

SUPPLEMENTARY INFORMATION

CONTROLLABLE GENOME EDITING WITH SPLIT-ENGINEERED BASE EDITORS

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Supplementary Figure 1. Base editing efficiency of evoA1-seBE-T2A constructs in human cells at diverse loci and off-target sites. The frequency of individual base calls at each locus of interest are shown, colored using a heat map from white (0%) to red (100%). The parent sequence is shown with PAM (yellow) and sgRNA protospacer (black) noted. When the PAM is at right, the coding strand cytosine (C) targeted for mutation is highlighted in red. When the PAM is at left, the non-coding strand cytosine is targeted, and the associated coding strand (G) is highlighted in red. The data in Fig. 3b show the quantification of conversion at the target base only, with individual loci shown in Extended Data Fig. 5a. Results across each locus with individual replicates are shown using untreated cells (n = 1), along with intact evoA1-BE4max or evoA1-seBE-T2A with or without rapamycin (n = 3 each). The loci analyzed and desired mutations are (a) CDA E67R targeting the active site residue, (b) CDA Q104* nonsense mutation, (c) IDH1 R132H neomorphic mutation, (d) TDG Q51* nonsense mutation, (e) TDG Q172* nonsense mutation, (f) TET2 nonsense mutation Q180*, (g) IDH2 R172K neomorphic mutation, (h) validated EMX1 targeting site, (i) validated EMX1 off-target site 1 (OT1) (j) validated EMX1 off-target site 2 (OT2), (k) validated FANCF targeting site, (l) validated FANCF off-target site 1 (OT1), (m) validated FANCF off-target site 2 (OT2).

Supplementary Figure 1

a		CDA E67R																												
		P61			L62				G63			I64				C65			A66			E67								
untreated	A	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.1	0.0	99.9	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.1	100.0	100.0	0.0
	C	99.9	100.0	99.9	0.0	100.0	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	0.0	99.9	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	100.0
	G	0.0	0.0	0.0	99.9	0.0	0.0	100.0	99.9	99.9	0.0	0.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0
	T	0.0	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	0.0	100.0	0.0	100.0	0.0	99.9	0.0	0.1	100.0	0.0	0.0	0.0	0.0	0.0	0.0
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

		PAM			20				15			10				5			1						
		C	C	C	G	C	T	G	G	G	C	A	T	C	T	G	T	G	C	T	G	A	A	C	
evoA1-seB:max Replicate 1	A	0.0	0.0	0.0	0.0	0.0	0.0	0.7	3.6	0.6	0.0	99.2	0.0	0.1	0.0	2.7	0.0	59.5	0.0	0.0	59.2	99.7	99.8	0.0	0.0
	C	99.9	99.8	99.8	0.0	99.8	0.0	0.0	0.0	0.0	99.3	0.0	0.0	99.1	0.0	0.0	0.2	99.2	0.0	0.1	0.0	0.0	0.0	99.8	
	G	0.0	0.0	0.0	99.8	0.0	0.0	98.6	95.6	98.7	0.0	0.0	0.0	0.0	0.0	96.3	0.0	39.2	0.0	0.0	39.8	0.0	0.0	0.0	
	T	0.0	0.1	0.0	0.0	0.0	99.8	0.0	0.2	0.0	0.0	0.0	99.2	0.0	99.0	0.1	99.1	0.3	0.0	99.4	0.3	0.0	0.0	0.0	
	-	0.1	0.1	0.1	0.1	0.2	0.2	0.6	0.6	0.7	0.7	0.7	0.8	0.8	0.9	0.9	0.9	0.8	0.7	0.6	0.5	0.3	0.2	0.2	

		PAM			20				15			10				5			1						
		C	C	C	G	C	T	G	G	G	C	A	T	C	T	G	T	G	C	T	G	A	A	C	
evoA1-seB:max Replicate 2	A	0.0	0.0	0.0	0.0	0.1	0.0	1.1	2.8	0.4	0.0	99.6	0.0	0.0	0.0	3.1	0.0	59.1	0.0	0.0	58.8	99.8	99.9	0.0	0.0
	C	100.0	99.9	99.9	0.0	99.9	0.0	0.0	0.0	0.0	99.6	0.0	0.0	99.5	0.0	0.1	0.2	99.5	0.0	0.2	0.0	0.0	0.0	99.8	
	G	0.0	0.0	0.0	99.9	0.0	0.1	98.6	96.7	99.2	0.0	0.0	0.0	0.0	0.0	96.3	0.0	39.7	0.0	0.0	40.3	0.0	0.0	0.0	
	T	0.0	0.1	0.0	0.0	0.0	99.9	0.1	0.2	0.1	0.0	0.0	99.5	0.0	99.4	0.0	99.3	0.4	0.0	99.5	0.3	0.0	0.0	0.0	
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.2	0.1	0.3	0.4	0.4	0.5	0.6	0.6	0.6	0.6	0.5	0.5	0.4	0.2	0.1	0.1	

		PAM			20				15			10				5			1						
		C	C	C	G	C	T	G	G	G	C	A	T	C	T	G	T	G	C	T	G	A	A	C	
evoA1-seB:max Replicate 3	A	0.0	0.0	0.0	0.1	0.0	0.0	0.8	3.2	0.5	0.0	99.4	0.0	0.0	0.0	2.9	0.0	57.5	0.0	0.0	57.6	99.7	99.7	0.0	0.0
	C	99.9	99.9	99.9	0.0	99.9	0.0	0.0	0.0	0.0	99.6	0.0	0.0	99.4	0.0	0.1	0.2	99.4	0.0	0.2	0.0	0.0	0.0	99.8	
	G	0.0	0.0	0.0	99.9	0.0	0.0	98.6	96.2	99.0	0.0	0.0	0.0	0.0	0.0	96.5	0.0	41.5	0.0	0.0	41.6	0.0	0.0	0.0	
	T	0.0	0.1	0.1	0.0	0.0	99.9	0.0	0.1	0.0	0.0	0.0	99.4	0.0	99.3	0.0	99.3	0.3	0.0	99.5	0.3	0.0	0.0	0.0	
	-	0.1	0.1	0.1	0.1	0.1	0.1	0.5	0.5	0.5	0.4	0.5	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.5	0.4	0.3	0.2	

		PAM			20				15			10				5			1						
		C	C	C	G	C	T	G	G	G	C	A	T	C	T	G	T	G	C	T	G	A	A	C	
evoA1-seB: T2A +Rap Replicate 1	A	0.0	0.0	0.0	0.1	0.0	0.0	0.4	1.9	0.2	0.0	99.8	0.0	0.0	0.0	1.0	0.0	38.0	0.0	0.0	38.7	100.0	100.0	0.0	0.0
	C	100.0	100.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	99.8	0.0	0.0	99.8	0.0	0.1	0.1	99.9	0.0	0.0	0.0	0.0	0.0	0.0	100.0
	G	0.0	0.0	0.0	99.9	0.0	0.0	99.4	97.8	99.6	0.0	0.0	0.0	0.0	0.0	98.9	0.0	61.8	0.0	0.0	61.2	0.0	0.0	0.0	0.0
	T	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.1	0.0	0.0	0.0	99.8	0.0	99.8	0.0	99.8	0.1	0.0	99.9	0.1	0.0	0.0	0.0	0.0
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0

		PAM			20				15			10				5			1						
		C	C	C	G	C	T	G	G	G	C	A	T	C	T	G	T	G	C	T	G	A	A	C	
evoA1-seB: T2A +Rap Replicate 2	A	0.1	0.0	0.0	0.1	0.0	0.0	0.3	1.4	0.3	0.0	100.0	0.0	0.0	0.0	1.0	0.1	29.2	0.0	0.0	30.0	100.0	100.0	0.0	0.0
	C	99.9	100.0	99.9	0.0	99.9	0.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.1	100.0	0.0	0.0	0.0	0.0	0.0	99.9
	G	0.0	0.0	0.0	99.9	0.0	0.0	99.6	98.6	99.7	0.0	0.0	0.0	0.0	0.0	99.0	0.0	70.6	0.0	0.0	69.9	0.0	0.0	0.0	0.0
	T	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	100.0	0.0	99.9	0.0	99.8	0.1	0.0	100.0	0.1	0.0	0.0	0.0	0.0
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

		PAM			20				15			10				5			1						
		C	C	C	G	C	T	G	G	G	C	A	T	C	T	G	T	G	C	T	G	A	A	C	
evoA1-seB: T2A +Rap Replicate 3	A	0.0	0.0	0.1	0.0	0.0	0.0	0.5	1.8	0.4	0.0	99.9	0.0	0.0	0.0	1.3	0.1	37.8	0.0	0.0	38.9	99.9	99.9	0.0	0.0
	C	99.9	100.0	99.9	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	99.9	0.0	0.0	0.1	99.9	0.0	0.0	0.0	0.0	0.1	99.9	
	G	0.0	0.0	0.0	100.0	0.0	0.0	99.5	98.1	99.5	0.0	0.0	0.0	0.0	0.0	98.7	0.0	62.0	0.0	0.1	61.1	0.0	0.0	0.0	
	T	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.1	0.0	0.0	99.9	0.0	99.9	0.0	99.9	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.0
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0

		PAM			20				15			10				5			1						
		C	C	C	G	C	T	G	G	G	C	A	T	C	T	G	T	G	C	T	G	A	A	C	
evoA1-seB: T2A +Rap Replicate 1	A	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.0	0.0	100.0	0.0	0.0	0.0	0.1	0.0	4.0	0.0	0.0	5.5	100.0	100.0	0.0	0.0
	C	100.0	100.0	100.0	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	0.0	100.0	0.0	0.1	0.0	0.0	0.0	100.0
	G	0.0	0.0	0.0	100.0	0.0	0.0	99.9	99.8	99.9	0.0	0.0	0.0	0.0	0.0	99.9	0.0	96.0	0.0	0.0	94.5	0.0	0.0	0.0	0.0
	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	100.0	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	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

		PAM			20				15			10				5			1						
		C	C	C	G	C	T	G	G	G	C	A	T	C	T	G	T	G	C	T	G	A	A	C	
evoA1-seB: T2A +Rap Replicate 2	A	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.1	0.1	0.0	99.9	0.0	0.0	0.0	0.1	0.1	3.2	0.0	0.0	4.4	99.9	99.9	0.0	0.0
	C	99.9	100.0	99.9	0.0	99.9	0.0	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	0.0	0.0	100.0
	G	0.0	0.0	0.0	99.9	0.0	0.0	99.8	99.9	99.9	0.0	0.0	0.0	0.0	0.0	99.9	0.1	96.8	0.0	0.0	95.5	0.0	0.1	0.0	0.0
	T	0.0	0.0	0.0	0.0	0.0	99.9	0.1	0.0	0.0	0.0	0.0	100.0	0.0	99.9	0.0	99.8	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	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

		PAM			20				15			10				5			1			
		C	C	C	G	C	T	G	G	G	C	A	T	C	T	G	T	G	C	T	G	A
evoA1-seB: T2A +Rap Replicate 3	A	0.0	0.0	0.0	0.1	0																

Supplementary Figure 1

b		CDA Q104*																							
		C102				R103			Q104			V105			M106			R107			E108				
untreated		C	T	G	C	A	G	G	C	A	A	G	T	C	A	T	G	A	G	A	G	A	G	G	
	A	0.0	0.0	0.1	0.0	99.9	0.0	0.1	0.0	100.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	0.0
	C	100.0	0.0	0.0	99.9	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	0.0	0.0	99.9	0.0	0.1	100.0	99.9	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0	100.0
	T	0.0	100.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	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	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

evoA1_sEBE-max	Replicate 1	PAM																							
		I	C	T	G	C	A	G	G	C	A	A	G	T	C	A	T	G	A	G	A	G	A	G	G
A	0.1	0.0	0.0	0.6	99.4	0.2	0.0	0.4	99.1	99.1	0.0	0.0	0.1	99.5	0.0	0.2	99.8	0.1	99.9	0.0	100.0	0.1	0.0	0.0	0.0
C	78.7	0.0	0.0	36.3	0.0	0.1	0.0	39.8	0.0	0.0	0.0	0.0	91.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
G	0.0	0.0	99.6	0.3	0.1	99.0	99.1	1.8	0.0	0.0	0.0	99.0	0.0	0.0	0.0	99.4	0.0	99.8	0.0	99.9	0.0	99.8	99.9	99.9	99.9
T	20.8	99.6	0.0	62.2	0.0	0.0	0.0	56.6	0.0	0.0	0.0	99.2	7.9	0.0	99.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
-	0.4	0.4	0.4	0.6	0.6	0.8	0.8	1.4	0.9	0.9	1.0	0.8	0.7	0.5	0.4	0.4	0.2	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0

evoA1_sEBE-max	Replicate 2	PAM																							
		I	C	T	G	C	A	G	G	C	A	A	G	T	C	A	T	G	A	G	A	G	A	G	G
A	0.3	0.0	0.1	0.8	99.5	0.3	0.0	0.2	99.3	99.2	0.0	0.0	0.3	99.4	0.0	0.2	99.7	0.0	99.7	0.1	99.8	0.2	0.0	0.0	0.0
C	79.9	0.0	0.0	41.7	0.0	0.0	0.0	45.3	0.0	0.1	0.0	0.0	91.9	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.0
G	0.1	0.0	99.5	0.2	0.0	99.1	99.2	1.4	0.0	0.0	0.0	99.2	0.0	0.0	0.0	99.5	0.1	99.8	0.0	99.8	0.1	99.7	100.0	100.0	
T	19.3	99.6	0.0	56.8	0.0	0.1	0.1	52.2	0.0	0.0	0.0	99.2	7.1	0.0	99.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
-	0.5	0.4	0.4	0.5	0.4	0.6	0.7	0.9	0.7	0.8	0.8	0.8	0.7	0.5	0.3	0.3	0.2	0.2	0.3	0.2	0.2	0.1	0.0	0.0	0.0

evoA1_sEBE-max	Replicate 3	PAM																							
		I	C	T	G	C	A	G	G	C	A	A	G	T	C	A	T	G	A	G	A	G	A	G	G
A	0.1	0.0	0.0	0.5	99.4	0.3	0.0	0.5	99.1	99.1	0.0	0.0	0.0	0.0	99.4	0.0	0.1	99.7	0.1	99.7	0.0	99.9	0.1	0.0	0.0
C	78.0	0.0	0.0	37.0	0.0	0.0	0.0	40.5	0.0	0.0	0.0	0.0	91.5	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0
G	0.0	0.0	99.6	0.5	0.0	99.1	99.2	1.9	0.0	0.0	0.0	99.2	0.0	0.0	0.0	99.5	0.0	99.7	0.0	99.9	0.0	99.8	99.9	99.9	
T	21.5	99.6	0.0	61.5	0.0	0.0	0.0	55.9	0.0	0.0	0.0	99.3	7.9	0.0	99.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
-	0.4	0.3	0.4	0.6	0.6	0.7	0.8	1.2	0.8	0.9	0.8	0.7	0.6	0.5	0.4	0.4	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.0	0.0

evoA1_sEBE-T2A+Rap	Replicate 1	PAM																							
		I	C	T	G	C	A	G	G	C	A	A	G	T	C	A	T	G	A	G	A	G	A	G	G
A	0.1	0.0	0.0	0.1	99.8	0.1	0.0	0.3	99.8	99.8	0.0	0.0	0.0	0.0	99.8	0.0	0.0	99.9	0.0	99.9	0.0	100.0	0.1	0.0	0.0
C	85.7	0.0	0.0	51.8	0.0	0.0	0.0	57.1	0.0	0.0	0.0	0.0	0.0	92.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
G	0.0	0.0	99.9	0.1	0.0	99.8	99.9	1.3	0.0	0.0	0.0	99.8	0.0	0.0	0.0	99.9	0.0	99.9	0.0	99.9	0.0	99.9	100.0	100.0	
T	14.1	99.9	0.0	47.8	0.0	0.0	0.0	40.9	0.0	0.0	0.0	99.8	7.5	0.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
-	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.4	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0

evoA1_sEBE-T2A+Rap	Replicate 2	PAM																							
		I	C	T	G	C	A	G	G	C	A	A	G	T	C	A	T	G	A	G	A	G	A	G	G
A	0.1	0.0	0.0	0.3	99.8	0.0	0.0	0.2	99.9	99.8	0.0	0.0	0.0	0.0	99.8	0.0	0.0	99.9	0.0	99.9	0.0	100.0	0.0	0.0	0.1
C	89.2	0.0	0.0	63.9	0.0	0.0	0.0	68.1	0.0	0.0	0.0	0.0	0.0	94.8	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0
G	0.0	0.0	99.9	0.2	0.1	99.8	99.8	1.1	0.0	0.0	0.0	99.8	0.0	0.0	0.0	99.9	0.1	100.0	0.0	100.0	0.0	100.0	99.9	99.9	
T	10.7	100.0	0.0	35.5	0.0	0.0	0.0	30.3	0.0	0.0	0.0	99.8	5.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
-	0.1	0.0	0.1	0.1	0.1	0.2	0.2	0.3	0.1	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

evoA1_sEBE-T2A+Rap	Replicate 3	PAM																							
		I	C	T	G	C	A	G	G	C	A	A	G	T	C	A	T	G	A	G	A	G	A	G	G
A	0.0	0.0	0.1	0.0	0.0	0.0	0.5	1.8	0.4	0.0	99.9	0.0	0.0	0.0	1.3	0.1	37.8	0.0	0.0	38.9	99.9	99.9	99.9	99.9	
C	99.9	100.0	99.9	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.1	99.9	0.0	0.0	0.1	0.0	0.0	0.0
G	0.0	0.0	0.0	100.0	0.0	0.0	99.5	98.1	99.5	0.0	0.0	0.0	0.0	0.0	0.0	98.7	0.0	62.0	0.0	0.1	61.1	0.0	0.0	0.0	0.0
T	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.1	0.0	0.0	0.0	99.9	0.0	99.9	0.0	99.9	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.0
-	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0

evoA1_sEBE-T2A+Rap	Replicate 1	PAM																							
		I	C	T	G	C	A	G	G	C	A	A	G	T	C	A	T	G	A	G	A	G	A	G	G
A	0.0	0.0	0.1	0.0	99.9	0.0	0.0	0.0	99.9	99.9	0.0	0.0	0.1	99.9	0.0	0.0	99.9	0.1	99.8	0.0	100.0	0.0	0.0	0.0	0.0
C	99.0	0.0	0.0	93.2	0.0	0.0	0.0	95.9	0.0	0.0	0.0	0.0	0.0	99.7	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0
G	0.0	0.0	99.9	0.0	0.0	100.0	99.9	0.1	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	99.9	0.0	100.0	0.0	99.9	100.0	100.0
T	0.9	99.9	0.0	6.8	0.0	0.0	0.1	4.0	0.0	0.1	0.0	100.0	0.3	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	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

evoA1_sEBE-T2A+Rap	Replicate 2	PAM																							
		I	C	T	G	C	A	G	G	C	A	A	G	T	C	A	T	G	A	G	A	G	A	G	G
A	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	99.9	99.9	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	99.8	0.0	100.0	0.0	0.0	0.0
C	98.8	0.0	0.0	91.9	0.0	0.0	0.0	95.1	0.0	0.0	0.0	0.0	0.0	99.6	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0
G	0.0	0.0	100.0	0.0	0.0	100.0	99.9	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	99.9	99.9	
T	1.2	100.0	0.0	8.0	0.0	0.0	0.1	4.9	0.0	0.0	0.0	100.0	0.4	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

evoA1_sEBE-T2A+Rap	Replicate 3	PAM																							
		I	C	T	G	C	A	G	G	C	A	A	G	T	C	A	T	G	A	G	A	G	A	G	G
A	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	99.9	99.9	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	99.8	0.0	100.0	0.0	0.0	0.0
C	98.8	0.0	0.0	91.9	0.0	0.0	0.0	95.1	0.0	0.0	0.0	0.0	0.0	99.6	0										

Supplementary Figure 1

c		IDHI R132H																								
		P127			I128			I129			I130			G131			R132			H133			A134			
		C	C	T	A	T	C	A	T	C	A	T	A	G	G	T	C	G	T	C	A	T	G	C		
untreated	A	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
	C	100.0	99.9	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	0.0	99.9	0.0	
	G	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.0	100.0	100.0	0.0	0.0	99.9	0.5	0.0	0.0	0.4	100.0	0.0	0.0	
	T	0.0	0.0	100.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	99.6	0.0	0.0	0.0	100.0	0.0	0.0	99.4	0.0	0.0	99.6	0.0	0.0	99.6	0.0
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
evoA1-seBE: Replicate 1		PAM			20			15			10			5			1									
		C	C	T	A	T	C	A	T	C	A	T	A	G	G	T	C	G	T	C	A	T	G	C		
	A	0.0	0.0	0.0	100.0	0.0	0.0	98.6	0.0	0.0	98.4	0.0	97.0	23.9	0.7	0.0	0.0	7.4	0.0	0.0	97.6	0.0	30.3	0.1		
	C	99.9	99.9	0.0	0.0	0.0	99.9	0.0	0.0	98.6	0.0	0.0	0.0	0.6	0.0	0.0	96.4	0.0	0.0	97.2	0.0	0.0	0.3	98.7		
	G	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.1	71.8	95.8	0.0	0.0	89.8	0.0	0.0	0.0	0.0	67.6	0.1		
-	0.0	0.0	0.0	0.0	0.0	0.0	0.1	1.3	1.3	1.5	1.7	2.9	3.4	3.4	3.5	2.8	2.8	2.0	2.7	2.3	2.3	1.5	0.9			
evoA1-seBE: Replicate 2		C	C	T	A	T	C	A	T	C	A	T	A	G	G	T	C	G	T	C	A	T	G	C		
	A	0.0	0.0	0.0	99.9	0.0	0.0	99.0	0.1	0.0	98.8	0.0	97.9	21.4	0.6	0.0	0.0	6.0	0.0	0.0	98.0	0.0	24.6	0.1		
	C	99.9	99.9	0.0	0.0	0.0	99.8	0.0	0.1	99.1	0.0	0.0	0.0	0.5	0.0	0.0	97.3	0.0	0.0	97.9	0.0	0.0	0.4	98.6		
	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	75.2	96.7	0.0	0.0	91.9	0.0	0.0	0.0	0.0	73.5	0.0		
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.9	0.8	1.1	1.2	2.0	2.6	2.7	2.7	2.6	2.1	2.1	2.0	1.9	1.8	1.3	1.0		
evoA1-seBE: Replicate 3		C	C	T	A	T	C	A	T	C	A	T	A	G	G	T	C	G	T	C	A	T	G	C		
	A	0.0	0.0	0.0	99.9	0.0	0.0	98.8	0.0	0.0	98.6	0.0	97.4	21.5	0.8	0.0	0.0	5.9	0.0	0.0	97.7	0.0	25.3	0.1		
	C	100.0	99.9	0.0	0.0	0.0	99.9	0.1	0.1	98.8	0.0	0.0	0.1	0.7	0.1	0.1	96.7	0.0	0.1	97.4	0.0	0.0	0.4	98.8		
	G	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	74.6	96.0	0.1	0.0	91.3	0.1	0.0	0.0	0.0	72.9	0.1		
	-	0.0	0.0	0.0	0.0	0.0	0.0	1.1	1.1	1.2	1.4	1.4	2.5	3.0	3.1	3.1	3.2	2.6	2.5	2.5	2.2	2.2	1.1	0.7		
evoA1-seBE: T2A +Rap Replicate 1		PAM			20			15			10			5			1									
		C	C	T	A	T	C	A	T	C	A	T	A	G	G	T	C	G	T	C	A	T	G	C		
	A	0.0	0.0	0.0	100.0	0.0	0.0	99.2	0.0	0.0	98.9	0.0	98.2	18.5	0.3	0.0	0.0	7.4	0.1	0.0	98.8	0.0	26.5	0.1		
	C	100.0	99.9	0.0	0.0	0.0	99.9	0.0	0.0	99.2	0.0	0.0	0.0	0.2	0.0	0.0	98.0	0.0	0.0	98.6	0.0	0.0	0.2	99.1		
	-	0.0	0.0	0.0	0.0	0.0	0.1	0.7	0.6	0.7	1.0	1.1	1.7	2.0	2.0	2.0	2.0	1.4	1.4	1.3	1.2	1.2	0.8	0.6		
evoA1-seBE: T2A +Rap Replicate 2		C	C	T	A	T	C	A	T	C	A	T	A	G	G	T	C	G	T	C	A	T	G	C		
	A	0.0	0.0	0.0	100.0	0.0	0.0	99.5	0.0	0.0	99.3	0.0	98.6	13.6	0.3	0.0	0.0	5.2	0.1	0.0	99.0	0.0	18.7	0.1		
	C	99.9	100.0	0.1	0.0	0.0	99.9	0.0	0.0	99.4	0.0	0.0	0.1	0.1	0.0	0.0	98.5	0.0	0.1	98.9	0.0	0.0	0.2	99.6		
	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	84.7	98.2	0.0	0.0	93.6	0.0	0.0	0.0	0.0	80.5	0.0		
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.5	0.5	0.6	0.7	0.8	1.3	1.5	1.5	1.5	1.5	1.1	1.1	1.1	0.9	0.9	0.5	0.3		
evoA1-seBE: T2A +Rap Replicate 3		C	C	T	A	T	C	A	T	C	A	T	A	G	G	T	C	G	T	C	A	T	G	C		
	A	0.0	0.0	0.0	100.0	0.0	0.0	99.3	0.0	0.0	99.2	0.0	98.4	15.9	0.5	0.0	0.0	6.8	0.0	0.0	98.9	0.0	22.6	0.0		
	C	100.0	100.0	0.0	0.0	0.0	99.9	0.0	0.0	99.2	0.0	0.0	0.1	0.1	0.0	0.0	98.3	0.0	0.0	98.7	0.0	0.0	0.1	99.4		
	G	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	82.2	97.7	0.0	0.0	91.8	0.0	0.0	0.0	0.0	76.8	0.0		
	-	0.0	0.0	0.0	0.0	0.0	0.1	0.6	0.7	0.7	0.8	0.8	1.5	1.8	1.8	1.8	1.7	1.3	1.3	1.2	1.1	1.1	0.5	0.3		
evoA1-seBE: T2A +Rap Replicate 1		PAM			20			15			10			5			1									
		C	C	T	A	T	C	A	T	C	A	T	A	G	G	T	C	G	T	C	A	T	G	C		
	A	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	100.0	0.9	0.1	0.0	0.0	0.4	0.0	0.0	100.0	0.0	1.9	0.0		
	C	100.0	100.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	99.9	0.0	0.0	0.0	100.0		
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0		
evoA1-seBE: T2A +Rap Replicate 2		C	C	T	A	T	C	A	T	C	A	T	A	G	G	T	C	G	T	C	A	T	G	C		
	A	0.0	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	100.0	0.0	99.9	0.6	0.0	0.0	0.0	0.2	0.0	0.0	99.9	0.0	1.3	0.0		
	C	100.0	100.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	0.0	100.0		
	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	99.4	99.9	0.0	0.0	99.8	0.0	0.0	0.0	0.0	98.7	0.0		
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0		
evoA1-seBE: T2A +Rap Replicate 3		C	C	T	A	T	C	A	T	C	A	T	A	G	G	T	C	G	T	C	A	T	G	C		
	A	0.0	0.0	0.0	100.0	0.0	0.0	99.9	0.0	0.0	100.0	0.0	99.9	0.9	0.0	0.0	0.0	0.2	0.0	0.0	99.9	0.0	1.5	0.0		
	C	99.9	100.0	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	100.0	0.0	0.1	100.0	0.0	0.0	0.0	100.0		
	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	99.1	100.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	98.5	0.0		
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0		

