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Supplemental information

CABE-RY: A PAM-flexible dual-mutation base editor for reliable modeling of multi-nucleotide variants

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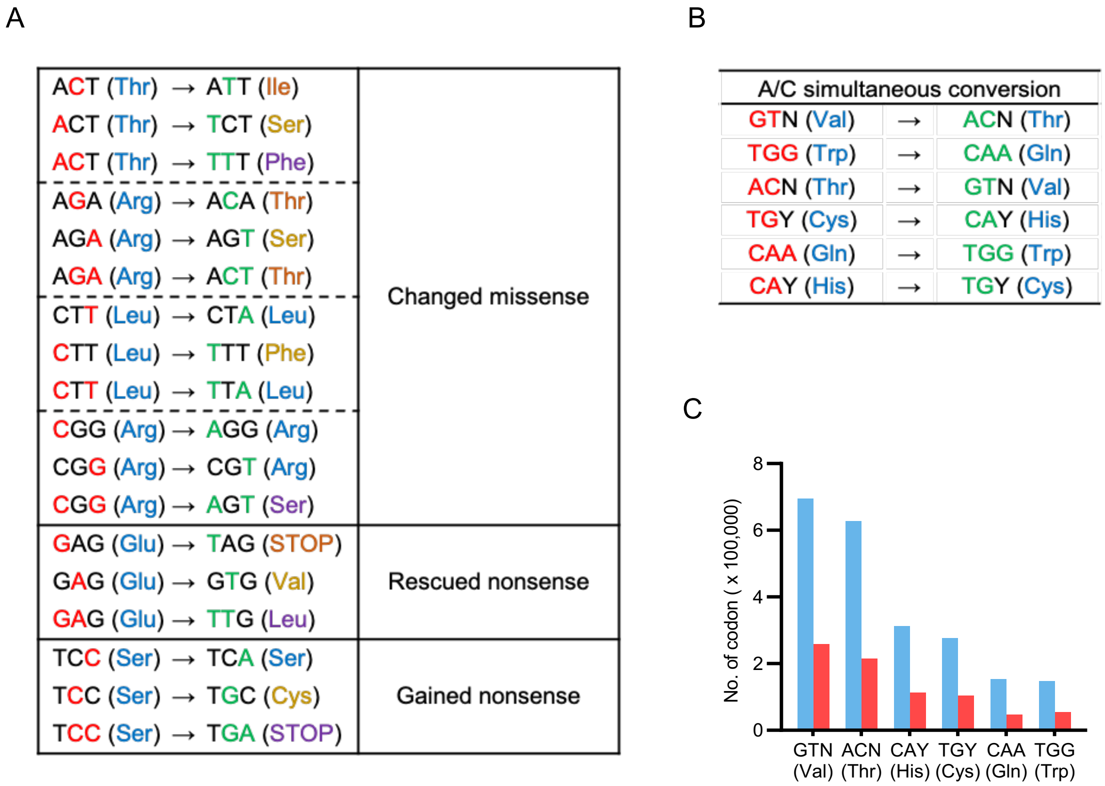


A

ACT (Thr) → ATT (Ile)	Changed missense
ACT (Thr) → TCT (Ser)	
ACT (Thr) → TTT (Phe)	
AGA (Arg) → ACA (Thr)	
AGA (Arg) → AGT (Ser)	
AGA (Arg) → ACT (Thr)	
CTT (Leu) → CTA (Leu)	
CTT (Leu) → TTT (Phe)	
CTT (Leu) → TTA (Leu)	
CGG (Arg) → AGG (Arg)	
CGG (Arg) → CGT (Arg)	
CGG (Arg) → AGT (Ser)	
GAG (Glu) → TAG (STOP)	Rescued nonsense
GAG (Glu) → GTG (Val)	
GAG (Glu) → TTG (Leu)	
TCC (Ser) → TCA (Ser)	Gained nonsense
TCC (Ser) → TGC (Cys)	
TCC (Ser) → TGA (STOP)	

B

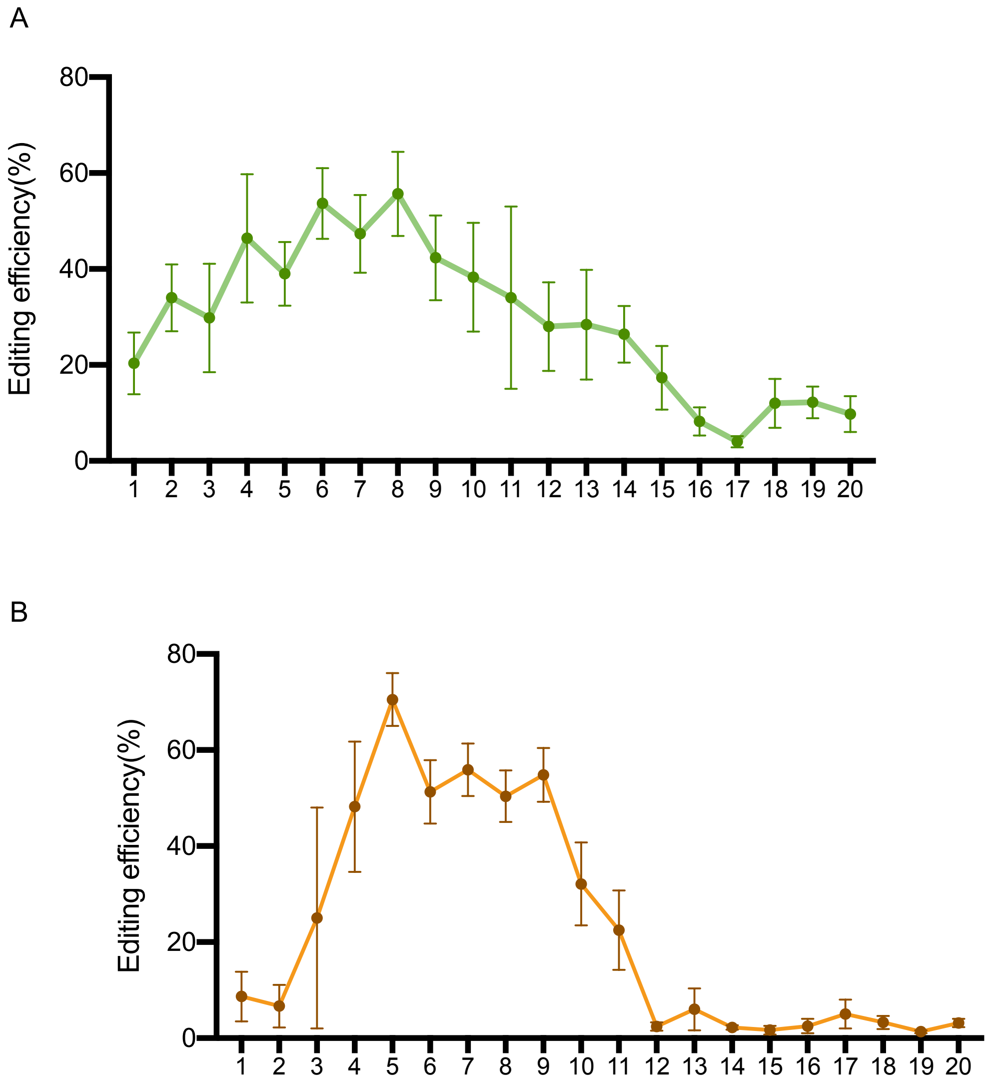
A/C simultaneous conversion		
GTN (Val)	→	ACN (Thr)
TGG (Trp)	→	CAA (Gln)
ACN (Thr)	→	GTN (Val)
TGY (Cys)	→	CAY (His)
CAA (Gln)	→	TGG (Trp)
CAY (His)	→	TGY (Cys)

