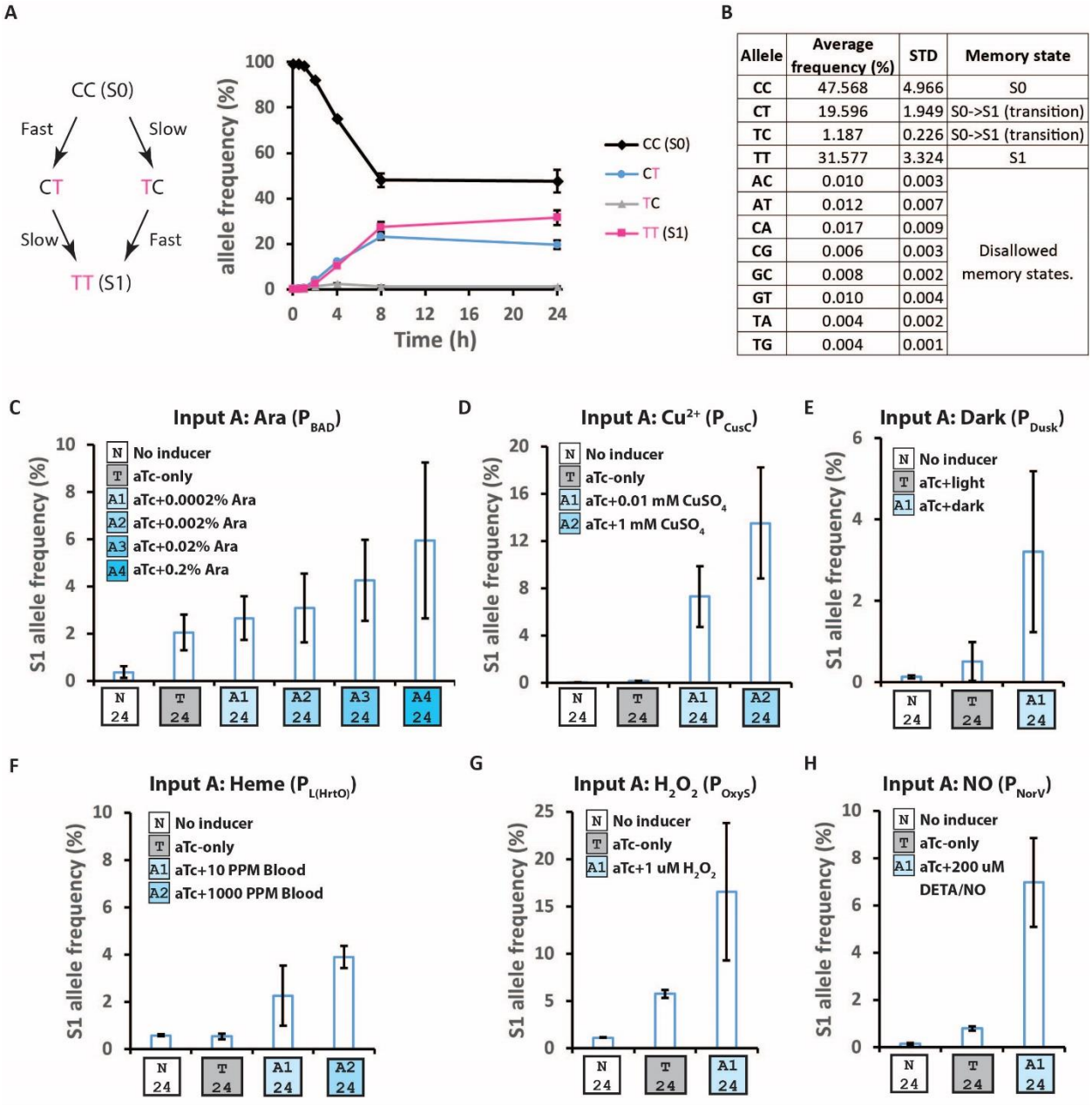
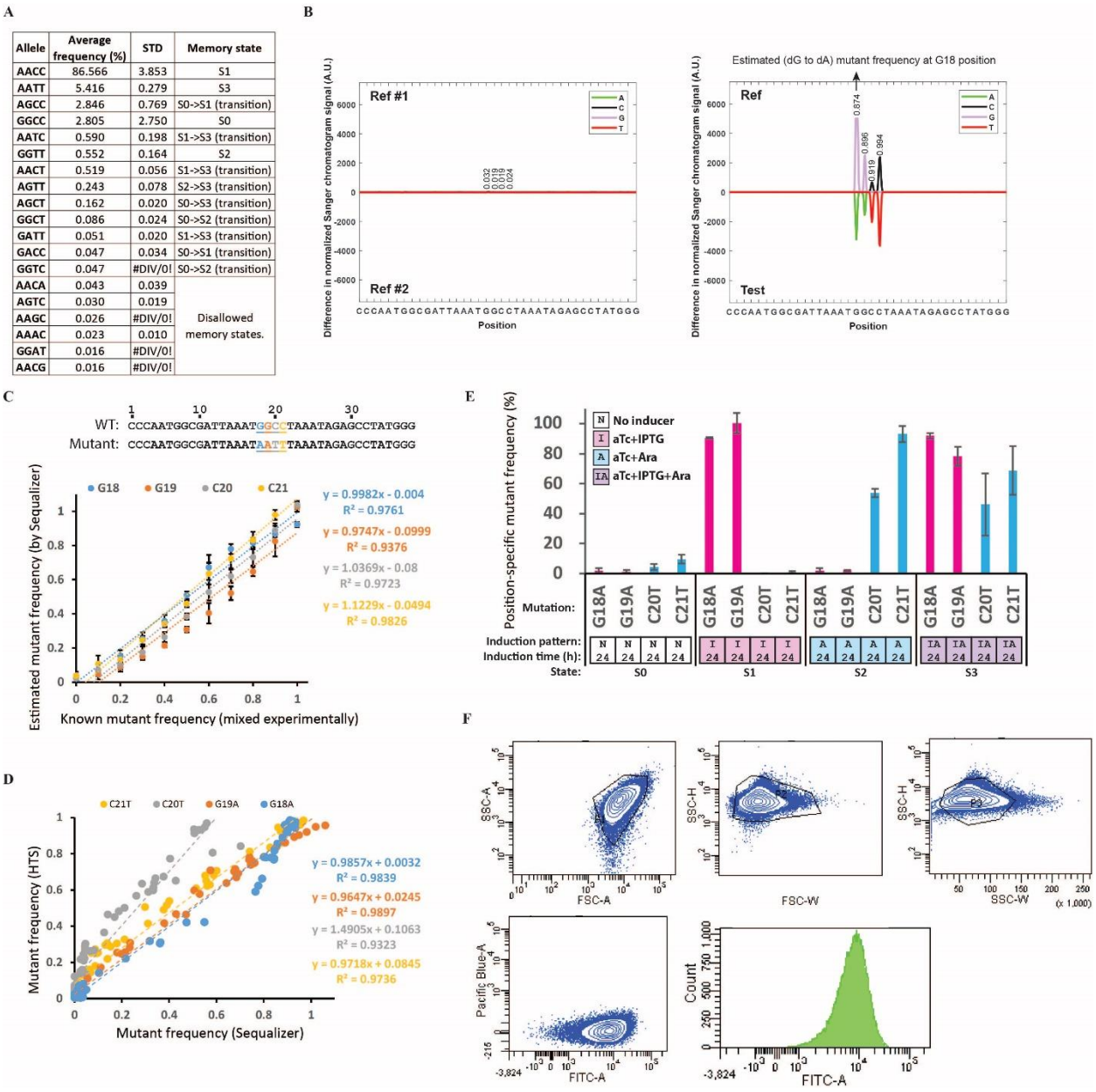


Allele	Average frequency (%)	STD	Memory state
CC	47.568	4.966	S0
CT	19.596	1.949	S0->S1 (transition)
TC	1.187	0.226	S0->S1 (transition)
TT	31.577	3.324	S1
AC	0.010	0.003	Disallowed memory states.
AT	0.012	0.007	
CA	0.017	0.009	
CG	0.006	0.003	
GC	0.008	0.002	
GT	0.010	0.004	
TA	0.004	0.002	
TG	0.004	0.001	

Figure S1. Related to Figure 1 | Dynamics of molecular recording and recording biologically relevant information by DOMINO operators. A) Dynamics of S0 (CC), S1 (TT), and the transient intermediate states (CT, and TC) for the experiment shown in Figure 1E. Different positions along the target site are mutated with different dynamics, with one of the positions being edited significantly faster than the other. **B)** The mutational profile for the last time point of the experiment shown in Figure S1A. Disallowed memory states correspond to mutations that are not expected to be generated as a result of precise base editing. The levels of these mutations are

comparable with the error rate of Illumina sequencing, suggesting that they likely originated from sequencing artifacts (i.e., errors during library preparation by PCR or sequencing). **C)** Recording various biological signal in *E. coli* by replacing the input promoter in the DOMINO operator with different signal-responsive promoters. The name of each inducer and its corresponding promoter sensor are indicated in the title of each plot. Error bars indicate standard deviation for three biological replicates.