Supplementary Figure 1

d *TDG Q51**

	P49				A/T50			Q51			E52			P53			V54			Q55													
	C	C	T	G	C	T	C	A	G	G	A	A	C	C	A	G	T	G	C	A	A	G	G										
untreated	A	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	100.0	100.0	0.0	0.0	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	0.0	0.0	0.0	0.0	0.0	
	C	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	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	
	G	0.0	0.0	0.0	67.3	0.0	0.0	0.0	0.1	100.0	100.0	0.0	0.0	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	100.0	100.0	0.0	0.0	0.0	
	T	0.0	0.0	100.0	32.7	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	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	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				5			10			15			20			PAM						
	C	C	T	G	C	T	C	A	G	G	A	A	C	C	A	G	T	G	C	A	A	G	G
evoA1-seBE Replicate 1	A	0.1	0.1	0.0	0.0	0.3	0.0	0.0	99.0	0.1	0.1	99.2	99.2	0.0	0.0	99.6	0.0	0.0	0.0	100.0	100.0	0.2	0.0
	C	82.8	58.2	0.0	0.0	47.2	0.0	47.2	0.0	0.0	0.0	0.0	99.2	96.9	0.0	0.0	0.0	0.0	99.8	0.0	0.0	0.1	0.0
	G	0.0	0.1	0.0	65.9	0.4	0.0	0.3	0.0	99.1	99.0	0.0	0.0	0.0	0.0	99.6	0.0	99.9	0.0	0.0	0.0	99.7	100.0
	T	16.8	41.1	99.6	33.6	51.6	99.1	51.4	0.0	0.0	0.0	0.0	0.0	0.0	2.5	0.0	0.0	99.7	0.0	0.2	0.0	0.0	0.0
	-	0.2	0.5	0.4	0.5	0.6	0.9	1.1	0.0	0.8	0.9	0.8	0.8	0.7	0.6	0.4	0.3	0.3	0.0	0.0	0.0	0.0	0.0

	1				5			10			15			20			PAM							
	C	C	T	G	C	T	C	A	G	G	A	A	C	C	A	G	T	G	C	A	A	G	G	
evoA1-seBE Replicate 2	A	0.0	0.1	0.0	0.0	0.1	0.0	0.1	99.4	0.2	0.0	99.5	99.5	0.0	0.0	99.7	0.0	0.0	0.0	100.0	100.0	0.2	0.0	
	C	83.9	61.7	0.0	0.0	51.8	0.0	52.0	0.0	0.0	0.0	0.0	99.5	96.3	0.0	0.0	0.0	0.0	99.7	0.0	0.0	0.0	0.0	
	G	0.0	0.0	0.0	65.8	0.4	0.0	0.2	0.0	99.2	99.4	0.0	0.0	0.0	0.0	0.0	99.6	0.1	99.9	0.0	0.0	0.0	99.8	99.9
	T	15.7	37.6	99.5	32.7	46.9	99.2	46.6	0.0	0.0	0.0	0.0	0.0	0.0	3.2	0.0	0.1	99.8	0.0	0.3	0.0	0.0	0.0	0.0
	-	0.3	0.5	0.5	0.4	0.8	0.8	1.2	0.6	0.6	0.5	0.5	0.5	0.5	0.4	0.2	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0

	1				5			10			15			20			PAM							
	C	C	T	G	C	T	C	A	G	G	A	A	C	C	A	G	T	G	C	A	A	G	G	
evoA1-seBE Replicate 3	A	0.1	0.1	0.0	0.0	0.1	0.0	0.1	99.3	0.1	0.1	99.4	99.4	0.0	0.0	99.6	0.0	0.0	0.0	100.0	100.0	0.4	0.0	
	C	83.8	60.9	0.0	0.0	52.2	0.0	52.4	0.0	0.0	0.0	0.0	99.4	97.3	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	
	G	0.1	0.0	0.0	67.1	0.6	0.0	0.2	0.0	99.1	99.3	0.0	0.0	0.0	0.0	0.0	99.6	0.1	100.0	0.0	0.0	0.0	99.6	100.0
	T	15.8	38.5	99.6	32.5	46.3	99.1	46.3	0.0	0.0	0.0	0.0	0.0	0.1	2.3	0.0	0.0	99.7	0.0	0.1	0.0	0.0	0.0	0.0
	-	0.2	0.5	0.3	0.4	0.7	0.8	1.1	0.6	0.6	0.6	0.6	0.6	0.5	0.4	0.3	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.0

	1				5			10			15			20			PAM							
	C	C	T	G	C	T	C	A	G	G	A	A	C	C	A	G	T	G	C	A	A	G	G	
evoA1-seBE T2A +Rap Replicate 1	A	0.2	0.0	0.0	0.0	0.0	0.0	0.0	99.7	0.0	0.0	99.6	99.7	0.0	0.0	99.8	0.0	0.0	0.0	100.0	100.0	0.0	0.0	
	C	86.9	70.4	0.0	0.0	65.1	0.0	65.2	0.0	0.0	0.0	0.0	99.7	97.9	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	
	G	0.1	0.0	0.0	67.9	0.1	0.0	0.1	0.0	99.7	99.6	0.0	0.0	0.0	0.0	0.1	99.9	0.0	100.0	0.0	0.0	0.0	100.0	100.0
	T	12.7	29.4	99.8	31.8	34.5	99.6	34.2	0.0	0.0	0.0	0.0	0.0	0.0	1.8	0.0	0.0	100.0	0.0	0.1	0.0	0.0	0.0	0.0
	-	0.1	0.2	0.2	0.2	0.3	0.3	0.5	0.3	0.3	0.4	0.4	0.3	0.3	0.2	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0

	1				5			10			15			20			PAM							
	C	C	T	G	C	T	C	A	G	G	A	A	C	C	A	G	T	G	C	A	A	G	G	
evoA1-seBE T2A +Rap Replicate 2	A	0.0	0.1	0.0	0.0	0.1	0.0	0.0	99.8	0.1	0.0	99.7	99.8	0.0	0.0	99.9	0.0	0.0	0.0	100.0	100.0	0.0	0.0	
	C	89.7	77.9	0.0	0.0	74.4	0.0	74.3	0.0	0.0	0.0	0.0	99.8	98.6	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	
	G	0.0	0.0	0.0	66.9	0.2	0.1	0.1	0.0	99.6	99.7	0.0	0.0	0.0	0.0	0.0	99.8	0.1	100.0	0.0	0.0	0.0	100.0	100.0
	T	10.2	21.9	99.8	32.9	25.2	99.6	25.3	0.0	0.0	0.1	0.0	0.0	0.0	1.2	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0
	-	0.1	0.1	0.1	0.1	0.2	0.2	0.3	0.2	0.2	0.3	0.2	0.2	0.2	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0

	1				5			10			15			20			PAM							
	C	C	T	G	C	T	C	A	G	G	A	A	C	C	A	G	T	G	C	A	A	G	G	
evoA1-seBE T2A +Rap Replicate 3	A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.8	0.0	0.0	99.8	99.7	0.0	0.0	100.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0	
	C	89.6	76.5	0.0	0.0	71.0	0.0	71.4	0.0	0.0	0.0	0.0	99.7	98.5	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	
	G	0.0	0.0	0.0	66.7	0.2	0.0	0.0	0.0	99.7	99.8	0.0	0.0	0.0	0.0	0.0	100.0	0.1	100.0	0.0	0.0	0.0	100.0	100.0
	T	10.2	23.2	99.9	33.2	28.6	99.8	28.4	0.0	0.0	0.0	0.0	0.0	0.0	1.4	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0
	-	0.2	0.2	0.1	0.1	0.2	0.2	0.3	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

	1				5			10			15			20			PAM							
	C	C	T	G	C	T	C	A	G	G	A	A	C	C	A	G	T	G	C	A	A	G	G	
evoA1-seBE T2A +Rap Replicate 1	A	0.1	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0	
	C	99.2	97.6	0.0	0.0	96.8	0.0	96.8	0.0	0.0	0.0	0.0	0.0	100.0	99.9	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	
	G	0.0	0.0	0.0	65.0	0.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	100.0	100.0
	T	0.7	2.4	100.0	34.9	3.2	100.0	3.2	0.0	0.0	0.0	0.0	0.0	0.0	0.1	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	0.0	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				5			10			15			20			PAM							
	C	C	T	G	C	T	C	A	G	G	A	A	C	C	A	G	T	G	C	A	A	G	G	
evoA1-seBE T2A +Rap Replicate 2	A	0.0	0.0	0.0	0.0	0.1	0.0	0.1	100.0	0.0	0.0	99.9	99.9	0.1	0.0	99.9	0.1	0.0	0.0	100.0	100.0	0.0	0.0	
	C	99.7	97.9	0.0	0.0	97.3	0.0	97.4	0.0	0.0	0.0	0.0	0.0	99.9	99.8	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	
	G	0.0	0.0	0.0	65.7	0.0	0.1	0.0	0.0	100.0	99.9	0.0	0.1	0.0	0.0	0.0	99.9	0.1	100.0	0.0	0.0	0.0	99.9	100.0
	T	0.3	2.0	100.0	34.2	2.5	99.8	2.4	0.0	0.0	0.1	0.0	0.0	0.0	0.1	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	0.0	0.0	0.0	0.0	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				5			10			15			20			PAM						
	C	C	T	G	C	T	C	A	G	G	A	A	C	C	A	G	T	G	C	A	A	G	G
evoA1-seBE T2A +Rap Replicate 3	A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.1	100.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0
	C	99.4	98.2	0.0	0.0	97.7	0.0	97.7	0.0	0.0	0.0	0.0	0.0	1									

Supplementary Figure 1

<i>e</i>		TDG Q172*																										
		E170				V171				Q172				K173				N174				H175				M176		
untreated		T	G	A	G	G	T	C	C	A	G	C	T	G	A	A	C	C	A	T	A	T	G	G				
	A	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.0	99.9	0.0	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			
	C	0.0	0.0	0.0	0.0	0.0	0.0	99.7	99.8	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	99.9	100.0	0.0	0.1	0.0	0.1	0.0	0.0			
	G	0.0	99.9	0.1	100.0	99.9	0.2	0.1	0.0	0.1	99.9	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	100.0	99.9			
	T	100.0	0.0	0.0	0.0	0.0	99.8	0.2	0.2	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.1	0.0	0.0	99.9	0.0	99.9	0.0	99.9	0.1			
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0				

evoA1-seB:max Replicate 1		I	G	A	G	G	T	C	C	A	G	G	C	T	G	A	A	C	C	A	T	A	T	G	G
	A	0.0	0.0	99.5	0.0	0.0	0.0	0.5	0.1	99.4	0.0	0.0	0.0	0.0	99.6	99.7	0.1	0.1	99.9	0.0	99.9	0.0	99.9	0.0	0.0
	C	0.0	0.0	0.0	0.0	0.0	0.0	37.3	42.3	0.0	0.0	95.9	0.0	0.0	0.0	0.0	0.0	99.5	99.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	0.0	99.5	0.0	99.5	99.5	0.0	2.4	0.1	0.1	99.5	0.1	0.0	99.6	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	99.9	99.9
	T	99.5	0.1	0.0	0.0	0.0	99.5	59.2	57.0	0.0	0.0	3.5	99.5	0.0	0.0	0.0	0.1	0.6	0.0	99.9	0.0	99.9	0.0	99.9	0.0
-	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.4	0.4	0.3	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1	

evoA1-seB:max Replicate 2		C	C	T	G	C	T	C	A	G	G	A	A	C	C	A	G	T	G	C	A	A	G	G	
	A	0.0	0.1	99.9	0.0	0.0	0.1	0.6	0.2	99.7	0.0	0.1	0.0	0.1	99.6	99.7	0.0	0.1	99.9	0.0	100.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	0.0	0.0	0.0	43.3	48.8	0.0	0.0	95.9	0.0	0.0	0.1	0.0	99.8	99.2	0.0	0.0	0.0	0.0	0.0	0.0	
	G	0.0	99.8	0.0	99.8	99.7	0.5	2.6	0.1	0.1	99.7	0.2	0.0	99.6	0.1	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	100.0	99.9
	T	99.8	0.0	0.0	0.0	0.0	99.2	53.3	50.6	0.0	0.0	3.6	99.7	0.0	0.0	0.0	0.1	0.1	0.6	0.0	99.9	0.0	100.0	0.0	0.0
-	0.1	0.1	0.1	0.2	0.3	0.3	0.3	0.4	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1	

evoA1-seB:max Replicate 3		C	C	T	G	C	T	C	A	G	G	A	A	C	C	A	G	T	G	C	A	A	G	G	
	A	0.0	0.0	99.6	0.1	0.0	0.1	0.5	0.2	99.7	0.0	0.0	0.0	0.1	99.7	99.7	0.0	0.0	99.8	0.0	99.9	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	0.0	0.0	0.0	42.0	47.0	0.0	0.0	95.7	0.0	0.0	0.0	0.0	99.8	99.2	0.0	0.0	0.0	0.0	0.0	0.0	
	G	0.0	99.5	0.0	99.5	99.6	0.3	2.4	0.1	0.0	99.7	0.1	0.0	99.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	99.9
	T	99.7	0.1	0.0	0.0	0.0	99.3	54.8	52.5	0.0	0.0	3.9	99.7	0.0	0.0	0.0	0.0	0.6	0.0	99.9	0.0	99.9	0.0	0.0	0.1
-	0.4	0.4	0.4	0.4	0.4	0.3	0.3	0.2	0.2	0.3	0.3	0.3	0.3	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1	

evoA1-seB: T2A +Rap Replicate 1		I	G	A	G	G	T	C	C	A	G	G	C	T	G	A	A	C	C	A	T	A	T	G	G
	A	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	99.9	0.2	0.1	100.0	0.0	100.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	0.0	0.0	0.0	53.2	56.9	0.0	0.0	96.6	0.0	0.0	0.0	0.0	99.7	99.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	0.0	99.9	0.0	99.9	99.9	0.0	0.4	0.1	0.0	100.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0
	T	99.9	0.0	0.0	0.0	0.0	100.0	46.3	43.0	0.0	0.0	3.4	100.0	0.0	0.0	0.0	0.0	0.8	0.0	100.0	0.0	100.0	0.0	0.0	0.0
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

evoA1-seB: T2A +Rap Replicate 2		C	C	T	G	C	T	C	A	G	G	A	A	C	C	A	G	T	G	C	A	A	G	G	
	A	0.0	0.0	99.9	0.0	0.0	0.1	0.1	0.0	99.9	0.0	0.0	0.0	0.0	99.9	99.9	0.0	0.0	99.9	0.0	99.9	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	0.0	0.0	0.0	66.9	70.4	0.0	0.0	97.9	0.0	0.0	0.0	0.0	99.9	99.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	0.0	99.9	0.0	99.9	99.9	0.4	0.4	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	99.9	99.9
	T	99.9	0.0	0.0	0.0	0.0	99.5	32.6	29.6	0.0	0.0	2.0	99.9	0.0	0.0	0.0	0.0	0.5	0.0	99.9	0.0	99.9	0.0	99.9	0.0
-	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	

evoA1-seB: T2A +Rap Replicate 3		C	C	T	G	C	T	C	A	G	G	A	A	C	C	A	G	T	G	C	A	A	G	G	
	A	0.1	0.0	99.9	0.0	0.0	0.0	0.2	0.0	99.9	0.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0	99.9	0.0	100.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	0.0	0.0	0.0	56.9	59.8	0.0	0.0	97.5	0.0	0.0	0.0	0.0	99.9	99.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	0.1	99.9	0.0	99.9	99.9	0.3	0.3	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.0	100.0	100.0
	T	99.8	0.0	0.0	0.0	0.0	99.6	42.6	40.0	0.0	0.0	2.4	99.9	0.0	0.0	0.0	0.1	0.6	0.0	99.9	0.0	99.9	0.0	0.0	0.0
-	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	

evoA1-seB: T2A +Rap Replicate 1		I	G	A	G	G	T	C	C	A	G	G	C	T	G	A	A	C	C	A	T	A	T	G	G
	A	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	100.0	0.1	0.1	100.0	0.0	100.0	0.0	0.0	0.0	0.0
	C	0.1	0.0	0.0	0.0	0.0	0.0	94.0	95.9	0.0	0.0	99.6	0.0	0.0	0.0	0.0	99.9	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	0.0	99.9	0.0	100.0	100.0	0.0	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	99.9	100.0
	T	99.9	0.0	0.0	0.0	0.0	100.0	5.9	4.0	0.0	0.0	0.4	100.0	0.0	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	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

evoA1-seB: T2A +Rap Replicate 2		C	C	T	G	C	T	C	A	G	G	A	A	C	C	A	G	T	G	C	A	A	G	G	
	A	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	100.0	99.9	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	0.0	0.0	0.0	95.7	97.5	0.0	0.0	99.8	0.0	0.0	0.0	0.1	100.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	0.0	100.0	0.0	100.0	100.0	0.3	0.1	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	0.0	100.0	100.0
	T	100.0	0.0	0.0	0.0	0.0	99.5	4.2	2.5	0.0	0.0	0.2	100.0	0.0	0.0	0.0	0.1	0.0	0.0	99.9	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	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

evoA1-seB: T2A +Rap Replicate 3		C	C	T	G	C	T	C	A	G	G	A	A	C	C	A	G	T	G	C	A	A	G	G	
	A	0.1	0.0	100.0	0.0	0.1	0.1	0.1	0.0	99.9	0.0	0.0	0.0	0.0	99.9	99.9	0.0	0.0	99.9	0.0	99.9	0.0	99.9	0.0	0.0
	C	0.0	0.0	0.0	0.0	0.0	0.1	94.4	96.6	0.0	0.0	99.8	0.1	0.0	0.1	0.0	100.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	0.0	100.0	0.0	100.0	100.0	0.3	0.1	0.0	0.1	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.0	100.0	99.9
	T	99.9	0.0	0.0	0.0	0.0	99.6	5.4	3.4	0.0	0.0	0.2	100.0	0.0	0.0	0.1	0.0	0.1	0.0	99.9	0.0	100.0	0.0		

Supplementary Figure 1

<i>f</i>		<i>TET2 Q180*</i>																											
		L179				Q180				I181				L182				N183				E184				Q185			
		G	C	T	T	C	A	G	A	T	T	C	T	G	A	A	T	G	A	G	C	A	G	G					
untreated	A	0.0	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	100.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0					
	C	0.0	99.9	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	100.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0					
	G	100.0	0.0	0.1	0.1	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.1	100.0	0.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	100.0					
	T	0.0	0.0	99.9	99.9	0.0	0.0	0.0	0.0	100.0	100.0	0.0	99.8	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0					
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0					

		I	C	T	T	C	A	G	A	T	T	C	T	G	A	A	T	G	A	G	C	A	G	G
evoA1-seBEMax Replicate 1	A	0.0	0.0	0.0	0.0	0.1	99.7	0.0	99.7	0.0	0.0	0.1	0.0	0.0	99.7	99.8	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0
	C	0.0	94.6	0.0	0.0	75.8	0.0	0.0	0.0	0.0	0.0	87.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	
	G	99.9	0.1	0.0	0.0	0.1	0.0	99.7	0.0	0.0	0.0	0.3	0.0	99.7	0.0	0.0	0.0	99.9	0.0	99.9	0.0	0.0	100.0	100.0
	T	0.0	5.2	99.8	99.8	23.7	0.0	0.0	0.0	99.6	99.7	11.9	99.7	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	-	0.1	0.1	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.3	0.3	0.2	0.2	0.2	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0

		G	C	T	T	C	A	G	A	T	T	C	T	G	A	A	T	G	A	G	C	A	G	G
evoA1-seBEMax Replicate 2	A	0.0	0.0	0.0	0.0	0.2	99.8	0.0	99.7	0.0	0.0	0.2	0.0	0.0	99.8	99.8	0.0	0.1	99.9	0.0	0.0	100.0	0.0	0.0
	C	0.0	93.8	0.0	0.0	73.4	0.0	0.0	0.0	0.0	0.0	86.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	
	G	99.9	0.1	0.0	0.0	0.3	0.0	99.7	0.0	0.0	0.0	0.3	0.0	99.8	0.0	0.0	0.0	99.8	0.0	99.9	0.0	0.0	100.0	99.9
	T	0.0	6.0	99.8	99.8	25.9	0.0	0.0	0.0	99.6	99.6	12.9	99.6	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	-	0.1	0.1	0.2	0.2	0.3	0.2	0.3	0.3	0.3	0.4	0.3	0.4	0.3	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.0	0.0

		G	C	T	T	C	A	G	A	T	T	C	T	G	A	A	T	G	A	G	C	A	G	G
evoA1-seBEMax Replicate 3	A	0.1	0.0	0.0	0.0	0.2	99.8	0.0	99.7	0.0	0.0	0.1	0.0	0.0	99.7	99.7	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0
	C	0.0	93.3	0.0	0.0	70.9	0.0	0.0	0.0	0.0	0.0	85.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	
	G	99.8	0.0	0.0	0.0	0.2	0.0	99.7	0.0	0.0	0.0	0.3	0.0	99.7	0.0	0.0	0.0	99.8	0.0	99.9	0.0	0.0	99.9	100.0
	T	0.0	6.5	99.8	99.8	28.5	0.0	0.0	0.0	99.7	99.7	14.2	99.6	0.0	0.0	0.0	99.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	-	0.1	0.1	0.1	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.4	0.3	0.3	0.3	0.3	0.3	0.2	0.1	0.1	0.1	0.1	0.0	0.0

		I	C	T	T	C	A	G	A	T	T	C	T	G	A	A	T	G	A	G	C	A	G	G
evoA1-seBE T2A+Rap Replicate 1	A	0.0	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	99.9	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0
	C	0.0	96.0	0.0	0.0	85.7	0.0	0.0	0.0	0.0	0.0	93.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	
	G	99.9	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	100.0	100.0
	T	0.0	3.9	99.9	99.9	14.1	0.0	0.0	0.0	99.9	99.8	6.5	99.8	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	-	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0

		G	C	T	T	C	A	G	A	T	T	C	T	G	A	A	T	G	A	G	C	A	G	G
evoA1-seBE T2A+Rap Replicate 2	A	0.0	0.0	0.0	0.0	0.0	100.0	0.0	99.9	0.0	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
	C	0.0	97.3	0.0	0.0	90.2	0.0	0.0	0.0	0.0	0.0	95.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	
	G	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.1	0.0	99.9	0.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	100.0	100.0
	T	0.0	2.7	99.9	99.9	9.7	0.0	0.0	0.0	99.9	99.9	4.5	99.9	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	0.0	0.0	0.0	0.0	0.0	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	C	T	T	C	A	G	A	T	T	C	T	G	A	A	T	G	A	G	C	A	G	G
evoA1-seBE T2A+Rap Replicate 3	A	0.0	0.0	0.0	0.0	0.1	100.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0
	C	0.0	98.4	0.0	0.0	93.1	0.0	0.0	0.0	0.0	0.0	96.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	
	G	99.9	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.1	0.0	100.0	0.0	0.0	0.0	99.9	0.0	99.9	0.0	0.0	100.0	99.9
	T	0.0	1.6	99.9	99.9	6.8	0.0	0.0	0.0	99.9	99.9	3.4	99.9	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	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

		I	C	T	T	C	A	G	A	T	T	C	T	G	A	A	T	G	A	G	C	A	G	G
evoA1-seBE T2A Rap Replicate 1	A	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	100.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0
	C	0.0	99.9	0.0	0.0	99.6	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	100.0	0.0	0.0	
	G	100.0	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	100.0	0.0	100.0	0.0	0.0	100.0	100.0
	T	0.0	0.1	100.0	100.0	0.4	0.0	0.0	0.0	100.0	100.0	0.1	99.9	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	0.0	0.0	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	C	T	T	C	A	G	A	T	T	C	T	G	A	A	T	G	A	G	C	A	G	G
evoA1-seBE T2A Rap Replicate 2	A	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	99.9	99.9	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0
	C	0.0	99.9	0.0	0.0	99.6	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	
	G	100.0	0.0	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	0.0	100.0	0.0	99.9	0.0	0.0	100.0	100.0
	T	0.0	0.1	100.0	100.0	0.4	0.0	0.0	0.0	100.0	100.0	0.1	100.0	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	0.0	0.0	0.0	0.0	0.0	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	C	T	T	C	A	G	A	T	T	C	T	G	A	A	T	G	A	G	C	A	G	G
evoA1-seBE T2A Rap Replicate 3	A	0.0	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	99.9	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0
	C	0.0	99.8	0.0	0.0	98.9	0.0	0.0	0.0	0.0	0.0	99.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	
	G	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	0.0	0.0	0.0	99.9	0.0	100.0	0.0	0.0	100.0	100.0
	T	0.0	0.2	99.9	99.9	1.0	0.0	0.0	0.0	100.0	100.0	0.4	99.9	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	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Supplementary Figure 1

		g																						
		P167			I168			T169			I170			G171			R172			H173				
untreated		C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C
	A	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	0.2	0.2	0.0	99.9	0.5	0.5	0.0	100.0	0.0	0.1	0.0
	C	99.9	100.0	100.0	0.0	0.0	100.0	0.0	99.9	100.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	100.0	0.0	99.9	0.0	99.9
	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	99.8	99.8	0.0	0.1	99.4	99.5	0.0	0.0	0.0	99.9	0.0
	T	0.1	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

evoA1-IBE:max Replicate 1		PAM			20			15			10			5			1							
		C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C
	A	0.0	0.0	0.0	99.9	0.0	0.0	99.6	0.0	0.0	99.6	0.0	0.0	18.0	7.6	0.0	99.1	48.9	49.1	0.0	99.4	0.0	7.9	0.0
	C	100.0	100.0	99.9	0.0	0.0	99.8	0.1	99.7	99.6	0.0	0.0	0.0	0.0	0.0	99.1	0.0	0.3	0.2	99.4	0.0	99.5	0.0	99.5
	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	81.2	91.5	0.0	0.0	49.1	49.4	0.0	0.0	0.0	91.6	0.0
T	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	99.4	99.3	0.1	0.1	0.1	0.0	0.8	0.5	0.0	0.0	0.0	0.1	0.1	
-	0.0	0.0	0.0	0.0	0.0	0.2	0.3	0.3	0.4	0.4	0.6	0.7	0.7	0.8	0.8	0.9	0.9	0.8	0.6	0.5	0.5	0.5	0.5	

evoA1-IBE:max Replicate 2		C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C
	A	0.0	0.0	0.0	99.9	0.0	0.0	99.7	0.0	0.0	99.7	0.0	0.0	13.1	5.6	0.0	99.3	40.1	39.8	0.0	99.5	0.0	5.3	0.0
	C	99.9	99.9	99.9	0.0	0.0	99.9	0.0	99.7	99.7	0.0	0.0	0.0	0.0	0.0	99.4	0.0	0.2	0.3	99.6	0.0	99.7	0.0	99.7
	G	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	86.3	93.8	0.0	0.0	58.4	58.8	0.0	0.0	0.0	94.4	0.0
	T	0.1	0.0	0.0	0.0	99.9	0.1	0.0	0.1	0.0	0.0	99.6	99.4	0.1	0.0	0.1	0.0	0.6	0.5	0.0	0.0	0.0	0.0	0.1
-	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.2	0.2	0.3	0.4	0.5	0.6	0.6	0.6	0.6	0.7	0.6	0.4	0.4	0.3	0.3	0.2	

