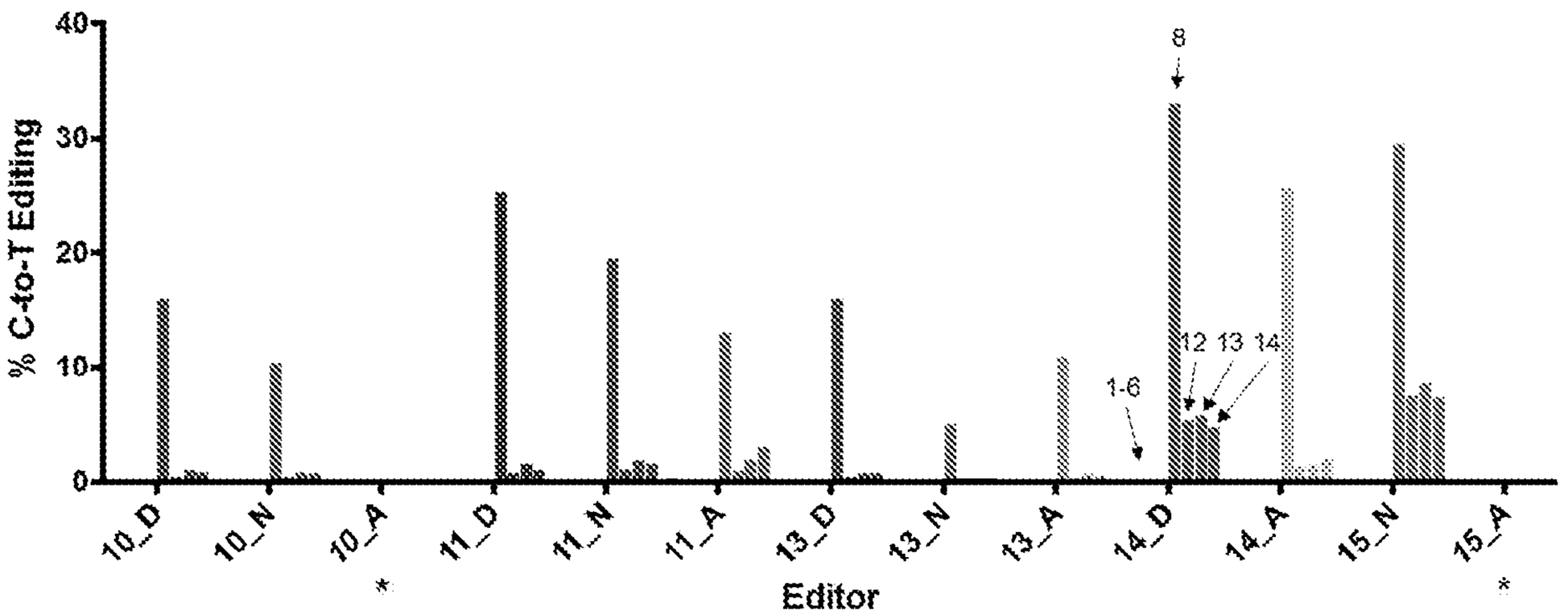


(*Data not obtained)

FIGURE 158

HEK2 Length 18

TTTCC$_1$AGC$_4$C$_5$C$_6$GC$_8$TGGC$_{12}$C$_{13}$C$_{14}$TGTAA



(*Data not obtained)

