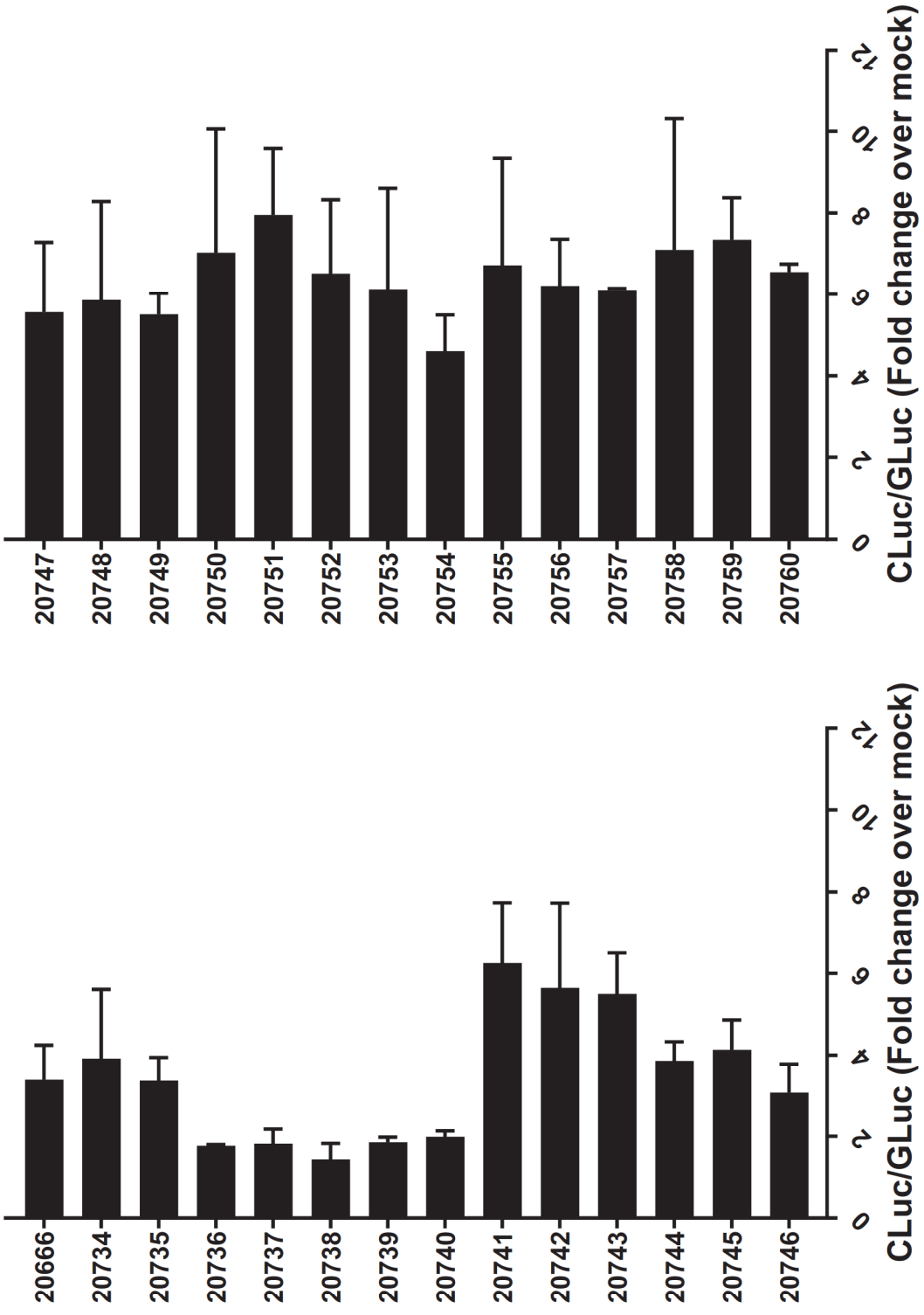