evoA1-IBE:max Replicate 3		C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C
	A	0.0	0.0	0.0	99.8	0.0	0.0	99.7	0.0	0.0	99.6	0.0	0.0	20.0	9.2	0.0	99.1	53.7	53.4	0.0	99.5	0.0	9.9	0.0
	C	99.9	99.9	99.9	0.0	0.0	99.8	0.0	99.8	99.6	0.0	0.0	0.0	0.1	0.1	99.2	0.0	0.4	0.4	99.4	0.0	99.7	0.0	99.7
	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	79.2	89.9	0.0	0.0	44.4	45.0	0.0	0.0	0.0	89.7	0.0
	T	0.0	0.0	0.0	0.1	99.9	0.1	0.0	0.0	0.0	0.0	99.4	99.3	0.0	0.0	0.0	0.0	0.7	0.5	0.0	0.0	0.0	0.0	0.0
-	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.3	0.3	0.5	0.7	0.7	0.8	0.8	0.8	0.8	0.7	0.5	0.5	0.3	0.3	0.3	

evoA1-seBE T2A +Rap Replicate 1		PAM			20			15			10			5			1							
		C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C
	A	0.0	0.0	0.0	100.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	9.1	3.5	0.0	99.8	30.7	30.2	0.0	99.9	0.0	4.2	0.0
	C	100.0	100.0	100.0	0.0	0.0	100.0	0.0	99.9	99.9	0.0	0.0	0.0	0.1	0.0	99.8	0.0	0.1	0.2	99.9	0.0	99.9	0.0	99.9
	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	90.7	96.3	0.0	0.0	68.7	69.3	0.0	0.0	0.0	95.8	0.0
T	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	99.8	99.9	0.0	0.0	0.0	0.0	0.3	0.2	0.0	0.0	0.0	0.0	0.0	
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	

evoA1-seBE T2A +Rap Replicate 2		C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C
	A	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	6.4	2.3	0.0	99.8	22.7	22.3	0.0	99.8	0.0	2.7	0.0
	C	99.9	100.0	100.0	0.0	0.0	99.9	0.1	99.9	99.9	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.2	0.2	99.9	0.0	99.9	0.0	99.9
	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	93.4	97.5	0.0	0.0	76.9	77.3	0.0	0.1	0.0	97.2	0.0
	T	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	99.9	99.9	0.0	0.0	0.0	0.0	0.1	0.2	0.0	0.0	0.0	0.0	0.0
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	

evoA1-seBE T2A +Rap Replicate 3		C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C
	A	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	10.2	3.3	0.0	99.7	35.9	35.3	0.0	99.8	0.0	4.9	0.0
	C	99.9	99.9	99.9	0.0	0.0	99.9	0.0	99.9	99.9	0.0	0.0	0.0	0.0	0.0	99.6	0.0	0.3	0.2	99.8	0.0	99.8	0.0	99.9
	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	89.5	96.4	0.0	0.1	63.3	64.1	0.0	0.0	0.0	95.0	0.0
	T	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	99.7	99.7	0.0	0.0	0.0	0.0	0.3	0.1	0.0	0.0	0.0	0.0	0.0
-	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.3	0.3	0.3	0.3	0.3	0.3	0.2	0.2	0.2	0.2	0.2	0.1	

evoA1-seBE T2A +Rap Replicate 1		PAM			20			15			10			5			1							
		C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C
	A	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.7	0.3	0.0	100.0	6.0	5.5	0.0	100.0	0.0	0.5	0.0
	C	100.0	100.0	100.0	0.0	0.0	100.0	0.0	99.9	100.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.1	0.0	99.9	0.0	100.0	0.0	99.9
	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	99.2	99.7	0.0	0.0	93.9	94.4	0.0	0.0	0.0	99.5	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	99.9	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

evoA1-seBE T2A +Rap Replicate 2		C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C
	A	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	0.5	0.1	0.0	99.9	4.0	3.5	0.0	99.8	0.0	0.2	0.0
	C	99.9	100.0	100.0	0.0	0.0	100.0	0.1	99.9	99.9	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.1	0.0	99.9	0.0	99.9	0.0	99.9
	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	99.4	99.8	0.0	0.1	95.9	96.4	0.0	0.1	0.0	99.8	0.0
	T	0.1	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	99.9	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	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

evoA1-seBE T2A +Rap Replicate 3		C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C
	A	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	0.7	0.3	0.0	99.9	5.7	5.1	0.0	99.9	0.0	0.2	0.0
	C	100.0	100.0	99.9	0.0	0.0	99.9	0.0	99.9	99.9	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.1	0.0	100.0	0.0	99.9	0.0	99.9
	G	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.3	99.7	0.0	0.1	94.2	94.8	0.0	0.0	0.0		

Supplementary Figure 1

<i>h</i>		<i>EMXI</i>																							
		E225			S226			E227			Q228			K229			K230			K231					
untreated		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	G	G	
	A	0.0	99.9	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	99.8	0.0	99.7	99.9	0.0	99.9	99.9	0.0	99.4	99.6	0.0	0.0	0.0
	C	0.0	0.0	0.0	0.0	99.8	99.8	0.0	0.0	0.0	99.8	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
	G	99.9	0.0	99.8	0.1	0.0	0.0	99.8	0.0	99.9	0.1	0.1	99.9	0.1	0.1	99.7	0.0	0.0	99.5	0.1	0.0	99.8	99.8	99.8	99.8
	T	0.0	0.0	0.1	99.7	0.2	0.1	0.1	0.0	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.1	0.1	0.0	0.1	0.1
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.4	0.4	0.0	0.0	0.0	0.0	

evoA1-seB:imx	Replicate 1	1			5			10			15			20			PAM						
		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	G	G		
A	0.5	99.7	0.1	0.0	0.4	0.2	0.0	99.6	0.0	1.1	99.6	0.0	99.8	99.8	0.1	99.8	99.8	0.0	99.7	99.8	0.0	0.0	0.0
C	0.1	0.0	0.0	0.1	46.1	47.3	0.0	0.0	0.0	93.0	0.0	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	99.1	0.0	99.6	2.1	1.5	0.5	99.5	0.0	99.5	0.2	0.0	99.7	0.0	0.0	99.7	0.0	0.0	99.7	0.0	0.0	99.9	99.9	99.9
T	0.0	0.0	0.1	97.4	51.6	51.6	0.0	0.0	0.0	5.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.0
-	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.3	0.3	0.2	0.2	0.2	0.2	0.1	0.1	0.3	0.2	0.2	0.0	0.0

evoA1-seB:imx	Replicate 2	G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	G	G
		A	0.4	99.7	0.1	0.0	0.5	0.3	0.1	99.7	0.0	0.0	99.7	0.0	99.7	99.8	0.1	99.9	99.9	0.0	99.7	99.8	0.0	0.0
C	0.1	0.0	0.0	0.0	52.8	54.3	0.0	0.0	0.0	95.2	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	
G	99.3	0.0	99.5	0.2	1.6	0.4	99.6	0.0	99.6	0.1	0.1	99.7	0.1	0.1	99.7	0.0	0.0	99.7	0.0	0.0	99.9	99.9	99.8	
T	0.0	0.0	0.2	99.6	44.7	44.7	0.1	0.0	0.1	4.5	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.1	0.1	0.1	0.0	0.1	0.2	
-	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.3	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.0	0.0	0.0	

evoA1-seB:imx	Replicate 3	G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	G	G
		A	0.5	99.8	0.0	0.0	0.6	0.1	0.0	99.8	0.0	0.1	99.6	0.0	99.6	99.8	0.0	99.8	99.8	0.0	99.5	99.7	0.0	0.0
C	0.1	0.0	0.0	0.0	45.0	46.2	0.0	0.0	0.0	94.7	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	
G	99.3	0.1	99.6	0.1	1.4	0.5	99.7	0.0	99.7	0.1	0.1	99.8	0.1	0.1	99.7	0.0	0.0	99.6	0.0	0.0	99.9	99.8	99.7	
T	0.1	0.0	0.2	99.7	52.9	53.0	0.1	0.0	0.1	4.9	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.1	0.1	0.1	0.0	0.1	0.2	
-	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.3	0.3	0.3	0.1	0.1	

evoA1-seB:imx	T2A+Rap	1			5			10			15			20			PAM						
		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	G	G		
A	0.1	99.9	0.0	0.1	0.1	0.0	0.0	99.9	0.0	0.1	99.8	0.0	99.9	99.9	0.0	99.9	99.9	0.0	99.8	99.8	0.0	0.0	0.0
C	0.0	0.0	0.0	0.1	65.6	65.8	0.0	0.0	0.0	96.1	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
G	99.8	0.0	99.9	1.7	0.3	0.0	99.9	0.0	99.8	0.2	0.0	99.9	0.0	0.0	99.9	0.0	0.0	99.8	0.0	0.0	99.9	99.9	99.9
T	0.0	0.0	0.1	98.1	34.0	34.0	0.0	0.0	0.0	2.3	0.0	0.0	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	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	0.0	0.2	0.2	0.2	0.0	0.0

evoA1-seB:imx	T2A+Rap	G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	G	G
		A	0.1	99.9	0.0	0.0	0.1	0.0	0.0	99.9	0.0	0.0	99.7	0.0	99.6	99.8	0.0	99.9	99.9	0.0	99.6	99.8	0.0	0.0
C	0.0	0.0	0.0	0.1	72.9	73.2	0.0	0.0	0.0	97.8	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	
G	99.8	0.1	99.8	0.1	0.6	0.1	99.9	0.0	99.8	0.1	0.1	99.9	0.2	0.1	99.7	0.0	0.0	99.7	0.0	0.0	99.8	99.8	99.6	
T	0.1	0.0	0.2	99.7	26.4	26.7	0.1	0.0	0.1	2.1	0.1	0.0	0.0	0.1	0.2	0.0	0.0	0.2	0.2	0.0	0.1	0.2	0.3	
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	

evoA1-seB:imx	T2A+Rap	G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	G	G
		A	0.0	99.9	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.8	0.0	99.6	99.8	0.0	99.9	99.9	0.0	99.6	99.8	0.0	0.0
C	0.0	0.0	0.0	0.0	60.3	60.3	0.0	0.0	0.0	96.6	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	
G	99.8	0.0	99.8	0.1	0.6	0.1	99.8	0.0	99.9	0.0	0.1	99.9	0.2	0.1	99.8	0.0	0.0	99.6	0.1	0.0	99.9	99.8	99.7	
T	0.0	0.0	0.1	99.8	39.0	39.5	0.2	0.0	0.1	3.3	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.2	0.1	0.0	0.1	0.1	0.3	
-	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.2	0.2	0.2	0.0	0.0	0.0	

evoA1-seB:imx	T2A+Rap	1			5			10			15			20			PAM						
		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	G	G		
A	0.0	99.9	0.0	0.0	0.0	0.0	0.0	99.9	0.0	1.3	99.9	0.0	99.9	99.9	0.0	99.9	99.9	0.0	99.7	99.8	0.0	0.0	0.0
C	0.0	0.0	0.0	0.1	94.6	94.8	0.0	0.0	0.0	98.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
G	100.0	0.1	99.9	1.9	0.0	0.0	100.0	0.0	99.9	0.2	0.0	99.9	0.0	0.0	99.9	0.0	0.0	99.8	0.0	0.0	99.8	99.8	99.9
T	0.0	0.0	0.1	97.9	5.3	5.1	0.0	0.0	0.0	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.0
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.2	0.2	0.0	0.0

evoA1-seB:imx	T2A+Rap	G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	G	G
		A	0.0	99.9	0.0	0.1	0.0	0.0	0.0	100.0	0.0	0.0	99.8	0.0	99.7	99.9	0.0	100.0	99.9	0.0	99.6	99.8	0.0	0.0
C	0.0	0.0	0.0	0.1	96.0	96.2	0.0	0.0	0.0	99.7	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	
G	99.9	0.0	99.8	0.2	0.1	0.0	99.8	0.0	99.9	0.0	0.1	100.0	0.1	0.0	99.7	0.0	0.1	99.6	0.0	0.0	99.9	99.7	99.6	
T	0.0	0.0	0.2	99.7	3.9	3.8	0.1	0.0	0.1	0.2	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.2	0.2	0.0	0.0	0.2	0.3	
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.2	0.2	0.0	0.0	0.0	

evoA1-seB:imx	T2A+Rap	G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	G	G
		A	0.0	99.9	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.8	0.0	99.7	99.9	0.0	99.9	99.9	0.0	99.6	99.7	0.0	0.0
C	0.0	0.0	0.0	0.0	94.8	94.9	0.0	0.0	0.0	99.7	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	
G	99.9	0.1	99.8	0.2	0.1	0.0	99.9	0.0	99.8	0.1	0.1	100.0	0.2	0.1	99.9	0.0	0.0	99.6	0.0	0.0	99.8	99.8	99.7	
T	0.0	0.0	0.1	99.7	5.1	5.0	0.1	0.0	0.1	0.2	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.1	0.1	0.0	0.1	0.1	0.2	
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.3	0.3	0.3	0.1	0.0	

Supplementary Figure 1

<i>k</i>		FANCF																							
		E2			S3			L4			L5			Q6			H7			L8					
untreated		G	G	A	A	T	C	C	C	T	T	C	T	G	C	A	G	C	A	C	C	T	G	G	
	A	0.0	0.0	99.9	100.0	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	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	99.9	99.9	99.9	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	100.0	0.0	100.0	100.0	0.0	0.0	0.0	0.0
	G	100.0	100.0	0.1	0.0	0.0	0.0	0.0	0.0	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	0.0	100.0	99.9
	T	0.0	0.0	0.0	0.0	99.9	0.1	0.1	0.1	0.0	99.9	100.0	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
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

		PAM																							
		I	5	10	15	20	T	G	T	C	T	A	G	C	A	C	T	G	G						
evoA1-seBE Replicate 1	A	0.1	0.1	98.3	98.1	0.0	0.1	0.2	0.2	0.0	0.0	0.0	0.0	98.6	0.0	0.0	99.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	0.0	0.0	64.1	64.8	64.5	0.0	0.0	72.9	0.0	0.0	96.3	0.0	0.0	98.1	0.0	99.3	99.3	0.0	0.0	0.0	0.0
	G	98.6	98.4	0.0	0.0	0.0	0.1	0.2	0.2	0.0	0.0	0.1	0.0	98.1	0.0	0.0	98.6	0.0	0.0	0.0	0.0	0.0	0.0	99.7	99.7
	T	0.0	0.0	0.0	0.0	98.1	33.6	32.5	32.6	97.9	97.9	24.3	97.9	0.0	2.1	0.0	0.0	0.8	0.0	0.0	0.0	0.0	99.3	0.0	0.0
	-	1.3	1.5	1.6	1.8	1.9	2.0	2.4	2.5	2.0	2.1	2.6	2.1	1.9	1.5	1.4	1.3	1.1	0.9	0.7	0.7	0.6	0.2	0.0	0.2

		PAM																							
		I	5	10	15	20	T	G	T	C	T	A	G	C	A	C	T	G	G						
evoA1-seBE Replicate 2	A	0.1	0.2	98.7	98.6	0.0	0.1	0.3	0.2	0.0	0.0	0.1	0.0	0.0	99.1	0.0	0.0	99.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	0.0	0.1	66.8	67.6	67.4	0.1	0.0	75.8	0.0	0.0	97.4	0.0	0.0	98.5	0.1	99.6	99.6	0.0	0.0	0.0	0.0
	G	98.8	98.6	0.0	0.0	0.0	0.1	0.2	0.2	0.0	0.0	0.1	0.0	98.8	0.0	0.0	99.1	0.0	0.1	0.0	0.0	0.0	0.0	99.8	99.8
	T	0.0	0.0	0.0	0.0	98.4	31.4	30.0	30.1	98.2	98.2	21.9	98.5	0.0	1.7	0.0	0.0	0.7	0.0	0.0	0.0	0.0	99.6	0.0	0.0
	-	1.1	1.2	1.3	1.4	1.5	1.6	1.9	2.1	1.7	1.7	2.1	1.5	1.1	1.0	0.9	0.8	0.8	0.6	0.4	0.4	0.4	0.2	0.0	0.2

		PAM																							
		I	5	10	15	20	T	G	T	C	T	A	G	C	A	C	T	G	G						
evoA1-seBE Replicate 3	A	0.2	0.1	98.6	98.5	0.0	0.2	0.2	0.2	0.0	0.0	0.0	0.0	0.0	98.8	0.0	0.0	99.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	0.0	0.0	59.5	60.5	60.2	0.0	0.0	69.7	0.0	0.0	96.7	0.0	0.0	98.1	0.0	99.5	99.6	0.0	0.0	0.0	0.0
	G	98.7	98.5	0.0	0.0	0.0	0.1	0.2	0.3	0.0	0.0	0.1	0.1	98.4	0.0	0.0	99.0	0.0	0.0	0.0	0.0	0.0	0.0	99.8	99.8
	T	0.0	0.1	0.0	0.0	98.4	38.3	36.7	36.8	97.9	98.0	27.7	98.2	0.0	2.1	0.0	0.0	0.9	0.1	0.0	0.0	0.0	99.5	0.0	0.0
	-	1.1	1.3	1.4	1.5	1.6	2.0	2.3	2.4	2.0	2.0	2.4	1.7	1.5	1.3	1.2	1.0	0.9	0.7	0.5	0.4	0.4	0.2	0.0	0.2

		PAM																							
		I	5	10	15	20	T	G	T	C	T	A	G	C	A	C	T	G	G						
evoA1-seBE T2A+Rap Replicate 1	A	0.0	0.0	99.7	99.6	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	99.7	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	0.0	0.0	83.1	83.5	83.1	0.0	0.0	90.1	0.0	0.0	99.2	0.0	0.0	99.5	0.0	99.8	99.8	0.0	0.0	0.0	0.0
	G	99.7	99.6	0.0	0.0	0.0	0.0	0.1	0.1	0.0	0.0	0.1	0.0	99.6	0.0	0.0	99.7	0.0	0.0	0.0	0.0	0.0	100.0	99.9	
	T	0.0	0.0	0.0	0.0	99.6	16.4	15.8	16.2	99.6	99.5	9.3	99.6	0.0	0.5	0.0	0.0	0.2	0.0	0.0	0.0	0.0	99.8	0.0	0.0
	-	0.3	0.3	0.3	0.3	0.4	0.4	0.5	0.6	0.4	0.4	0.5	0.4	0.4	0.3	0.3	0.3	0.3	0.2	0.1	0.1	0.1	0.0	0.0	0.0

		PAM																							
		I	5	10	15	20	T	G	T	C	T	A	G	C	A	C	T	G	G						
evoA1-seBE T2A+Rap Replicate 2	A	0.0	0.0	99.6	99.6	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	99.8	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	0.0	0.0	86.3	86.5	86.6	0.0	0.0	93.0	0.0	0.0	99.3	0.0	0.0	99.7	0.0	99.8	99.8	0.0	0.0	0.0	0.0
	G	99.7	99.6	0.0	0.0	0.0	0.0	0.1	0.1	0.0	0.0	0.1	0.0	99.7	0.0	0.0	99.7	0.0	0.0	0.0	0.0	0.0	0.0	99.9	99.9
	T	0.1	0.0	0.0	0.0	99.6	13.2	12.8	12.8	99.6	99.6	6.4	99.6	0.0	0.4	0.0	0.0	0.1	0.0	0.0	0.0	0.0	99.8	0.0	0.0
	-	0.3	0.3	0.3	0.4	0.4	0.4	0.5	0.5	0.4	0.4	0.5	0.3	0.3	0.3	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.1

		PAM																							
		I	5	10	15	20	T	G	T	C	T	A	G	C	A	C	T	G	G						
evoA1-seBE T2A+Rap Replicate 3	A	0.1	0.0	99.6	99.6	0.0	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	99.7	0.1	0.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	0.0	0.1	77.9	78.3	77.9	0.0	0.0	87.5	0.0	0.0	99.1	0.0	0.0	99.5	0.0	99.8	99.8	0.0	0.0	0.0	0.0
	G	99.6	99.6	0.0	0.0	0.0	0.1	0.1	0.2	0.0	0.0	0.0	0.0	99.6	0.0	0.0	99.5	0.0	0.0	0.0	0.0	0.0	0.0	99.9	99.9
	T	0.0	0.0	0.0	0.0	99.5	21.4	21.0	21.3	99.5	99.5	11.9	99.5	0.1	0.5	0.0	0.0	0.1	0.0	0.0	0.0	0.0	99.8	0.0	0.0
	-	0.3	0.3	0.3	0.4	0.4	0.5	0.5	0.5	0.5	0.4	0.6	0.4	0.4	0.3	0.3	0.4	0.4	0.3	0.2	0.2	0.2	0.2	0.1	0.1

		PAM																							
		I	5	10	15	20	T	G	T	C	T	A	G	C	A	C	T	G	G						
evoA1-seBE T2A+Rap Replicate 1	A	0.0	0.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	0.0	0.0	97.0	97.2	97.0	0.0	0.0	99.5	0.0	0.0	99.9	0.0	0.0	99.9	0.0	100.0	100.0	0.1	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	99.9	0.0	0.0	99.9	0.0	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	3.0	2.8	2.9	100.0	99.9	0.5	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0
	-	0.0	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	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0

		PAM																							
		I	5	10	15	20	T	G	T	C	T	A	G	C	A	C	T	G	G						
evoA1-seBE T2A+Rap Replicate 2	A	0.0	0.0	99.9	99.9	0.0	0.0	0.1	0.1	0.0	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	0.0	0.1
	C	0.0	0.0	0.0	0.0	0.0	96.7	96.9	96.8	0.0	0.0	99.3	0.0	0.0	99.8	0.0	0.0	99.8	0.0	99.9	99.9	0.0	0.0	0.0	0.0
	G	99.9	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.1	99.9	99.8	
	T	0.0	0.0	0.0	0.0	99.9	3.2	2.9	3.0	99.9	99.9	0.6	99.8	0.0	0.1	0.1	0.0	0.1	0.0	0.0	0.0	0.0	99.8	0.0	0.0
	-	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	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

		PAM																							
		I	5	10	15	20	T	G	T	C	T	A	G	C	A	C	T	G	G						
evoA1-seBE T2A+Rap Replicate 3	A	0.0	0.0	99.9	99.9	0.0	0.0	0.1	0.0	0.0	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	0.0	0.0
	C	0.0	0.0	0.0	0.0	0.0	96.3	96.5	96.4	0.0	0.0	99.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	99.9	99.9	0.0	0.0	0.0	0.0
	G	100.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	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	3.6	3.4	3.4	99.9	99.9	0.8	99.8	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.

Supplementary Figure 1

I		FANCF_OTI																											
untreated		C	C	T	G	G	T	G	C	T	G	C	A	G	A	C	G	G	G	G	T	T	C	C	C	C	C	C	
	A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	99.9	0.0	99.8	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.1	0.0	0.0
	C	99.7	99.8	0.2	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	99.9	99.9	0.0	0.0
	G	0.1	0.1	0.1	99.9	99.9	0.2	100.0	0.0	0.2	99.8	0.0	0.0	99.8	0.1	0.0	99.9	99.6	99.6	99.7	0.0	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	T	0.1	0.1	99.6	0.0	0.0	99.8	0.0	0.1	99.8	0.1	0.0	0.0	0.1	0.0	0.1	0.0	0.2	0.3	0.2	99.9	99.4	0.1	0.0	0.0	0.0	0.0	0.0	0.0
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
evoA1-seBE: T2A +Rap Replicate 1		C	C	T	G	G	T	G	C	T	G	C	A	G	A	C	G	G	G	G	T	T	C	C	C	C	C	C	C
	A	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.3	0.0	99.8	4.8	99.8	0.0	7.6	7.5	8.1	4.4	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0
	C	99.9	99.9	0.1	0.0	0.0	0.0	0.0	99.8	0.0	0.0	99.9	0.0	0.0	0.0	99.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.7	99.8
	G	0.0	0.0	0.0	99.8	99.8	0.0	99.9	0.0	0.0	99.6	0.0	0.0	94.9	0.0	0.0	92.2	92.2	91.6	95.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	T	0.0	0.0	99.8	0.0	0.1	99.9	0.0	0.1	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	99.8	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
-	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
evoA1-seBE: T2A +Rap Replicate 2		C	C	T	G	G	T	G	C	T	G	C	A	G	A	C	G	G	G	G	T	T	C	C	C	C	C	C	C
	A	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	99.8	4.8	99.6	0.0	9.1	8.7	9.7	4.5	0.0	0.1	0.0	0.0	0.0	0.0	0.1	0.0	0.0
	C	99.8	99.8	0.0	0.0	0.0	0.0	0.0	99.8	0.0	0.0	99.9	0.1	0.0	0.0	99.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	99.8	99.8
	G	0.1	0.1	0.2	99.9	99.9	0.2	99.6	0.0	0.2	99.9	0.0	0.0	94.9	0.2	0.0	90.8	91.0	89.9	95.2	0.0	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	T	0.1	0.1	99.7	0.0	0.0	99.7	0.1	0.0	99.6	0.0	0.0	0.0	0.2	0.0	0.1	0.0	0.2	0.3	0.2	99.8	99.4	0.1	0.0	0.0	0.0	0.0	0.1	0.0
-	0.0	0.0	0.0	0.1	0.1	0.1	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	
evoA1-seBE: T2A +Rap Replicate 3		C	C	T	G	G	T	G	C	T	G	C	A	G	A	C	G	G	G	G	T	T	C	C	C	C	C	C	C
	A	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.1	0.0	99.8	4.1	99.6	0.0	7.4	7.3	7.9	3.5	0.0	0.1	0.0	0.0	0.0	0.0	0.1	0.0	0.0
	C	99.9	99.8	0.1	0.0	0.0	0.0	0.0	99.8	0.0	0.0	99.7	0.0	0.0	0.0	99.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.4	99.6
	G	0.1	0.0	0.1	99.9	99.9	0.1	99.6	0.0	0.2	99.8	0.0	0.0	95.5	0.1	0.0	92.3	92.3	91.6	96.0	0.0	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.0
	T	0.0	0.1	99.8	0.0	0.1	99.7	0.0	0.0	99.7	0.0	0.0	0.0	0.1	0.1	0.1	0.0	0.1	0.3	0.2	99.7	99.2	0.2	0.1	0.0	0.0	0.0	0.0	0.0
-	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	
evoA1-seBE: T2A +Rap Replicate 1		C	C	T	G	G	T	G	C	T	G	C	A	G	A	C	G	G	G	G	T	T	C	C	C	C	C	C	C
	A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	3.1	99.9	0.0	4.4	4.8	5.0	2.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	99.9	99.9	0.1	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.9	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	99.9	99.9
	G	0.0	0.0	0.1	99.9	99.8	0.0	99.9	0.0	0.0	99.9	0.0	0.0	96.8	0.0	0.0	95.4	95.0	94.8	97.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	T	0.0	0.0	99.8	0.0	0.1	99.9	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	99.8	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
-	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.1	
evoA1-seBE: T2A +Rap Replicate 2		C	C	T	G	G	T	G	C	T	G	C	A	G	A	C	G	G	G	G	T	T	C	C	C	C	C	C	C
	A	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.1	0.0	99.9	1.6	99.7	0.0	2.6	2.8	2.9	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0
	C	99.8	99.8	0.1	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	0.0	99.7	0.0	0.0	0.0	0.0	0.0	0.0	0.1	99.8	99.9	0.0	0.0	0.0	0.0
	G	0.1	0.1	0.1	99.9	99.9	0.2	99.9	0.0	0.2	99.8	0.0	0.0	98.1	0.1	0.1	97.3	96.9	96.7	98.5	0.0	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.0
	T	0.1	0.1	99.8	0.0	0.1	99.7	0.0	0.0	99.7	0.0	0.0	0.0	0.2	0.1	0.1	0.0	0.2	0.4	0.2	99.9	99.3	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	0.1	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	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
evoA1-seBE: T2A +Rap Replicate 3		C	C	T	G	G	T	G	C	T	G	C	A	G	A	C	G	G	G	G	T	T	C	C	C	C	C	C	C
	A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.8	2.9	99.6	0.0	4.9	4.8	4.9	2.8	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	99.8	99.8	0.1	0.0	0.0	0.0	0.0	99.8	0.0	0.0	99.7	0.0	0.0	0.0	99.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.7	99.7
	G	0.1	0.1	0.1	99.9	99.9	0.3	99.8	0.0	0.3	99.8	0.0	0.0	96.8	0.1	0.0	94.8	94.9	94.4	96.8	0.1	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	T	0.1	0.1	99.8	0.0	0.0	99.6	0.0	0.0	99.5	0.1	0.0	0.0	0.2	0.1	0.1	0.1	0.2	0.4	0.2	99.7	99.3	0.1	0.1	0.0	0.0	0.0	0.0	0.0
-	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	
evoA1-seBE: T2A +Rap Replicate 1		C	C	T	G	G	T	G	C	T	G	C	A	G	A	C	G	G	G	G	T	T	C	C	C	C	C	C	C
	A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.1	99.9	0.0	0.1												