Allele	Average frequency (%)	STD	Memory state
AACC	86.566	3.853	S1
AATT	5.416	0.279	S3
AGCC	2.846	0.769	S0->S1 (transition)
GGCC	2.805	2.750	S0
AATC	0.590	0.198	S1->S3 (transition)
GGTT	0.552	0.164	S2
AACT	0.519	0.056	S1->S3 (transition)
AGTT	0.243	0.078	S2->S3 (transition)
AGCT	0.162	0.020	S0->S3 (transition)
GGCT	0.086	0.024	S0->S2 (transition)
GATT	0.051	0.020	S1->S3 (transition)
GACC	0.047	0.034	S0->S1 (transition)
GGTC	0.047	#DIV/0!	S0->S2 (transition)
AACA	0.043	0.039	Disallowed memory states.
AGTC	0.030	0.019	
AAGC	0.026	#DIV/0!	
AAAC	0.023	0.010	
GGAT	0.016	#DIV/0!	
AACG	0.016	#DIV/0!	

Figure S2. Related to Figure 2 | Observed memory states in order-independent DOMINO AND gate and using Sequalizer to estimate position-specific mutant frequencies from Sanger chromatograms. A) The mutational profile for an exemplary time point (72-hour IPTG induction) for the experiment shown in Figure 2B. Disallowed memory states correspond to mutations that are not expected to be produced as a result of precise base editing. The levels of these mutations are comparable with the error rate of Illumina sequencing, suggesting that they likely originated from sequencing artifacts (i.e., errors during library preparation by PCR or sequencing). The intermediate memory states can be used as transient states in shorter recording timescales or

discarded in longer timescales because, given enough time, they potentially could be converted to the final memory state. **B)** Sequalizer analysis comparing two instances of WT unmutated (i.e., Ref samples) sequences (left) and a WT unmutated (Ref) sequence vs. a Test sample containing a mixture of mutated and unmutated sequences (right). The y-axis shows differences between normalized Sanger chromatograms for the samples being compared (Ref #1 vs. Ref #2 or Ref vs. Test). Peaks in these plots indicate differences in the normalized chromatograms and thus mutations in the corresponding positions. For example, the peak marked by a black arrow in the bottom plot indicates mutations of dG at position 18 in the Ref to dA in the Test sample. The numbers above the target positions (i.e., positions 18-21) show the estimated mutant frequency in that position based on the Sequalizer algorithm, which takes into account the height of the Sanger chromatogram peaks in a given position to normalize the calculated difference values. The MATLAB script and additional description for Sequalizer is provided in Supplementary File 1.**C)** Standard curves obtained by analyzing samples containing known mutant ratios by Sequalizer. Two plasmids encoding the pure WT and mutant sequences (as indicated) were mixed at the following mutant:WT ratios: 0:10, 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1, and 10:0. The mixtures were Sanger-sequenced and the obtained chromatograms were analyzed by Sequalizer. The estimated mutant frequencies at the four target positions were plotted against the known (i.e., experimentally mixed) mutant ratios. Error bars indicate standard deviation for six independent replicates. **D)** Position-specific mutant allele frequencies for the last time point (96 h) of the experiment shown in Figure 2B estimated from Sanger sequencing analysis by Sequalizer (see Supplementary File 1). This data demonstrates the expected outcomes of AND gate behavior at the population level. The x-axis shows dC-to-dT or dG-to-dA mutations in the specified positions. For example, the G18A mutation means that there is a dG-to-dA mutation in position 18 of the target sequence. **E)** The position-specific mutant frequencies measured by Sequalizer vs. HTS at four target positions for samples from the experiment described in Figure 2B. **F)** The gating strategy used to analyze flow cytometry data in this study.

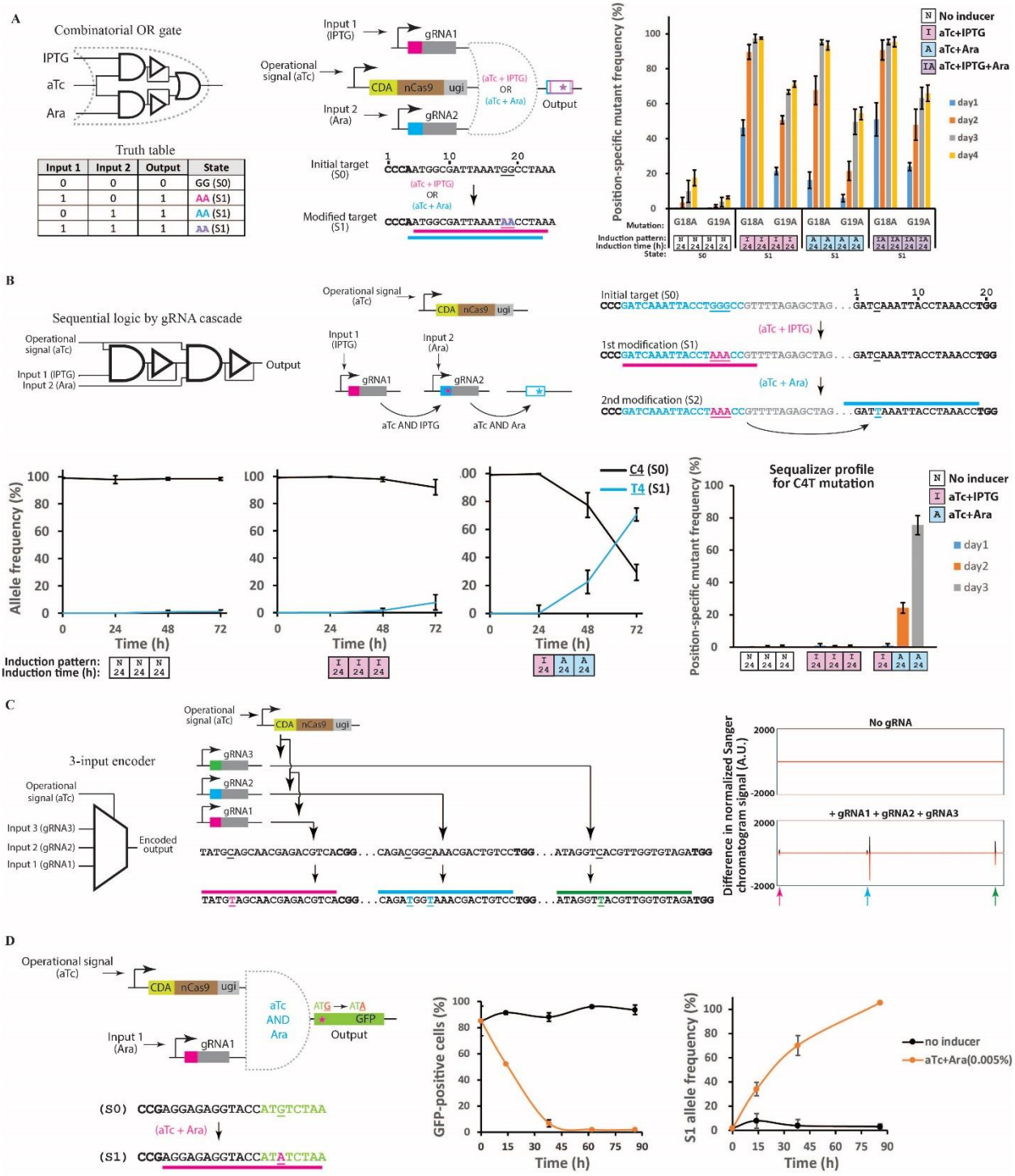


Figure S3. Related to Figures 2 and 3 | Examples of additional circuits built using DOMINO operators. A) Left: Schematic representation and truth table for a DOMINO OR gate. Right: Sequalizer results for the circuit shown in (A). *E. coli* cells were induced for four days using the indicated patterns, and position-specific mutant frequencies were assessed by Sequalizer analysis