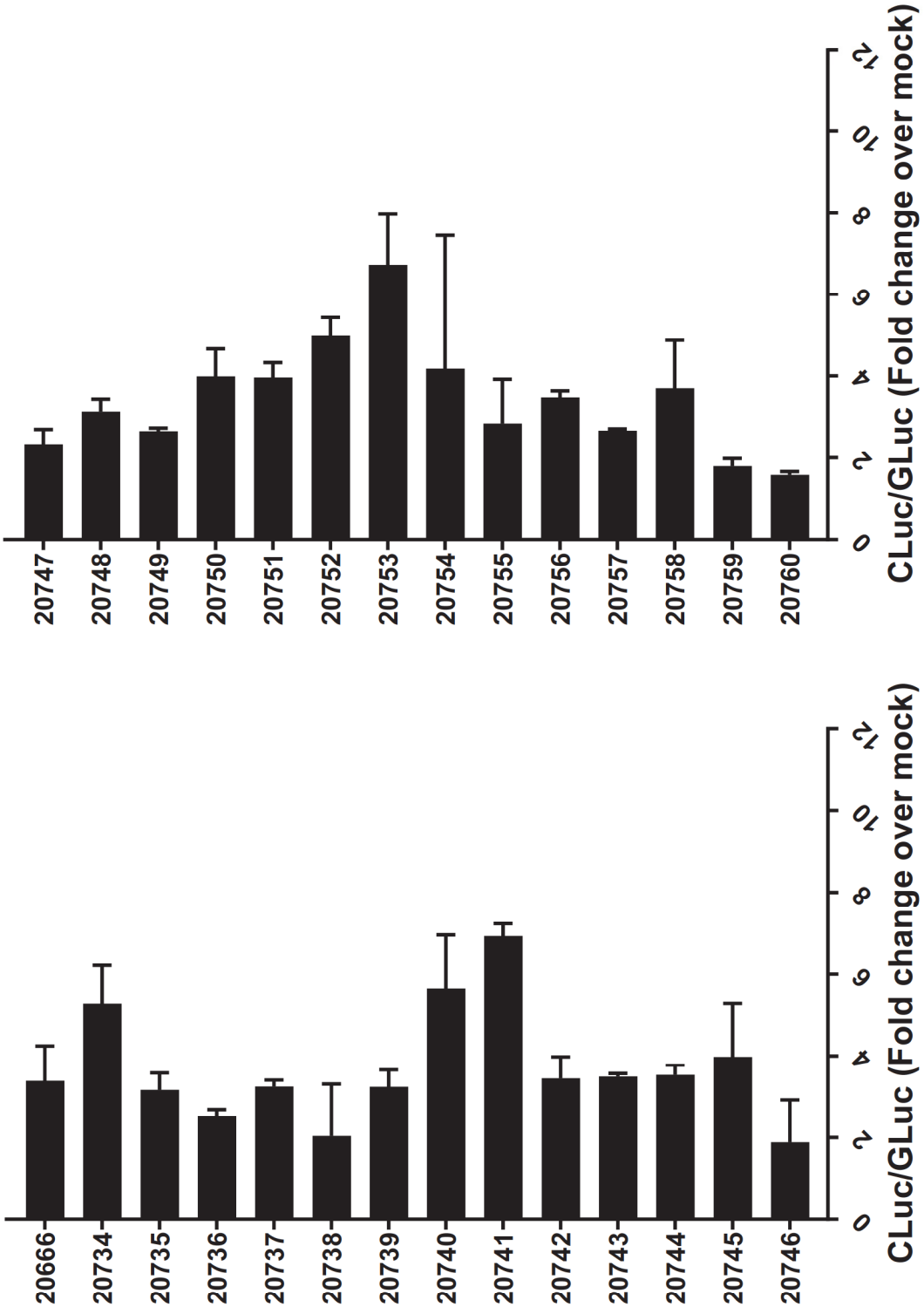