Supplementary Figure 1

m		FANCF_OT2																							
		E2			S3			L4			L5			Q6			H7			L8					
		A	C	C	A	T	C	C	C	T	C	T	G	C	A	G	C	A	C	C	A	G	G		
untreated	A	99.9	0.2	0.2	99.4	0.0	0.4	0.1	0.0	0.0	0.1	0.1	0.1	0.0	0.0	99.8	0.0	0.0	100.0	0.0	0.0	99.9	0.0	0.1	
	C	0.0	99.7	99.8	0.6	0.0	99.6	99.8	100.0	0.0	99.9	99.9	0.1	0.0	99.9	0.1	0.0	100.0	0.0	99.9	100.0	0.0	0.0	0.0	
	G	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	100.0	0.0	0.1	100.0	0.0	0.0	0.0	0.0	0.0	0.1	100.0	99.9	
	T	0.0	0.0	0.0	0.0	100.0	0.1	0.0	0.0	99.9	0.0	0.0	99.7	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	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			5			10			15			20			PAM								
		A	C	C	A	T	C	C	C	T	C	T	G	C	A	G	C	A	C	C	A	G	G		
evoA1-seBE Replicate 1	A	99.9	0.0	0.1	99.9	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.1	0.0	100.0	0.0	0.0	0.0	
	C	0.0	99.7	97.7	0.0	0.0	97.3	97.2	97.3	0.0	97.6	98.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	99.9	100.0	0.0	0.0	0.0	
	G	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0	
	T	0.0	0.1	2.2	0.0	99.9	2.6	2.6	2.6	99.9	2.3	1.8	99.9	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	-	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

		1			5			10			15			20			PAM								
		A	C	C	A	T	C	C	C	T	C	T	G	C	A	G	C	A	C	C	A	G	G		
evoA1-seBE Replicate 2	A	100.0	0.4	0.3	99.3	0.0	0.4	0.2	0.1	0.0	0.2	0.1	0.0	0.0	0.1	99.8	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0
	C	0.0	99.5	97.7	0.7	0.0	96.8	97.1	97.2	0.0	97.5	98.0	0.2	0.0	99.9	0.2	0.0	100.0	0.0	100.0	100.0	0.0	0.0	0.0	0.0
	G	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	99.9	0.0
	T	0.0	0.1	2.0	0.0	100.0	2.8	2.7	2.7	100.0	2.3	1.8	99.8	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	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

		1			5			10			15			20			PAM								
		A	C	C	A	T	C	C	C	T	C	T	G	C	A	G	C	A	C	C	A	G	G		
evoA1-seBE Replicate 3	A	99.8	0.2	0.1	99.1	0.0	0.3	0.1	0.1	0.0	0.2	0.1	0.1	0.0	0.0	99.8	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	0.0
	C	0.0	99.3	96.7	0.7	0.0	95.8	96.0	96.0	0.1	96.4	97.1	0.1	0.0	99.8	0.1	0.0	99.9	0.0	99.9	99.9	0.0	0.0	0.0	0.0
	G	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.1	0.0	0.0	0.0	99.9	100.0	0.0
	T	0.0	0.2	3.0	0.0	99.8	3.8	3.8	3.8	99.7	3.2	2.6	99.7	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	-	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.2	0.1	0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0

		1			5			10			15			20			PAM								
		A	C	C	A	T	C	C	C	T	C	T	G	C	A	G	C	A	C	C	A	G	G		
evoA1-seBE T2A +Rap Replicate 1	A	99.9	0.1	0.0	99.9	0.0	0.1	0.1	0.1	0.0	0.1	0.1	0.0	0.0	100.0	0.1	0.0	100.0	0.1	0.0	99.9	0.0	0.1	0.1	
	C	0.0	99.3	99.9	0.1	0.0	99.8	99.9	99.8	0.0	99.8	99.9	0.0	0.0	99.9	0.0	0.0	99.9	0.0	99.9	99.9	0.0	0.0	0.0	0.0
	G	0.1	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	0.0	99.9	0.0	0.0	0.0	0.0	0.1	100.0	99.8	
	T	0.0	0.1	0.0	0.0	99.9	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	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			5			10			15			20			PAM								
		A	C	C	A	T	C	C	C	T	C	T	G	C	A	G	C	A	C	C	A	G	G		
evoA1-seBE T2A +Rap Replicate 2	A	99.9	0.4	0.2	99.0	0.0	0.6	0.2	0.1	0.0	0.3	0.1	0.1	0.0	0.0	99.8	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	0.0
	C	0.0	99.5	99.2	0.9	0.0	98.6	99.0	99.2	0.0	99.1	99.4	0.2	0.0	99.9	0.1	0.0	99.9	0.0	100.0	100.0	0.0	0.0	0.0	0.0
	G	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0	
	T	0.0	0.1	0.5	0.0	99.9	0.8	0.7	0.7	99.9	0.6	0.4	99.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	-	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

		1			5			10			15			20			PAM								
		A	C	C	A	T	C	C	C	T	C	T	G	C	A	G	C	A	C	C	A	G	G		
evoA1-seBE T2A +Rap Replicate 3	A	99.9	0.3	0.2	99.4	0.0	0.4	0.1	0.1	0.0	0.2	0.1	0.1	0.0	0.0	99.8	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0
	C	0.1	99.6	98.8	0.6	0.0	98.1	98.3	98.4	0.0	98.7	99.1	0.2	0.0	99.9	0.1	0.0	100.0	0.0	99.9	100.0	0.0	0.0	0.0	0.0
	G	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	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	0.1	1.1	0.0	100.0	1.5	1.5	1.5	100.0	1.1	0.9	99.7	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	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			5			10			15			20			PAM								
		A	C	C	A	T	C	C	C	T	C	T	G	C	A	G	C	A	C	C	A	G	G		
evoA1-seBE T2A +Rap Replicate 1	A	99.9	0.1	0.0	99.9	0.0	0.1	0.0	0.0	0.0	0.2	0.1	0.0	0.1	0.0	100.0	0.1	0.1	100.0	0.1	0.0	99.8	0.0	0.1	
	C	0.0	99.8	99.9	0.1	0.0	99.9	99.9	99.9	0.0	99.8	99.9	0.0	0.0	99.9	0.0	0.0	99.9	0.0	99.9	100.0	0.0	0.0	0.0	0.0
	G	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.1	100.0	99.8	
	T	0.0	0.1	0.0	0.0	99.9	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.1	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	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			5			10			15			20			PAM								
		A	C	C	A	T	C	C	C	T	C	T	G	C	A	G	C	A	C	C	A	G	G		
evoA1-seBE T2A +Rap Replicate 2	A	99.9	0.6	0.1	99.1	0.0	0.6	0.3	0.2	0.0	0.2	0.1	0.1	0.0	0.0	99.7	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0
	C	0.0	99.3	99.8	0.7	0.0	99.3	99.7	99.8	0.0	99.8	99.9	0.2	0.0	99.9	0.3	0.0	100.0	0.0	100.0	100.0	0.0	0.0	0.0	0.0
	G	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	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	0.1	0.0	0.0	99.9	0.0	0.0	99.7	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	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			5			10			15			20			PAM								
		A	C	C	A	T	C	C	C	T	C	T	G	C	A	G	C	A	C	C	A	G	G		
evoA1-seBE T2A +Rap Replicate 3	A	99.9	0.4	0.1	99.3	0.0	0.4	0.1	0.1	0.0	0.1	0.2	0.2	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	0.0
	C	0.1	99.6	99.9	0.7	0.0	99.5	99.8	99.9																

Supplementary Figure 2. Base editing efficiency of evoA1-seBE-IRES constructs in human cells at diverse loci and off-target sites. The frequency of individual base calls at each locus of interest are shown, colored using a heat map from white (0%) to red (100%). The parent sequence is shown with PAM (yellow) and sgRNA protospacer (black) noted. When the PAM is at right, the coding strand cytosine (C) targeted for mutation is highlighted in red. When the PAM is at left, the non-coding strand cytosine is targeted, and the associated coding strand (G) is highlighted in red. The data in Fig. 3c show the quantification of conversion at the target base only, with individual loci shown in Extended Data Fig. 5b. Results across each locus with individual replicates are shown using untreated cells (n = 1), along with intact evoA1-BE or evoA1-seBE-IRES with or without rapamycin (n = 3 each). The loci analyzed and desired mutations are (a) CDA E67R targeting the active site residue, (b) CDA Q104* nonsense mutation, (c) IDH2 R172K neomorphic mutation, (d) validated EMX1 targeting site, (e) validated EMX1 OT1 (f) validated EMX1 OT2.

Supplementary Figure 2

a *CDA E67R*

	P61			L62			G63			I64			C65			A66			E67			
	C	C	C	G	C	T	G	G	C	A	T	C	T	G	T	G	C	T	G	A	A	C
untreated	A	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.1	0.0	99.9	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.0
	C	99.9	100.0	99.9	0.0	100.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0
	G	0.0	0.0	0.0	99.9	0.0	0.0	100.0	99.9	99.9	0.0	0.0	0.0	0.0	100.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0
	T	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	99.9	0.0	0.1	100.0	0.0	0.0
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

evoA1-seBE Replicate 1	PAM			20			15			10			5			1						
	C	C	C	G	C	T	G	G	C	A	T	C	T	G	T	G	C	T	G	A	A	C
A	0.0	0.0	0.0	0.1	0.0	0.0	0.9	4.4	0.8	0.0	99.2	0.0	0.0	0.0	2.7	0.1	53.9	0.0	0.0	53.8	99.6	99.8
C	99.9	99.9	99.9	0.0	99.9	0.0	0.0	0.0	0.0	99.3	0.0	0.0	99.2	0.0	0.0	0.1	0.3	99.3	0.0	0.2	0.0	0.0
G	0.0	0.0	0.0	99.8	0.0	0.0	98.5	94.9	98.6	0.0	0.0	0.0	0.0	96.4	0.0	44.6	0.0	0.0	45.0	0.0	0.0	0.0
T	0.0	0.0	0.0	0.0	0.0	99.8	0.0	0.2	0.0	0.0	99.2	0.1	99.3	0.0	99.1	0.5	0.0	99.4	0.6	0.0	0.0	0.0
-	0.1	0.1	0.1	0.1	0.1	0.2	0.5	0.5	0.6	0.6	0.7	0.7	0.7	0.7	0.7	0.7	0.6	0.5	0.5	0.3	0.2	0.2

evoA1-seBE Replicate 2	PAM			20			15			10			5			1						
	C	C	C	G	C	T	G	G	C	A	T	C	T	G	T	G	C	T	G	A	A	C
A	0.0	0.0	0.0	0.0	0.0	0.0	0.9	4.2	0.7	0.0	99.2	0.1	0.0	0.0	2.6	0.0	53.2	0.0	0.0	53.2	99.6	99.7
C	99.9	99.8	99.9	0.0	99.8	0.0	0.0	0.1	0.1	99.5	0.0	0.0	99.2	0.0	0.1	0.2	99.1	0.0	0.2	0.0	0.0	0.0
G	0.0	0.0	0.0	99.9	0.0	0.0	98.5	95.2	98.8	0.0	0.0	0.0	0.0	96.5	0.0	45.3	0.0	0.0	45.8	0.0	0.0	0.0
T	0.0	0.1	0.0	0.0	0.0	99.8	0.1	0.1	0.0	0.0	0.1	99.2	0.1	99.2	0.1	99.1	0.4	0.0	99.3	0.1	0.0	0.0
-	0.1	0.1	0.1	0.1	0.2	0.5	0.5	0.5	0.5	0.5	0.7	0.7	0.7	0.8	0.8	0.9	0.8	0.7	0.7	0.3	0.3	0.3

evoA1-seBE Replicate 3	PAM			20			15			10			5			1						
	C	C	C	G	C	T	G	G	C	A	T	C	T	G	T	G	C	T	G	A	A	C
A	0.0	0.0	0.0	0.0	0.0	0.0	0.9	4.1	0.5	0.0	99.2	0.0	0.0	0.0	3.0	0.0	54.7	0.0	0.0	54.2	99.4	99.5
C	99.9	99.8	99.8	0.0	99.8	0.0	0.0	0.1	0.1	99.3	0.0	0.0	99.1	0.0	0.1	0.0	0.2	99.0	0.1	0.1	0.0	0.0
G	0.0	0.0	0.0	99.8	0.0	0.0	98.5	95.0	98.7	0.0	0.0	0.0	0.0	95.9	0.0	43.7	0.0	0.0	44.3	0.0	0.0	0.0
T	0.0	0.0	0.0	0.0	0.0	99.8	0.1	0.3	0.0	0.0	0.0	99.1	0.0	99.0	0.0	99.0	0.4	0.0	99.1	0.4	0.0	0.1
-	0.1	0.1	0.1	0.1	0.1	0.2	0.5	0.5	0.6	0.7	0.7	0.9	0.9	1.0	0.9	1.0	1.1	0.9	0.9	0.6	0.5	0.4

evoA1-seBE IRES +Rap Rep 1	PAM			20			15			10			5			1						
	C	C	C	G	C	T	G	G	C	A	T	C	T	G	T	G	C	T	G	A	A	C
A	0.0	0.0	0.0	0.0	0.0	0.0	0.4	2.7	0.4	0.0	99.9	0.0	0.0	0.9	0.0	34.3	0.0	0.0	34.8	100.0	99.9	
C	99.9	99.9	99.9	0.0	99.9	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.1	0.1	99.9	0.0	0.0	0.0	0.0	0.0
G	0.0	0.0	0.0	99.9	0.0	0.0	99.4	97.1	99.5	0.0	0.0	0.0	0.0	98.9	0.0	65.3	0.0	0.0	65.0	0.0	0.0	0.0
T	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	99.9	0.0	99.9	0.0	99.8	0.2	0.0	99.9	0.0	0.0	0.0
-	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0

evoA1-seBE IRES +Rap Rep 2	PAM			20			15			10			5			1						
	C	C	C	G	C	T	G	G	C	A	T	C	T	G	T	G	C	T	G	A	A	C
A	0.0	0.0	0.0	0.0	0.0	0.0	0.6	2.2	0.5	0.0	99.8	0.0	0.0	1.2	0.0	34.1	0.0	0.0	35.3	99.9	99.9	
C	100.0	100.0	99.9	0.0	100.0	0.0	0.0	0.0	0.0	99.8	0.0	0.0	99.8	0.0	0.1	0.1	99.8	0.0	0.1	0.0	0.0	0.0
G	0.0	0.0	0.0	99.9	0.0	0.0	99.3	97.6	99.3	0.0	0.0	0.0	0.0	98.6	0.0	65.6	0.0	0.0	64.5	0.0	0.0	0.0
T	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	99.8	0.0	99.8	0.0	99.7	0.1	0.0	99.8	0.0	0.0	0.0
-	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.2	0.2	0.2	0.2	0.2	0.1	0.1

evoA1-seBE IRES +Rap Rep 3	PAM			20			15			10			5			1						
	C	C	C	G	C	T	G	G	C	A	T	C	T	G	T	G	C	T	G	A	A	C
A	0.0	0.0	0.0	0.0	0.0	0.0	0.5	2.2	0.5	0.0	99.8	0.0	0.0	1.1	0.0	35.0	0.0	0.0	35.9	100.0	100.0	
C	99.9	99.9	99.9	0.0	100.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.0
G	0.0	0.0	0.0	99.9	0.0	0.0	99.4	97.7	99.4	0.0	0.0	0.0	0.0	98.8	0.0	64.8	0.0	0.0	64.0	0.0	0.0	0.0
T	0.0	0.1	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	99.9	0.0	99.9	0.0	99.8	0.0	0.0	99.9	0.0	0.0	0.0
-	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	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

evoA1-seBE IRES -Rap Rep 1	PAM			20			15			10			5			1						
	C	C	C	G	C	T	G	G	C	A	T	C	T	G	T	G	C	T	G	A	A	C
A	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	1.4	0.0	0.0	2.1	100.0	100.0	
C	100.0	99.9	100.0	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	0.0	0.0	0.0	0.0
G	0.0	0.0	0.0	99.9	0.0	0.0	100.0	99.9	100.0	0.0	0.0	0.0	0.0	100.0	0.0	98.5	0.0	0.0	97.9	0.0	0.0	0.0
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	100.0	0.0	99.9	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	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

evoA1-seBE IRES -Rap Rep 2	PAM			20			15			10			5			1						
	C	C	C	G	C	T	G	G	C	A	T	C	T	G	T	G	C	T	G	A	A	C
A	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	1.0	0.0	0.0	1.2	100.0	100.0	
C	100.0	100.0	100.0	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	0.0	0.0	0.0	0.0
G	0.0	0.0	0.0	99.9	0.0	0.0	100.0	99.9	100.0	0.0	0.0	0.0	0.0	99.9	0.0	99.0	0.0	0.0	98.7	0.0	0.0	0.0
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	100.0	0.0	99.9	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	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

evoA1-seBE IRES -Rap Rep 3	PAM			20			15			10			5			1					
	C	C	C	G	C	T	G	G	C	A	T	C	T	G	T	G	C	T	G	A	A
A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	100.0	0.0	0.0	0.0	0.0	1.4	0.0	0.0	1.9	100.0	100.0
C	100.0	100.0	99.9	0.0	100.0	0.0	0.0	0.0	0.0	99.9	0.										

Supplementary Figure 2

b		CDA Q104*																											
		C102				R103				Q104				V105				M106				R107				E108			
		C	T	G	C	A	G	G	C	A	A	G	T	C	A	T	G	A	G	A	G	A	G	A	G	A	G	A	G
untreated	A	0.0	0.0	0.1	0.0	99.9	0.0	0.1	0.0	100.0	100.0	0.0	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
	C	100.0	0.0	0.0	99.9	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	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	0.0	0.0	99.9	0.0	0.1	100.0	99.9	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	100.0	0.0	100.0	100.0
	T	0.0	100.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	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	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
evoA1-seBE- Replicate 1	A	0.2	0.0	0.1	0.8	99.3	0.2	0.0	0.3	99.1	99.1	0.0	0.0	0.2	99.4	0.0	0.1	99.7	0.1	99.7	0.0	99.8	0.0	99.8	0.1	0.0	0.0	0.0	0.0
	C	79.9	0.0	0.0	43.9	0.0	0.0	0.0	47.0	0.0	0.0	0.0	0.0	91.9	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
	G	0.0	0.0	99.4	0.4	0.0	99.0	99.1	1.9	0.0	0.0	99.2	0.0	0.0	0.0	0.0	99.4	0.0	99.6	0.0	99.8	0.0	99.8	0.0	99.7	99.9	0.0	0.0	0.0
	T	19.3	99.6	0.0	54.2	0.0	0.1	0.0	49.4	0.0	0.0	99.2	7.2	0.0	99.5	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0
	-	0.5	0.4	0.4	0.7	0.6	0.8	0.8	1.4	0.9	0.9	0.8	0.7	0.6	0.5	0.5	0.3	0.3	0.2	0.3	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.0
evoA1-seBE- Replicate 2	A	0.3	0.0	0.0	0.7	99.2	0.4	0.1	0.5	99.1	99.2	0.0	0.0	0.0	99.5	0.0	0.1	99.6	0.1	99.8	0.0	99.9	0.1	99.9	0.1	0.0	0.0	0.0	0.0
	C	79.9	0.0	0.0	44.5	0.0	0.0	0.0	47.7	0.0	0.0	0.0	0.0	90.9	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
	G	0.0	0.0	99.4	0.3	0.0	98.7	99.0	1.8	0.0	0.0	99.2	0.0	0.0	0.0	0.0	99.4	0.0	99.6	0.0	99.8	0.0	99.8	0.0	99.8	100.0	0.0	0.0	0.0
	T	19.2	99.5	0.0	53.7	0.0	0.1	0.0	48.8	0.0	0.0	99.3	8.4	0.0	99.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	-	0.6	0.5	0.5	0.8	0.8	0.9	0.9	1.2	0.9	0.8	0.8	0.7	0.7	0.5	0.4	0.4	0.3	0.3	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0
evoA1-seBE- Replicate 3	A	0.1	0.0	0.0	0.7	99.2	0.2	0.0	0.3	99.3	99.3	0.0	0.0	0.0	99.6	0.0	0.0	99.7	0.2	99.9	0.1	99.9	0.1	99.9	0.2	0.0	0.0	0.0	0.0
	C	81.7	0.0	0.0	47.9	0.0	0.0	0.0	51.3	0.0	0.0	0.0	0.0	91.9	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
	G	0.0	0.0	99.4	0.2	0.0	99.0	99.1	1.7	0.0	0.0	99.3	0.0	0.2	0.0	0.0	99.6	0.0	99.7	0.0	99.8	0.0	99.7	99.9	99.9	0.0	0.0	0.0	
	T	17.6	99.4	0.0	50.4	0.0	0.0	0.0	45.3	0.0	0.0	99.4	7.5	0.0	99.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	-	0.6	0.6	0.5	0.8	0.7	0.7	0.8	1.4	0.7	0.7	0.7	0.6	0.5	0.4	0.3	0.3	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0
evoA1-seBE- IRES +Rap Rep 1	A	0.1	0.0	0.0	0.1	99.8	0.0	0.0	0.1	99.7	99.8	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	99.9	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0
	C	88.7	0.0	0.0	63.4	0.0	0.0	0.0	68.2	0.0	0.0	0.0	0.0	94.9	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
	G	0.0	0.0	99.7	0.1	0.0	99.8	99.7	0.9	0.0	0.0	99.8	0.0	0.0	0.0	0.0	99.9	0.1	99.9	0.0	100.0	0.0	100.0	0.0	99.9	100.0	0.0	0.0	
	T	11.1	99.8	0.1	36.1	0.0	0.0	0.0	30.4	0.0	0.0	99.8	5.0	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	0.0
	-	0.2	0.1	0.2	0.3	0.2	0.2	0.3	0.4	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
evoA1-seBE- IRES +Rap Rep 2	A	0.1	0.0	0.0	0.3	99.6	0.1	0.0	0.1	99.6	99.8	0.0	0.0	0.0	99.8	0.0	0.0	99.9	0.0	100.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0
	C	88.4	0.0	0.0	61.8	0.0	0.0	0.0	66.3	0.0	0.0	0.0	0.0	94.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	0.0	0.0	99.7	0.2	0.1	99.5	99.5	1.3	0.0	0.0	99.8	0.0	0.0	0.0	0.0	99.9	0.0	99.9	0.0	100.0	0.0	100.0	0.0	99.9	100.0	0.0	0.0	
	T	11.2	99.7	0.0	37.4	0.0	0.0	0.0	31.7	0.0	0.0	99.8	5.4	0.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	-	0.3	0.3	0.3	0.4	0.3	0.4	0.5	0.7	0.4	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
evoA1-seBE- IRES +Rap Rep 3	A	0.0	0.0	0.0	0.2	99.8	0.1	0.0	0.1	99.9	99.9	0.0	0.0	0.0	99.8	0.0	0.0	99.9	0.0	99.9	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0
	C	88.7	0.0	0.0	62.2	0.0	0.0	0.0	66.4	0.0	0.0	0.0	0.0	94.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	0.0	0.0	99.9	0.1	0.0	99.8	99.9	0.7	0.0	0.0	99.9	0.0	0.0	0.0	0.0	99.9	0.1	100.0	0.0	100.0	0.0	100.0	0.0	100.0	100.0	0.0	0.0	
	T	11.2	99.9	0.0	37.4	0.0	0.0	0.0	32.5	0.0	0.0	99.8	5.7	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	0.0
	-	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	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
evoA1-seBE- IRES -Rap Rep 1	A	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0
	C	99.8	0.0	0.0	97.6	0.0	0.0	0.0	98.6	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	0.0	0.0	0.0	0.0	0.0	0.0
	G	0.0	0.0	100.0	0.0	0.0	100.0	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	100.0	0.0	100.0	0.0	100.0	100.0	0.0	0.0	
	T	0.2	100.0	0.0	2.4	0.0	0.0	0.0	1.4	0.0	0.0	0.0	100.0	0.2	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	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
evoA1-seBE- IRES -Rap Rep 2	A	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0
	C	99.8	0.0	0.0	97.8	0.0	0.0	0.0	98.8	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	0.0	0.0	0.0	0.0	0.0	0.0
	G	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	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0	100.0	0.0	0.0	
	T	0.2	100.0	0.0	2.2	0.0	0.0																						