Supplemental Figure 1. Further analysis of MNVs.

(A) Examples of the differences in functional impacts on the protein between MNVs and individual SNVs.

(B) Six amino acid changes can be achieved uniquely by simultaneous A/C conversion.

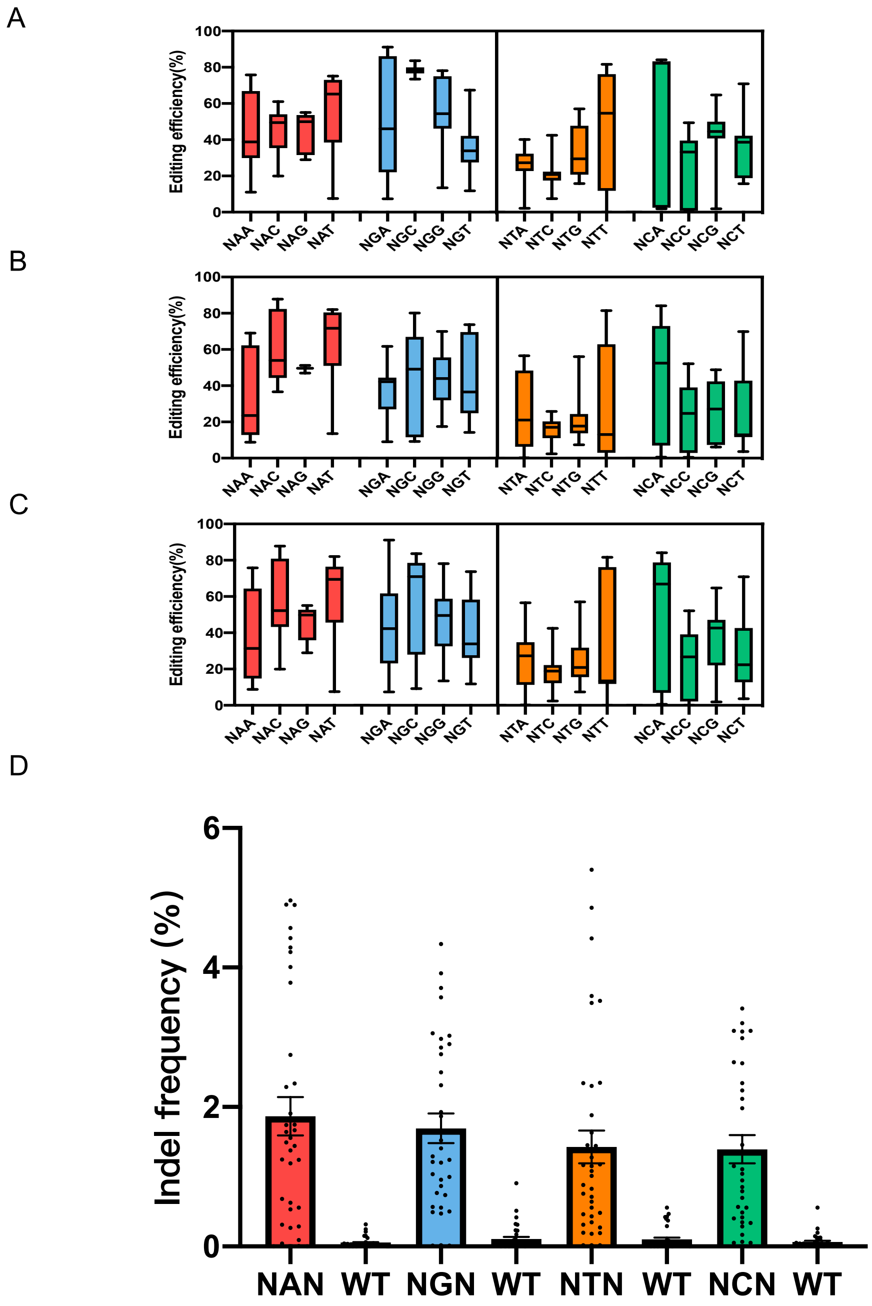
(C) The PAM-flexible dual-mutation base editor can target more specific codons in the human genome than existing editors.



Supplemental Figure 2. Mean nuclease activity plots for a single base editor across NNN PAMs in human cells.

(A) Mean nuclease activity plots for ABE8e(V106W)-RY across NNN PAMs in human cells. The error bars represent the standard error of the mean (SEM) values.