CLuc/GLuc (Fold change over mock)
0
2
4
6
8
10
12
20747
20748
20749
20750
20751
20752
20753
20754
20755
20756
20757
20758
20759
20760
CLuc/GLuc (Fold change over mock)
0
2
4
6
8
10
12
20666
20734
20735
20736
20737
20738
20739
20740
20741
20742
20743
20744
20745
20746

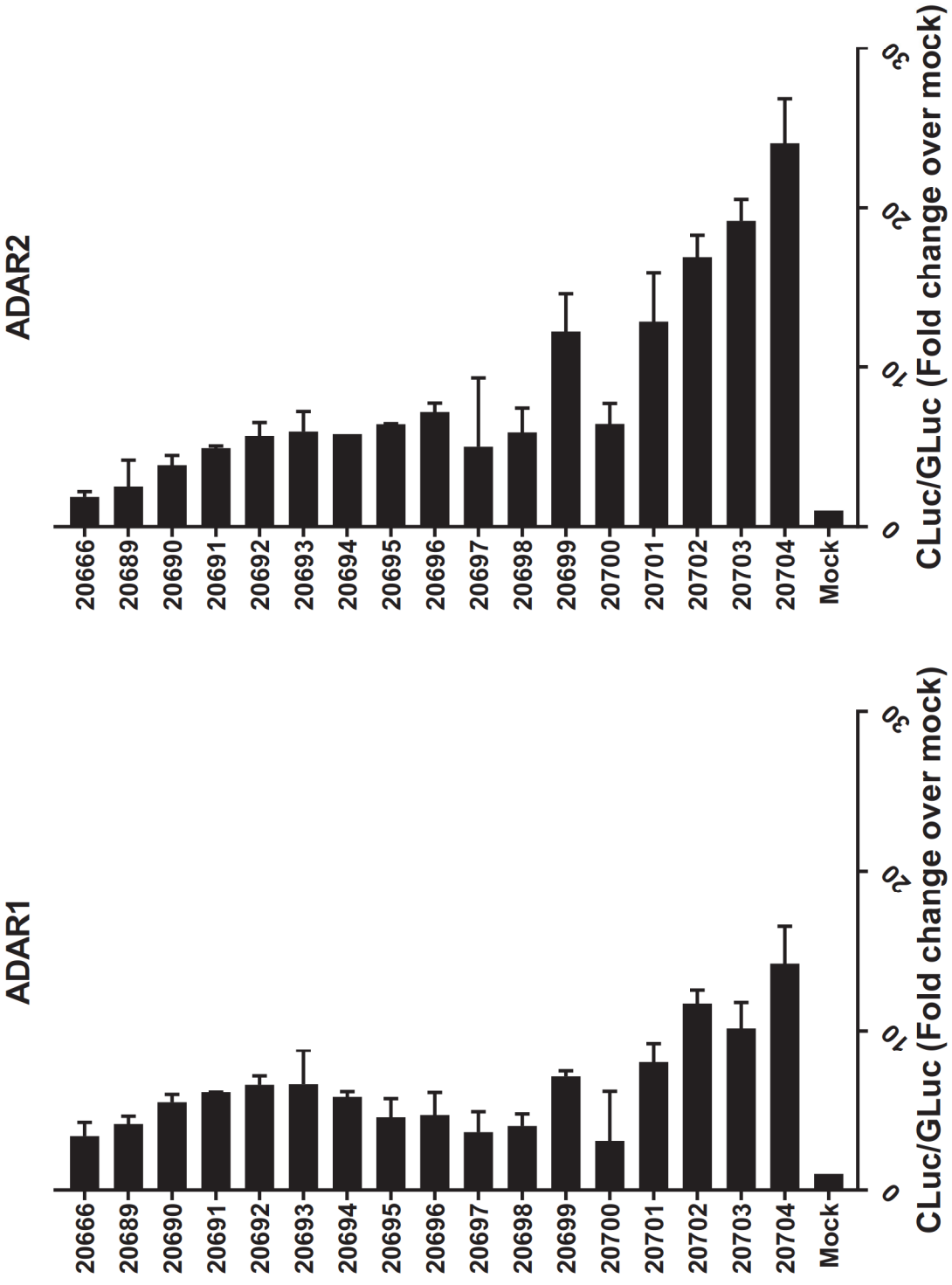
(a)

FIG. 1


20666
20734
20735
20736
20737
20738
20739
20740
20741
20742
20743
20744
20745
20746
CLuc/GLuc (Fold change over mock)
0
2
4
6
8
10
12
20747
20748
20749
20750
20751
20752
20753
20754
20755
20756
20757
20758
20759
20760
CLuc/GLuc (Fold change over mock)