of Sanger chromatograms. Error bars indicate standard deviation for three biological replicates. **B)** A sequential AND gate built by a cascade of gRNAs, in which the first (IPTG-inducible) gRNA edits and activates a downstream gRNA, which can then edit a downstream target. As demonstrated in this example, gRNA outputs of a DOMINO cascade can be independently regulated by using inducible promoters, such as an Ara-inducible promoter. This offers greater flexibility compared to using mutations as DOMINO outputs (e.g., designs shown in Figures 2 and 3). The dynamics of allele frequencies (i.e., memory states) were assessed by HTS (bottom-left panel), and the population-averaged C4T mutation frequency was assessed by Sequalizer (bottom-right panel). Error bars indicate standard deviation for three biological replicates. **C)** A multi-input encoder circuit, which converts the presence of three input gRNAs into *cis*-encoded mutations in the same DNA target locus (*lacZ* ORF in *E. coli* in this case). The circuit can be used to encode multiple transcriptional signals from various loci across a genome into DNA memory within a confined region. The multiplexed and *cis*-encoded signals can then be read and decoded by HTS or Sanger sequencing to reveal information about the original signals. The plots on the right show the Sequalizer output for cells containing no gRNA (top) and those containing three constitutively expressed input gRNAs (bottom). Mutations in gRNA target sites are reflected as peaks in the bottom Sequalizer plot. This circuit is an example of a DOMINO circuit with more than two inputs; we envision that circuits can be readily extended to accommodate additional inputs for *in vivo* memory applications and storing information (spatial, temporal, or artificial) across a genome. **D)** Regulation of gene expression by manipulating functional elements by DOMINO. Conditional conversion of a canonical, efficient initiation codon (ATG) to ATA (which is a non-efficient initiation codon) by an Ara-inducible DOMINO operator was used to down-regulate GFP expression in *E. coli*. Over time, in induced samples the number of GFP-positive cells decreased, and the frequency of mutants increased, whereas in non-induced samples these quantities changed minimally. For GFP measurements, samples were grown for six hours in LB with no inducers before flow cytometry to ensure removal of any repression (i.e., CRISPRi) effect enacted by bound CDA-nCas9-ugi. Error bars indicate standard deviation of three biological replicates.

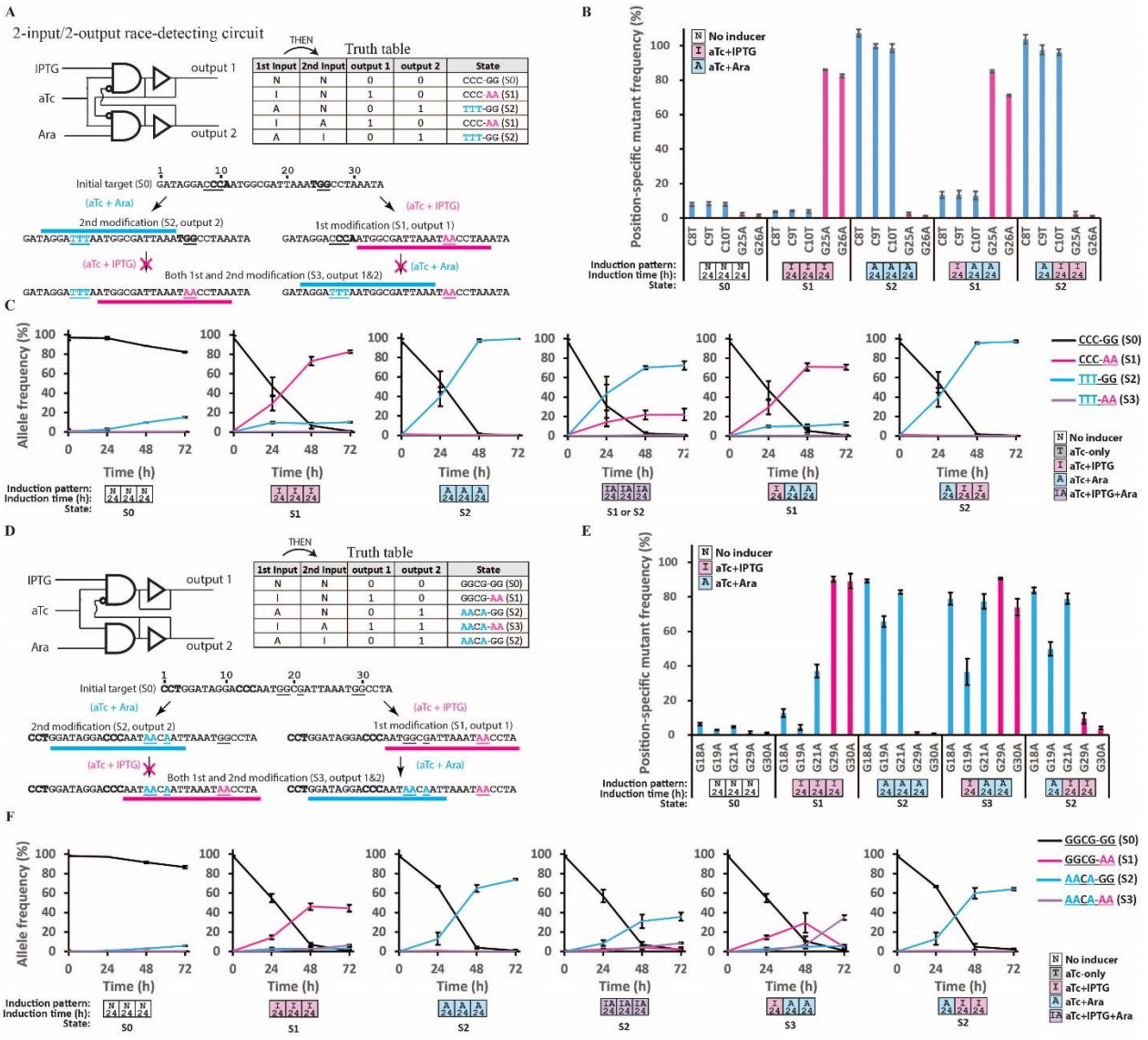


Figure S4. Related to Figure 3 | Additional examples of sequential DOMINO logic circuits. A) Two-input/Two-output race-detecting circuit. In this design, the PAM domain for each gRNA is placed within the WRITE window of the other, in such a way that editing mediated by one gRNA destroys the PAM domain for the other gRNA, thus preventing binding and subsequent editing by latter gRNA. Induction of cells harboring this circuit with IPTG results in the transition of the target register from the initial unmodified state (state S0) to the first modified state (state S1). Subsequent induction of these cells with the second inducer (Ara) leads to transition to the doubly mutated state (state S3). On the other hand, when cells are first induced with Ara, they are converted to an alternative singly modified state (state S2). However, subsequent induction of these cells with IPTG does not result in a transition. Thus, the final mutational signature generated

by this circuit is only determined by the first input, allowing one to infer the order of addition of the inputs from the mutational signatures generated. **B)** Sequalizer analysis of *E. coli* cells harboring the circuit shown in (A) that were induced with different patterns of the inputs as indicated, showing that the output of the circuit depends on the identity of the first inducer. Specifically, cells that were first induced with IPTG were converted to state S1, independent of addition of the second inducer (Ara) at a later stage. Those cells that were first induced with Ara were converted to state S2 independent of IPTG induction. **C)** Dynamics of allele frequencies (memory states) measured by HTS for cells harboring the sequential logic circuit shown in (A). In each subplot, the dominant allele in the last time point was used to determine the dominant memory state. The slight increase in the mutant frequency in the positions corresponding to targets of the Ara-inducible gRNA in cells that were induced with IPTG AND THEN Ara ([I][A][A] induction pattern in (B)) is likely due to leakiness of the Ara-inducible promoter during IPTG induction period (i.e., before ending the propagation delay of the first operator), which would lead to expression of the second gRNA and aberrant transition of a small subpopulation of cells to state S2. The HTS data (C) demonstrated that this was indeed the case, as doubly edited alleles (i.e., state S3, corresponding to editing events by both gRNAs) were extremely rare. Thus, because editing by one gRNA should destroy the PAM domain for the second gRNA, the race-detecting logic still holds within each single DNA molecule. **D)** Another example of sequential DOMINO logic, in which sequential induction of cells with IPTG AND THEN Ara results in the step-wise transition between two modified states (states S1 and S3, respectively). However, the induction of cells with the same inducers but in reverse order (Ara AND THEN IPTG) only results in a one-step transition to a different state (S2). In this circuit, which is an intermediate circuit between the sequential AND gate (Figure 3A) and the race-detecting circuit (Figure S4A), editing mediated by one gRNA destroys the binding site of the other gRNA, whereas editing mediated by the second gRNA does not interfere with the binding or editing of the first gRNA. **E)** Sequalizer analysis of *E. coli* cells harboring the circuit shown in (D) that were induced with different patterns of the inputs as indicated. **F)** Dynamics of allele frequencies (memory states) measured by HTS for cells harboring the sequential logic circuit shown in (D). Similar to the circuit shown in (A), the HTS data show that the circuit logic holds at the level of individual DNA molecules despite the leakiness of one of the promoters and apparent increase in unwanted memory states in Sequalizer results. Error bars indicate standard deviation for three biological replicates.