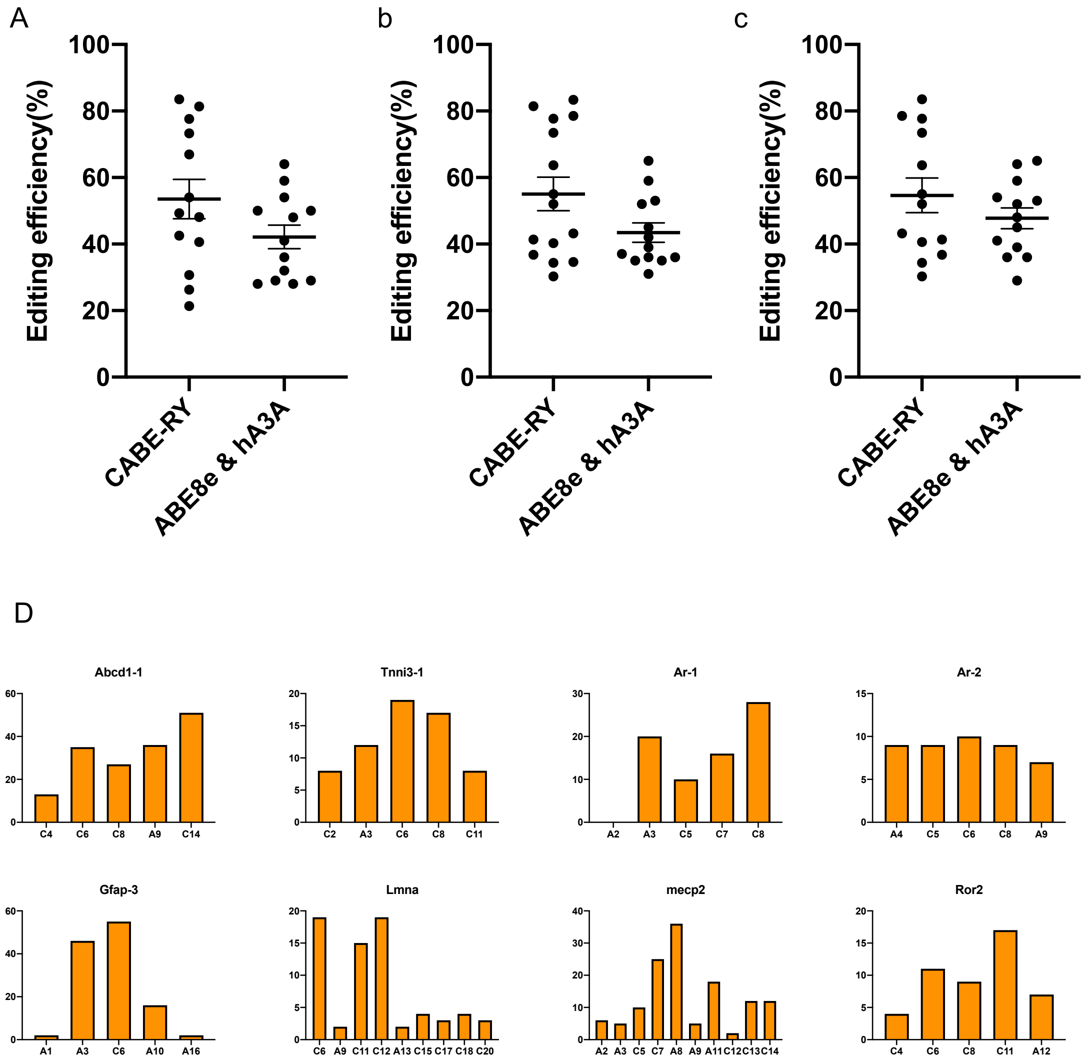
(B) Mean nuclease activity plots for A3A(Y130F)-RY across NNN PAMs in human cells. The error bars represent the standard error of the mean (SEM) values.



Supplemental Figure 3. Other characteristics of CABE-RY at 48 endogenous target sites.

(A, B, C) Aggregate distribution of C-to-T edits (A), A-to-G edits (B) and overall edits (C) across the editing window with CABE-RY.

(D) Box plots indicating the average indel frequencies. The error bars represent the standard error of the mean (SEM) values.



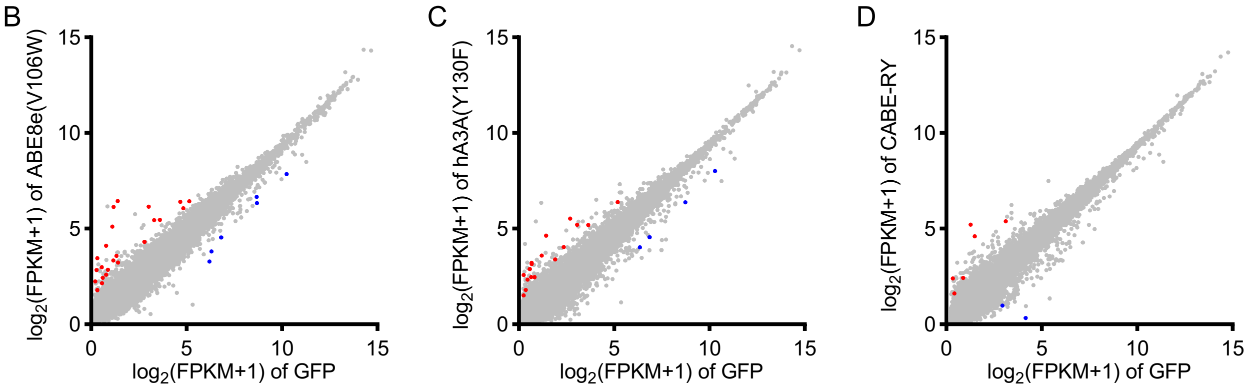
Supplemental Figure 4. Further analysis of CABE-RY.

(A, B, C) Comparison of simultaneous A/C conversion between CABE-RY and coexpressed ABE8e(V106W)-RY and hA3A(Y130F)-RY in HEK 293T cells. The scatter plot shows the efficiency of C-to-T (A), A-to-G (B) and overall edits (C) across the editing window with CABE-RY.