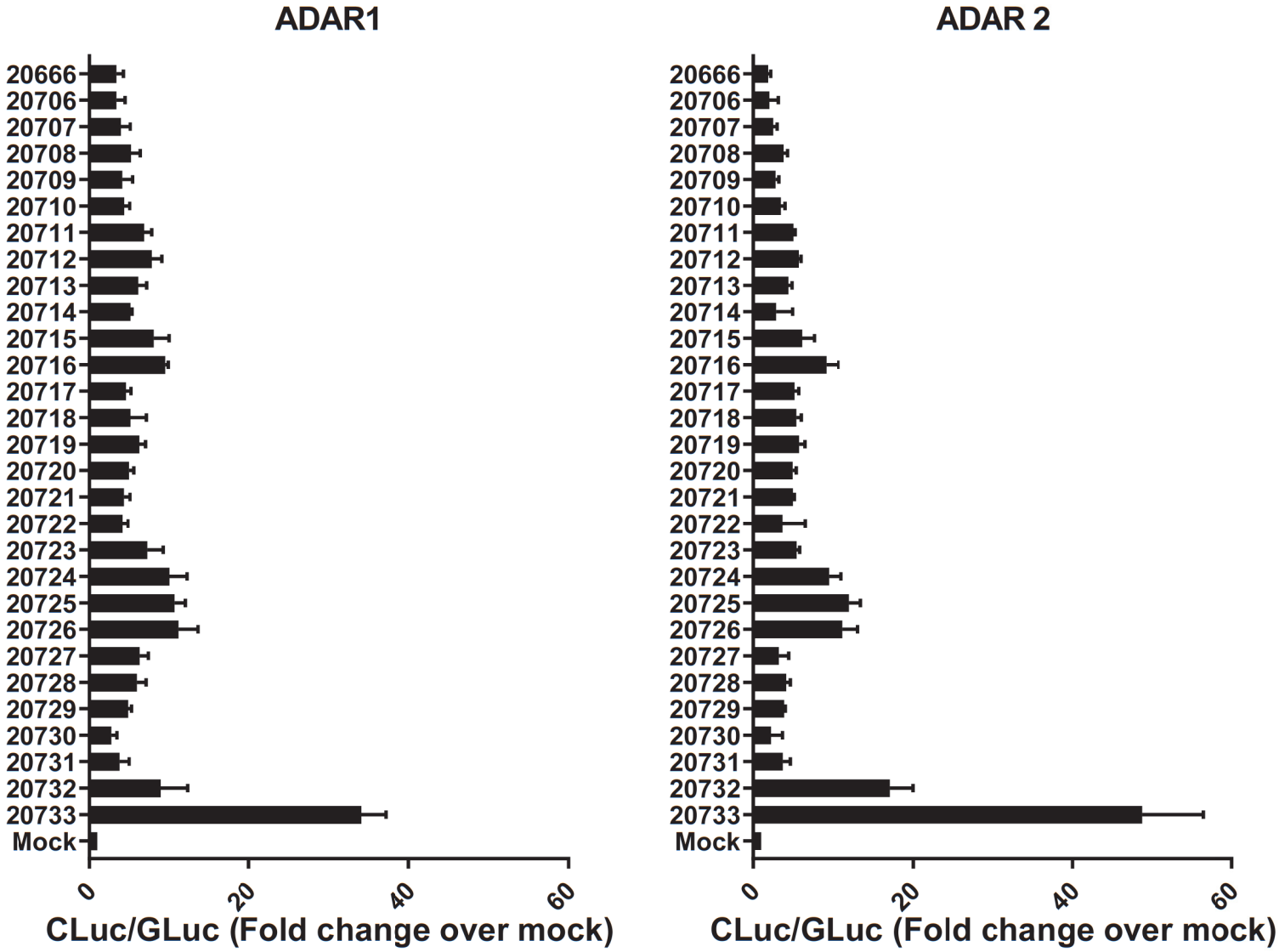
(b)

FIG. 1


ADAR1
ADAR2
CLuc/GLuc (Fold change over mock)
0
10
20
30
20666
20689
20690
20691
20692
20693
20694
20695
20696
20697
20698
20699
20700
20701
20702
20703
20704
Mock