FIGURE 159

EMX 19

	10_D	10_N	10_A	11_D	11_N	11_A	13_D	13_N	13_A	14_D	14_A	15_N	15_A
C3	0.025	0.039	2.662	0.012	0.013	0.041	0.02	0.013	0.012	0.033	0.012	0.02	0.021
C9	20.899	13.15	10.456	27.535	18.921	13.072	19.043	1.591	3.638	29.39	14.271	20.95	13.924
C10	20.226	10.784	5.206	26.909	16.026	6.748	18.445	1.266	2.658	28.933	2.934	13.039	3.051
C12	20.453	11.385	9.095	26.849	16.893	9.983	18.589	1.437	3.127	29.165	8.695	18.597	9.07
C13	6.39	3.396	1.085	8.946	4.126	1.3	6.317	0.257	0.659	18.973	0.547	3.247	0.8
C18	4.757	2.603	2.013	5.304	3.233	1.914	2.805	0.235	0.367	4.302	0.992	1.848	0.994
indels (%)	0.028979	6.0862	28.9183	0.038623	9.8557	28.6068	0.94296	1.4573	3.78	0.024623	27.6872	13.0741	31.3295
C3	0.02499276	0.03662638	1.89219485	0.01199537	0.01171876	0.02927121	0.01981141	0.01281055	0.0115464	0.03299187	0.00867754	0.01738518	0.01442081
C9	20.8929437	12.3496647	7.43230255	27.5243652	17.056203	9.3325191	18.8634321	1.56781436	3.5004836	29.3827633	10.3197597	18.2109761	9.56168042
C10	20.2201387	10.1276642	3.7005133	26.8986069	14.4465255	4.81761314	18.271071	1.24755058	2.5575276	28.9258758	2.12165755	11.3342681	2.09513696
C12	20.4470729	10.6920861	6.46488062	26.8386301	15.2280766	7.12718316	18.4137132	1.4160586	3.0087994	29.1578187	6.28759796	16.1656096	6.22841435
C13	6.38814824	3.18931265	0.77123645	8.94254479	3.71935382	0.9281116	6.25743322	0.25325474	0.6340898	18.9683283	0.39555102	2.82248397	0.549364
C18	4.75562147	2.44457621	1.43087462	5.30195144	2.91436522	1.36646585	2.77854997	0.23157535	0.3531274	4.30094072	0.71734298	1.60639063	0.68258477

FIGURE 160

EMX 18

	10_D	10_N	10_A	11_D	11_N	11_A	13_D	13_N	13_A	14_D	14_A	15_N	15_A
C3	0.023	0.008	0.032	0.044	0.035	0.016	0.03	0.016	0.016	0.018	0.02	0.017	0.01
C9	21.333	13.606	10.333	27.294	17.216	14.646	22.315	1.297	5.485	29.094	14.566	21.847	13.66
C10	20.865	11.831	5.528	26.409	15.041	6.931	21.548	0.932	4.309	28.456	2.996	13.762	3.337
C12	20.773	12.165	7.147	26.572	16.178	10.157	21.839	1.202	5.059	28.937	10.88	19.625	9.359
C13	6.538	3.591	0.848	8.562	4.096	1.387	7.426	0.129	0.729	18.993	0.945	3.353	0.809
C18	5.174	2.54	1.788	5.313	3.146	2.196	3.443	0.243	0.565	4.517	0.647	2.03	1.154
indels (%)	0.039639	5.7886	23.1911	0.035862	7.9573	30.2671	1.1014	1.1121	4.6798	0.040521	29.8821	14.2217	26.5552
C3	0.02299088	0.00753691	0.02457885	0.04398422	0.03221495	0.01115726	0.02966958	0.01582206	0.01525123	0.01799271	0.01402358	0.01458231	0.00734448
C9	21.3245438	12.8184031	7.93666364	27.2842118	15.8460712	10.2130805	22.0692226	1.28257606	5.22831297	29.0822108	10.2133733	18.7399852	10.0325597
C10	20.8567293	11.1461507	4.24599599	26.3995292	13.8441425	4.8331873	21.3106703	0.92163523	4.10734742	28.4444693	2.10073228	11.8048096	2.45085298
C12	20.7647658	11.4608168	5.48953208	26.5624707	14.890668	7.08277065	21.5984653	1.18863256	4.82224892	28.9252744	7.62882752	16.8339914	6.87369883
C13	6.5354084	3.38313137	0.65133947	8.5589295	3.77006899	0.96719532	7.34421004	0.12756539	0.69488426	18.9853038	0.66261416	2.8761464	0.59416843
C18	5.17194908	2.39296956	1.37334313	5.31109465	2.89566334	1.53133448	3.4050788	0.2402976	0.53855913	4.51516967	0.45366281	1.74129949	0.84755299