(D) Editing efficiency of CABE-RY in the N2a cell line.

A

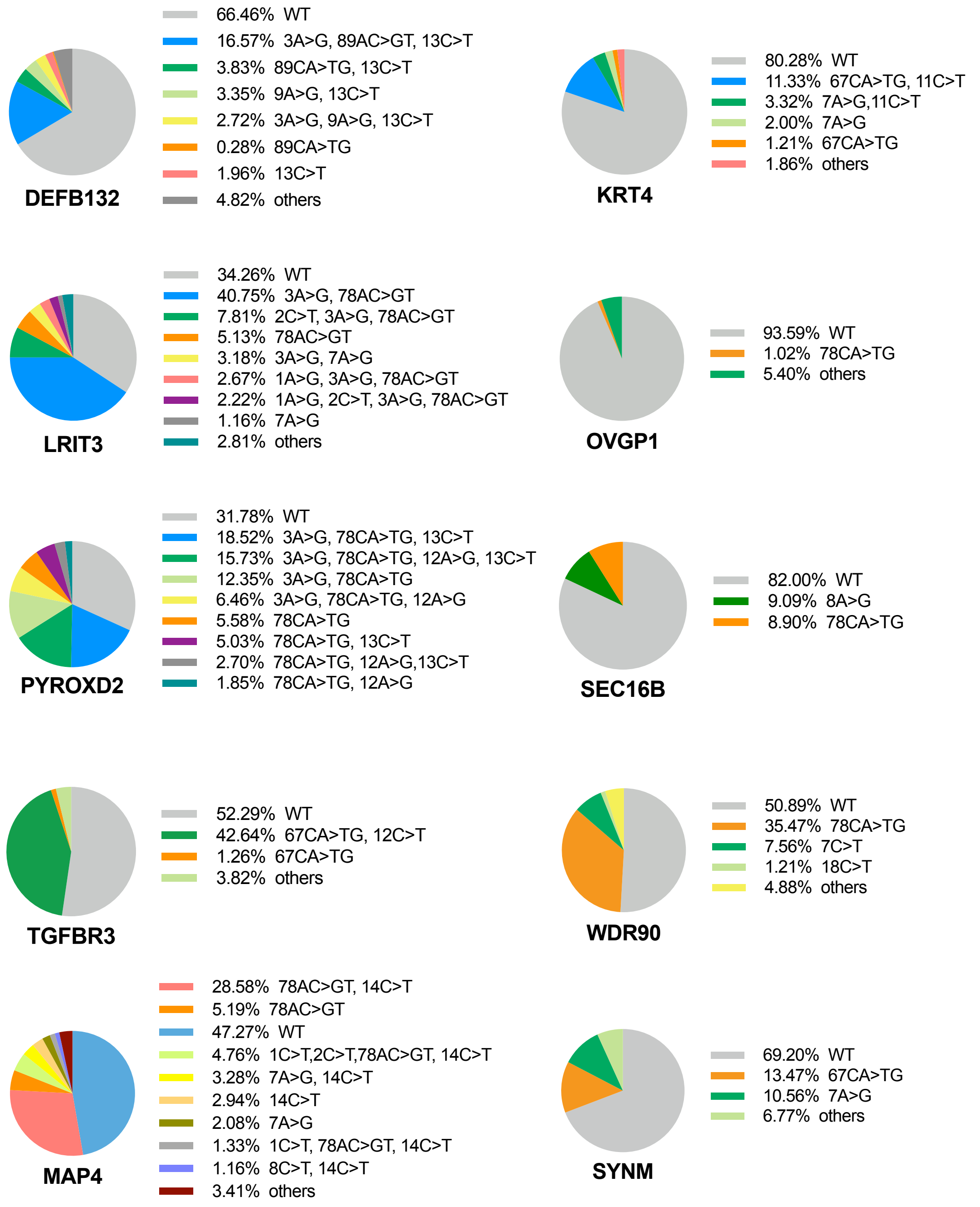
Sample	Raw reads	Mapped reads	Off-target edits (totals)	Off-target edits (A-to-I)	Off-target edits (C-to-U)
GFP-1	24,043,676	21,021,190	428	325	16
GFP-2	22,677,528	20,233,880	618	475	19
ABE8e(V106W)-1	21,999,661	17,071,710	8,462	8,350	21
ABE8e(V106W)-2	19,862,432	15,371,901	9,765	9,633	21
hA3A(Y130F)-1	20,294,961	15,491,241	508	331	72
hA3A(Y130F)-2	20,592,803	15,613,140	506	313	116
CABE-RY-1	21,168,535	17,376,848	2,944	2,853	17
CABE-RY-2	20,020,981	16,466,648	2,748	2,637	24



Supplemental Figure 5. Further description of the RNA-seq data for transcriptome-wide off-target analysis.