These examples demonstrate that sequential DOMINO logic circuits can be used to program and commit cells to defined states based on the order of inputs. In these scenarios, if conversion of the whole population to a final state is desired, one can perform each induction step for periods longer than the operator's propagation delay to allow the full conversion of cells to a given state before moving to the next induction step. Alternatively, the ratio between edited alleles in a population can be tuned by controlling the induction time of each of the inputs, while ensuring that the desired logic is applied at the level of each individual DNA molecule. This control over the degree of commitment of cells to different states could be useful for dividing biological tasks between distinct subpopulations in a community. For example, one subpopulation of cells could be edited to activate metabolic pathway 1 and the other subpopulation of cells could be edited to activate metabolic pathway 2. The relative ratio of activation could be tuned by using the abovementioned DOMINO circuit, thus controlling the degree of commitment of cell populations to different pathways.

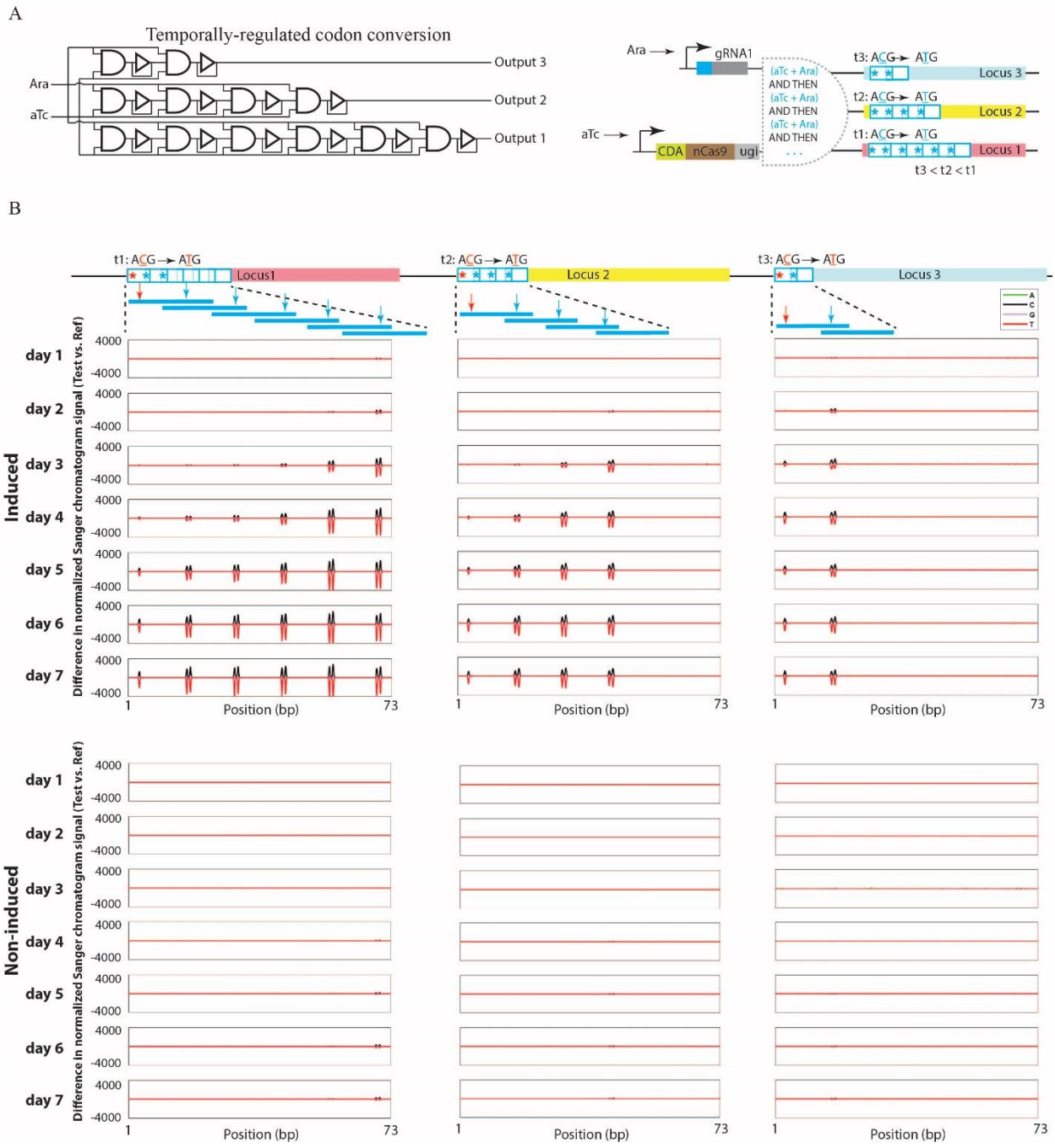


Figure S5. Related to Figure 4 | Using DOMINO delay elements to control the temporal order of ACG-to-ATG mutations in three different loci. A) Schematic representation of the time-dependent codon conversion experiment. Three loci with different numbers of delay elements (i.e., overlapping repeats) in their N-termini were placed in a synthetic operon. A gRNA was designed so that it could bind to the 3'-distal repeat element in each array. Sequential recruitment and editing of the repeat elements by this gRNA led to the progressive accumulation of mutations within the

repeat elements toward the 5'-end and eventual editing of the upstream ACG codons to ATG. In this circuit, because there were different numbers of delay elements in each array, the delay times differed; thus, temporal regulation is achieved. The time required for ACG-to-ATG conversion for locus 1 (t1) is expected to be longer than the time required for locus 2 (t2), which itself is expected to be longer than the time required for the conversion in locus 3 (t3). **B)** *E. coli* cells harboring the indicated circuit in (A) were induced and then mutation accumulation in the arrays was monitored by Sanger sequencing and Sequalizer over time. Upon induction of the circuit, time-dependent accumulation of mutations was observed in all three repeat arrays. The position corresponding to the start codon (shown by the red arrow) in the third locus, which possessed only two repeats in its N-terminus array, was the first that accumulated significant levels of mutations. This was followed by locus 2, which contained four delay elements and so experienced a longer delay compared to locus 3. Locus 1, possessing six repeats, was thus subject to the longest delay and was the last locus in which mutations in the position corresponding to the cryptic start codon accumulated. On the other hand, in non-induced cells, only low levels of mutations accumulated in the downstream repeat of each array and only at the later time points of the experiment, likely due to the background activity of the promoters. Nevertheless, no mutations were detected in positions corresponding to cryptic start codons in non-induced cells.