(a)

FIG. 2


ADAR1
ADAR 2
20666
20706
20707
20708
20709
20710
20711
20712
20713
20714
20715
20716
20717
20718
20719
20720
20721
20722
20723
20724
20725
20726
20727
20728
20729
20730
20731
20732
20733
Mock
0
20
40
60
CLuc/GLuc (Fold change over mock)

(b)

FIG. 2

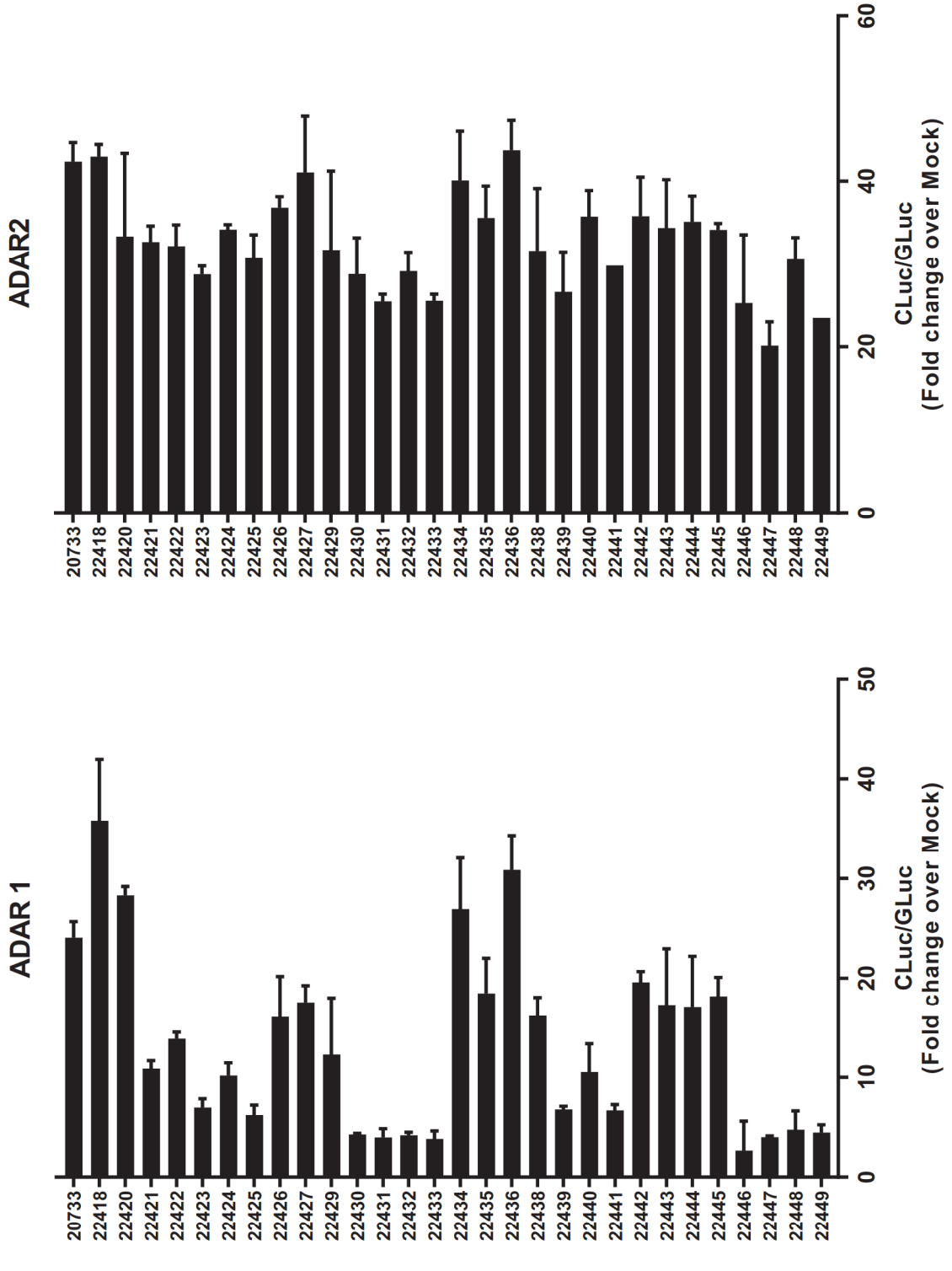

ADAR 1
CLuc/GLuc
(Fold change over Mock)
0
10
20
30
40
50
20733
22418
22420
22421
22422
22423
22424
22425
22426
22427
22429
22430
22431
22432
22433
22434
22435
22436
22438
22439
22440
22441
22442
22443
22444
22445
22446
22447
22448
22449
ADAR2
CLuc/GLuc
(Fold change over Mock)
0
20
40
60
20733
22418
22420
22421
22422
22423
22424
22425
22426
22427
22429
22430
22431
22432
22433
22434
22435
22436
22438
22439
22440
22441
22442
22443
22444
22445
22446
22447
22448
22449