Supplementary Figure 2

		c																							
		IDH2 R172K																							
untreated		P167			I168			T169			I170			G171			R172			H173					
	A	C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C	
		A	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	0.2	0.2	0.0	99.9	0.5	0.5	0.0	100.0	0.0	0.1	0.0
		C	99.9	100.0	100.0	0.0	0.0	100.0	0.0	99.9	100.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	100.0	0.0	99.9	0.0	99.9
		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	99.8	99.8	0.0	0.1	99.4	99.5	0.0	0.0	0.0	0.0	99.9
	T	0.1	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

evoA1-seBE Replicate 1		PAM			20			15			10			5			1								
	A	C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C	
		A	0.0	0.0	0.0	99.9	0.0	0.0	99.6	0.0	0.0	99.5	0.0	0.0	14.8	6.7	0.0	99.3	40.6	40.6	0.0	99.3	0.0	6.9	0.0
		C	99.9	99.9	99.9	0.0	0.0	99.8	0.0	99.6	99.6	0.0	0.0	0.0	0.1	0.0	99.3	0.0	0.5	0.3	99.3	0.0	99.6	0.0	99.6
		G	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	84.5	92.6	0.0	0.0	57.2	57.6	0.0	0.0	0.0	0.0	92.7
	T	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.1	0.0	0.0	99.4	99.4	0.1	0.0	0.1	0.0	0.9	0.7	0.0	0.0	0.0	0.1	0.0	
	-	0.0	0.0	0.0	0.0	0.0	0.1	0.3	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.6	0.7	0.8	0.8	0.6	0.7	0.6	0.4	0.3	

evoA1-seBE Replicate 2		PAM			20			15			10			5			1								
	A	C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C	
		A	0.0	0.0	0.0	99.9	0.0	0.0	99.7	0.0	0.0	99.7	0.0	0.0	15.3	7.4	0.0	99.2	38.9	39.1	0.0	99.4	0.0	6.7	0.0
		C	99.9	99.9	99.9	0.0	0.0	99.8	0.1	99.8	99.7	0.0	0.0	0.0	0.1	0.0	99.3	0.0	0.3	0.4	99.3	0.0	99.6	0.0	99.6
		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	84.1	91.8	0.0	0.0	59.1	59.2	0.0	0.0	0.0	0.0	92.9
	T	0.0	0.0	0.1	0.0	99.9	0.0	0.0	0.0	0.0	0.0	99.5	99.4	0.1	0.0	0.0	0.0	0.8	0.5	0.0	0.0	0.0	0.1	0.0	
	-	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.2	0.3	0.3	0.5	0.6	0.6	0.7	0.7	0.8	0.8	0.8	0.6	0.7	0.6	0.4	0.3	

evoA1-seBE Replicate 3		PAM			20			15			10			5			1								
	A	C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C	
		A	0.0	0.0	0.0	99.9	0.0	0.0	99.6	0.0	0.0	99.6	0.0	0.0	13.3	5.5	0.0	99.4	35.7	35.9	0.0	99.4	0.0	6.3	0.0
		C	99.9	99.9	99.9	0.0	0.0	99.8	0.0	99.6	99.6	0.0	0.0	0.0	0.1	0.0	99.3	0.0	0.3	0.4	99.4	0.0	99.5	0.0	99.6
		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	86.0	93.8	0.0	0.0	62.3	62.4	0.0	0.0	0.0	0.0	93.2
	T	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	99.5	99.4	0.1	0.0	0.1	0.0	0.9	0.7	0.0	0.0	0.0	0.1	0.0	
	-	0.0	0.1	0.1	0.1	0.1	0.2	0.3	0.3	0.3	0.4	0.5	0.5	0.6	0.6	0.6	0.6	0.7	0.7	0.6	0.7	0.6	0.4	0.3	

evoA1-seBE IRES +Rap Rep 1		PAM			20			15			10			5			1								
	A	C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C	
		A	0.0	0.0	0.0	100.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	7.7	2.7	0.0	99.9	25.7	24.9	0.0	99.9	0.0	3.3	0.0
		C	100.0	100.0	100.0	0.0	0.0	100.0	0.0	99.9	99.9	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.2	0.3	99.9	0.0	100.0	0.0	100.0
		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	92.1	97.1	0.0	0.0	73.8	74.5	0.0	0.0	0.0	0.0	96.6
	T	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	99.9	99.9	0.0	0.0	0.0	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	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	0.0	0.0	0.0	

evoA1-seBE IRES +Rap Rep 2		PAM			20			15			10			5			1								
	A	C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C	
		A	0.0	0.0	0.0	100.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	7.1	2.5	0.0	99.8	24.2	23.5	0.0	99.8	0.0	3.0	0.0
		C	100.0	100.0	100.0	0.0	0.0	100.0	0.1	99.9	99.9	0.0	0.0	0.0	0.0	0.0	99.8	0.0	0.2	0.3	99.8	0.0	99.9	0.0	99.9
		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	92.7	97.2	0.0	0.0	75.2	75.9	0.0	0.0	0.0	0.0	96.9
	T	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	99.8	99.8	0.0	0.0	0.0	0.0	0.2	0.2	0.0	0.0	0.1	0.0	0.0	
	-	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.1	0.1	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	

evoA1-seBE IRES +Rap Rep 3		PAM			20			15			10			5			1								
	A	C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C	
		A	0.0	0.0	0.0	100.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	6.6	2.5	0.0	99.8	22.4	22.0	0.0	99.9	0.0	2.8	0.0
		C	100.0	100.0	100.0	0.0	0.0	100.0	0.1	99.9	100.0	0.0	0.0	0.0	0.0	0.0	99.8	0.0	0.2	0.2	99.9	0.0	99.9	0.0	100.0
		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	93.3	97.4	0.0	0.0	77.1	77.6	0.0	0.0	0.0	0.0	97.1
	T	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	99.9	99.9	0.0	0.0	0.0	0.0	0.1	0.1	0.0	0.0	0.1	0.0	0.0	
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	

evoA1-seBE IRES -Rap Rep 1		PAM			20			15			10			5			1								
	A	C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C	
		A	0.0	0.0	0.0	100.0	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	0.3	0.1	0.0	100.0	1.4	1.2	0.0	100.0	0.0	0.1	0.0
		C	100.0	100.0	100.0	0.0	0.0	99.9	0.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	99.9	0.0	100.0
		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	99.7	99.9	0.0	0.0	98.6	98.7	0.0	0.0	0.0	0.0	99.9
	T	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

evoA1-seBE IRES -Rap Rep 2		PAM			20			15			10			5			1								
	A	C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C	
		A	0.0	0.0	0.0	100.0	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	0.2	0.0	0.0	100.0	1.5	1.4	0.0	100.0	0.0	0.1	0.0
		C	100.0	100.0	100.0	0.0	0.0	100.0	0.1	100.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	99.9	0.0	100.0
		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	99.8	99.9	0.0	0.0	98.5	98.5	0.0	0.0	0.0	0.0	99.9
	T	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

evoA1-seBE IRES -Rap Rep 3		PAM			20			15		
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Supplementary Figure 2

d		EMXI																																		
		E225					S226					E227					Q228					K229					K230					K231				
		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	A	A	G	A	A	A	G	A	A					
untreated	A	0.0	99.9	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.8	0.0	99.7	99.9	0.0	99.9	99.9	0.0	99.9	99.9	0.0	99.4	99.6	0.0	0.0	0.0	0.0	0.0	0.0							
	C	0.0	0.0	0.0	0.0	99.8	99.8	0.0	0.0	0.0	99.8	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0							
	G	99.9	0.0	99.8	0.1	0.0	0.0	99.8	0.0	99.9	0.1	0.1	99.9	0.1	0.1	99.7	0.0	0.0	99.5	0.1	0.0	99.8	99.8	99.8	99.8	99.8	99.8	99.8	99.8							
	T	0.0	0.0	0.1	99.7	0.2	0.1	0.1	0.0	0.1	0.1	0.0	0.0	0.0	0.2	0.0	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							
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.4	0.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0							

evoA1-seBE- Replicate 1	PAM																												
	I					5					10					15					20								
	G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	A	A	G	A	A	A	G	A
A	0.4	99.8	0.0	0.0	0.5	0.2	0.0	99.6	0.0	0.0	99.7	0.0	99.7	99.8	0.0	99.8	99.8	0.0	99.4	99.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
C	0.2	0.0	0.0	0.0	55.8	56.9	0.0	0.0	0.0	95.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
G	99.1	0.1	99.8	0.3	1.1	0.3	99.7	0.1	99.7	0.0	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.5	0.0	0.0	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	
T	0.1	0.0	0.0	99.4	42.4	42.3	0.0	0.0	0.0	3.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

evoA1-seBE- Replicate 2	PAM																												
	I					5					10					15					20								
	G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	A	A	G	A	A	A	G	A
A	0.5	99.7	0.0	0.0	0.5	0.3	0.0	99.7	0.0	0.1	99.7	0.0	99.8	99.8	0.0	99.9	99.8	0.0	99.6	99.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
C	0.1	0.0	0.0	0.0	55.8	57.4	0.0	0.0	0.0	95.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
G	99.1	0.1	99.8	0.3	1.5	0.5	99.7	0.1	99.7	0.0	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.5	0.0	0.0	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	
T	0.1	0.0	0.0	99.5	41.9	41.5	0.0	0.0	0.0	4.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

evoA1-seBE- Replicate 3	PAM																												
	I					5					10					15					20								
	G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	A	A	G	A	A	A	G	A
A	0.6	99.7	0.0	0.0	0.6	0.1	0.0	99.7	0.1	0.0	99.7	0.0	99.8	99.7	0.0	99.8	99.8	0.0	99.6	99.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
C	0.1	0.0	0.0	0.0	60.1	60.0	0.0	0.0	0.0	95.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
G	99.1	0.1	99.8	0.2	1.3	0.3	99.7	0.0	99.7	0.0	0.0	99.7	0.0	0.0	99.8	0.0	0.0	99.6	0.0	0.0	99.8	99.9	99.8	99.8	99.8	99.8	99.8	99.8	
T	0.1	0.0	0.0	99.6	39.2	39.2	0.0	0.0	0.0	4.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

evoA1-seBE- IRES +Rap Rep 1	PAM																												
	I					5					10					15					20								
	G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	A	A	G	A	A	A	G	A
A	0.1	99.9	0.0	0.0	0.1	0.0	0.0	99.9	0.0	0.0	99.9	0.0	99.9	99.9	0.0	100.0	99.9	0.0	99.6	99.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
C	0.0	0.0	0.0	0.0	72.5	72.6	0.0	0.0	0.0	97.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
G	99.9	0.1	100.0	0.2	0.1	0.0	99.9	0.0	99.9	0.0	0.1	99.9	0.0	0.0	99.9	0.0	0.0	99.6	0.0	0.0	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	
T	0.0	0.0	0.0	99.7	27.2	27.2	0.0	0.0	0.0	2.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

evoA1-seBE- IRES +Rap Rep 2	PAM																												
	I					5					10					15					20								
	G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	A	A	G	A	A	A	G	A
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	99.9	0.0	99.7	99.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
C	0.0	0.0	0.0	0.0	74.3	74.2	0.0	0.0	0.0	97.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
G	99.9	0.0	99.9	0.2	0.2	0.0	99.9	0.0	99.9	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	99.7	0.0	0.0	100.0	100.0	99.9	99.9	99.9	99.9	99.9	99.9	
T	0.0	0.0	0.0	99.7	25.3	25.6	0.0	0.0	0.0	2.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

evoA1-seBE- IRES +Rap Rep 3	PAM																												
	I					5					10					15					20								
	G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	A	A	G	A	A	A	G	A
A	0.1	99.7	0.0	0.0	0.0	0.0	0.0	99.8	0.0	0.0	99.8	0.0	99.7	99.7	0.0	99.7	99.8	0.0	99.5	99.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
C	0.0	0.0	0.0	0.0	74.1	74.2	0.0	0.0	0.0	97.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
G	99.7	0.1	99.8	0.2	0.3	0.0	99.8	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.7	0.0	0.0	99.5	0.0	0.0	99.7	99.8	99.8	99.7	99.8	99.7	99.8	99.7	
T	0.1	0.0	0.0	99.6	25.3	25.6	0.0	0.0	0.0	2.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

evoA1-seBE- IRES -Rap Rep 1	PAM																												
	I					5					10					15					20								
	G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	A	A	G	A	A	A	G	A
A	0.0	100.0	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	99.8	99.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
C	0.0	0.0	0.0	0.0	97.9	98.1	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	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	100.0	0.2	0.0	0.0	99.9	0.0	99.9	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	99.7	0.0	0.0	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	
T	0.1	0.0	0.0	99.8	2.1	1.8	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

evoA1-seBE- IRES -Rap Rep 2	PAM																								
	I					5					10					15					20				
	G	A	G	T	C	C	G	A	G																

Supplementary Figure 3. Base editing efficiency of AID'-seBE-IRES constructs in human cells at diverse loci and off-target sites. The frequency of individual base calls at each locus of interest are shown, colored using a heat map from white (0%) to red (100%). The parent sequence is shown with PAM (yellow) and sgRNA protospacer (black) noted. When the PAM is at right, the coding strand cytosine (C) targeted for mutation is highlighted in red. When the PAM is at left, the non-coding strand cytosine is targeted, and the associated coding strand (G) is highlighted in red. The data in Fig. 3c show the quantification of conversion at the target base only, with individual loci shown in Extended Data Fig. 5c. Results across each locus with individual replicates are shown using untreated cells (n = 1), along with intact AID'-BE4max or AID'-seBE-IRES with or without rapamycin (n = 3 each). The loci analyzed and desired mutations are (a) CDA E67R targeting the active site residue, (b) CDA Q104* nonsense mutation, (c) IDH2 R172K neomorphic mutation, (d) validated EMX1 targeting site, (e) validated EMX1 OT1 (f) validated EMX1 OT2.

Supplementary Figure 3

a		<i>CDA E67R</i>																								
		P61			L62			G63			I64			C65			A66			E67						
		C	C	C	G	C	T	G	G	G	C	A	T	C	T	G	G	C	T	G	A	A		C		
untreated	A	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.1	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.0	0.0		
	C	99.9	100.0	99.9	0.0	100.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	100.0		
	G	0.0	0.0	0.0	99.9	0.0	0.0	100.0	99.9	99.9	0.0	0.0	0.0	0.0	100.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	99.9	0.0		
	T	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	99.9	0.0	0.1	100.0	0.0	0.0	0.0	0.0		
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	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-seB4max Replicate 1	A	0.0	0.1	0.4	0.2	0.1	0.0	1.8	0.9	11.2	0.1	99.7	0.0	0.1	0.0	37.3	0.0	38.7	0.1	0.0	37.9	99.7	99.8	0.0		
	C	99.9	99.8	99.6	0.0	99.8	0.0	0.0	0.0	0.0	99.6	0.0	0.0	99.4	0.0	0.2	0.1	0.1	98.9	0.0	0.0	0.0	0.0	99.0		
	G	0.0	0.0	0.0	99.7	0.0	0.0	97.6	98.7	88.5	0.0	0.0	0.0	0.0	0.0	61.8	0.0	60.6	0.0	0.0	61.6	0.0	0.0	0.0		
	T	0.1	0.0	0.0	0.1	0.0	99.9	0.3	0.1	0.1	0.0	99.7	0.1	99.5	0.2	99.4	0.1	0.5	99.6	0.2	0.0	0.0	0.0	0.8		
	-	0.0	0.1	0.1	0.1	0.1	0.1	0.3	0.2	0.2	0.3	0.3	0.4	0.4	0.4	0.4	0.5	0.5	0.4	0.4	0.5	0.2	0.2	0.2	0.2	
AID-seB4max Replicate 2	A	0.0	0.3	0.7	0.2	0.1	0.0	2.6	1.0	11.9	0.2	99.5	0.0	0.1	0.0	41.0	0.0	42.4	0.2	0.0	41.8	99.5	99.5	0.1		
	C	99.9	99.7	99.3	0.0	99.8	0.0	0.0	0.0	0.0	99.4	0.0	0.0	99.2	0.0	0.5	0.0	0.1	98.5	0.0	0.0	0.0	0.0	98.6		
	G	0.0	0.0	0.0	99.8	0.0	0.0	96.4	98.5	87.5	0.0	0.0	0.0	0.0	0.0	57.5	0.0	56.5	0.1	0.0	57.3	0.0	0.0	0.1		
	T	0.0	0.0	0.0	0.0	0.0	99.9	0.6	0.1	0.2	0.0	99.5	0.1	99.4	0.2	99.1	0.2	0.5	99.2	0.2	0.2	0.0	0.0	0.8		
	-	0.0	0.0	0.0	0.0	0.1	0.1	0.4	0.3	0.3	0.4	0.4	0.5	0.6	0.7	0.8	0.8	0.8	0.8	0.8	0.7	0.5	0.5	0.5	0.5	
AID-seB4max Replicate 3	A	0.0	0.0	0.1	0.3	0.0	0.0	2.6	1.2	13.2	0.0	99.6	0.0	0.0	0.0	45.0	0.0	46.6	0.1	0.0	45.8	99.5	99.6	0.1		
	C	99.8	99.9	99.8	0.0	99.9	0.0	0.0	0.0	0.1	99.6	0.0	0.0	99.3	0.0	0.5	0.0	0.1	98.4	0.0	0.1	0.0	0.0	98.5		
	G	0.0	0.0	0.0	99.6	0.0	0.0	97.0	98.5	86.3	0.0	0.0	0.0	0.0	0.0	53.6	0.0	52.5	0.1	0.0	53.5	0.0	0.0	0.0		
	T	0.1	0.0	0.0	0.0	0.0	99.9	0.6	0.3	0.1	0.0	99.4	0.1	99.4	0.2	99.3	0.2	0.7	99.4	0.1	0.0	0.0	0.1	1.1		
	-	0.1	0.0	0.1	0.0	0.1	0.1	0.4	0.3	0.3	0.3	0.3	0.5	0.5	0.6	0.6	0.7	0.7	0.7	0.6	0.6	0.4	0.3	0.3	0.3	
AID-seBE-IRE5 +Rap Replicate 1	A	0.0	0.2	0.6	0.1	0.1	0.0	0.4	0.2	2.3	0.2	99.8	0.0	0.1	0.0	16.3	0.0	17.1	0.1	0.0	16.2	99.9	99.9	0.0		
	C	99.9	99.8	99.3	0.0	99.8	0.0	0.0	0.0	0.0	99.6	0.0	0.0	99.7	0.0	0.2	0.0	0.0	99.6	0.0	0.0	0.0	0.0	99.6		
	G	0.0	0.0	0.0	99.9	0.0	0.0	98.8	99.5	97.5	0.0	0.0	0.0	0.0	0.0	83.3	0.0	82.7	0.0	0.0	83.6	0.0	0.0	0.0		
	T	0.1	0.0	0.0	0.0	0.0	99.9	0.6	0.2	0.1	0.0	99.8	0.0	99.8	0.1	99.8	0.1	0.2	99.8	0.1	0.0	0.0	0.0	0.3		
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.1	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	
AID-seBE-IRE5 +Rap Replicate 2	A	0.0	0.2	0.4	0.1	0.1	0.0	0.4	0.1	1.7	0.1	99.9	0.0	0.1	0.0	12.7	0.0	13.3	0.1	0.0	12.5	99.9	99.9	0.0		
	C	100.0	99.8	99.6	0.0	99.9	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.8	0.0	0.3	0.0	0.0	99.7	0.0	0.0	0.0	0.0	99.9		
	G	0.0	0.0	0.0	99.9	0.0	0.0	99.1	99.7	98.2	0.0	0.0	0.0	0.0	0.0	87.0	0.0	86.6	0.0	0.0	87.3	0.0	0.0	0.0		
	T	0.0	0.0	0.0	0.0	0.0	99.9	0.5	0.2	0.1	0.0	99.9	0.0	99.9	0.0	99.8	0.0	0.1	99.9	0.1	0.0	0.0	0.0	0.1		
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	
AID-seBE-IRE5 +Rap Replicate 3	A	0.0	0.0	0.0	0.1	0.0	0.0	0.5	0.2	2.5	0.0	99.9	0.0	0.0	0.0	15.5	0.0	16.1	0.0	0.0	15.4	99.9	99.9	0.0		
	C	99.9	99.9	99.9	0.0	99.9	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.2	0.0	0.0	99.8	0.0	0.0	0.0	0.0	99.8		
	G	0.0	0.0	0.0	99.9	0.0	0.0	99.4	99.7	97.4	0.0	0.0	0.0	0.0	0.0	84.2	0.0	83.8	0.0	0.0	84.6	0.0	0.0	0.0		
	T	0.0	0.0	0.0	0.0	0.0	99.9	0.1	0.0	0.0	0.0	99.9	0.0	99.9	0.0	99.9	0.0	0.1	99.9	0.0	0.0	0.0	0.0	0.1		
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
AID-seBE-IRE5 NoRap Replicate 1	A	0.0	0.1	0.4	0.0	0.1	0.0	0.0	0.0	0.1	0.1	100.0	0.0	0.0	0.0	0.4	0.0	0.4	0.0	0.0	0.5	100.0	100.0	0.0		
	C	100.0	99.9	99.6	0.0	99.9	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	99.9		
	G	0.0	0.0	0.0	99.9	0.0	0.0	99.6	99.9	99.8	0.0	0.0	0.0	0.0	0.0	99.6	0.0	99.6	0.0	0.0	99.4	0.0	0.0	0.0		
	T	0.0	0.0	0.0	0.0	0.0	100.0	0.4	0.1	0.1	0.0	0.0	100.0	0.0	100.0	0.0	99.9	0.0	100.0	0.1	0.0	0.0	0.0	0.0		
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
AID-seBE-IRE5 NoRap Replicate 2	A	0.0	0.2	0.7	0.0	0.2	0.0	0.0	0.0	0.2	0.2	100.0	0.0	0.1	0.0	0.3	0.0	0.3	0.1	0.0	0.3	100.0	100.0	0.1		
	C	100.0	99.8	99.2	0.0	99.8	0.0	0.0	0.0	0.0	99.7	0.0	0.0	99.9	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	99.9		
	G	0.0	0.0	0.0	99.9	0.0	0.0	99.3	99.8	99.7	0.0	0.0	0.0	0.0	0.0	99.7	0.0	99.6	0.0	0.0	99.5	0.0	0.0	0.0		
	T	0.0	0.0	0.0	0.1	0.0	100.0	0.6	0.2	0.1	0.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.2	0.0	0.0	0.0	0.0		
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	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-seBE-IRE5 NoRap Replicate 3	A	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.1	0.0	99.9	0.0	0.0	0.0	0.3	0.0	0.4	0.0	0.0	0.4	100.0	100.0	0.0		
	C	100.0	100.0	99.9	0.0	100.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	99.9		
	G	0.0	0.0	0.0	99.9	0.0	0.0	99.9	100.0	99.8	0.0	0.0	0.0	0.0	0.0	99.7	0.0	99.5	0.0	0.0	99.6	0.0	0.0	0.0		
	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	100.0	0.0	99.9	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	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

Supplementary Figure 3

b **CDA Q104***

		C102			R103			Q104			V105			M106			R107			E108		
		C	T	G	C	A	G	C	A	A	G	T	C	A	T	G	A	G	A	G	A	G
untreated	A	0.0	0.0	0.1	0.0	99.9	0.0	0.1	0.0	100.0	100.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	100.0	0.0	100.0
	C	100.0	0.0	0.0	99.9	0.0	0.0	0.0	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	0.0
	G	0.0	0.0	99.9	0.0	0.1	100.0	99.9	0.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	100.0	0.0
	T	0.0	100.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	0.0	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	0.0	0.0	0.0	0.0	0.0

		1			5			10			15			20			PAM					
		C	T	G	C	A	G	C	A	A	G	T	C	A	T	G	A	G	A	G	A	G
AID-seB4max Replicate 1	A	0.4	0.0	1.0	0.5	99.0	0.5	0.5	0.3	99.3	99.3	0.1	0.1	0.1	99.6	0.0	0.0	99.9	0.1	100.0	0.0	100.0
	C	88.0	0.0	0.0	65.8	0.0	0.0	0.0	66.3	0.0	0.0	0.0	97.8	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	0.1	0.0	98.0	0.2	0.0	98.2	98.3	1.0	0.0	0.0	0.0	99.4	0.0	0.0	99.4	0.0	99.6	0.0	99.4	0.0	99.7
	T	10.3	99.1	0.1	32.5	0.0	0.3	0.0	31.1	0.0	0.0	0.0	99.6	1.8	0.0	99.8	0.4	0.0	0.3	0.0	0.5	0.0
	-	1.2	0.8	0.8	1.0	1.0	1.0	1.1	1.3	0.7	0.7	0.5	0.4	0.2	0.2	0.2	0.1	0.1	0.1	0.0	0.0	0.0

		1			5			10			15			20			PAM					
		C	T	G	C	A	G	C	A	A	G	T	C	A	T	G	A	G	A	G	A	G
AID-seB4max Replicate 2	A	0.3	0.0	0.6	0.4	99.0	0.4	0.5	0.4	99.1	99.1	0.0	0.0	0.2	99.6	0.0	0.0	99.8	0.0	99.9	0.0	100.0
	C	89.6	0.0	0.1	63.7	0.0	0.0	0.0	63.3	0.0	0.0	0.0	98.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	0.0	0.0	98.3	0.1	0.0	98.0	98.3	1.7	0.0	0.0	0.0	99.1	0.0	0.1	0.0	99.4	0.0	99.7	0.0	98.8	0.0
	T	8.5	99.1	0.1	34.8	0.0	0.6	0.1	33.4	0.0	0.0	0.1	99.4	1.3	0.0	99.7	0.4	0.0	0.2	0.0	1.1	0.0
	-	1.5	0.8	0.9	1.0	0.9	1.0	1.1	1.2	0.9	0.9	0.8	0.5	0.4	0.2	0.2	0.1	0.1	0.1	0.0	0.0	0.0

		1			5			10			15			20			PAM					
		C	T	G	C	A	G	C	A	A	G	T	C	A	T	G	A	G	A	G	A	G
AID-seB4max Replicate 3	A	0.3	0.1	0.8	0.3	98.7	0.6	0.6	0.3	98.9	98.9	0.1	0.0	0.2	99.4	0.0	0.1	99.8	0.1	99.9	0.0	100.0
	C	85.5	0.0	0.0	55.5	0.0	0.0	0.0	55.5	0.0	0.0	0.0	97.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	0.1	0.0	98.0	0.2	0.1	97.5	97.8	1.5	0.0	0.0	0.0	98.9	0.0	0.0	0.0	99.3	0.0	99.5	0.0	99.1	0.0
	T	12.5	98.9	0.2	42.8	0.0	0.6	0.2	41.1	0.0	0.0	0.1	99.3	1.9	0.0	99.5	0.3	0.0	0.4	0.0	0.9	0.0
	-	1.6	1.0	1.0	1.2	1.1	1.3	1.3	1.6	1.1	1.0	0.9	0.7	0.6	0.6	0.5	0.4	0.2	0.1	0.1	0.0	0.0

		1			5			10			15			20			PAM					
		C	T	G	C	A	G	C	A	A	G	T	C	A	T	G	A	G	A	G	A	G
AID-seBE-IRE5 +Rap Replicate 1	A	0.1	0.0	0.1	0.0	99.9	0.1	0.1	0.1	99.9	99.9	0.0	0.0	0.1	99.9	0.0	0.0	99.9	0.0	100.0	0.0	100.0
	C	92.6	0.0	0.0	72.0	0.0	0.0	0.0	72.2	0.0	0.0	0.0	99.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	0.0	0.0	99.7	0.0	0.0	99.6	99.7	0.3	0.0	0.0	0.0	99.9	0.0	0.0	0.0	99.8	0.0	99.8	0.0	99.7	99.9
	T	7.1	99.9	0.0	27.9	0.0	0.3	0.1	27.3	0.0	0.0	0.0	99.9	0.3	0.0	100.0	0.2	0.0	0.2	0.0	0.3	0.1
	-	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

		1			5			10			15			20			PAM					
		C	T	G	C	A	G	C	A	A	G	T	C	A	T	G	A	G	A	G	A	G
AID-seBE-IRE5 +Rap Replicate 2	A	0.1	0.0	0.0	0.1	99.8	0.0	0.1	0.1	99.8	99.9	0.0	0.0	0.0	99.9	0.0	0.0	100.0	0.0	100.0	0.0	100.0
	C	94.6	0.0	0.0	76.0	0.0	0.0	0.0	76.4	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
	G	0.0	0.0	99.8	0.0	0.0	99.5	99.7	0.4	0.0	0.0	0.0	99.9	0.0	0.0	0.0	99.7	0.0	99.9	0.0	99.5	99.8
	T	5.0	99.8	0.1	23.8	0.0	0.3	0.1	22.9	0.0	0.0	0.0	100.0	0.2	0.0	100.0	0.2	0.0	0.1	0.0	0.4	0.2
	-	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

		1			5			10			15			20			PAM					
		C	T	G	C	A	G	C	A	A	G	T	C	A	T	G	A	G	A	G	A	G
AID-seBE-IRE5 +Rap Replicate 3	A	0.2	0.0	0.1	0.1	99.9	0.0	0.0	0.1	100.0	99.9	0.0	0.0	0.1	99.9	0.0	0.0	100.0	0.0	99.9	0.0	100.0
	C	93.5	0.0	0.0	73.1	0.0	0.0	0.0	73.2	0.0	0.0	0.0	99.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	0.0	0.0	99.8	0.0	0.0	99.5	99.8	0.3	0.0	0.0	0.0	99.8	0.0	0.0	0.0	99.7	0.0	99.6	0.0	99.2	99.7
	T	6.1	99.9	0.1	26.7	0.0	0.4	0.1	26.3	0.0	0.0	0.1	100.0	0.2	0.0	100.0	0.3	0.0	0.4	0.0	0.8	0.3
	-	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