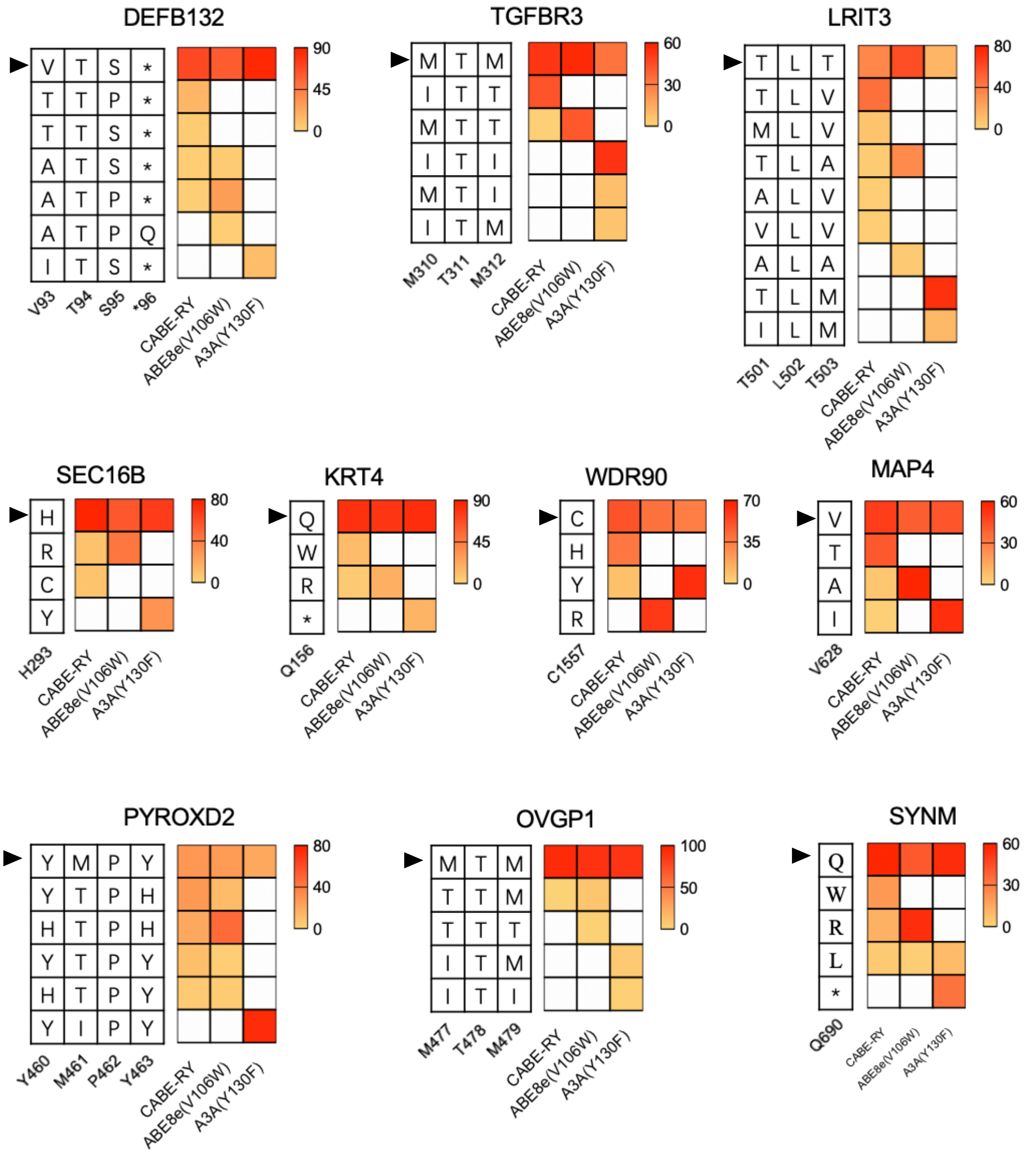
(A) Sequencing information and the number of off-target edits for each sample.

(B, C, D) Transcriptome-wide expression levels of ABE8e(V106W) (B), hA3A(Y130F) (C) and CABE-RY (D) compared to GFP (control). Shown is the mean of two biological replicates. The upregulated genes are labeled in red, and the downregulated genes are labeled in blue.



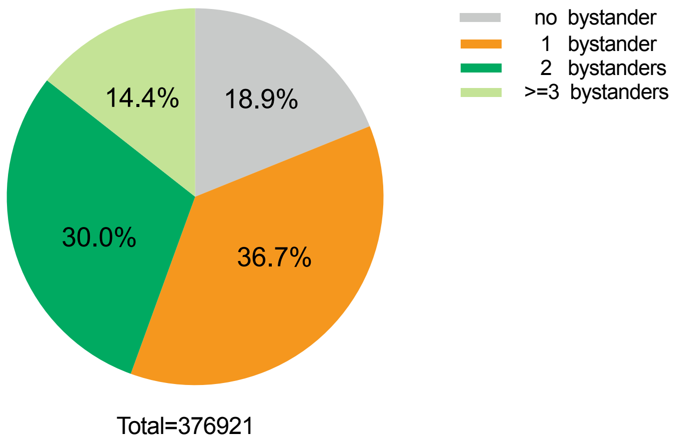
Supplemental Figure 6. Mutation types of simulated MNVs.

The pie chart shows the proportions of mutation types at the ten sites. Only alleles with at least 1% abundance are included. The proportion of perfect MNV is indicated with orange.



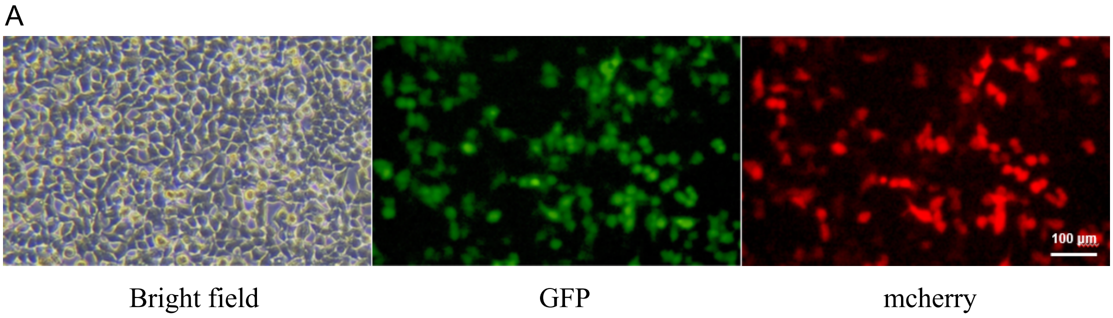
Supplemental Figure 7. Amino acid changes in MNV models.

The amino acid edits are summarized in the map on the left; the mean frequencies of amino acid edits are shown in the heatmap. The wild-type (unedited) allele is indicated with a black triangle. Only alleles with at least 1% abundance are included in the heatmap.



Supplemental Figure 8. Bystander effect in gnomAD.