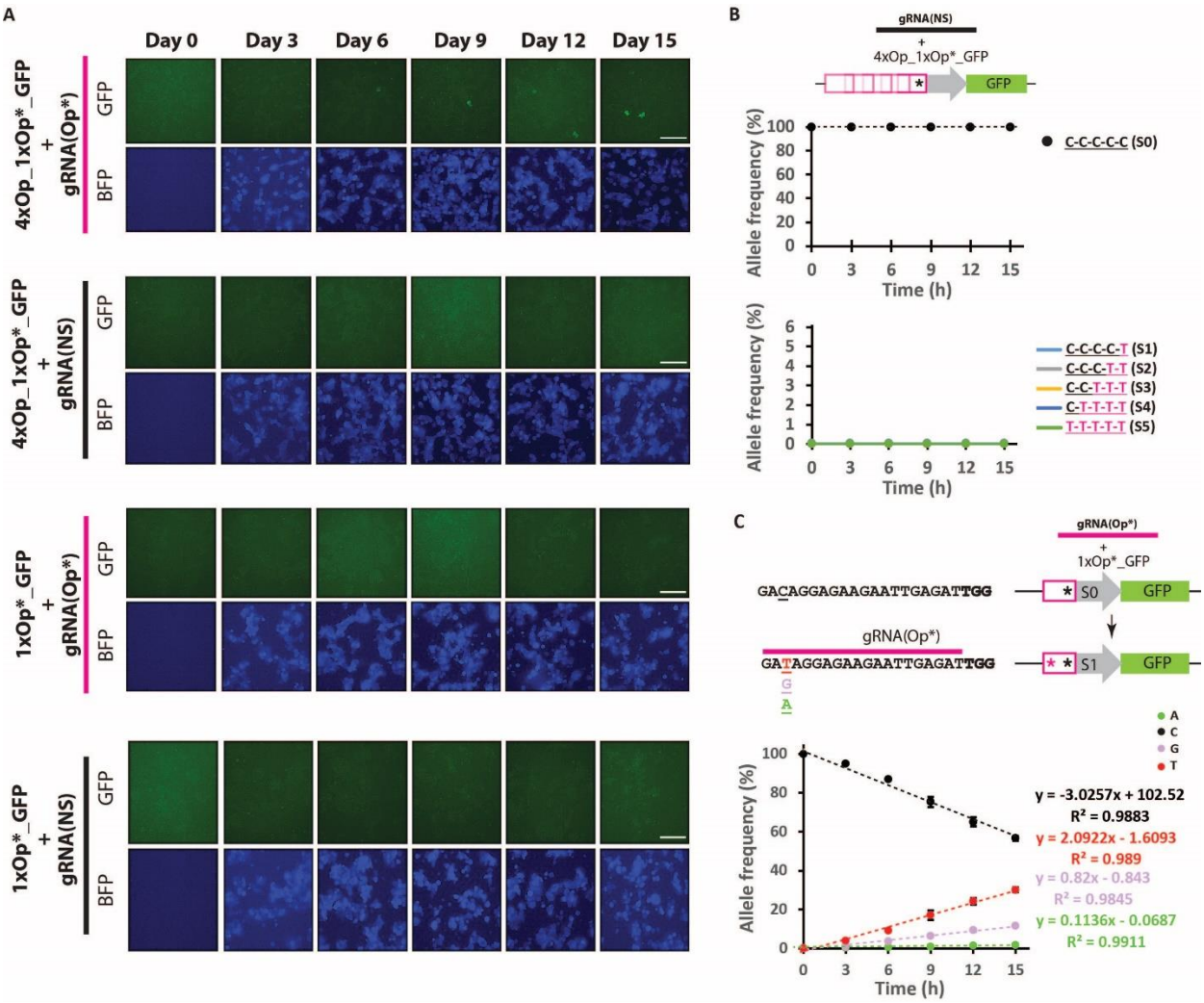


Figure S6. Related to Figure 5 | Representative microscopy images and additional data for the Non-destructive DNA-state reporter circuit. A) Representative microscopy images for cells harboring the 4xOp_1xOp*_GFP reporter and the Op*-specific gRNA [gRNA(Op*)] or a non-specific gRNA [gRNA(NS)]. Scale bars indicate 100 μm. **B)** Dynamics of allele frequencies (memory states) for cells harboring the 4xOp_1xOp*_GFP reporter and gRNA(NS) which were used as a negative control. **C)** Dynamics of allele frequencies (memory states) for cells harboring the 1xOp*_GFP reporter and gRNA(Op*). The mutable dC residue within the gRNA target site was mutated at a constant rate into dT and constant but at lower rates into dG and dA, reflecting the promiscuous repair of deaminated cytidine lesions in mammalian cells. The linear decrease in dC allele frequency, as well as the linear increases in dT, dG, and dA allele frequencies, can be used as an analog readout of the duration (or intensity) of gRNA expression.

Table S1. Related to STAR Methods | Plasmids used in this study

Name	Plasmid Code	Marker	Used in
P_{tetO}_CDA-nCas9-ugi	pFF1454	Cam	Figures 1-4 Figures S1-S5
P_{lacO}_DOMINO	pFF1630	Carb	Figure 1 Figure S1A-B
P_{BAD}_DOMINO	pFF1631	Carb	Figure S1C
P_{CusC}_DOMINO	pFF1633	Carb	Figure S1D
P_{Dusk}_DOMINO	pFF1635	Carb	Figure S1E
$P_{L(HrtO)}$_DOMINO	pFF1632	Carb	Figure S1F
P_{OxyS}_DOMINO	pFF1638	Carb	Figure S1G
P_{NorV}_DOMINO	pFF1637	Carb	Figure S1H
Comb_AND_gate	pFF1581	Carb	Figure 2A-B
Comb_AND_gate_gRNA_output	pFF1590	Carb	Figure 2C
Seq_AND_gate	pFF1610	Carb	Figure 3A-C
Race_detecting	pFF1684	Cam	Figure S4A-C
Mixed_seq_logic	pFF1685	Carb	Figure S4D-F
3x_propagation_delay_seq_AND	pFF1588	Carb	Figure 4
gRNA(Op*)	pYH383	Carb Hygro	Figure 5 Figure S6
gRNA(NS)	pYH384	Carb Hygro	Figure 5 Figure S6
4xOp*_1xOp_GFP_pCMV_nCas9_CDA_ugi_VP64	pYH396	Carb Puro	Figure 5 Figure S6
1xOp*_GFP_pCMV_nCas9_CDA_ugi_VP64	pYH404	Carb Puro	Figure 5 Figure S6
OR_gate	pFF1583	Carb	Figure S3A
gRNA_cascade	pFF1586	Carb	Figure S3B
Multiplexer	pFF1572	Carb	Figure S3C
ATG_conversion	PFF1604	Carb	Figure S3D
Temporal_start_codon_conversion	pFF1573	Carb	Figure S5

Table S2. Related to STAR Methods | Synthetic parts and their corresponding sequences used in this study

Part name	Type	Sequence	Source
P_{lacO} ($P_{LlacO-1}$)	IPTG-inducible promoter	AATTGTGAGCGGATAACAATTGACATTGTGAGCGGATAACAAGATACTGAGC ACATCAGCAGGACGCACTGACC	(Lutz and Bujard, 1997)
P_{tetO}	aTc-inducible promoter	TCCCTATCAGTGATAGAGAAAAGAATTCAAAAGATCTAAAGAGGAGAAAGGA TCT	(Lutz and Bujard, 1997)
P_{BAD}	Ara-inducible promoter	ACATTGATTATTTGCACGGCGTCACACTTTGCTATGCCATAGCATTTTTATCCA TAAGATTAGCGGATCCTACCTGACGCTTTTTATCGCAACTCTCTACTGTTTCTC CATA	*E. coli* genome
P_{CusC}	Cu-inducible promoter	GCGGGATCAGATGGCAATCGCTTATTGGCAAAATGACAATTTTGTCATTTTTCT GTCACCGGAAAATCAGAGCCTGGCGAGTAAAGTTGGCGGCATAA	*E. coli* genome
P_{Dusk}	Dark-inducible promoter		(Ohlendorf et al., 2012)
$P_{L(HrtO)}$	Heme-inducible promoter		(Mimee et al., 2018)
P_{OxyS}	Peroxide-inducible promoter	CCATCGCCACGATAGTTCATGGCGATAGGTAGAATAGCAATGAACGATTATCC CTATCAAGCATTCTGACTGATAATTGCTCACAG	*E. coli* genome
P_{NorV}	Nitrogen Oxide-inducible promoter	AAACTCATCTTTGCCTCACTGTCAATTTGACTATAGATATTGTCATATCGACCA TTTGATTGATAGTCATTTTGACTACTCATTAATGGGCATAATTTTATTTATAGA GTAAAAACAATCAGATAAAAAACTGGCACGCAATCTGCAATTAGCAAGAC	*E. coli* genome
4xOp_1xOp*_pMLP	4xOp_1xOp* array upstream of minimal MLP promoter	GACAGGAGAAGAATTGAGACAGGAGAAGAATTGAGACAGGAGAAGAATTGA GACAGGAGAAGAATTGAGACAGGAGAAGAATTGAGATTGGTGGGGGGCTATA AAAGGGGGTGGGGGCGTTCGTCCTCACTCTAGATCTGCGATCTAAGTAAGCTT GGCATTCCGGTACTGTTGGTAAAGCCACCATGGC	This work
1xOp*_pMLP	1xOp* upstream of minimal MLP promoter	GACAGGAGAAGAATTGAGATTGGTGGGGGGCTATAAAAGGGGGTGGGGGCGT TCGTCCTCACTCTAGATCTGCGATCTAAGTAAGCTTGGCATTCCGGTACTGTTG GTAAAGCCACCATGGC	This work
pU6	Constitutive RNA Pol III promoter	TGTACAAAAAAGCAGGCTTTAAAGGAACCAATTCAGTCGACTGGATCCGGTAC CAAGGTCGGGCAGGAAGAGGGCCTATTTCCCATGATTCCTTCATATTTGCATA TACGATACAAGGCTGTTAGAGAGATAATTAGAATTAATTTGACTGTAAACACA AAGATATTAGTACAAAATACGTGACGTAGAAAGTAATAATTTCTTGGGTAGTT TGCAGTTTTAAAATTATGTTTTAAAATGGACTATCATATGCTTACCGTAACTTG AAAGTATTTCGATTTCTTGGCTTTATATATCTTGTGGAAAGGACGAAACACC	
CDA-nCas9-ugi For use in bacterial experiments. The	read-write head ORF	ATGAGCTCAGAGACTGGCCCAGTGGCTGTGGACCCCACATTGAGACGGCGGA TCGAGCCCCATGAGTTTGAGGTATTCTTCGATCCGAGAGAGCTCCGCAAGGAG ACCTGCCTGCTTTACGAAATTAATTGGGGGGGCCGGCACTCCATTTGGCGACA TACATCACAGAACACTAACAAGCACGTCGAAGTCAACTTCATCGAGAAGTTCA CGACAGAAAGATATTTCTGTCCGAACACAAGGTGCAGCATTACCTGGTTTCTC AGCTGGAGCCCATGCGGCGAATGTAGTAGGGCCATCACTGAATTCCTGTCAAG GTATCCCCACGTCACTCTGTTTATTTACATCGCAAGGCTGTACCACCACGCTGA CCCCCGCAATCGACAAGGCCTGCGGGATTTGATCTCTTCAGGTGTGACTATCC	(Komor et al., 2016)