		1			5			10			15			20			PAM					
		C	T	G	C	A	G	C	A	A	G	T	C	A	T	G	A	G	A	G	A	G
AID-seBE-IRE5 NoRap Replicate 1	A	0.1	0.0	0.0	0.0	99.9	0.0	0.0	0.0	100.0	100.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	100.0	0.0	99.9
	C	99.7	0.0	0.0	99.1	0.0	0.0	0.0	99.2	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
	G	0.0	0.0	99.9	0.0	0.1	99.8	99.9	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	99.9	0.0	99.9	0.0	99.7	99.9
	T	0.2	99.9	0.0	0.8	0.0	0.1	0.0	0.8	0.0	0.0	0.1	100.0	0.0	0.0	99.9	0.1	0.0	0.1	0.0	0.3	0.1
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

		1			5			10			15			20			PAM					
		C	T	G	C	A	G	C	A	A	G	T	C	A	T	G	A	G	A	G	A	G
AID-seBE-IRE5 NoRap Replicate 2	A	0.1	0.0	0.1	0.1	100.0	0.0	0.1	0.1	100.0	99.9	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	99.9	0.0	100.0
	C	99.8	0.1	0.0	99.5	0.0	0.0	0.0	99.5	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
	G	0.0	0.0	99.9	0.0	0.0	99.8	99.9	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	99.8	0.0	99.7	0.0	99.4	99.8
	T	0.1	99.9	0.0	0.4	0.0	0.1	0.1	0.4	0.0	0.0	0.1	99.9	0.0	0.0	100.0	0.2	0.0	0.3	0.0	0.6	0.2
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

		1			5			10			15			20			PAM					
		C	T	G	C	A	G	C	A	A	G	T	C	A	T	G	A	G	A	G	A	G
AID-seBE-IRE5 NoRap Replicate 3	A	0.1	0.0	0.0	0.0	100.0	0.0	0.0	0.1	100.0	100.0	0.0	0.0	0.1	100.0	0.0	0.0	100.0	0.0	100.0	0.0	100.0
	C	99.7	0.0	0.0	99.3	0.0	0.0	0.0	99.2	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	0.0	0.0	100.0	0.0	0.0	99.7	99.9	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	99.6	0.0	99.7	0.0	99.3	99.9
	T	0.2	100.0	0.0	0.6	0.0	0.3	0.1	0.7	0.0	0.0	0.1	100.0	0.0	0.0	100.0	0.3	0.0	0.3	0.0	0.7	0.3
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Supplementary Figure 3

c		IDH2 R172K																												
untreated		P167			I168			T169			I170			G171			R172			H173										
		C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C						
	A	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	0.2	0.2	0.0	99.9	0.5	0.5	0.0	100.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	
	C	99.9	100.0	100.0	0.0	0.0	100.0	0.0	99.9	100.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	100.0	0.0	99.9	0.0	0.0	0.0	99.9	0.0	99.9	
	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	99.8	99.8	0.0	0.1	99.4	99.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0
	T	0.1	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	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-seB4max Replicate 1		PAM			20			15			10			5			1													
		C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C						
	A	0.1	0.2	0.4	99.9	0.0	0.1	99.7	0.1	0.2	99.6	0.0	0.0	10.0	31.7	0.2	99.2	31.4	32.2	0.1	99.4	0.1	30.2	0.1						
	C	99.6	99.7	99.5	0.0	0.0	99.6	0.0	99.5	99.4	0.0	0.0	0.0	0.0	0.1	98.8	0.0	0.0	0.1	98.9	0.0	99.0	0.0	98.8						
	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	89.4	67.2	0.0	0.0	67.5	66.7	0.0	0.0	0.0	0.0	68.9						
	T	0.2	0.0	0.0	0.0	99.9	0.1	0.0	0.1	0.1	0.0	99.5	99.4	0.1	0.3	0.3	0.0	0.3	0.2	0.0	0.3	0.3	0.1	0.4						
-	0.0	0.1	0.1	0.1	0.1	0.2	0.3	0.1	0.4	0.4	0.5	0.5	0.5	0.7	0.7	0.7	0.7	0.8	0.7	0.6	0.6	0.7	0.7							
AID-seB4max Replicate 2		C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C						
	A	0.0	0.0	0.0	99.9	0.0	0.0	99.7	0.0	0.0	99.7	0.0	0.0	10.1	38.0	0.0	99.3	37.7	38.3	0.1	99.3	0.0	35.6	0.1						
	C	99.7	100.0	99.9	0.0	0.0	99.8	0.1	99.7	99.7	0.0	0.0	0.0	0.0	0.3	99.1	0.0	0.1	0.3	98.7	0.1	99.0	0.0	98.7						
	G	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	89.4	60.7	0.0	0.0	61.4	60.4	0.0	0.0	0.0	0.0	63.7						
	T	0.2	0.0	0.0	0.0	100.0	0.1	0.0	0.1	0.1	0.0	99.6	99.5	0.0	0.3	0.2	0.0	0.1	0.2	0.6	0.1	0.2	0.4	0.5						
	-	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.2	0.2	0.2	0.4	0.5	0.5	0.6	0.6	0.6	0.7	0.7	0.6	0.6	0.6	0.7	0.7						
AID-seB4max Replicate 3		C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C						
	A	0.0	0.0	0.1	99.9	0.0	0.0	99.8	0.0	0.0	99.7	0.0	0.0	8.2	30.0	0.1	99.4	29.7	30.3	0.1	99.5	0.0	28.2	0.0						
	C	99.7	99.9	99.9	0.1	0.0	99.9	0.1	99.7	99.7	0.0	0.0	0.0	0.0	0.3	99.3	0.0	0.0	0.2	99.2	0.0	99.3	0.0	99.1						
	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	91.3	69.0	0.0	0.0	69.6	68.8	0.0	0.0	0.0	0.0	71.3						
	T	0.2	0.0	0.0	0.0	100.0	0.0	0.0	0.1	0.1	0.0	99.6	99.5	0.0	0.2	0.2	0.0	0.1	0.2	0.3	0.0	0.3	0.0	0.4						
	-	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.2	0.3	0.3	0.4	0.5	0.4	0.5	0.5	0.5	0.5	0.6	0.5	0.5	0.4	0.4	0.4						
AID-seB4max + Rap Replicate 1		PAM			20			15			10			5			1													
		C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C						
	A	0.1	0.2	0.4	99.9	0.0	0.0	99.9	0.1	0.2	100.0	0.0	0.0	2.6	14.8	0.2	99.9	14.6	15.0	0.1	99.9	0.1	13.6	0.1						
	C	99.9	99.8	99.6	0.1	0.0	99.9	0.1	99.9	99.8	0.0	0.0	0.0	0.0	0.1	99.7	0.0	0.0	0.1	99.7	0.0	99.8	0.0	99.7						
	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	97.3	85.0	0.0	0.0	85.1	84.7	0.0	0.0	0.0	0.0	86.1						
	T	0.1	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	100.0	99.9	0.1	0.1	0.0	0.0	0.1	0.1	0.0	0.1	0.1	0.1	0.1						
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.1	0.1							
AID-seB4max + Rap Replicate 2		C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C						
	A	0.0	0.0	0.1	99.9	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	2.6	14.6	0.0	99.8	14.6	14.9	0.1	99.8	0.0	13.5	0.0						
	C	99.9	99.9	99.9	0.1	0.0	99.9	0.1	99.9	99.9	0.0	0.0	0.0	0.0	0.1	99.8	0.0	0.0	0.1	99.8	0.0	99.8	0.0	99.8						
	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	97.3	85.2	0.0	0.1	85.2	84.9	0.0	0.0	0.0	0.0	86.3						
	T	0.1	0.0	0.0	0.0	100.0	0.1	0.0	0.0	0.0	0.0	99.9	99.9	0.0	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0						
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1						
AID-seB4max + Rap Replicate 3		C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C						
	A	0.0	0.0	0.0	99.9	0.0	0.0	99.8	0.0	0.0	99.9	0.0	0.0	2.3	14.2	0.0	99.8	14.2	14.5	0.0	99.8	0.0	13.1	0.0						
	C	99.9	100.0	99.9	0.1	0.0	100.0	0.1	99.9	99.9	0.0	0.0	0.0	0.0	0.0	99.7	0.0	0.0	0.1	99.8	0.0	99.8	0.0	99.8						
	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	97.5	85.5	0.0	0.1	85.6	85.3	0.0	0.0	0.0	0.0	86.8						
	T	0.1	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	99.9	99.8	0.0	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0						
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1						
AID-seB4max IRES NoRap Replicate 1		PAM			20			15			10			5			1													
		C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C						
	A	0.1	0.2	0.3	99.9	0.0	0.0	99.9	0.0	0.1	100.0	0.0	0.0	0.1	0.3	0.2	100.0	0.3	0.3	0.1	99.9	0.0	0.3	0.1						
	C	99.9	99.8	99.7	0.0	0.0	99.9	0.0	100.0	99.9	0.0	0.0	0.0	0.0	0.0	99.7	0.0	0.0	0.0	99.9	0.0	99.9	0.0	99.9						
	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	99.8	99.7	0.0	0.0	99.6	99.6	0.0	0.0	0.0	0.0	99.6						
	T	0.0	0.0	0.0	0.0	100.0	31.0	0.0	0.0	0.0	0.0	100.0	99.9	0.1	0.0	0.0	0.0	0.1	0.1	0.0	0.0	0.0	0.0	0.1						
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0							
AID-seB4max IRES NoRap Replicate 2		C	C	C	A	T	C	A	C	C	A	T	T	G	G	C	A	G	G	C	A	C	G	C						
	A	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	0.2	0.9	0.0	99.9	0.9	1.0	0.0	100.0	0.0	0.9	0.0						
	C	99.9	100.0	100.0	0.0	0.0	100.0	0.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	99.9	0.0	99.8	0.0	99.9						
	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	99.7	99.0	0.0	0.0	99.0	99.0	0.0	0.0	0.0	0.0	99.1						
	T	0.1	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0						
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0																			

Supplementary Figure 3

d		EMXI																										
		E225				S226				E227				Q228				K229				K230				K231		
		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	A	A	G	G	G	
untreated	A	0.0	99.9	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.8	0.0	99.7	99.9	0.0	99.9	99.9	0.0	99.4	99.6	0.0	99.4	99.6	0.0	0.0	0.0	
	C	0.0	0.0	0.0	0.0	99.8	99.8	0.0	0.0	0.0	99.8	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	
	G	99.9	0.0	99.8	0.1	0.0	0.0	99.8	0.0	99.9	0.1	0.1	99.9	0.1	0.1	99.7	0.0	0.0	99.5	0.1	0.0	99.8	99.8	99.8	99.8	99.8		
	T	0.0	0.0	0.1	99.7	0.2	0.1	0.1	0.0	0.1	0.1	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	0.1	0.1	0.0	0.1	0.1	0.0	0.1		
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.4	0.4	0.0	0.0	0.0	0.0		

AID-seBEMax Replicate 1		1				5				10				15				20				PAM					
		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	G	G			
AID-seBEMax Replicate 1	A	0.6	99.3	0.8	0.1	0.7	0.5	0.1	99.2	0.5	0.6	99.4	0.2	99.4	99.5	0.1	99.6	99.7	0.0	99.6	99.6	0.1	99.6	99.6	0.1	0.0	0.4
	C	0.0	0.0	0.0	0.0	70.7	76.0	0.0	0.0	0.0	70.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	98.2	0.0	98.3	0.0	0.3	0.2	98.1	0.0	98.5	0.6	0.0	98.9	0.0	0.0	99.1	0.0	0.0	99.2	0.0	0.0	99.0	99.3	99.1	99.0	99.1	
	T	0.5	0.0	0.1	99.2	27.6	22.4	0.9	0.0	0.2	27.9	0.0	0.3	0.0	0.0	0.0	0.4	0.0	0.0	0.3	0.0	0.0	0.0	0.7	0.5	0.3	
	-	0.7	0.7	0.8	0.8	0.8	0.9	0.8	0.8	0.8	0.8	0.6	0.6	0.5	0.4	0.5	0.4	0.4	0.3	0.5	0.4	0.4	0.2	0.2	0.2	0.2	

AID-seBEMax Replicate 2		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	G	G	
		A	0.6	99.3	0.9	0.1	0.7	0.3	0.1	99.1	0.3	0.6	99.1	0.1	99.4	99.5	0.0	99.7	99.7	0.1	99.5	99.6	0.0	0.0	0.0
C	0.0	0.0	0.1	0.1	55.2	64.8	0.0	0.0	0.0	54.4	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	
G	98.5	0.0	98.2	0.2	0.3	0.2	98.9	0.0	98.7	0.9	0.0	99.1	0.0	0.0	99.5	0.0	0.0	99.5	0.0	0.0	99.7	99.8	99.2	99.2	99.2
T	0.1	0.0	0.1	99.8	42.9	33.8	0.1	0.0	0.0	43.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.0	0.2	0.1	0.1	

AID-seBEMax Replicate 3		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	G	G		
		A	0.5	99.4	0.6	0.0	0.5	0.1	0.2	99.4	0.3	0.3	99.4	0.1	99.6	99.6	0.1	99.6	99.7	0.0	99.5	99.5	0.1	99.5	99.5	0.1
C	0.0	0.0	0.1	0.0	65.0	73.5	0.0	0.0	0.0	64.9	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
G	98.8	0.0	98.7	0.2	0.2	0.2	99.1	0.0	99.1	0.7	0.0	99.3	0.0	0.0	99.5	0.0	0.0	99.4	0.0	0.0	99.5	99.7	99.6	99.6	99.6	
T	0.1	0.0	0.1	99.8	33.7	25.6	0.1	0.0	0.0	33.4	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.1	0.0		

AID-seBE-IREs +Rap Replicate 1		1				5				10				15				20				PAM				
		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	G	G		
AID-seBE-IREs +Rap Replicate 1	A	0.0	99.9	0.1	0.0	0.2	0.2	0.0	99.9	0.0	0.1	99.9	0.0	99.9	99.9	0.0	99.9	99.9	0.0	99.8	99.8	0.0	99.8	99.8	0.0	0.1
	C	0.0	0.0	0.0	0.0	85.5	88.7	0.0	0.0	0.0	85.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	99.8	0.0	99.8	0.1	0.0	0.0	99.6	0.0	99.9	0.1	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.7	0.0	0.0	99.6	99.8	99.8	99.8	99.8
	T	0.1	0.0	0.0	99.8	14.1	11.0	0.3	0.0	0.1	14.2	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.0	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	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.1	0.1	0.1	

AID-seBE-IREs +Rap Replicate 2		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	G	G	
		A	0.0	99.9	0.0	0.0	0.1	0.0	0.0	99.9	0.0	0.1	99.9	0.0	99.9	99.9	0.0	99.9	99.9	0.0	99.7	99.8	0.0	99.7	99.8
C	0.0	0.0	0.0	0.0	85.2	88.6	0.0	0.0	0.0	85.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
G	99.8	0.0	99.9	0.1	0.0	0.0	99.8	0.0	99.8	0.1	0.1	99.9	0.0	0.0	99.9	0.0	0.0	99.7	0.0	0.0	99.8	99.9	99.9	99.9	99.9
T	0.1	0.0	0.0	99.8	14.7	11.2	0.1	0.0	0.1	14.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.1	0.1	

AID-seBE-IREs +Rap Replicate 3		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	G	G	
		A	0.1	99.9	0.0	0.0	0.1	0.2	0.0	99.9	0.0	0.1	99.9	0.0	99.9	99.9	0.0	99.9	99.9	0.0	99.8	99.8	0.0	99.8	99.8
C	0.0	0.0	0.0	0.0	86.2	89.2	0.0	0.0	0.0	85.9	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
G	99.8	0.0	99.9	0.1	0.1	0.0	99.8	0.0	99.9	0.1	0.0	99.9	0.0	0.0	99.9	0.0	0.0	99.8	0.0	0.0	99.7	99.8	99.8	99.8	99.8
T	0.1	0.0	0.1	99.8	13.6	10.5	0.1	0.0	0.0	13.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.1	0.1	

AID-seBE-IREs NoRap Replicate 1		1				5				10				15				20				PAM				
		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	G	G		
AID-seBE-IREs NoRap Replicate 1	A	0.0	99.9	0.0	0.0	0.2	0.4	0.0	99.9	0.0	0.1	99.9	0.0	99.9	100.0	0.0	99.9	100.0	0.0	99.9	99.9	0.0	99.9	99.9	0.0	0.0
	C	0.0	0.0	0.0	0.0	98.4	98.2	0.0	0.0	0.0	99.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
	G	99.7	0.0	100.0	0.1	0.0	0.0	99.6	0.0	99.9	0.0	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.7	0.0	0.0	99.4	99.7	99.9	99.9	99.9
	T	0.3	0.0	0.0	99.9	1.4	1.4	0.3	0.0	0.1	0.4	0.0	0.1	0.0	0.0	0.2	0.0	0.0	0.2	0.0	0.1	0.0	0.6	0.3	0.1	
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.0	0.0	

AID-seBE-IREs NoRap Replicate 2		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	G	G	
		A	0.0	99.9	0.0	0.0	0.1	0.2	0.0	100.0	0.0	0.0	99.9	0.0	99.9	100.0	0.0	100.0	100.0	0.0	99.8	99.7	0.0	0.0	0.0
C	0.0	0.0	0.0	0.0	99.7	99.6	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	0.0	0.0	0.0	0.0	0.0	
G	99.9	0.0	99.9	0.1	0.0	0.0	99.8	0.0	99.9	0.0	0.0	99.9	0.1	0.0	99.9	0.0	0.0	99.7	0.0	0.0	99.7	99.9	99.9	99.9	99.9
T	0.1	0.0	0.1	99.9	0.2	0.2	0.1	0.0	0.1	0.2	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.1	0.0	0.2	0.1	0.1	

AID-seBE-IREs NoRap Replicate 3		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G	G	G	
		A	0.0	99.9	0.0	0.0	0.1	0.3	0.0	99.9	0.0	0.0	99.9	0.0	99.9	99.9	0.0	99.9	100.0	0.0	99.8	99.8	0.0	0.0	0.0
C	0.0	0.0	0.0	0.0	99.4	99.4	0.0	0.0	0.0	99.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
G	99.8	0.0	99.9	0.2	0.0	0.0	99.7	0.0	99.9	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	99.8	0.0	0.0	99.7	99.8	99.9	99.9	99.9
T	0.2	0.0	0.0	99.8	0.4	0.3	0.2	0.0	0.0	0.3	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.1	0.0	0.3	0.1	0.1	

Supplementary Figure 3

e		EMXI_OTI																						
untreated		T	T	C	T	T	C	T	T	C	T	G	C	T	T	A	G	A	C	T	C	T	T	G
	A	0.0	0.0	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	0.1	100.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	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	0.0	0.0	0.0	99.9	0.0	100.0	0.0	0.0	0.0
	G	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	100.0
	T	100.0	100.0	0.0	99.9	100.0	0.0	100.0	100.0	0.0	100.0	0.0	0.0	100.0	99.9	0.0	0.0	0.0	0.0	100.0	0.0	99.9	100.0	0.0
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
AID-seBE ^{max} Replicate 1		T	T	C	T	T	C	T	T	C	T	G	C	T	T	A	G	A	C	T	C	T	T	G
	A	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.0	9.1	0.1	0.0	0.0	100.0	8.8	100.0	0.0	0.0	0.3	0.0	0.0	11.0
	C	0.0	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.7	0.0	0.0	0.0	0.0	0.0	99.3	0.0	99.4	0.0	0.0	0.3
	G	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	90.7	0.0	0.0	0.0	0.0	91.0	0.0	0.0	0.0	0.0	0.0	0.0	88.7
	T	99.9	99.9	0.0	99.9	99.9	0.0	99.9	99.9	0.1	99.9	0.1	0.2	99.9	100.0	0.0	0.1	0.0	0.7	100.0	0.3	99.9	99.9	0.1
-	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
AID-seBE ^{max} Replicate 2		T	T	C	T	T	C	T	T	C	T	G	C	T	T	A	G	A	C	T	C	T	T	G
	A	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.2	0.0	10.7	0.1	0.0	0.0	100.0	10.4	99.9	0.0	0.0	0.3	0.0	0.0	14.7
	C	0.0	0.0	99.9	0.0	0.0	99.8	0.0	0.0	99.7	0.0	0.1	99.6	0.0	0.0	0.0	0.1	0.0	99.1	0.0	99.3	0.0	0.0	0.3
	G	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	89.1	0.0	0.0	0.0	0.0	89.3	0.0	0.0	0.1	0.0	0.0	0.0	84.9
	T	99.9	99.9	0.0	100.0	100.0	0.1	100.0	99.9	0.1	99.9	0.1	0.3	100.0	100.0	0.0	0.1	0.0	0.8	99.8	0.4	99.9	99.9	0.1
-	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	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	
AID-seBE ^{max} Replicate 3		T	T	C	T	T	C	T	T	C	T	G	C	T	T	A	G	A	C	T	C	T	T	G
	A	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.0	9.0	0.0	0.0	0.0	100.0	8.9	99.9	0.0	0.0	0.2	0.0	0.0	11.7
	C	0.0	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.8	0.0	0.1	99.6	0.0	0.0	0.0	0.0	0.0	99.3	0.0	99.4	0.0	0.0	0.2
	G	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	90.8	0.0	0.0	0.0	0.0	90.8	0.0	0.0	0.0	0.0	0.0	0.0	88.0
	T	99.9	100.0	0.1	99.9	100.0	0.1	100.0	99.9	0.0	99.9	0.1	0.3	99.9	99.9	0.0	0.2	0.0	0.6	99.9	0.4	99.9	99.9	0.1
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.1	0.0	0.0	0.0	0.0	0.1	0.1	
AID-seBE- ^{RES} +Rap Replicate 1		T	T	C	T	T	C	T	T	C	T	G	C	T	T	A	G	A	C	T	C	T	T	G
	A	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.9	0.0	0.0	0.0	100.0	0.9	100.0	0.0	0.0	0.1	0.0	0.0	1.6
	C	0.0	0.0	99.8	0.0	0.0	99.8	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	99.8	0.0	0.0	0.0
	G	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.1	0.0	0.0	0.0	0.0	99.0	0.0	0.0	0.0	0.0	0.0	0.0	98.4
	T	99.9	99.9	0.0	100.0	100.0	0.0	100.0	100.0	0.0	100.0	0.0	0.0	100.0	100.0	0.0	0.1	0.0	0.0	100.0	0.0	100.0	99.9	0.0
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	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-seBE- ^{RES} +Rap Replicate 2		T	T	C	T	T	C	T	T	C	T	G	C	T	T	A	G	A	C	T	C	T	T	G
	A	0.0	0.0	0.1	0.0	0.0	0.2	0.0	0.0	0.1	0.0	0.6	0.0	0.0	0.0	100.0	0.6	100.0	0.0	0.0	0.2	0.0	0.0	1.0
	C	0.0	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	100.0	0.0	99.8	0.0	0.0	0.0
	G	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.3	0.0	0.0	0.0	0.0	99.2	0.0	0.0	0.0	0.0	0.0	0.0	98.9
	T	99.9	100.0	0.0	99.9	100.0	0.0	99.9	99.9	0.0	100.0	0.1	0.0	100.0	100.0	0.0	0.1	0.0	0.0	100.0	0.0	100.0	99.9	0.0
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
AID-seBE- ^{RES} +Rap Replicate 3		T	T	C	T	T	C	T	T	C	T	G	C	T	T	A	G	A	C	T	C	T	T	G
	A	0.0	0.0	0.2	0.0	0.0	0.2	0.0	0.0	0.2	0.0	0.9	0.0	0.0	0.0	99.9	0.9	100.0	0.1	0.0	0.4	0.0	0.0	1.1
	C	0.1	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.8	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	99.8	0.0	99.5	0.0	0.0	0.0
	G	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.0	0.0	0.0	0.0	0.0	98.9	0.0	0.0	0.0	0.0	0.0	0.0	98.8
	T	99.9	99.9	0.0	99.9	100.0	0.0	100.0	99.9	0.0	99.9	0.1	0.0	100.0	99.9	0.0	0.2	0.0	0.1	100.0	0.0	100.0	100.0	0.1
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
AID-seBE- ^{RES} NoRap Replicate 1		T	T	C	T	T	C	T	T	C	T	G	C	T	T	A	G	A	C	T	C	T	T	G
	A	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.2	0.0	0.0	0.0
	C	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	99.8	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	99.8	0.0	0.0	0.0
	G	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	99.9
	T	99.9	99.9	0.0	99.9	100.0	0.0	99.9	99.9	0.0	99.9	0.1	0.0	100.0	100.0	0.0	0.1	0.0	0.0	100.0	0.0	100.0	100.0	0.0
-	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
AID-seBE- ^{RES} NoRap Replicate 2		T	T	C	T	T	C	T	T	C	T	G	C	T	T	A	G	A	C	T	C	T	T	G
	A	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	100.0	0.0	100.0	0.1	0.0	0.2	0.0	0.0	0.1
	C	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	99.9	0.0	99.8	0.0	0.0	0.0
	G	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0	99.9
	T	100.0	100.0	0.0	100.0	100.0	0.0	100.0	99.9	0.0	99.9	0.0	0.0	100.0	100.0	0.0	0.1	0.0	0.0	100.0	0.0	100.0	100.0	0.0
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
AID-seBE- ^{RES} NoRap Replicate 3		T	T	C	T	T	C	T	T	C	T	G	C	T	T	A	G	A	C	T	C	T	T	G
	A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	100.0	0.1	99.9	0.0	0.0	0.0	0.0	0.0	0.1
	C	0.0	0.0	100.0	0.0	0.0	100.0	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	100.0	0.0	0.0	0.0
	G	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	99.9
	T	99.9	100.0	0.0	100.0	100.0	0.0	100.0	99.9	0.0	99.9	0.0	0.0	100.0	99.9	0.0	0.0	0.0	0.0	99.9	0.0	99.9	99.9	0.0
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