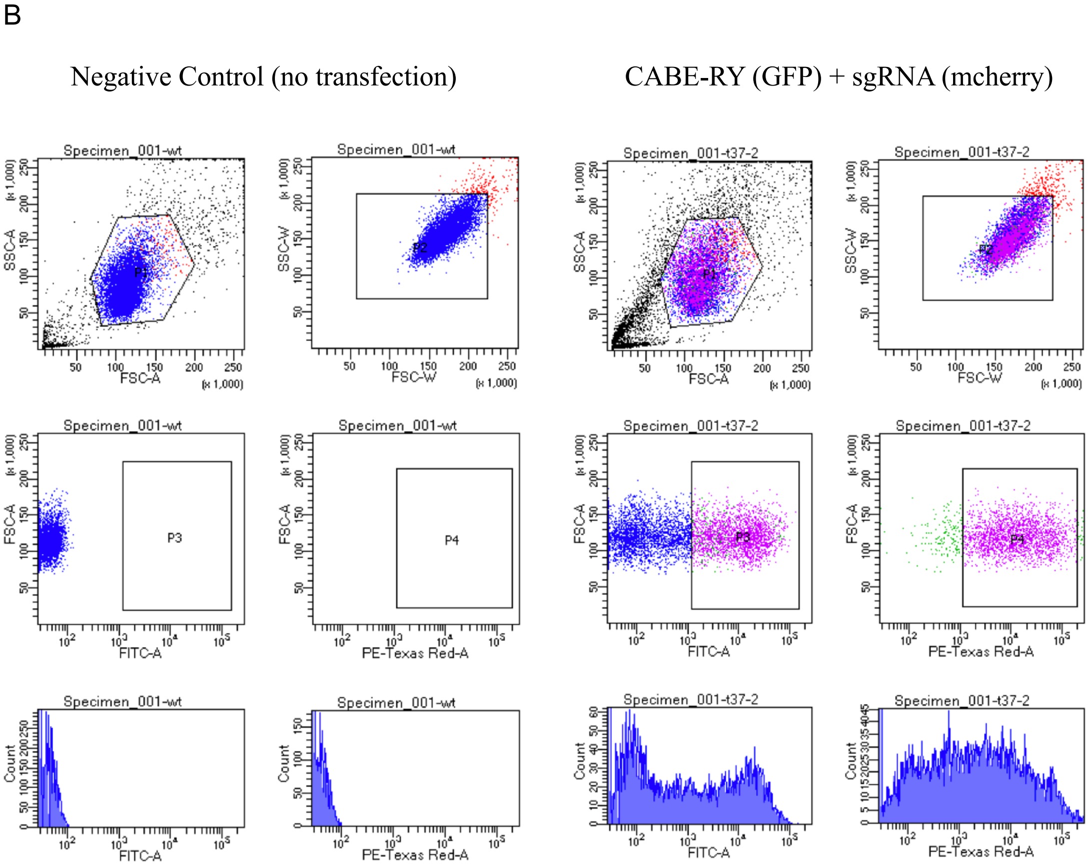
The pie chart shows the proportions of bystanders obtained for modeling of two adjacent MNVs in gnomAD. The main editing window (5-10 for C-to-T, 3-8 for A-to-G) was used for analysis.



Bright field

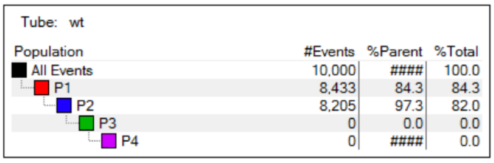
GFP

mcherry



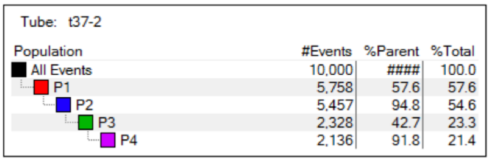
Negative Control (no transfection)

CABE-RY (GFP) + sgRNA (mcherry)



Tube: wt

Population	#Events	%Parent	%Total
■ All Events	10,000	####	100.0
🟥 P1	8,433	84.3	84.3
🟦 P2	8,205	97.3	82.0
🟩 P3	0	0.0	0.0
🟪 P4	0	####	0.0



Tube: t37-2

Population	#Events	%Parent	%Total
■ All Events	10,000	####	100.0
🟥 P1	5,758	57.6	57.6
🟦 P2	5,457	94.8	54.6
🟩 P3	2,328	42.7	23.3
🟪 P4	2,136	91.8	21.4

Supplemental Figure 9. Profiles for transfection and FACS analysis.

(A) Images of transfected HEK293T cells with fluorescence markers.

(B) FACS gating profiles for GFP- and mCherry-positive HEK293T cells.

Supplementary Sequences 1. DNA sequences used this study for cell transfection. Within base editor sequences, BPNLS sequences are highlighted in cyan, A3A(Y130F) sequences are in pink, TadA8e sequences are in yellow, linkers are in blue, SpRY are in red, UGIs are in tan, P2A sequences are in grey, EGFP sequences are in green and BSD sequences are in purple.

CABE-RY

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Supplemental Table 1. sgRNA sequences.