APOBEC1 CDA protein used as the writing module.		AAATTATGACTGAGCAGGAGTCAGGATACTGCTGGAGAAACTTTGTGAATTAT AGCCCGAGTAATGAAGCCCACTGGCCTAGGTATCCCCATCTGTGGGTACGACT GTACGTTCTTGAACTGTACTGCATCATACTGGGCCTGCCTCCTTGTCTCAACAT TCTGAGAAGGAAGCAGCCACAGCTGACATTCTTTACCATCGCTCTTCAGTCTT GTCATTACCAGCGACTGCCCCCACACATTCTCTGGGCCACCGGGTTGAAAAGC GGCAGCGAGACTCCCGGGACCTCAGAGTCCGCCACACCCGAAAGTGATAAAA AGTATTCTATTGGTTTAGCCATCGGCACTAATTCCGTTGGATGGGCTGTCATAA CCGATGAATACAAAGTACCTTCAAAGAAATTTAAGGTGTTGGGGAACACAGA CCGTCATTCGATTAAAAAGAATCTTATCGGTGCCCTCCTATTCGATAGTGGCG AAACGGCAGAGGCGACTCGCCTGAAACGAACCGCTCGGAGAAGGTATACACG TCGCAAGAACCGAATATGTTACTTACAAGAAATTTTTAGCAATGAGATGGCCA AAGTTGACGATTCTTTCTTTCACCGTTTGGAAGAGTCCTTCCTTGTCGAAGAGG ACAAGAAACATGAACGGCACCCCATCTTTGGAAACATAGTAGATGAGGTGGC ATATCATGAAAAGTACCCAACGATTTATCACCTCAGAAAAAAGCTAGTTGACT CAACTGATAAAGCGGACCTGAGGTTAATCTACTTGGCTCTTGCCCATATGATA AAGTTCCGTGGGCACTTTCTCATTGAGGGTGATCTAAATCCGGACAACTCGGA TGTCGACAAACTGTTCATCCAGTTAGTACAAACCTATAATCAGTTGTTTGAAG AGAACCCTATAAATGCAAGTGGCGTGGATGCGAAGGCTATTCTTAGCGCCCGC CTCTCTAAATCCCGACGGCTAGAAAACCTGATCGCACAATTACCCGGAGAGAA GAAAAATGGGTTGTTCGGTAACCTTATAGCGCTCTCACTAGGCCTGACACCAA ATTTTAAGTCGAACTTCGACTTAGCTGAAGATGCCAAATTGCAGCTTAGTAAG GACACGTACGATGACGATCTCGACAATCTACTGGCACAAATTGGAGATCAGTA TGCGGACTTATTTTTGGCTGCCAAAAACCTTAGCGATGCAATCCTCCTATCTGA CATACTGAGAGTTAATACTGAGATTACCAAGGCGCCGTTATCCGCTTCAATGA TCAAAAGGTACGATGAACATCACCAAGACTTGACACTTCTCAAGGCCCTAGTC CGTCAGCAACTGCCTGAGAAATATAAGGAAATATTCTTTGATCAGTCGAAAAA CGGGTACGCAGGTTATATTGACGGCGGAGCGAGTCAAGAGGAATTCTACAAG TTTATCAAACCCATATTAGAGAAGATGGATGGGACGGAAGAGTTGCTTGTAAA ACTCAATCGCGAAGATCTACTGCGAAAGCAGCGGACTTTCGACAACGGTAGC ATTCCACATCAAATCCACTTAGGCGAATTGCATGCTATACTTAGAAGGCAGGA GGATTTTTATCCGTTCCTCAAAGACAATCGTGAAAAGATTGAGAAAATCCTAA CCTTTCGCATACCTTACTATGTGGGACCCCTGGCCCGAGGGAACTCTCGGTTC GCATGGATGACAAGAAAGTCCGAAGAAACGATTACTCCATGGAATTTTGAGG AAGTTGTCGATAAAGGTGCGTCAGCTCAATCGTTCATCGAGAGGATGACCAAC TTTGACAAGAATTTACCGAACGAAAAAGTATTGCCTAAGCACAGTTTACTTTA CGAGTATTTCACAGTGTACAATGAACTCACGAAAGTTAAGTATGTCACTGAGG GCATGCGTAAACCCGCCTTTCTAAGCGGAGAACAGAAGAAAGCAATAGTAGA TCTGTTATTCAAGACCAACCGCAAAGTGACAGTTAAGCAATTGAAAGAGGACT ACTTTAAGAAAATTGAATGCTTCGATTCTGTCGAGATCTCCGGGGTAGAAGAT CGATTTAATGCGTCACTTGGTACGTATCATGACCTCCTAAAGATAATTAAAGA TAAGGACTTCCTGGATAACGAAGAGAATGAAGATATCTTAGAAGATATAGTGT TGACTCTTACCCTCTTTGAAGATCGGGAAATGATTGAGGAAAGACTAAAAACA TACGCTCACCTGTTCGACGATAAGGTTATGAAACAGTTAAAGAGGCGTCGCTA TACGGGCTGGGGACGATTGTCGCGGAAACTTATCAACGGGATAAGAGACAAG CAAAGTGGTAAAACTATTCTCGATTTTCTAAAGAGCGACGGCTTCGCCAATAG GAACTTTATGCAGCTGATCCATGATGACTCTTTAACCTTCAAAGAGGATATAC AAAAGGCACAGGTTTCCGGACAAGGGGACTCATTGCACGAACATATTGCGAA TCTTGCTGGTTCGCCAGCCATCAAAAAGGGCATACTCCAGACAGTCAAAGTAG TGGATGAGCTAGTTAAGGTCATGGGACGTCACAAACCGGAAAACATTGTAATC GAGATGGCACGCGAAAATCAAACGACTCAGAAGGGGCAAAAAAACAGTCGA GAGCGGATGAAGAGAATAGAAGAGGGTATTAAAGAACTGGGCAGCCAGATCT TAAAGGAGCATCCTGTGGAAAATACCCAATTGCAGAACGAGAAACTTTACCTC TATTACCTACAAAATGGAAGGGACATGTATGTTGATCAGGAACTGGACATAAA CCGTTTATCTGATTACGACGTCGATCACATTGTACCCCAATCCTTTTTGAAGGA CGATTCAATCGACAATAAAGTGCTTACACGCTCGGATAAGAACCGAGGGAAA AGTGACAATGTTCCAAGCGAGGAAGTCGTAAAGAAAATGAAGAACTATTGGC GGCAGCTCCTAAATGCGAAACTGATAACGCAAAGAAAGTTCGATAACTTAACT AAAGCTGAGAGGGGTGGCTTGTCTGAACTTGACAAGGCCGGATTTATTAAACG TCAGCTCGTGGAAACCCGCCAAATCACAAAGCATGTTGCACAGATACTAGATT CCCGAATGAATACGAAATACGACGAGAACGATAAGCTGATTCGGGAAGTCAA AGTAATCACTTTAAAGTCAAAATTGGTGTCGGACTTCAGAAAGGATTTTCAAT TCTATAAAGTTAGGGAGATAAATAACTACCACCATGCGCACGACGCTTATCTT	