FIGURE 161

EMX 17

	10_D	10_N	10_A	11_D	11_N	11_A	13_D	13_N	13_A	14_D	14_A	15_N	15_A
C3	0.016	0.014	0.044	0.012	0.018	0.012	0.013	0.016	0.03	0.014	0.011	0.016	0.005
C9	12.742	6.895	2.862	17.142	10.77	5.941	10.177	1.471	3.395	18.719	11.13	11.103	11.493
C10	11.901	6.427	2.199	16.385	10.277	5.064	9.741	1.393	3.216	18.206	8.1	10.086	7.747
C12	11.548	6.014	1.916	15.933	9.872	4.041	9.468	1.287	2.986	18.492	9.847	10.751	10.523
C13	1.993	0.768	0.252	2.696	1.357	0.599	1.155	0.083	0.285	10.532	0.971	3.674	1.082
C18	1.457	0.613	0.361	1.471	0.987	0.773	0.667	0.043	0.245	1.978	0.729	0.545	0.621
indels (%)	0.017245	0.052423	1.7787	0.025203	0.11499	2.7876	0.14938	0.019738	0.041079	0.04713	4.2923	0.37931	6.7995
C3	0.01599724	0.01399266	0.04321737	0.01199698	0.0179793	0.01166549	0.01298058	0.01599684	0.02998768	0.0139934	0.01052785	0.01593931	0.00466003
C9	12.7398026	6.89138543	2.81109361	17.1376797	10.7576156	5.77538868	10.1617976	1.47070965	3.39360537	18.7101777	10.652267	11.0608852	10.7115335
C10	11.8989477	6.42363077	2.15988639	16.3808705	10.2651825	4.92283594	9.72644889	1.39272505	3.2146789	18.1974195	7.7523237	10.0477428	7.22024274
C12	11.5460085	6.01084728	1.88192011	15.9289844	9.86064819	3.92835308	9.4538567	1.28674597	2.98477338	18.4832847	9.42433722	10.7102204	9.80748862
C13	1.99265631	0.76759739	0.24751768	2.69532053	1.35543959	0.58230228	1.15327466	0.08298362	0.28488292	10.5270363	0.92932177	3.66006415	1.00842941
C18	1.45674874	0.61267865	0.35457889	1.47062926	0.98586505	0.75145185	0.66600364	0.04299151	0.24489936	1.97706777	0.69770913	0.54293276	0.57877511

FIGURE 162

Hek2 23

	10_D	10_N	10_A	11_D	11_N	11_A	13_D	13_N	13_A	14_D	14_A	15_N	15_A
C1	0.042	0.021	0	0.039	0.084	0	0.045	0.07	0.04	0.045	0.056	0.057	0
C4	0.016	0.018	0	0.023	0.013	0	0.027	0.022	0.016	0.035	0.008	0.016	0
C5	0.031	0.018	0	0.037	0.052	0	0.048	0.021	0.044	0.047	0.157	0.017	0
C6	0.064	0.045	0	0.064	0.02	0	0.077	0.068	0.051	0.078	0.032	0.08	0
C8	12.758	2.444	0	19.198	3.66	0	14.134	0.423	2.22	22.158	0.977	7.763	0
C12	1.418	0.291	0	2.281	0.446	0	2.163	0.101	0.21	6.745	0.235	0.809	0
C13	3.282	0.603	0	5.021	1.121	0	5.713	0.042	0.308	8.933	0.599	0.921	0
C14	2.898	0.641	0	4.719	1.38	0	5.614	0.096	0.38	8.268	1.066	0.746	0
indels (%)	0.052343	11.0664		0.041898			2.2549	6.3138	13.9681	0.085777	59.2508	11.3052	
C1	0.04197802	0.01867606	0	0.03898366	0.084	0	0.0439853	0.06558034	0.03441276	0.0449614	0.02281955	0.05055604	0
C4	0.01599163	0.01600805	0	0.02299036	0.013	0	0.02639118	0.02061096	0.0137651	0.03496998	0.00325994	0.01419117	0
C5	0.03098377	0.01600805	0	0.0369845	0.052	0	0.04691765	0.0196741	0.03785404	0.04695968	0.06397624	0.01507812	0
C6	0.0639665	0.04002012	0	0.06397319	0.02	0	0.07526373	0.06370662	0.04387627	0.07793309	0.01303974	0.07095584	0
C8	12.7513221	2.17353718	0	19.1899564	3.66	0	13.8152924	0.39629263	1.90990818	22.1389935	0.39811968	6.88537732	0
C12	1.41725778	0.25879678	0	2.28004431	0.446	0	2.11422651	0.09462306	0.18066699	6.73921434	0.09576062	0.71754093	0
C13	3.2802821	0.53626961	0	5.0188963	1.121	0	5.58417756	0.0393482	0.26497825	8.92533754	0.24408771	0.81687911	0
C14	2.8964831	0.57006438	0	4.71702283	1.38	0	5.48740991	0.08993875	0.32692122	8.26090796	0.43438647	0.66166321	0