Number	Site	Protospacer sequence
1	NGG SITE 1	GAACACAAAGCATAGACTGC
2	NTT SITE 1	ACATCATCAGATATTCTGCA
3	NTC SITE 1	GCTGCAAACAAGTGCAGAAT
4	NTG SITE 1	TGGCAGGACGTCTGCCCAAT
5	NAC SITE 1	ACCAACAATAGAGGCCCATT
6	NAG SITE 1	GTTTACATAAAAGATCTTCA
7	NGT SITE 1	AATACAAATAGTTAAGAACA
8	NGC SITE 1	CTGGAACACAAAGCATAGAC
9	NCT SITE 1	TCCTAAACCAGTGTCAGGGA
10	NCC SITE 1	AAAGATCTTCACAGGCTACC
11	NCG SITE 1	CCAACAATAGAGGCCCATTA
12	NAT SITE 1	CTGTCAAACTGTGCGTATGA
13	NAA SITE 1	TACCAACAATAGAGGCCCAT
14	NCA SITE 1	CTGCAGCCCAAGCCTCAGTG
15	NGA SITE 1	AGGTCCTAAACCAGTGTCAG
16	NTA SITE 1	CTACCAACAATAGAGGCCCA
17	NTT SITE 2	GACAGTTCCTTCCAATTCCA
18	NTC SITE 2	AACAACAGTACTTGCGACAG
19	NTG SITE 2	GCAGCAGCCTGGAAAAGTAC
20	NGT SITE 2	TTGGAACTCCTGCTTGCAAG
21	NGC SITE 2	AAGGCCAAGCTTGCCTGCCC
22	NCC SITE 2	GAGATGCAGCGAATGTGAAA
23	NCT SITE 2	TCATCTTAGGCCTTCAAGGA
24	NGG SITE 2	CCTGCCCTGCATTTTATCAA
25	NCG SITE 2	GAGCAGGGAAGAAGGAATCA
26	NAT SITE 2	TACTTGCGACAGTTCCTTCC
27	NAC SITE 2	CATTTCCCTCTACGCTCGCT
28	NAG SITE 2	TTGAACAACAGTACTTGCGA
29	NAA SITE 2	CCTGCTTGCAAGTGTCAACC
30	NCA SITE 2	GATGCAGCGAATGTGAAATC
31	NGA SITE 2	GAAAAGTACTTGGGGACCAA
32	NTA SITE 2	CCTCTTCTGGAAAGGGGTAC
33	NTT SITE 3	CTTAGGGGGCACTTCGACCA
34	NTC SITE 3	TCCACCCGCTGTGCGTCCCA
35	NTG SITE 3	TGGCCGAATGCAAAGGTTCT
36	NGT SITE 3	TCGGCCAATGGGGCACAAGG
37	NGC SITE 3	CCCAAAAGTGGGGCGTACA
38	NCC SITE 3	GAGTTCCACCCGCTGTGCGT
39	NCT SITE 3	TGGACTCAGATGCTCCAACG
40	NGG SITE 3	GGTTACACCAAAGGGCTAGA

41	NCG SITE 3	ATGCAAAGGTTCTCTGCTAG
42	NAT SITE 3	GTAACCTCCCTTGAAAGGGG
43	NAC SITE 3	GGAGCATCTGAGTCCAGGGG
44	NAG SITE 3	ACAGCGGGTGGAACTCCCAA
45	NAA SITE 3	CTGCTAGACGACAGCGCAGG
46	NCA SITE 3	TGCGTCCCACTCCTTGTGCC
47	NGA SITE 3	GAATGCAAAGGTTCTCTGCT
48	NTA SITE 3	CCGAATGCAAAGGTTCTCTG
49	DEFB132	ATTATGATGTTACGGTCGTT
50	KRT4	AGGTGCAGTTCTTAGAGCAA
51	LRIT3	ACATTGACGTGGAATATGAT
52	OVGP1	CATGGTCATTGCCCCAGTGA
53	PYROXD2	ATAGGGCATGTACTGAGTGA
54	SEC16B	TGGTGCATGTAGGTCCCAGC
55	TGFBR3	TTGGTCATTGTCATAGATCT
56	WDR90	CCTGTGCAGGGGTGGCTCAC
57	MAP4	CCTGTGACGGTTTCTAAAGG
58	SYNM	AGGGGCAGGGTGGGCCGGGG

Supplemental Table 2. pegRNA sequences.

pegRNA	**spacer sequence**	**3 ‘extension sequence**	**PBS length(nt)**	**RT template length(nt)**
DEFB132	CAGTGGTTATTATGATGTTA	ACAAACGACCACAACATCATAATAA	13	12
KRT4	GCTGGTGCCTTTATCAACAC	CTCTAAGAACCACACCTGTGTTGAT	13	12
LRIT3	AAGAGAGTGTGACATTGACG	CATATTCCACACCAATGTCACACTC	13	12
OVGP1	AGAGAAGACTGAGATCACTG	AAGTCATGGTTGTTGCCCCAGTGAT	13	12
PYROXD2	TTGCCTCCAGCCAGCGTATA	ACTCAGTACACACCCTATACGCTGG	13	12
SEC16B	TTTCGGGCCAGGAGGTCAGC	GGGACCTACACACACCAGCTGACCT	13	12
TGFBR3	AATGTCATCTCTTATTGATT	TCTATGACAACAACCAAATCAATAA	13	12
WDR90	ACGGAAGGTTGTCCCTGTGC	GAGCCACCCCCACACAGGGACAACC	13	12
MAP4	CTTTTTCCCCGTTCCTGTGA	TTTAGAAACCACCACAGGAACGGGG	13	12
SYNM	TGTCCGCCCTCACCAGAGAG	CGGCCCACCCCACCCCTCTCTGGTG	13	12
nicking sgRNA	**spacer sequence**			
DEFB132	AACCACTGGCAATCAAGGAG			
KRT4	TGGTCGTCTGCTGCTGGAGC			
LRIT3	CAGGTCCTTCCCACCATACT			
OVGP1	AGGGATACAGTTTCCTTTGT			
PYROXD2	TTCCTCGCTGGACCCCACCC			
SEC16B	CATGCTGTGCAGTTCAACAA			
TGFBR3	GAATCTGGTGAAGTGGGCTT			
WDR90	CCAGGTCAGACTGTCCTCTC			
MAP4	GATTCTGTGTTAGAAAAACT			
SYNM	CGGAACTGCCACCAGCACCC			

Supplemental Table 3. Primer sequences.