		AATGCCGTCGTAGGGACCGCACTCATTAAGAAATACCCGAAGCTAGAAAGTG AGTTTGTGTATGGTGATTACAAAGTTTATGACGTCCGTAAGATGATCGCGAAA AGCGAACAGGAGATAGGCAAGGCTACAGCCAAATACTTCTTTTATTCTAACAT TATGAATTTCTTTAAGACGGAAATCACTCTGGCAAACGGAGAGATACGCAAAC GACCTTTAATTGAAACCAATGGGGAGACAGGTGAAATCGTATGGGATAAGGG CCGGGACTTCGCGACGGTGAGAAAAGTTTTGTCCATGCCCCAAGTCAACATAG TAAAGAAAACTGAGGTGCAGACCGGAGGGTTTTCAAAGGAATCGATTCTTCCA AAAAGGAATAGTGATAAGCTCATCGCTCGTAAAAAGGACTGGGACCCGAAAA AGTACGGTGGCTTCGATAGCCCTACAGTTGCCTATTCTGTCCTAGTAGTGGCA AAAGTTGAGAAGGGAAAATCCAAGAAACTGAAGTCAGTCAAAGAATTATTGG GGATAACGATTATGGAGCGCTCGTCTTTTGAAAAGAACCCCATCGACTTCCTT GAGGCGAAAGGTTACAAGGAAGTAAAAAAGGATCTCATAATTAAACTACCAA AGTATAGTCTGTTTGAGTTAGAAAATGGCCGAAAACGGATGTTGGCTAGCGCC GGAGAGCTTCAAAAGGGGAACGAACTCGCACTACCGTCTAAATACGTGAATTT CCTGTATTTAGCGTCCCATTACGAGAAGTTGAAAGGTTCACCTGAAGATAACG AACAGAAGCAACTTTTTGTTGAGCAGCACAAACATTATCTCGACGAAATCATA GAGCAAATTTCGGAATTCAGTAAGAGAGTCATCCTAGCTGATGCCAATCTGGA CAAAGTATTAAGCGCATACAACAAGCACAGGGATAAACCCATACGTGAGCAG GCGGAAAATATTATCCATTTGTTTACTCTTACCAACCTCGGCGCTCCAGCCGCA TTCAAGTATTTTGACACAACGATAGATCGCAAACGATACACTTCTACCAAGGA GGTGCTAGACGCGACACTGATTCACCAATCCATCACGGGATTATATGAAACTC GGATAGATTTGTCACAGCTTGGGGGTGACTCTGGTGGTTCTACTAATCTGTCA GATATTATTGAAAAGGAGACCGGTAAGCAACTGGTTATCCAGGAATCCATCCT CATGCTCCCAGAGGAGGTGGAAGAAGTCATTGGGAACAAGCCGGAAAGCGAT ATACTCGTGCACACCGCCTACGACGAGAGCACCGACGAGAATGTCATGCTTCT GACTAGCGACGCCCCTGAATACAAGCCTTGGGCTCTGGTCATACAGGATAGCA ACGGTGAGAACAAGATTAAGATGCTCTCTGGTGGTTCTCCCAAGAAGAAGAG GAAAGTCTAA	
nCas9-CDA-ugi-VP64 For use in mammalian cell experiments. PmCDA protein (Nishida et al., 2016) and minimal VP64 (Farzadfard et al., 2013) domain were used as the write and the transactivation modules, respectively.	read-write-transactivator ORF	ATGGCACCGAAGAAGAAGCGTAAAGTCGGAATCCACGGAGTTCCTGCGGCAA TGGACAAGAAGTACTCCATTGGGCTCGCTATCGGCACAAACAGCGTCGGTTGG GCCGTCATTACGGACGAGTACAAGGTGCCGAGCAAAAAATTCAAAGTTCTGG GCAATACCGATCGCCACAGCATAAAGAAGAACCTCATTGGCGCCCTCCTGTTC GACTCCGGGGAGACGGCCGAAGCCACGCGGCTCAAAAGAACAGCACGGCGCA GATATACCCGCAGAAAGAATCGGATCTGCTACCTGCAGGAGATCTTTAGTAAT GAGATGGCTAAGGTGGATGACTCTTTCTTCCATAGGCTGGAGGAGTCCTTTTT GGTGGAGGAGGATAAAAAGCACGAGCGCCACCCAATCTTTGGCAATATCGTG GACGAGGTGGCGTACCATGAAAAGTACCCAACCATATATCATCTGAGGAAGA AGCTTGTAGACAGTACTGATAAGGCTGACTTGCGGTTGATCTATCTCGCGCTG GCGCATATGATCAAATTTCGGGGACACTTCCTCATCGAGGGGGACCTGAACCC AGACAACAGCGATGTCGACAAACTCTTTATCCAACTGGTTCAGACTTACAATC AGCTTTTCGAAGAGAACCCGATCAACGCATCCGGAGTTGACGCCAAAGCAAT CCTGAGCGCTAGGCTGTCCAAATCCCGGCGGCTCGAAAACCTCATCGCACAGC TCCCTGGGGAGAAGAAGAACGGCCTGTTTGGTAATCTTATCGCCCTGTCACTC GGGCTGACCCCCAACTTTAAATCTAACTTCGACCTGGCCGAAGATGCCAAGCT TCAACTGAGCAAAGACACCTACGATGATGATCTCGACAATCTGCTGGCCCAGA TCGGCGACCAGTACGCAGACCTTTTTTTGGCGGCAAAGAACCTGTCAGACGCC ATTCTGCTGAGTGATATTCTGCGAGTGAACACGGAGATCACCAAAGCTCCGCT GAGCGCTAGTATGATCAAGCGCTATGATGAGCACCACCAAGACTTGACTTTGC TGAAGGCCCTTGTCAGACAGCAACTGCCTGAGAAGTACAAGGAAATTTTCTTC GATCAGTCTAAAAATGGCTACGCCGGATACATTGATGGCGGAGCAAGCCAGG AGGAATTTTACAAATTTATTAAGCCCATCTTGGAAAAAATGGACGGCACCGAG GAGCTGCTGGTAAAGCTTAACAGAGAAGATCTGTTGCGCAAACAGCGCACTTT CGACAATGGAAGCATCCCCCACCAGATTCACCTGGGCGAACTGCACGCTATCC TCAGGCGGCAAGAGGATTTCTACCCCTTTTTGAAAGATAACAGGGAAAAGATT GAGAAAATCCTCACATTTCGGATACCCTACTATGTAGGCCCCCTCGCCCGGGG AAATTCCAGATTCGCGTGGATGACTCGCAAATCAGAAGAGACCATCACTCCCT GGAACTTCGAGGAAGTCGTGGATAAGGGGGCCTCTGCCCAGTCCTTCATCGAA AGGATGACTAACTTTGATAAAAATCTGCCTAACGAAAAGGTGCTTCCTAAACA CTCTCTGCTGTACGAGTACTTCACAGTTTATAACGAGCTCACCAAGGTCAAAT ACGTCACAGAAGGGATGAGAAAGCCAGCATTCCTGTCTGGAGAGCAGAAGAA AGCTATCGTGGACCTCCTCTTCAAGACGAACCGGAAAGTTACCGTGAAACAGC TCAAAGAAGACTATTTCAAAAAGATTGAATGTTTCGACTCTGTTGAAATCAGC	This work