Supplementary Figure 3

f		EMXI_OT2																													
untreated		C	C	A	T	T	C	T	T	C	T	T	C	T	G	C	T	C	A	G	A	C	G	T							
	A	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.8	0.0	99.7	0.0	0.0	0.1								
	C	100.0	100.0	0.2	0.0	0.0	99.9	0.0	0.1	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	100.0	0.2	0.0	0.2	100.0	0.0	0.2							
	G	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	99.9	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	99.9	0.0						
	T	0.0	0.0	0.0	100.0	99.9	0.0	99.9	99.9	0.0	100.0	99.9	0.0	99.9	0.0	0.0	100.0	0.0	0.0	0.1	0.0	0.0	0.0	0.1	99.7	0.0					
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	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-seBEmax Replicate 1		PAM					20					15					10					5					1				
		C	C	A	T	T	C	T	T	C	T	T	C	T	G	C	T	C	A	G	A	C	G	T							
	A	0.1	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	9.8	0.1	0.1	0.0	99.6	10.5	99.6	0.1	10.5	0.1							
	C	99.2	99.1	0.0	0.0	0.0	99.4	0.0	0.0	99.5	0.1	0.0	99.4	0.0	0.1	98.4	0.1	99.0	0.0	0.2	0.0	91.7	0.1	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	89.6	0.1	0.0	0.0	0.0	88.4	0.0	0.5	88.8	0.0							
	T	0.7	0.8	0.0	99.9	99.8	0.3	99.8	99.7	0.3	99.6	99.6	0.1	99.5	0.1	1.0	99.4	0.5	0.0	0.6	0.0	7.2	0.1	99.4	0.0						
-	0.0	0.1	0.1	0.1	0.1	0.2	0.2	0.4	0.4	0.5	0.5	0.6	0.8	0.6	0.7	0.7	0.8	0.7	0.8	0.7	0.8	0.7	0.5	0.4							
AID-seBEmax Replicate 2		C	C	A	T	T	C	T	T	C	T	T	C	T	G	C	T	C	A	G	A	C	G	T							
	A	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	15.9	0.0	0.0	0.0	99.0	17.1	99.0	0.4	17.3	0.1							
	C	98.7	98.3	0.2	0.0	0.0	99.6	0.0	0.0	99.5	0.0	0.0	98.9	0.0	0.2	97.8	0.0	98.6	0.3	0.2	0.2	85.1	0.1	0.1							
	G	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	83.1	0.2	0.0	0.1	0.0	81.1	0.0	0.6	81.6	0.1							
	T	1.1	1.6	0.0	99.9	99.9	0.3	99.8	99.8	0.3	99.8	99.4	0.2	99.1	0.2	1.3	99.2	0.5	0.1	0.8	0.0	13.1	0.3	99.7	0.0						
	-	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.2	0.3	0.4	0.5	0.6	0.8	0.6	0.7	0.7	0.8	0.7	0.8	0.7	0.8	0.7	0.5						
AID-seBEmax Replicate 3		C	C	A	T	T	C	T	T	C	T	T	C	T	G	C	T	C	A	G	A	C	G	T							
	A	0.0	0.1	99.7	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.1	0.1	0.0	12.6	0.0	0.0	0.1	99.1	13.7	99.2	0.3	13.7	0.0							
	C	98.7	98.3	0.1	0.0	0.0	99.5	0.0	0.0	99.3	0.1	0.0	99.1	0.0	0.1	98.4	0.0	98.7	0.2	0.2	0.2	89.0	0.1	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	86.5	0.1	0.0	0.1	0.0	85.3	0.0	0.3	85.4	0.1							
	T	1.1	1.5	0.0	99.8	99.8	0.3	99.7	99.6	0.2	99.5	99.4	0.2	99.4	0.2	0.9	99.3	0.5	0.0	0.3	0.0	9.7	0.2	99.4	0.0						
	-	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.4	0.4	0.5	0.5	0.6	0.6	0.5	0.6	0.7	0.6	0.6	0.5	0.6	0.7	0.6	0.5	0.0						
AID-seBE-IREs +Rap Replicate 1		PAM					20					15					10					5					1				
		C	C	A	T	T	C	T	T	C	T	T	C	T	G	C	T	C	A	G	A	C	G	T							
	A	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	3.6	0.0	0.0	0.0	99.6	4.6	99.6	0.0	4.7	0.0							
	C	99.9	99.9	0.1	0.0	0.0	100.0	0.0	0.0	99.9	0.0	0.0	99.8	0.0	0.0	99.8	0.0	99.7	0.2	0.1	0.2	97.4	0.0	0.1							
	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	96.1	0.0	0.0	0.0	0.0	94.8	0.0	0.1	95.0	0.0							
	T	0.1	0.1	0.0	100.0	100.0	0.0	100.0	100.0	0.0	99.9	99.9	0.0	99.8	0.0	0.0	99.8	0.1	0.0	0.3	0.0	2.2	0.0	99.7	0.0						
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.1	0.2	0.2	0.2	0.2	0.2	0.2							
AID-seBE-IREs +Rap Replicate 2		C	C	A	T	T	C	T	T	C	T	T	C	T	G	C	T	C	A	G	A	C	G	T							
	A	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	3.8	0.0	0.0	0.0	99.9	4.9	99.9	0.1	5.1	0.0							
	C	99.8	99.8	0.0	0.0	0.0	99.9	0.0	0.0	99.8	0.0	0.0	99.6	0.0	0.0	99.8	0.0	99.9	0.0	0.1	0.0	97.1	0.0	0.1							
	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	95.9	0.0	0.0	0.0	0.0	94.7	0.0	0.1	94.8	0.0							
	T	0.1	0.2	0.0	99.9	99.9	0.0	99.9	99.9	0.0	99.8	99.7	0.0	99.7	0.1	0.1	99.8	0.0	0.0	0.3	0.0	2.6	0.0	99.8	0.0						
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.2	0.3	0.3	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1						
AID-seBE-IREs +Rap Replicate 3		C	C	A	T	T	C	T	T	C	T	T	C	T	G	C	T	C	A	G	A	C	G	T							
	A	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	3.2	0.0	0.0	0.0	99.6	4.1	99.7	0.0	4.0	0.0							
	C	99.9	99.9	0.1	0.0	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.8	0.0	99.7	0.1	0.0	0.1	97.4	0.0	0.0							
	G	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	96.4	0.0	0.0	0.0	0.0	95.4	0.0	0.1	95.7	0.0							
	T	0.0	0.1	0.0	99.9	99.9	0.0	99.9	99.8	0.0	99.8	99.8	0.0	99.8	0.1	0.0	99.8	0.0	0.0	0.3	0.0	2.2	0.1	99.8	0.0						
	-	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.3	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2						
AID-seBE-IREs NoRap Replicate 1		PAM					20					15					10					5					1				
		C	C	A	T	T	C	T	T	C	T	T	C	T	G	C	T	C	A	G	A	C	G	T							
	A	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.0	99.9	0.1	99.9	0.0	0.1	0.0							
	C	100.0	99.9	0.0	0.0	0.0	100.0	0.1	0.0	100.0	0.0	0.0	99.9	0.0	0.0	100.0	0.0	100.0	0.1	0.0	0.1	99.9	0.0	0.1							
	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	99.8	0.0	0.0	0.0	0.0	99.6	0.0	0.0	99.9	0.0							
	T	0.0	0.0	0.0	100.0	100.0	0.0	99.9	100.0	0.0	100.0	99.9	0.0	100.0	0.1	0.0	100.0	0.0	0.0	0.3	0.0	0.1	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	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-seBE-IREs NoRap Replicate 2		C	C	A	T	T	C	T	T	C	T	T	C	T	G	C	T	C	A	G	A	C	G	T							
	A	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	100.0	0.0	99.9	0.0	0.0	0.0							
	C	100.0	100.0	0.0	0.0	0.1	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	99.9	0.0	0.0							
	G	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	99.6	0.0	0.0	99.9	0.0							
	T	0.0	0.0	0.0	100.0	99.9	0.0	100.0	100.0	0.0	100.0	100.0	0.0	100.0	0.1	0.0	100.0	0.0	0.0	0.4	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	0.0	0.0	0.0	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-seBE-IREs NoRap Replicate 3		C	C	A	T	T	C	T	T	C	T	T	C	T	G	C	T	C	A	G	A	C	G	T							
	A	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	99.7	0.1	99.7	0.0	0.1	0.0							
	C	100.0	99.9	0.1	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	100.0	0.3	0.0	0.3	99.9	0.0	0.0							
	G	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	99.5	0.0	0.0	99.9	0.0							
	T	0.0	0.1	0.0	100.0	100.0	0.0	100.0	100.0	0.0	100.0	100.0	0.0	100.0	0.1	0.0	100.0	0.0	0.0	0.4	0.0	0.1	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	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0						

Supplementary Figure 4. R-loop assay to examine sgRNA-independent off-target activity. The on-target activity at EMX1 and sg-RNA independent off-target activity at the dSaCas9-site is provided. The frequency of individual base calls at each locus of interest are shown, colored using a heat map from white (0%) to red (100%). The parent sequence is shown with PAM (yellow) and sgRNA proto-spacer (black) noted, with the SpCas9 NGG PAM for EMX1 and the NNGRRT for the dSaCas9 targeting site. The PAM is at right, with the coding strand cytosine (C) targeted for mutation is highlighted in red. The data in Fig. 4c and Extended Data Fig. 4d show the quantification of conversion at the listed base only. Results across each locus and with individual replicates are shown using untreated cells (n = 1), along with intact BE4max or seBE-IRES constructs with or without rapamycin (n = 3 each). The loci analyzed are the validated EMX1 targeting site with (a) evoA1, (b) AID' or (c) A3A editors or the dSaCas9 site with (d) evoA1, (e) AID' or (f) A3A editors.

Supplementary Figure 4

a *AID constructs, EMXI on-target*

		E225		S226		E227		Q228		K229		K230		K231									
		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	G	G	G	
untreated	A	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.7	99.9	0.0	99.9	99.9	0.0	99.4	99.6	0.0	0.0	
	C	0.0	0.0	0.0	0.0	99.8	99.8	0.0	0.0	0.0	99.8	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	0.0	99.8	0.1	0.0	0.0	99.8	0.0	99.9	0.1	0.1	99.9	0.1	0.1	99.7	0.0	0.0	99.5	0.1	0.0	99.8	99.8
	T	0.0	0.0	0.1	99.7	0.2	0.1	0.1	0.0	0.1	0.1	0.0	0.0	0.0	0.2	0.0	0.0	0.1	0.1	0.0	0.1	0.1	0.1
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.4	0.4	0.0	0.0	0.0	0.0

		1		5		10		15		20 PAM													
		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	G	G	G	
AID-seBE ^{max} Replicate 1	A	0.3	99.3	0.4	0.1	0.6	0.2	0.1	99.3	0.2	0.4	99.3	0.1	99.5	99.5	0.1	99.6	99.6	0.1	99.4	99.5	0.1	0.1
	C	0.0	0.0	0.0	0.0	78.0	84.0	0.0	0.1	0.0	77.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
	G	99.0	0.1	98.9	0.2	0.1	0.0	99.2	0.0	99.1	0.3	0.0	99.2	0.0	0.1	99.4	0.0	0.0	99.5	0.0	0.0	99.3	99.6
	T	0.2	0.0	0.1	99.1	20.8	15.2	0.1	0.0	0.1	21.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.1	0.0	0.2	0.1
	-	0.5	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.5	0.5	0.4	0.4	0.4	0.3	0.3	0.3	0.4	0.4	0.4	0.1

		1		5		10		15		20 PAM													
		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	G	G	G	
AID-seBE ^{max} Replicate 2	A	0.2	99.4	0.3	0.0	0.3	0.1	0.1	99.4	0.1	0.2	99.5	0.0	99.6	99.6	0.0	99.7	99.7	0.0	99.5	99.5	0.0	0.0
	C	0.0	0.1	0.0	0.0	82.1	87.2	0.0	0.0	0.0	82.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
	G	99.2	0.0	99.1	0.2	0.1	0.0	99.3	0.0	99.4	0.2	0.0	99.4	0.0	0.0	99.6	0.0	0.0	99.7	0.0	0.1	99.5	99.7
	T	0.1	0.0	0.1	99.3	17.1	12.1	0.1	0.0	0.0	17.0	0.0	0.1	0.0	0.0	0.1	0.0	0.1	0.1	0.0	0.0	0.2	0.1
	-	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.4	0.4	0.4	0.3	0.3	0.2	0.2	0.2	0.4	0.4	0.4	0.1

		1		5		10		15		20 PAM													
		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	G	G	G	
AID-seBE ^{max} Replicate 3	A	0.8	99.1	1.2	0.1	1.4	0.5	0.1	99.2	0.4	0.5	99.1	0.2	99.2	99.3	0.2	99.6	99.5	0.1	99.4	99.5	0.2	0.1
	C	0.0	0.0	0.0	0.1	59.5	69.4	0.1	0.1	0.0	59.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
	G	98.4	0.1	97.9	0.2	0.4	0.2	98.8	0.0	98.6	0.6	0.1	99.1	0.1	0.2	99.1	0.1	0.1	99.3	0.1	0.1	98.9	99.2
	T	0.3	0.2	0.4	99.1	38.1	29.2	0.4	0.1	0.3	38.4	0.1	0.1	0.1	0.1	0.3	0.0	0.1	0.3	0.2	0.0	0.5	0.6
	-	0.6	0.6	0.6	0.6	0.7	0.7	0.6	0.7	0.7	0.7	0.6	0.6	0.5	0.5	0.4	0.3	0.2	0.2	0.4	0.3	0.3	0.1

		1		5		10		15		20 PAM													
		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	G	G	G	
AID-seBE-IRE5 +Rap Replicate 1	A	0.0	99.7	0.1	0.0	0.2	0.1	0.0	99.7	0.0	0.1	99.7	0.0	99.8	99.8	0.0	99.8	99.9	0.0	99.8	99.8	0.0	0.1
	C	0.0	0.0	0.0	0.0	83.0	87.2	0.0	0.1	0.0	82.7	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	0.1	99.7	0.2	0.1	0.0	99.7	0.0	99.7	0.1	0.0	99.7	0.0	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.6	99.8
	T	0.1	0.0	0.1	99.6	16.5	12.4	0.1	0.0	0.0	16.8	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.2	0.1
	-	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.1

		1		5		10		15		20 PAM													
		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	G	G	G	
AID-seBE-IRE5 +Rap Replicate 2	A	0.0	99.8	0.1	0.1	0.1	0.2	0.0	99.8	0.0	0.2	99.8	0.0	99.8	99.8	0.0	99.8	99.9	0.0	99.7	99.7	0.0	0.1
	C	0.0	0.0	0.0	0.1	86.2	89.7	0.0	0.0	0.0	86.0	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	0.0	99.7	0.2	0.1	0.0	99.6	0.0	99.8	0.1	0.0	99.7	0.0	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.6	99.7
	T	0.1	0.0	0.1	99.6	13.5	10.0	0.2	0.0	0.1	13.6	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.2
	-	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.1

		1		5		10		15		20 PAM													
		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	G	G	G	
AID-seBE-IRE5 +Rap Replicate 3	A	0.1	99.6	0.1	0.0	0.2	0.1	0.1	99.5	0.1	0.2	99.5	0.0	99.6	99.6	0.0	99.7	99.8	0.0	99.6	99.6	0.0	0.1
	C	0.0	0.1	0.0	0.0	75.5	81.4	0.0	0.0	0.0	75.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
	G	99.5	0.0	99.5	0.1	0.1	0.0	99.3	0.1	99.5	0.3	0.0	99.5	0.0	0.0	99.6	0.0	0.0	99.7	0.0	0.0	99.4	99.7
	T	0.2	0.0	0.1	99.5	23.8	18.1	0.2	0.0	0.0	24.1	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.2	0.1
	-	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.3	0.3	0.3	0.2	0.2	0.2	0.3	0.3	0.3	0.1

		1		5		10		15		20 PAM													
		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	G	G	G	
AID-seBE-IRE5 NoRap Replicate 1	A	0.0	99.8	0.0	0.1	0.1	0.2	0.0	99.8	0.1	0.0	99.8	0.0	99.9	99.8	0.0	99.9	99.9	0.0	99.7	99.7	0.0	0.1
	C	0.0	0.0	0.0	0.0	99.5	99.5	0.0	0.1	0.0	99.5	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
	G	99.8	0.1	99.8	0.4	0.0	0.0	99.7	0.1	99.8	0.0	0.0	99.8	0.0	0.1	99.8	0.0	0.0	99.8	0.0	0.0	99.6	99.7
	T	0.2	0.0	0.1	99.5	0.4	0.3	0.2	0.0	0.1	0.4	0.1	0.2	0.0	0.1	0.1	0.0	0.0	0.1	0.1	0.0	0.3	0.2
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1

		1		5		10		15		20 PAM													
		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	G	G	G	
AID-seBE-IRE5 NoRap Replicate 2	A	0.0	99.9	0.0	0.0	0.1	0.1	0.0	99.8	0.1	0.1	99.9	0.0	99.9	99.9	0.0	99.9	99.9	0.0	99.7	99.7	0.0	0.0
	C	0.0	0.0	0.0	0.1	99.6	99.5	0.0	0.1	0.0	99.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
	G	99.8	0.1	99.8	0.2	0.0	0.0	99.8	0.0	99.8	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	99.5	99.8
	T	0.2	0.0	0.1	99.7	0.3	0.3	0.1	0.0	0.0	0.3	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.1	0.0	0.3	0.2
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.2	0.2	0.1

		1		5		10		15		20 PAM													
		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	G	G	G	
AID-seBE-IRE5 NoRap Replicate 3	A	0.0	99.8	0.0	0.1	0.1	0.1	0.0	99.8	0.0	0.0	99.9	0.0	99.9	99.9	0.0	99.9	99.9	0.0	99.9	99.8	0.0	0.1
	C	0.0	0.0	0.0	0.0	98.4	98.5	0.0	0.1	0.0	98.5	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	0.1	99.9	0.2	0.0	0.0	99.8	0.1	99.9	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	99.6	99.8
	T	0.1	0.0	0.1	99.7	1.5	1.4	0.1	0.0	0.0	1.5	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.3	0.1
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1

Supplementary Figure 4

b		<i>evoA1 constructs, EMXI on-target</i>																				
		E225			S226			E227			Q228			K229			K230			K231		
		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G
untreated	A	0.0	99.9	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.8	0.0	99.7	99.9	0.0	99.9	99.9	0.0	99.4	99.6	0.0
	C	0.0	0.0	0.0	0.0	99.8	99.8	0.0	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
	G	99.9	0.0	99.8	0.1	0.0	0.0	99.8	0.0	99.9	0.1	0.1	99.9	0.1	0.1	99.7	0.0	0.0	99.5	0.1	0.0	99.8
	T	0.0	0.0	0.1	99.7	0.2	0.1	0.1	0.0	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.1	0.1	0.0
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.4	0.4	0.0

		1			5			10			15			20			PAM					
		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G
evoA1-BE4max Replicate 1	A	0.4	99.7	0.0	0.0	0.9	0.3	0.1	99.6	0.1	0.1	99.7	0.0	99.8	99.8	0.0	99.8	99.8	0.0	99.7	99.7	0.0
	C	0.1	0.0	0.0	0.1	55.7	56.9	0.0	0.0	0.0	95.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	99.2	0.1	99.7	0.2	1.6	0.5	99.6	0.0	99.6	0.0	99.7	0.0	99.7	0.0	99.8	0.0	0.0	99.8	0.0	0.1	99.6
	T	0.1	0.0	0.1	99.5	41.5	41.9	0.1	0.0	0.0	4.2	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.2
	-	0.2	0.2	0.2	0.3	0.3	0.4	0.3	0.3	0.3	0.3	0.3	0.3	0.2	0.2	0.1	0.1	0.1	0.1	0.2	0.2	0.2

		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G
evoA1-BE4max Replicate 2	A	0.3	99.6	0.0	0.0	0.5	0.3	0.0	99.7	0.0	0.1	99.7	0.0	99.8	99.8	0.0	99.8	99.9	0.0	99.7	99.7	0.0
	C	0.0	0.0	0.0	0.0	63.2	63.8	0.0	0.0	0.0	95.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	99.3	0.1	99.7	0.2	1.4	0.2	99.6	0.0	99.7	0.1	0.0	99.7	0.0	0.0	99.7	0.0	0.0	99.8	0.0	0.1	99.6
	T	0.2	0.0	0.1	99.5	34.7	35.4	0.1	0.0	0.1	3.7	0.1	0.1	0.0	0.1	0.0	0.1	0.0	0.1	0.1	0.0	0.2
	-	0.3	0.2	0.3	0.2	0.2	0.3	0.2	0.2	0.2	0.3	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.2	0.2

		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G
evoA1-BE4max Replicate 3	A	0.5	99.8	0.0	0.0	0.7	0.4	0.1	99.7	0.1	0.1	99.7	0.0	99.7	99.7	0.0	99.8	99.8	0.0	99.7	99.7	0.0
	C	0.0	0.0	0.0	0.0	45.2	46.3	0.0	0.0	0.0	92.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	99.3	0.0	99.7	0.2	1.4	0.2	99.5	0.0	99.6	0.1	0.0	99.7	0.0	0.0	99.7	0.0	0.0	99.8	0.0	0.0	99.6
	T	0.1	0.0	0.1	99.6	52.5	52.9	0.1	0.0	0.1	7.1	0.0	0.1	0.0	0.1	0.0	0.0	0.1	0.0	0.1	0.0	0.2
	-	0.1	0.1	0.1	0.2	0.2	0.3	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.2	0.2

		1			5			10			15			20			PAM					
		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G
evoA1-seBE- IRES +Rep Rep	A	0.1	99.8	0.0	0.1	0.1	0.1	0.0	99.8	0.0	0.0	99.8	0.0	99.9	99.9	0.0	99.9	99.9	0.0	99.7	99.7	0.0
	C	0.0	0.0	0.0	0.0	74.1	74.1	0.0	0.0	0.0	97.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	99.8	0.0	99.8	0.2	0.5	0.1	99.8	0.1	99.9	0.0	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.9	0.0	0.0	99.7
	T	0.1	0.0	0.1	99.7	25.3	25.7	0.1	0.0	0.0	2.4	0.1	0.1	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.1
	-	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.2	0.2	0.2

		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G
evoA1-seBE- IRES +Rep Rep	A	0.1	99.8	0.0	0.1	0.1	0.1	0.0	99.8	0.0	0.1	99.8	0.0	99.8	99.8	0.0	99.9	99.9	0.0	99.8	99.7	0.0
	C	0.0	0.1	0.0	0.1	75.5	75.5	0.0	0.1	0.0	97.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	99.6	0.0	99.8	0.3	0.5	0.1	99.7	0.0	99.8	0.0	0.0	99.8	0.0	0.1	99.8	0.0	0.0	99.9	0.0	0.1	99.6
	T	0.2	0.0	0.1	99.6	23.9	24.2	0.1	0.0	0.1	2.6	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.1	0.0	0.2
	-	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.1	0.1	0.1

		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G
evoA1-seBE- IRES +Rep Rep	A	0.2	99.8	0.0	0.0	0.1	0.1	0.0	99.8	0.0	0.1	99.7	0.0	99.8	99.8	0.0	99.8	99.8	0.0	99.7	99.7	0.0
	C	0.0	0.0	0.0	0.0	69.1	69.1	0.0	0.0	0.0	97.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	99.6	0.0	99.7	0.2	0.4	0.0	99.7	0.0	99.8	0.0	0.1	99.7	0.0	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.6
	T	0.1	0.0	0.1	99.6	30.3	30.6	0.1	0.0	0.0	2.8	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.1	0.0	0.2
	-	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	0.2	0.1

		1			5			10			15			20			PAM					
		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G
evoA1-seBE- IRES -Rep Rep 1	A	0.0	99.8	0.0	0.0	0.1	0.1	0.0	99.8	0.0	0.1	99.9	0.0	99.9	99.9	0.0	99.9	99.9	0.0	99.8	99.8	0.0
	C	0.0	0.0	0.0	0.1	98.9	98.9	0.0	0.1	0.0	99.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	99.8	0.1	99.9	0.2	0.0	0.0	99.8	0.1	99.9	0.0	0.0	99.9	0.1	0.0	99.9	0.0	0.0	99.9	0.0	0.1	99.7
	T	0.1	0.0	0.1	99.7	0.9	0.9	0.1	0.0	0.0	0.3	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.2
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1

		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G
evoA1-seBE- IRES -Rep Rep 2	A	0.0	99.9	0.0	0.0	0.1	0.1	0.1	99.9	0.1	0.1	99.9	0.0	99.9	99.9	0.0	99.9	99.9	0.0	99.8	99.8	0.0
	C	0.0	0.0	0.0	0.1	99.3	99.2	0.0	0.0	0.0	99.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	99.8	0.0	99.9	0.2	0.0	0.0	99.7	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.6
	T	0.2	0.0	0.1	99.7	0.6	0.6	0.2	0.0	0.1	0.1	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.1	0.0	0.2
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1

		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	G	A	A	G
evoA1-seBE- IRES -Rep Rep 3	A	0.0	99.9	0.0	0.1	0.1	0.2	0.0	99.8	0.1	0.0	99.9	0.0	99.9	99.8	0.0	99.9	99.9	0.0	99.8	99.8	0.0
	C	0.0	0.0	0.0	0.1	98.5	98.5	0.0	0.1	0.0	99.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	99.8	0.1	99.9	0.3	0.0	0.0	99.8	0.1	99.8	0.0	0.0	99.9	0.0	0.1	99.9	0.0	0.0	99.9	0.0	0.0	99.6
	T	0.1	0.0	0.1	99.6	1.4	1.3	0.1	0.0	0.1	0.4	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.1	0.0	0.3
	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1