FIGURE 163

Hek2 20

	10_D	10_N	10_A	11_D	11_N	11_A	13_D	13_N	13_A	14_D	14_A	15_N	15_A
C1	0.024	0.051	0	0.036	0.116	0.126	0.035	0.022	0.042	0.032	0.02	0.133	0
C4	0.054	0.023	0	0.026	0.011	0.01	0.019	0.019	0.011	0.025	0.016	0.016	0
C5	0.033	0.017	0	0.051	0.054	0.048	0.046	0.02	0.029	0.035	0.075	0.043	0
C6	0.096	0.083	0	0.058	0.032	0.022	0.055	0.016	0.047	0.139	0.166	0.083	0
C8	19.339	9.265	0	23.342	13.199	1.173	17.974	3.225	7.353	32.768	2.835	20.891	0
C12	1.402	0.551	0	1.491	1.036	0.713	1.68	0.188	0.471	8.549	0.3	2.967	0
C13	2.377	1.409	0	2.974	2.174	2.814	3.043	0.356	0.895	10.654	1.81	3.81	0
C14	2.129	1.545	0	2.604	2.523	5.582	3.076	0.316	0.955	8.964	4.97	3.086	0
indels (%)	0.10237	3.2815	24.3902	0.10375	4.3674	66.4779	1.8097	1.6132	3.0719	0.093678	63.4082	5.4543	
C1	0.02397543	0.04932644	0	0.03596265	0.11093382	0.04223785	0.03436661	0.0216451	0.0407098	0.03197002	0.00731836	0.12574578	0
C4	0.05394472	0.02224526	0	0.02597303	0.01051959	0.00335221	0.01865616	0.01869349	0.01066209	0.02497658	0.00585469	0.01512731	0
C5	0.03296622	0.01644215	0	0.05094709	0.0516416	0.01609061	0.04516754	0.01967736	0.02810915	0.03496721	0.02744385	0.04065465	0
C6	0.09590172	0.08027636	0	0.05793983	0.03060243	0.00737486	0.05400467	0.01574189	0.04555621	0.13886979	0.06074239	0.07847293	0
C8	19.3192027	8.96096903	0	23.3177827	12.6225469	0.39321423	17.6487245	3.1729743	7.12712319	32.7373036	1.03737753	19.7515422	0
C12	1.40056477	0.53291894	0	1.48945309	0.99075374	0.23901257	1.64959704	0.18496718	0.45653135	8.54099147	0.1097754	2.80517092	0
C13	2.37456667	1.36276367	0	2.97091448	2.07905272	0.94331189	2.98793083	0.35025701	0.8675065	10.6440195	0.66231158	3.60219117	0
C14	2.12682054	1.49430083	0	2.60129835	2.4128105	1.87120362	3.02033363	0.31090229	0.92566336	8.9556027	1.81861246	2.9176803	0