GGAGTGGAGGATCGCTTCAACGCATCCCTGGGAACGTATCACGATCTCCTGAA
AATCATTAAAGACAAGGACTTCCTGGACAATGAGGAGAACGAGGACATTCTT
GAGGACATTGTCCTCACCCTTACGTTGTTTGAAGATAGGGAGATGATTGAAGA
ACGCTTGAAAACTTACGCTCATCTCTTCGACGACAAAGTCATGAAACAGCTCA
AGAGGCGCCGATATACAGGATGGGGGCGGCTGTCAAGAAAACTGATCAATGG
GATCCGAGACAAGCAGAGTGGAAAGACAATCCTGGATTTTCTTAAGTCCGATG
GATTTGCCAACCGGAACTTCATGCAGTTGATCCATGATGACTCTCTCACCTTTA
AGGAGGACATCCAGAAAGCACAAGTTTCTGGCCAGGGGGACAGTCTTCACGA
GCACATCGCTAATCTTGCAGGTAGCCCAGCTATCAAAAAGGGAATACTGCAGA
CCGTTAAGGTCGTGGATGAACTCGTCAAAGTAATGGGAAGGCATAAGCCCGA
GAATATCGTTATCGAGATGGCCCGAGAGAACCAAACTACCCAGAAGGGACAG
AAGAACAGTAGGGAAAGGATGAAGAGGATTGAAGAGGGTATAAAAGAACTG
GGGTCCCAAATCCTTAAGGAACACCCAGTTGAAAACACCCAGCTTCAGAATG
AGAAGCTCTACCTGTACTACCTGCAGAACGGCAGGGACATGTACGTGGATCAG
GAACTGGACATCAATCGGCTCTCCGACTACGACGTGGATCATATCGTGCCCCA
GTCTTTTCTCAAAGATGATTCTATTGATAATAAAGTGTTGACAAGATCCGATA
AAAATAGAGGGAAGAGTGATAACGTCCCCTCAGAAGAAGTTGTCAAGAAAAT
GAAAAATTATTGGCGGCAGCTGCTGAACGCCAAACTGATCACACAACGGAAG
TTCGATAATCTGACTAAGGCTGAACGAGGTGGCCTGTCTGAGTTGGATAAAGC
CGGCTTCATCAAAAGGCAGCTTGTTGAGACACGCCAGATCACCAAGCACGTG
GCCCAAATTCTCGATTCACGCATGAACACCAAGTACGATGAAAATGACAAACT
GATTCGAGAGGTGAAAGTTATTACTCTGAAGTCTAAGCTGGTCTCAGATTTCA
GAAAGGACTTTCAGTTTTATAAGGTGAGAGAGATCAACAATTACCACCATGCG
CATGATGCCTACCTGAATGCAGTGGTAGGCACTGCACTTATCAAAAAATATCC
CAAGCTTGAATCTGAATTTGTTTACGGAGACTATAAAGTGTACGATGTTAGGA
AAATGATCGCAAAGTCTGAGCAGGAAATAGGCAAGGCCACCGCTAAGTACTT
CTTTTACAGCAATATTATGAATTTTTTCAAGACCGAGATTACACTGGCCAATGG
AGAGATTCGGAAGCGACCACTTATCGAAACAAACGGAGAAACAGGAGAAATC
GTGTGGGACAAGGGTAGGGATTTCGCGACAGTCCGGAAGGTCCTGTCCATGCC
GCAGGTGAACATCGTTAAAAAGACCGAAGTACAGACCGGAGGCTTCTCCAAG
GAAAGTATCCTCCCGAAAAGGAACAGCGACAAGCTGATCGCACGCAAAAAAG
ATTGGGACCCCAAGAAATACGGCGGATTCGATTCTCCTACAGTCGCTTACAGT
GTACTGGTTGTGGCCAAAGTGGAGAAAGGGAAGTCTAAAAAACTCAAAAGCG
TCAAGGAACTGCTGGGCATCACAATCATGGAGCGATCAAGCTTCGAAAAAAA
CCCCATCGACTTTCTCGAGGCGAAAGGATATAAAGAGGTCAAAAAAGACCTC
ATCATTAAGCTTCCCAAGTACTCTCTCTTTGAGCTTGAAAACGGCCGGAAACG
AATGCTCGCTAGTGCGGGCGAGCTGCAGAAAGGTAACGAGCTGGCACTGCCC
TCTAAATACGTTAATTTCTTGTATCTGGCCAGCCACTATGAAAAGCTCAAAGG
GTCTCCCGAAGATAATGAGCAGAAGCAGCTGTTCGTGGAACAACACAAACAC
TACCTTGATGAGATCATCGAGCAAATAAGCGAATTCTCCAAAAGAGTGATCCT
CGCCGACGCTAACCTCGATAAGGTGCTTTCTGCTTACAATAAGCACAGGGATA
AGCCCATCAGGGAGCAGGCAGAAAACATTATCCACTTGTTTACTCTGACCAAC
TTGGGCGCGCCTGCAGCCTTCAAGTACTTCGACACCACCATAGACAGAAAGCG
GTACACCTCTACAAAGGAGGTCCTGGACGCCACACTGATTCATCAGTCAATTA
CGGGGCTCTATGAAACAAGAATCGACCTCTCTCAGCTCGGTGGAGACAGCAG
GGCTGACCCCAAGAAGAAGAGGAAGGTGGGTGGAGGAGGTACCGGCGGTGG
AGGCTCAGCAGAATACGTACGAGCTCTGTTTGACTTCAATGGGAATGACGAGG
AGGATCTCCCCTTTAAGAAGGGCGATATTCTCCGCATCAGAGATAAGCCCGAA
GAACAATGGTGGAATGCCGAGGATAGCGAAGGGAAAAGGGGCATGATTCTGG
TGCCATATGTGGAGAAATATTCCGGTGACTACAAAGACCATGATGGGGATTAC
AAAGACCACGACATCGACTACAAAGACGACGACGATAAATCAGGGATGACAG
ACGCCGAGTACGTGCGCATTCATGAGAAACTGGATATTTACACCTTCAAGAAG
CAGTTCTTCAACAACAAGAAATCTGTGTCACACCGCTGCTACGTGCTGTTTGA
GTTGAAGCGAAGGGGCGAAAGAAGGGCTTGCTTTTGGGGCTATGCCGTCAAC
AAGCCCCAAAGTGGCACCGAGAGAGGAATACACGCTGAGATATTCAGTATCC
GAAAGGTGGAAGAGTATCTTCGGGATAATCCTGGGCAGTTTACGATCAACTGG
TATTCCAGCTGGAGTCCTTGCGCTGATTGTGCCGAGAAAATTCTGGAATGGTA
TAATCAGGAACTTCGGGGAAACGGGCACACATTGAAAATCTGGGCCTGCAAG
CTGTACTACGAGAAGAATGCCCGGAACCAGATAGGACTCTGGAATCTGAGGG
ACAATGGTGTAGGCCTGAACGTGATGGTTTCCGAGCACTATCAGTGTTGTCGG
AAGATTTTCATCCAAAGCTCTCATAACCAGCTCAATGAAAACCGCTGGTTGGA
GAAAACACTGAAACGTGCGGAGAAGTGGAGATCCGAGCTGAGCATCATGATC

		CAGGTCAAGATTCTGCATACCACTAAGTCTCCAGCCGTTGGTCCCAAGAAGAA AAGAAAAGTCGGTACCATGACCAACCTTTCCGACATCATAGAGAAGGAAACA GGCAAACAGTTGGTCATCCAAGAGTCGATACTCATGCTTCCTGAAGAAGTTGA GGAGGTCATTGGGAATAAGCCGGAAAGTGACATTCTCGTACACACTGCGTATG ATGAGAGCACCGATGAGAACGTGATGCTGCTCACGTCAGATGCCCCAGAGTA CAAACCCTGGGCTCTGGTGATTCAGGACTCTAATGGAGAGAACAAGATCAAG ATGCTATCTGGTGGTTCTCCCAAGAAGAAGAGGAAAGTCGAGGATCCAAAGA AGAAAAGGAAGGTTGAAGACCCCAAGAAAAAGAGGAAGGTGGATGGGATCG GCTCAGGCAGCAACGGCGGTGGAGGTTCAGACGCTTTGGACGATTTCGATCTC GATATGCTCGGTTCTGACGCCCTGGATGATTTCGATCTGGATATGCTCGGCAG CGACGCTCTCGACGATTTCGACCTCGACATGCTCGGGTCAGATGCCTTGGATG ATTTTGACCTGGATATGCTC	

Table S3. Related to STAR Methods | HTS primers and their corresponding sequences used in this study

name	Type	Sequence	Used in
FF_oligo_2525	HTS_Primer_Forward	ACACTCTTTCCCTACACGACGCTCTTCCGATCTNNNNNTGCTGCCCGACAACCACTA	Figures 1-4, S1, S3, and S4
FF_oligo_2526	HTS_Primer_Reverse	CGGCATTCCTGCTGAACCGCTCTTCCGATCTNNNNNTGAACAACCACCACTTCAAGTGGG	Figures 1-4, S1, S3, and S4
FF_oligo_2527	HTS_Primer_Forward	CACTCTTTCCCTACACGACGCTCTTCCGATCTNNNNNGGACAGCAGAGATCCAGTTTGGT	Figures 5 & S6
FF_oligo_2528	HTS_Primer_Reverse	GGCATTCCTGCTGAACCGCTCTTCCGATCTNNNNNTCGCAGATCTAGAGTGAGGACGAAC	Figures 5 & S6