Site	Forward sequence (5'-3')	Reverse sequence (5'-3')
NGG SITE 1	ATAACAAGACCTGGCTGAGC	TCAAGCAGGTGATTACAGGA
NTT SITE 1	CAGCATGTGGTAATTTTCCA	CACATGACAGTTAAGGTTTG
NTC SITE 1	CAAGACCTGGCTGAGCTAAC	TTTAGTCTTTCAAGCAGGTG
NTG SITE 1	AGGCTACCCCCTAAGTCTAG	GTTTCCTTTACAGGGCCAGC
NAC SITE 1	GATCTTCACAGGCTACCCCC	CCACATGCTGTCACAGTTAG
NAG SITE 1	GCAGTGTTTAGAAGGAGACT	GTTGGTAGAATGGCAGTGCA
NGT SITE 1	GGCCCTGTAAAGGAAACTGG	TGTTTAGTCTTTCAAGCAGG
NGC SITE 1	ATGATAACAAGACCTGGCTG	TCTTTCAAGCAGGTGATTAC
NCT SITE 1	AGAAGGAGACTTGTGCACAT	ATTGTTGGTAGAATGGCAGT
NCC SITE 1	GTTTAGAAGGAGACTTGTGC	GGTAGAATGGCAGTGCAATA
NCG SITE 1	AAAGATCTTCACAGGCTACC	CCAGCGGGCTGGAAAATTAC
NAT SITE 1	ATGTGGTAATTTTCCAGCCC	CAAGCACATGACAGTTAAGG
NAA SITE 1	CTTCACAGGCTACCCCCTAAG	GAAAATTACCACATGCTGTC
NCA SITE 1	CCTAAACCAGTGTCAGGGAG	TGCTTTGTGTTCCAGTTTCC
NGA SITE 1	GGAGACTTGTGCACATTCTA	TCTATTGTTGGTAGAATGGC
NTA SITE 1	CACAGGCTACCCCCTAAGTC	GGCTGGAAAATTACCACATG
NTT SITE 2	GTGGAACATGGTGAGTGCTT	TAGCAGAGGAATCAGGCAAG
NTC SITE 2	ACACTGCAATGTTTTTGTGG	AGGCAAGAAATAAGCAACTC
NTG SITE 2	GTGGAGATGCAGCGAATGTG	GAAAAGCACTCACCATGTTC
NGT SITE 2	GAGGAGTAGCCAAAGACCAT	TCCATAACAAAAGGAAGCAC
NGC SITE 2	TGAACCCTCTTCTGGAAAGG	CTGTTGTTCAAAGTTCCTTG
NCC SITE 2	GTGCTTCCTTTTGTTATGGA	GATTCCTTCTTCCCTGCTCC
NCT SITE 2	ATGGGGGTCCACACTGCAAT	CCGAAGTCACGAAGTAACTT
NGG SITE 2	CTCTTCTGGAAAGGGGTACC	GTCGCAAGTACTGTTGTTCA
NCG SITE 2	CTGGAAAGGGGTACCTATTA	TTGGAAGGAACTGTCGCAAG
NAT SITE 2	TGTTTTTGTGGAACATGGTG	GAATCAGGCAAGAAATAAGC
NAC SITE 2	GACTTGTGGAGATGCAGCGA	CACTCACCATGTTCCACAAA
NAG SITE 2	GGTCCACACTGCAATGTTTT	ATAAAGCCGAAGTCACGAAG
NAA SITE 2	GAGTAGCCAAAGACCATCAG	CTTCCATAACAAAAGGAAGC
NCA SITE 2	GCTTCCTTTTGTTATGGAAG	GATGATTCCTTCTTCCCTGC
NTA SITE 2	CTTGTGGAGATGCAGCGAAT	AAGCACTCACCATGTTCCAC
NGA SITE 2	AGATCTTGAACCCTCTTCTG	GTTCAAAGTTCCTTGAAGGC
NTT SITE 3	AGGAAGCAGTATCCGAAGGC	CCAATGGGGCACAAGGAGTG
NAC SITE 3	CAGTATCCGAAGGCAGCAGC	CATTCGGCCAATGGGGCACA
NGC SITE 3	ACAATTACTTAGGGGGCACT	ACTCAGCAGTATCTTCAGTG
NAG SITE 3	TACTTAGGGGGCACTTCGAC	AAGGGGAATACTCAGCAGTA

NGT SITE 3	GGCACTTCGACCATTTCTGA	TATCTTCAGTGCTCTTGCCT
NCT SITE 3	GACAACGCCAAGGAGTTGTG	AGCCCTTTGGTGTAACCTCC
NCC SITE 3	CGCCAAGGAGTTGTGTAAGG	TCTCGCCTTCTAGCCCTTTG
NTC SITE 3	GGAGTTGTGTAAGGCAGTGT	CCTAGGCTCTCGCCTTCTAG
NCA SITE 3	ACCATTTCTGACAACGCCAA	TTTGGTGTAACCTCCCTTGA
NTA SITE 3	CGTTGGAGCATCTGAGTCCA	GACGGCAGTTCAAGTGTCCC
NTG SITE 3	TGGAGCATCTGAGTCCAGGG	GGTAGACGGCAGTTCAAGTG
NAA SITE 3	GAGCATCTGAGTCCAGGGGA	GACAGGGTAGACGGCAGTTC
NCG SITE 3	GAACAGCTTCGGGGGGATTG	CTTGTAGAGAGACAGGGTAG
NGA SITE 3	GGGATTGCATGTACGCCCCA	CCAGTGCTCCGGACTTGTAG
NGG SITE 3	GTACGCCCCACTTTTGGGAG	GTCCAGTGCTCCGGACTTGT
NAT SITE 3	CACTCCTTGTGCCCCATTGG	GTTGTAGTAGTCGCGACTCT
DEFB132	GGGAGACAGCATTGTTCATG	TAAAGAGGAGCCTTGGCTAG
KRT4	GTTCTTGGGCCGTGTAGTTC	CCAAGGTATCTAGCTGCTTC
LRIT3	AGTAAGCTTCCTCCAGCCAG	GGGTTCCAAGCCATCTATGG
OVGP1	TGAGATCCACGGAAAGTGTG	AGGGGTCACAGACTGATAAC
PYROXD2	GTCCCAAGTCATCTCGGATG	CGTGCAGCTGTCTTTACCTC
SEC16B	GGGCAGAAATACATCTGTGG	TCCAGGGACACTGGGTCTTC
TGFBR3	TCATCGTTCTTAGCCCAAGG	AAGCCCACTTCACCAGATTC
WDR90	TGTTGCCTTCTCCACCGATG	GGGCTGCTTTACCTCTTTGC
MAP4	GCCCCTTGTAGGAGAACTCC	CCTAACTTACCTGAGGTCTC
SYNM	TGAAGGGCATCTCCTCCAAG	TCTTTGCTCAGCTCCTCCAG