FIGURE 164

Hek2 19

	10_D	10_N	10_A	11_D	11_N	11_A	13_D	13_N	13_A	14_D	14_A	15_N	15_A
C1	0.072	0.031	0	0.039	0.062	0.406	0.023	0.019	0.025	0.06	0.224	0.04	0
C4	0.034	0.019	0	0.021	0.06	0.018	0.039	0.033	0.025	0.012	0.009	0.008	0
C5	0.03	0.037	0	0.044	0.045	0.027	0.018	0.031	0.033	0.024	0.021	0.012	0
C6	0.053	0.066	0	0.042	0.071	0.164	0.033	0.031	0.046	0.098	0.117	0.034	0
C8	21.611	11.001	0	25.556	18.67	6.38	18.944	4.272	10.143	33.441	15.227	25.017	0
C12	1.049	0.704	0	1.345	1.022	1.548	1.154	0.195	0.489	6.54	1.177	6.539	0
C13	1.914	1.39	0	2.629	1.819	5.23	2.301	0.253	0.881	8.065	1.823	7.452	0
C14	1.545	1.212	0	2.238	1.761	9.623	1.98	0.151	0.975	6.517	4.174	6.365	0
indels (%)	0.056704	0.17936		0.04541	0.43984	50.2032	0.61981	0.18691	0.22381	0.14694	45.816	0.52493	
C1	0.07195917	0.0309444	0	0.03898229	0.0617273	0.20217501	0.02285744	0.01896449	0.02494405	0.05991184	0.12137216	0.03979003	0
C4	0.03398072	0.01896592	0	0.02099046	0.0597361	0.00896342	0.03875827	0.03293832	0.02494405	0.01198237	0.00487656	0.00795801	0
C5	0.02998299	0.03693364	0	0.04398002	0.04480207	0.01344514	0.01788843	0.03094206	0.03292614	0.02396473	0.01137864	0.01193701	0
C6	0.05296995	0.06588162	0	0.04198093	0.07068771	0.08166675	0.03279546	0.03094206	0.04589705	0.097856	0.06339528	0.03382152	0
C8	21.5987457	10.9812686	0	25.544395	18.5878819	3.17703584	18.8265832	4.2640152	10.120299	33.3918618	8.25059768	24.8856783	0
C12	1.04840518	0.70273731	0	1.34438924	1.01750484	0.77085446	1.14684739	0.19463553	0.48790557	6.53039012	0.63774568	6.50467483	0
C13	1.91291469	1.3875069	0	2.62780617	1.81099931	2.60437264	2.28673817	0.25252712	0.87902823	8.05314929	0.98777432	7.41288222	0
C14	1.54412392	1.20982616	0	2.23698372	1.75325442	4.79194606	1.96772776	0.15071777	0.97281785	6.50742392	2.26164016	6.33158821	0

FIGURE 165

Hek2 18

	10_D	10_N	10_A	11_D	11_N	11_A	13_D	13_N	13_A	14_D	14_A	15_N	15_A
C1	0.037	0.027	0	0.035	0.041	0.315	0.039	0.034	0.034	0.028	0.125	0.074	0
C4	0.014	0.016	0	0.007	0.018	0.017	0.018	0.038	0.019	0.014	0.021	0.035	0
C5	0.052	0.018	0	0.051	0.034	0.045	0.033	0.039	0.022	0.014	0.088	0.035	0
C6	0.056	0.035	0	0.032	0.08	0.047	0.082	0.051	0.07	0.081	0.208	0.107	0
C8	16.035	10.427	0	25.298	19.509	14.808	15.991	5.043	10.926	33.064	28.458	29.702	0
C12	0.571	0.503	0	0.802	1.161	1.138	0.513	0.228	0.317	5.485	1.471	7.611	0
C13	1.12	0.903	0	1.607	1.869	2.299	0.803	0.315	0.709	5.902	1.741	8.752	0
C14	0.877	0.819	0	1.132	1.609	3.468	0.751	0.375	0.636	4.806	2.316	7.414	0
indels (%)	0.076858	0.17892		0.048785	0.13947	11.5608	0.14868	0.1177	0.076621	0.23744	9.8678	0.50485	
C1	0.03697156	0.02695169	0	0.03498293	0.04094282	0.27858348	0.03894201	0.03395998	0.03397395	0.02793352	0.11266525	0.07362641	0
C4	0.01398924	0.01597137	0	0.00699659	0.0179749	0.01503466	0.01797324	0.03795527	0.01898544	0.01396676	0.01892776	0.0348233	0
C5	0.05196003	0.01796779	0	0.05097512	0.03395258	0.03979764	0.03295094	0.0389541	0.02198314	0.01396676	0.07931634	0.0348233	0
C6	0.05595696	0.03493738	0	0.03198439	0.07988842	0.04156642	0.08187808	0.05093997	0.06994637	0.08080767	0.18747498	0.10645981	0
C8	16.0226758	10.408344	0	25.2856584	19.4817908	13.0960767	15.9672246	5.03706439	10.9176284	32.9854928	25.6498215	29.5520495	0
C12	0.57056114	0.50210003	0	0.80160874	1.15938075	1.0064381	0.51223727	0.22773164	0.31675711	5.47197642	1.32584466	7.57257587	0
C13	1.11913919	0.90138435	0	1.60621603	1.86639331	2.03321721	0.8018061	0.31462925	0.70845676	5.88798629	1.5692016	8.70781553	0
C14	0.87632596	0.81753465	0	1.13144775	1.60675593	3.06707146	0.74988341	0.37455863	0.63551269	4.79458863	2.08746175	7.37657042	0

FIGURE 166