Supplementary Figure 4

c		<i>A3A constructs, EMXI on-target</i>																													
untreated		E225				S226				E227				Q228				K229				K230				K231					
		G	A	G	T	C	C	G	A	G	C	A	G	C	A	G	A	A	G	A	A	G	A	A	G	A	A	A	G	G	G
	A	0.8	99.9	0.0	0.0	0.0	0.9	0.2	0.2	99.1	0.0	0.3	99.2	0.2	99.7	99.9	0.0	99.9	99.9	0.0	99.9	99.9	0.0	99.4	99.6	0.0	0.0	0.0	0.0	0.0	
	C	0.0	0.0	0.0	0.0	99.8	99.8	0.0	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	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
	G	99.9	0.0	99.8	0.1	0.0	0.0	99.8	0.0	99.9	0.1	0.1	99.9	0.1	0.1	99.7	0.0	0.1	99.7	0.0	99.5	0.1	0.0	99.8	99.8	99.8	99.8	99.8	99.8	99.8	
T	0.0	0.0	0.1	99.7	0.2	0.1	0.1	0.0	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.1	0.1	0.0	0.1	0.1	0.0	0.1	0.1	0.1	0.1		
-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.4	0.4	0.4	0.0	0.4	0.4	0.4	0.0	0.0		
A3A-BE4max Replicate 1		1				5				10				15				20 PAM													
		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	A	G	A	A	G	A	A	A	G	G	G		
	A	0.8	99.4	0.1	0.0	0.0	61.8	62.0	0.1	0.1	0.0	72.1	0.0	0.1	0.1	0.0	0.0	0.1	99.5	99.6	0.2	99.5	99.6	0.0	0.0	0.0	0.0	0.0			
	C	0.0	0.1	0.0	0.0	0.0	62.3	62.5	0.0	0.0	0.0	71.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0			
	G	98.6	0.0	99.3	0.2	1.2	0.3	98.9	0.1	99.2	0.2	0.0	98.9	0.0	99.3	0.0	99.3	0.0	99.3	0.0	99.5	0.0	0.0	99.5	0.0	0.0	99.5	99.7			
T	0.2	0.0	0.1	99.1	35.4	36.7	0.1	0.0	0.1	26.5	0.0	0.1	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.0	0.2	0.1	0.2	0.1				
-	0.5	0.5	0.6	0.7	0.7	0.8	0.7	0.7	0.7	0.8	0.7	0.8	0.7	0.8	0.5	0.4	0.4	0.4	0.3	0.3	0.4	0.4	0.4	0.4	0.4	0.1	0.1				
A3A-BE4max Replicate 2		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	A	G	A	A	G	A	A	G	G	G			
	A	0.5	99.5	0.0	0.0	0.5	0.2	0.2	99.3	0.1	0.4	99.4	0.1	99.5	99.5	0.1	99.6	99.7	0.1	99.4	99.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0			
	C	0.0	0.0	0.0	0.0	71.5	71.1	0.1	0.0	0.0	78.8	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0			
	G	98.9	0.1	99.5	0.2	1.0	0.1	99.1	0.1	99.3	0.1	0.0	99.3	0.0	99.3	0.0	99.4	0.0	99.6	0.0	99.6	0.0	0.0	99.3	99.7	99.6	99.6	99.6			
	T	0.2	0.0	0.1	99.3	26.5	28.1	0.1	0.0	0.1	20.2	0.0	0.1	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.1	0.1	0.0	0.2	0.1	0.2	0.2	0.2			
-	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.5	0.6	0.5	0.5	0.4	0.4	0.4	0.3	0.2	0.2	0.5	0.4	0.4	0.4	0.4	0.4	0.4	0.2	0.1				
A3A-BE4max Replicate 3		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	A	G	A	A	G	A	A	G	G	G			
	A	0.4	99.4	0.0	0.1	0.6	0.4	0.2	99.1	0.1	0.6	99.2	0.2	99.5	99.5	0.2	99.7	99.7	0.1	99.4	99.5	0.0	0.0	0.0	0.1	0.1	0.1	0.1			
	C	0.1	0.0	0.0	0.0	62.3	62.5	0.0	0.0	0.0	71.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0			
	G	98.9	0.1	99.3	0.2	1.4	0.2	98.9	0.1	99.1	0.2	0.0	99.0	0.0	99.3	0.0	99.3	0.0	99.7	0.0	99.7	0.0	0.0	99.4	99.7	99.6	99.6	99.6			
	T	0.1	0.0	0.1	99.0	35.1	36.0	0.2	0.1	0.1	27.2	0.1	0.2	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.1	0.1	0.0	0.2	0.1	0.2	0.2	0.2			
-	0.5	0.5	0.6	0.7	0.7	0.9	0.7	0.7	0.7	0.7	0.6	0.6	0.4	0.4	0.4	0.4	0.2	0.2	0.2	0.2	0.4	0.4	0.4	0.4	0.4	0.1	0.1				
A3A-seBE-IRE5 +Rap Replicate 1		1				5				10				15				20 PAM													
		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	A	G	A	A	G	A	A	G	G	G			
	A	0.2	99.8	0.0	0.0	0.2	0.2	0.1	99.8	0.0	0.1	99.9	0.0	99.8	99.8	0.0	99.9	99.9	0.0	99.8	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.1			
	C	0.0	0.0	0.0	0.1	69.3	69.0	0.0	0.1	0.0	84.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0			
	G	99.5	0.0	99.8	0.2	0.5	0.1	99.6	0.1	99.8	0.1	0.0	99.8	0.0	0.1	99.8	0.0	99.8	0.0	99.8	0.0	0.0	0.0	99.6	99.7	99.8	99.8	99.8			
T	0.2	0.0	0.1	99.6	30.0	30.7	0.2	0.0	0.1	15.4	0.0	0.1	0.0	0.0	0.1	0.0	0.1	0.0	0.1	0.0	0.1	0.0	0.0	0.2	0.2	0.2	0.1				
-	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1	0.0	0.1	0.1	0.0	0.0	0.0				
A3A-seBE-IRE5 +Rap Replicate 2		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	A	G	A	A	G	A	A	G	G	G			
	A	0.1	99.8	0.0	0.0	0.1	0.2	0.1	99.8	0.0	0.1	99.8	0.0	99.8	99.8	0.0	99.8	99.8	0.0	99.7	99.7	0.0	0.0	0.0	0.0	0.0	0.0	0.1			
	C	0.0	0.0	0.0	0.0	73.8	73.5	0.0	0.0	0.0	86.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0			
	G	99.7	0.1	99.8	0.2	0.7	0.0	99.7	0.0	99.7	0.1	0.0	99.7	0.0	99.8	0.1	99.8	0.1	99.8	0.0	99.8	0.0	0.1	99.6	99.8	99.7	99.7	99.7			
	T	0.2	0.0	0.1	99.6	25.2	26.1	0.1	0.0	0.1	13.0	0.0	0.1	0.0	0.0	0.1	0.0	0.1	0.0	0.1	0.0	0.1	0.0	0.2	0.1	0.2	0.1	0.1			
-	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	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.1	0.1				
A3A-seBE-IRE5 +Rap Replicate 3		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	A	G	A	A	G	A	A	G	G	G			
	A	0.3	99.8	0.0	0.0	0.2	0.1	0.1	99.7	0.0	0.2	99.7	0.0	99.8	99.8	0.0	99.9	99.8	0.0	99.7	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0			
	C	0.0	0.0	0.0	0.0	58.6	59.3	0.0	0.0	0.0	77.1	0.0	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.0	0.0			
	G	99.5	0.1	99.7	0.0	0.5	0.0	99.4	0.0	99.6	0.1	0.0	99.6	0.0	99.6	0.0	99.8	0.0	99.8	0.0	99.7	0.0	0.0	99.8	99.8	99.8	99.8	99.8			
	T	0.1	0.0	0.0	99.8	40.5	40.2	0.3	0.0	0.1	22.3	0.0	0.1	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.1	0.1	0.1	0.1			
-	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.1				
A3A-seBE-IRE5 NoRap Replicate		1				5				10				15				20 PAM													
		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	A	G	A	A	G	A	A	G	G	G			
	A	0.0	99.9	0.0	0.0	0.1	0.1	0.0	99.9	0.0	0.0	99.9	0.0	99.9	99.9	0.0	99.9	99.9	0.0	99.9	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0			
	C	0.0	0.0	0.0	0.1	97.3	97.2	0.0	0.0	0.0	98.9	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			
	G	99.8	0.1	99.9	0.2	0.0	0.0	99.8	0.0	99.8	0.0	0.0	99.9	0.0	0.0	0.0	99.9	0.0	99.9	0.0	99.9	0.0	0.0	99.7	99.8	99.8	99.8	99.8			
T	0.1	0.0	0.0	99.6	2.6	2.6	0.1	0.0	0.1	1.0	0.0	0.1	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.2	0.1	0.2	0.1	0.1				
-	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.0	0.1	0.1	0.1	0.0	0.0				
A3A-seBE-IRE5 NoRap Replicate 2		G	A	G	T	C	C	G	A	G	C	A	G	A	A	G	A	A	A	G	A	A	G	A	A	G	G	G			
	A	0.0	99.9	0.0	0.1	0.1	0.1	0.1	99.9	0.0	0.1	99.9	0.0	99.9	99.9	0.0	99.9	99.9	0.0	99.7	99.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0			
	C	0.0	0.1	0.0	0.0	98.6	98.5	0.0	0.0	0.0	99.4	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0			
	G	99.9	0.1																												

Supplementary Figure 4

d <i>AID'-constructs, dSaCas9-target site</i>																												
		T	C	T	G	C	T	T	C	T	C	C	A	G	C	C	C	T	G	G	C	C	T	G	G	T		
untreated	A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.7	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0		
	C	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.7	0.0	99.7	99.6	0.0	0.0	99.6	99.5	99.6	0.0	0.0	0.0	99.3	99.4	0.0	0.0	0.0	0.0		
	G	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.6	0.0	0.0	0.0	0.0	99.5	99.3	0.0	0.0	0.0	99.2	99.2	99.1		
	T	99.7	4.8	99.8	0.1	8.6	99.6	99.6	3.1	99.6	3.5	2.8	0.0	0.1	8.2	0.3	2.2	99.4	0.1	0.1	0.0	0.0	99.1	0.3	0.2	0.2		
	-	0.3	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.4	0.4	0.4	0.5	0.6	0.6	0.6	0.7	0.7	0.7	0.8	1.3	
AID-BEImax Replicate 1			T	C	T	G	C	T	T	C	T	C	C	A	G	C	C	C	T	G	G	C	C	T	G	G	T	
	A	0.0	0.1	0.0	0.4	0.3	0.0	0.0	0.0	0.0	0.0	0.1	99.5	0.0	0.2	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0		
	C	0.0	94.4	0.0	0.0	90.3	0.0	0.0	96.5	0.1	96.0	96.7	0.0	0.0	91.1	99.1	97.3	0.0	0.0	0.0	99.2	99.2	0.1	0.0	0.0	0.0	0.0	
	G	0.0	0.1	0.0	99.2	0.5	0.0	0.0	0.0	0.0	0.1	0.0	0.0	99.3	0.0	0.0	0.0	0.0	99.1	99.1	0.0	0.0	0.0	0.0	98.7	98.8	98.8	
	T	99.6	4.8	99.7	0.1	8.6	99.6	99.6	3.1	99.6	3.5	2.8	0.0	0.1	8.2	0.3	2.2	99.4	0.1	0.1	0.0	0.0	99.1	0.3	0.2	0.2	98.4	
AID-BEImax Replicate 2	A	0.0	0.1	0.0	0.3	0.2	0.0	0.0	0.0	0.1	0.0	99.5	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.1	0.0		
	C	0.0	96.1	0.0	0.0	93.0	0.0	0.0	97.4	0.0	96.3	97.1	0.1	0.1	93.6	99.3	98.2	0.0	0.0	0.0	99.4	99.3	0.1	0.0	0.0	0.0	0.1	
	G	0.0	0.0	0.0	99.3	0.3	0.0	0.0	0.0	0.0	0.2	0.0	0.1	99.4	0.0	0.0	0.0	0.0	99.3	99.1	0.0	0.0	0.0	0.0	98.9	99.0	98.9	
	T	99.4	3.4	99.8	0.2	6.3	99.8	99.8	2.4	99.7	3.2	2.6	0.0	0.2	6.1	0.3	1.4	99.5	0.2	0.3	0.0	0.0	99.2	0.4	0.2	0.2	98.4	
	-	0.5	0.3	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.5	0.5	0.6	0.6	0.6	0.7	0.8	0.9
AID-BEImax Replicate 3	A	0.0	0.1	0.0	0.7	0.7	0.0	0.0	0.0	0.0	0.0	0.0	99.6	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.1	0.0	
	C	0.0	88.9	0.0	0.0	81.8	0.0	0.0	93.3	0.1	91.1	92.6	0.0	0.0	82.6	98.6	94.7	0.1	0.0	0.0	99.5	99.5	0.1	0.0	0.0	0.0	0.0	
	G	0.0	0.2	0.0	99.0	0.8	0.0	0.0	0.1	0.0	0.3	0.0	0.0	99.6	0.0	0.0	0.0	0.0	99.5	99.5	0.0	0.0	0.0	0.0	98.9	99.0	98.9	
	T	99.7	10.1	99.8	0.1	16.5	99.8	99.8	6.4	99.7	8.4	7.0	0.0	0.0	16.9	1.0	4.8	99.6	0.1	0.0	0.1	0.0	99.3	0.1	0.1	0.0	99.0	
	-	0.2	0.7	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.4	0.4	0.4	0.3	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.7	1.0
AID-seBE-IRE5 +Rep Replicate 1			T	C	T	G	C	T	T	C	T	C	C	A	G	C	C	C	T	G	G	C	C	T	G	G	T	
	A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.6	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	
	C	0.0	99.7	0.0	0.0	98.5	0.0	0.0	99.7	0.0	99.4	99.5	0.1	0.0	98.3	99.7	99.5	0.0	0.0	0.0	99.5	99.5	0.0	0.0	0.0	0.0	0.0	
	G	0.0	0.0	0.0	99.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.5	0.0	0.0	0.0	0.0	99.4	99.4	0.0	0.0	0.0	0.0	99.0	99.2	99.1	
	T	99.7	0.2	99.8	0.1	1.1	99.8	99.8	0.1	99.8	0.3	0.2	0.0	0.2	1.4	0.0	0.1	99.6	0.2	0.2	0.0	0.0	99.4	0.4	0.2	0.0	98.9	
AID-seBE-IRE5 +Rep Replicate 2	A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0		
	C	0.0	99.5	0.0	0.0	99.0	0.0	0.0	99.5	0.0	99.1	99.3	0.1	0.0	98.3	99.6	99.5	0.0	0.0	0.0	99.3	99.3	0.1	0.0	0.0	0.0	0.0	
	G	0.0	0.0	0.0	99.7	0.1	0.0	0.0	0.0	0.0	0.1	0.0	0.0	99.6	0.0	0.0	0.0	0.0	99.4	99.2	0.0	0.0	0.0	0.0	98.8	99.0	98.9	
	T	99.5	0.2	99.8	0.0	0.7	99.8	99.7	0.3	99.7	0.5	0.4	0.0	0.1	1.4	0.1	0.1	99.6	0.1	0.1	0.0	0.0	99.2	0.4	0.1	0.1	98.6	
	-	0.5	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.4	0.4	0.4	0.5	0.5	0.6	0.6	0.6	0.7	0.7	0.8	0.9	1.3
AID-seBE-IRE5 +Rep Replicate 3	A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	99.6	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		
	C	0.0	99.4	0.0	0.0	97.8	0.0	0.0	99.4	0.0	99.0	99.1	0.0	0.0	97.1	99.4	99.3	0.0	0.0	0.0	99.2	99.2	0.0	0.0	0.0	0.0	0.0	
	G	0.0	0.0	0.0	99.7	0.1	0.0	0.0	0.0	0.0	0.1	0.0	0.0	99.5	0.0	0.0	0.0	0.0	99.3	99.2	0.0	0.0	0.0	0.0	98.9	98.9	98.8	
	T	99.6	0.3	99.7	0.0	1.8	99.7	99.7	0.3	99.6	0.5	0.4	0.0	0.1	2.4	0.1	0.2	99.5	0.1	0.0	0.0	99.1	0.1	0.1	0.1	0.1	98.4	
	-	0.3	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.4	0.5	0.5	0.5	0.6	0.7	0.7	0.8	0.8	0.9	1.0	1.1	1.5	
AID-seBE-IRE5 NoRep Replicate 1			T	C	T	G	C	T	T	C	T	C	C	A	G	C	C	C	T	G	G	C	C	T	G	G	T	
	A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
	C	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.8	0.0	99.8	99.7	0.0	0.0	99.7	99.7	99.7	0.0	0.0	0.0	99.6	99.3	0.0	0.0	0.0	0.0	0.0	
	G	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.6	0.0	0.0	0.0	0.0	99.4	99.4	0.0	0.0	0.0	0.0	99.0	99.2	99.2	
	T	99.8	0.0	99.8	0.0	0.0	99.8	99.8	0.0	99.8	0.1	0.0	0.0	0.2	0.0	0.0	0.0	99.7	0.2	0.1	0.0	0.0	99.5	0.5	0.2	0.0	98.7	
AID-seBE-IRE5 NoRep Replicate 2	A	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.1	0.1	99.7	0.0	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	
	C	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.8	0.1	99.7	99.6	0.0	0.0	99.7	99.7	99.7	0.0	0.0	0.1	99.3	99.3	0.1	0.0	0.0	0.0	0.0	
	G	0.0	0.0	0.0	99.7	0.0	0.0	0.0	0.0	0.0	0.0	0.1	99.5	0.0	0.0	0.0	0.0	0.0	99.3	99.2	0.0	0.0	0.0	0.0	98.9	99.0	99.0	
	T	99.4	0.0	99.8	0.0	0.0	99.8	99.8	0.0	99.7	0.1	0.1	0.0	0.2	0.1	0.0	0.0	99.6	0.2	0.1	0.0	0.0	99.2	0.4	0.1	0.1	98.5	
	-	0.6	0.1	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.4	0.5	0.6	0.6	0.6	0.7	0.7	0.8	0.9	1.4
AID-seBE-IRE5 NoRep Replicate 3	A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	99.6	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	
	C	0.0	99.3	0.0	0.0	99.6	0.0	0.0	99.0	0.0	98.8	98.9	0.0	0.0	99.3	99.3	99.3	0.0	0.0	0.0	99.3	99.4	0.1	0.0	0.0	0.0	0.0	
	G	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.1	0.0	0.1	99.6	0.0	0.0	0.0	0.0	0.0	99.4	99.3	0.0	0.0	0.0	0.0	99.2	99.2	99.1	
	T	99.7	0.6	99.8	0.0	0.2	99.8	99.8	0.8	99.8	0.8	0.8	0.0	0.1	0.4	0.3	0.3	99.6	0.0	0.1	0.0	0.0	99.3	0.1	0.0	0.0	98.6	
	-	0.3	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.3	0.3	0.4	0.5	0.6	0.6	0.6	0.7	0.7	0.8	0.9	1.3	

Supplementary Figure 4

		e																								
		<i>evoA1-constructs, dSaCas9-target site</i>																								
untreated		T	C	T	G	C	T	T	C	T	C	C	A	G	C	C	C	T	G	G	C	C	T	G	G	T
	A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.7	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.7	0.0	99.7	99.6	0.0	0.0	99.6	99.5	99.6	0.0	0.0	0.0	99.3	99.4	0.0	0.0	0.0	0.0
	G	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	99.6	0.0	0.0	0.0	0.0	99.5	99.3	0.0	0.0	0.0	99.2	99.1
	T	99.7	3.0	99.8	0.0	0.0	99.7	99.7	6.1	99.7	14.6	9.0	0.0	0.2	1.2	1.8	0.7	99.5	0.1	0.1	0.0	0.0	99.3	0.3	0.1	0.0
-	0.3	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.4	0.4	0.4	0.5	0.6	0.6	0.6	0.7	0.7	0.7	0.8	
evoA1- <i>BE</i> max Replicate 1		T	C	T	G	C	T	T	C	T	C	C	A	G	C	C	C	T	G	G	C	C	T	G	G	T
	A	0.0	0.1	0.0	0.0	0.0	0.0	0.1	0.0	0.2	0.2	99.6	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	
	C	0.1	96.4	0.0	0.0	99.1	0.1	0.0	93.3	0.0	83.9	90.4	0.0	0.0	98.4	97.8	98.9	0.0	0.0	0.0	99.4	99.3	0.0	0.0	0.0	
	G	0.0	0.1	0.0	99.7	0.0	0.0	0.1	0.0	1.0	0.0	0.0	0.0	99.5	0.0	0.0	0.0	0.0	99.4	99.3	0.0	0.0	0.0	99.0	99.1	
	T	99.7	3.0	99.7	0.0	0.6	99.7	99.7	6.1	99.7	14.6	9.0	0.0	0.2	1.2	1.8	0.7	99.5	0.1	0.1	0.0	0.0	99.3	0.3	0.1	
-	0.3	0.4	0.2	0.2	0.2	0.3	0.4	0.3	0.3	0.5	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.6	0.6	0.6	0.7	0.7	0.7	0.8		
evoA1- <i>BE</i> max Replicate 2		T	C	T	G	C	T	T	C	T	C	C	A	G	C	C	C	T	G	G	C	C	T	G	G	T
	A	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.0	0.3	0.0	99.6	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	
	C	0.0	96.8	0.0	0.0	99.1	0.0	0.0	94.5	0.0	86.6	92.5	0.0	0.0	98.3	98.1	99.0	0.0	0.0	0.0	99.3	99.3	0.1	0.0	0.0	
	G	0.0	0.1	0.0	99.7	0.0	0.0	0.1	0.0	0.8	0.0	0.1	99.5	0.0	0.0	0.0	0.0	0.0	99.4	99.3	0.0	0.0	0.0	99.0	99.1	
	T	99.3	2.8	99.8	0.1	0.6	99.8	99.7	5.0	99.7	12.0	7.0	0.0	0.1	1.4	1.5	0.6	99.5	0.1	0.1	0.0	0.0	99.3	0.3	0.1	
-	0.7	0.3	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.4	0.3	0.3	0.3	0.3	0.4	0.4	0.5	0.6	0.6	0.6	0.6	0.7	0.7		
evoA1- <i>BE</i> max Replicate 3		T	C	T	G	C	T	T	C	T	C	C	A	G	C	C	C	T	G	G	C	C	T	G	G	T
	A	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.3	0.1	99.7	0.0	0.0	0.1	0.1	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	
	C	0.0	95.7	0.0	0.1	98.7	0.0	0.0	92.4	0.0	79.8	88.6	0.0	0.0	97.7	97.1	98.5	0.0	0.0	0.0	99.5	99.4	0.1	0.0	0.0	
	G	0.0	0.1	0.0	99.7	0.0	0.0	0.0	0.1	0.0	1.3	0.0	0.0	99.6	0.0	0.0	0.0	0.0	99.4	99.4	0.0	0.0	0.0	99.2	99.0	
	T	99.7	3.8	99.8	0.0	1.0	99.8	99.8	7.1	99.8	18.4	11.0	0.0	0.1	2.0	2.5	1.1	99.6	0.1	0.1	0.0	0.0	99.4	0.2	0.1	
-	0.3	0.3	0.1	0.2	0.2	0.2	0.2	0.3	0.2	0.2	0.3	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5	0.5	0.5	0.5	0.6	0.7		
evoA1- <i>seBE</i> - IRES +Rap Rep 1		T	C	T	G	C	T	T	C	T	C	C	A	G	C	C	C	T	G	G	C	C	T	G	G	T
	A	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	99.6	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	
	C	0.0	99.5	0.0	0.0	99.7	0.0	0.0	98.6	0.0	95.5	98.1	0.0	0.0	99.4	99.3	99.5	0.0	0.0	0.0	99.3	99.2	0.1	0.0	0.0	
	G	0.0	0.0	0.0	99.2	0.0	0.0	0.0	0.4	0.0	0.0	99.5	0.0	0.0	0.0	0.0	0.0	0.0	99.3	99.2	0.0	0.0	0.0	99.0	99.1	
	T	99.6	0.3	99.8	0.0	0.1	99.7	99.7	1.0	99.7	3.6	1.6	0.0	0.1	0.3	0.3	0.1	99.5	0.1	0.1	0.0	0.0	99.2	0.2	0.1	
-	0.3	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5	0.6	0.6	0.7	0.7	0.8	0.8	0.9		
evoA1- <i>seBE</i> - IRES +Rap Rep 2		T	C	T	G	C	T	T	C	T	C	C	A	G	C	C	C	T	G	G	C	C	T	G	G	T
	A	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	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	
	C	0.0	99.5	0.0	0.0	99.8	0.0	0.0	98.9	0.1	95.9	98.0	0.0	0.0	99.5	99.4	99.6	0.0	0.0	0.0	99.5	99.4	0.1	0.0	0.0	
	G	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.4	0.0	0.1	99.7	0.0	0.0	0.0	0.0	0.0	99.5	99.4	0.0	0.0	0.0	99.2	99.2	
	T	99.4	0.3	99.9	0.0	0.1	99.9	99.9	0.9	99.8	3.5	1.8	0.0	0.1	0.3	0.3	0.1	99.7	0.1	0.2	0.1	0.0	99.4	0.2	0.1	
-	0.6	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.4	0.4	0.5	0.5	0.6	0.7		
evoA1- <i>seBE</i> - IRES +Rap Rep 3		T	C	T	G	C	T	T	C	T	C	C	A	G	C	C	C	T	G	G	C	C	T	G	G	T
	A	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	99.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
	C	0.0	98.9	0.0	0.0	99.5	0.0	0.0	98.0	0.1	94.1	96.9	0.0	0.0	99.2	99.0	99.2	0.0	0.0	0.0	99.4	99.4	0.1	0.0	0.0	
	G	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.4	0.0	0.0	99.6	0.0	0.0	0.0	0.0	0.0	99.5	99.4	0.0	0.0	0.0	99.1	99.2	
	T	99.7	0.8	99.8	0.0	0.3	99.8	99.8	1.7	99.7	5.2	2.7	0.0	0.1	0.5	0.6	0.4	99.6	0.1	0.1	0.0	0.0	99.3	0.2	0.1	
-	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.4	0.5	0.6	0.6	0.6	0.7	0.7		
evoA1- <i>seBE</i> - IRES +Rap Rep 1		T	C	T	G	C	T	T	C	T	C	C	A	G	C	C	C	T	G	G	C	C	T	G	G	T
	A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	99.6	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	
	C	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.8	0.1	99.6	99.7	0.0	0.0	99.7	99.6	99.6	0.0	0.0	0.0	99.5	99.3	0.0	0.0	0.0	
	G	0.0	0.0	0.0	99.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	99.4	0.0	0.0	0.0	0.0	99.3	99.1	0.0	0.0	0.0	98.8	98.9	
	T	99.3	0.0	99.8	0.1	0.0	99.8	99.8	0.0	99.7	0.1	0.0	0.0	0.2	0.0	0.0	0.0	99.6	0.2	0.2	0.0	0.0	99.4	0.4	0.1	
-	0.3	0.1	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5	0.5	0.5	0.5	0.6	0.7	0.8		
evoA1- <i>seBE</i> - IRES +Rap Rep 2		T	C	T	G	C	T	T	C	T	C	C	A	G	C	C	C	T	G	G	C	C	T	G	G	T
	A	0.0	0.0	0.0	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	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	
	C	0.0	99.8	0.0	0.0	99.8	0.0	0.0	99.7	0.0	99.6	99.6	0.0	0.0	99.6	99.6	99.6	0.0	0.0	0.0	99.3	99.3	0.1	0.0	0.0	
	G	0.0	0.0	0.0	99.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	99.4	0.0	0.0	0.0	0.0	99.3	99.1	0.0	0.0	0.0	98.8	98.9	
	T	99.5	0.0	99.8	0.0	0.0	99.8	99.8	0.0	99.7	0.1	0.1	0.0	0.2	0.1	0.0	0.0	99.6	0.2	0.3	0.1	0.0	99.3	0.5	0.3	
-	0.5	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5	0.5	0.6	0.6	0.6	0.7	0.7		
evoA1- <i>seBE</i> - IRES +Rap Rep 3		T	C	T	G	C	T	T	C	T	C	C	A	G	C	C	C	T	G	G	C	C	T	G	G	T
	A	0.0	0.0	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	0.0	0.0	0.0	0.0	
	C	0.0	99.7	0.0	0.0	99.8	0.0	0.0	99.6	0.0	99.5	99.5	0.0	0.0	99.6	99.6	99.6	0.0	0.0	0.0	99.5	99.5	0.1	0.0	0.0	
	G	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.1	0.0	0.0	99.7	0.0	0.0	0.0	0.0	0.0	99.5	99.4	0.0	0.0	0.0	99.3	99.2	
	T	99.7	0.1	99.8	0.0	0.0	99.8	99.8	0.2	99.7	0.2	0.2	0.0	0.1	0.1	0.1	0.1	99.7	0.1	0.1	0.0	0.0	99.4	0.1	0.1	
-	0.3	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.3	0.4	0.5	0.5	0.5	0.5	0.6	0.7			

Supplementary Note: Vector Sequences

Bacterial DNA deaminase expression plasmids

AID*-pET41
AID*-INS1 pET41
AID*-INS2 pET41
AID*-INS3 pET41
AID*-INS- pET41
AID*-INS+ pET41
AID*-SPL2 pET41
AID*-SPL2_N pET41
AID*-SPL2_C pET41
A3A-pET41
A3A-INS2 pET41

Mammaian DNA deaminase expression plasmids

A3A-INS2 pLEXm
A3A(E72A)-INS2 pLEXm
A3A-SPL2_N pLEXm
A3A-SPL2_C pLEXm

Intact base editor constructs

evoA1-BE4max
AID'-BE4max
A3A-BE4max

Split engineered base editor constructs

evoA1-seBE-T2A
AID'-seBE-T2A
A3A-seBE-T2A
evoA1-seBE-IRES
AID'-seBE-IRES
A3A-seBE-IRES

gRNA and control constructs

LRcherry 2.1T empty
LRcherry 2.1 neomycin
LRG empty
dSaCas9-sgRNA

Lentiviral intact and split engineered constructs

Lentiviral evoA1-BE4max
Lentiviral seBE_N + sgRNA
Lentiviral seBE_C

Supplementary Vector Sequences

AID* pET41



taatacgaactcaactataggggaatttgtgagcggataacaattcccctctagaataattttgttttaactttaagaaggagatatacatAtgaaatcgaagAAGTAACCTGGTAATCT
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Supplementary Vector Sequences

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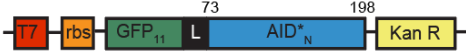
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Supplementary Vector Sequences

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Supplementary Vector Sequences

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Supplementary Vector Sequences

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