FIG. 3

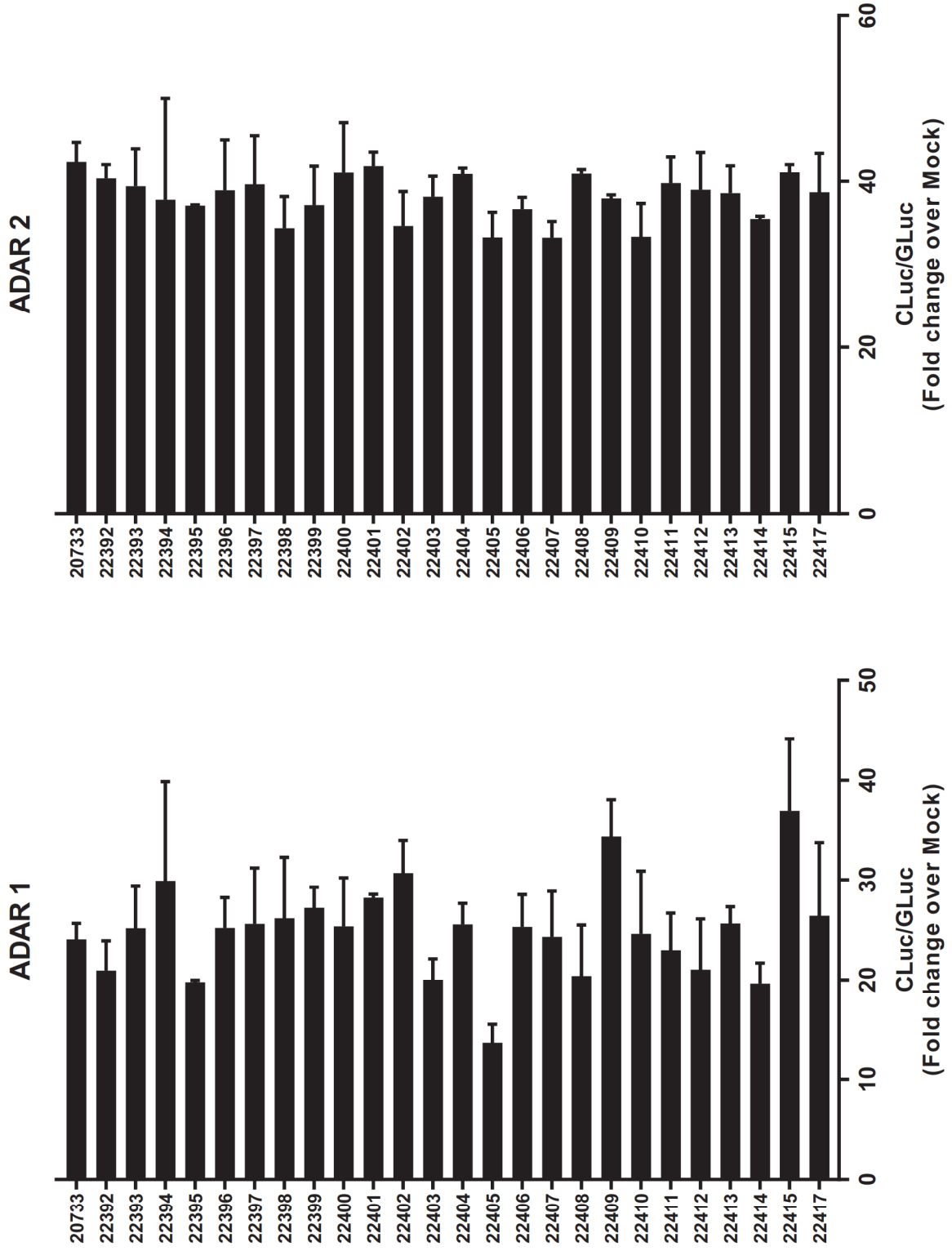
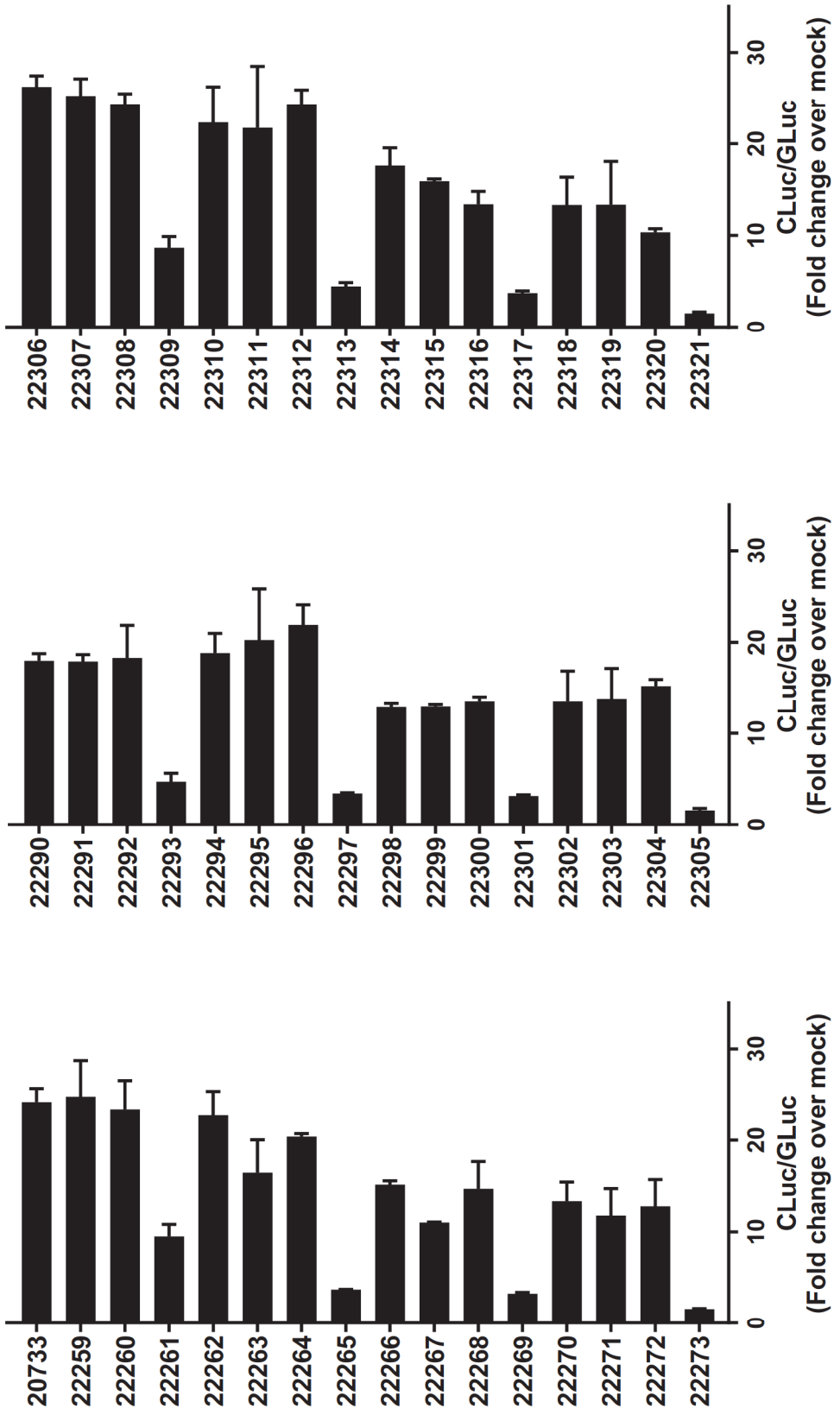
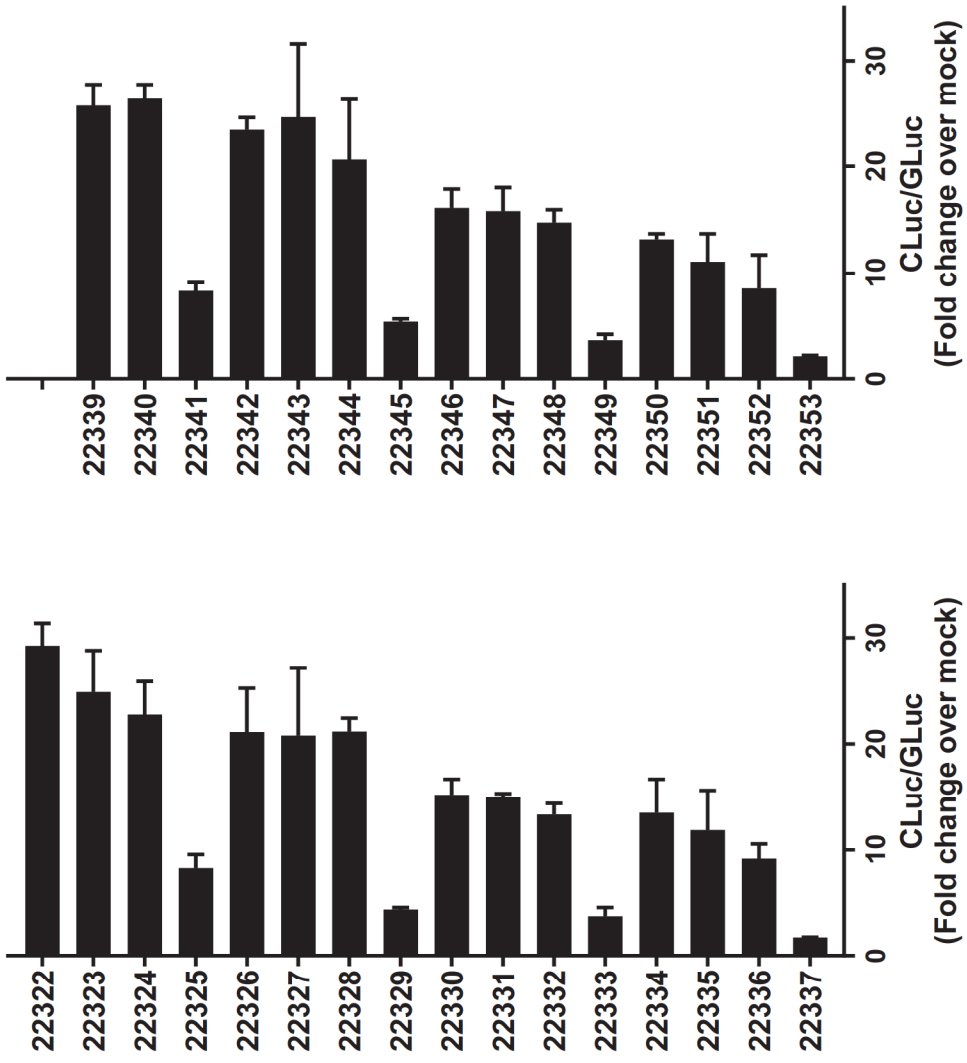

ADAR 1
CLuc/GLuc
(Fold change over Mock)
0
10
20
30
40
50
20733
22392
22393
22394
22395
22396
22397
22398
22399
22400
22401
22402
22403
22404
22405
22406
22407
22408
22409
22410
22411
22412
22413
22414
22415
22417
ADAR 2
CLuc/GLuc
(Fold change over Mock)
0
20
40
60
20733
22392
22393
22394
22395
22396
22397
22398
22399
22400
22401
22402
22403
22404
22405
22406
22407
22408
22409
22410
22411
22412
22413
22414
22415
22417

FIG. 4

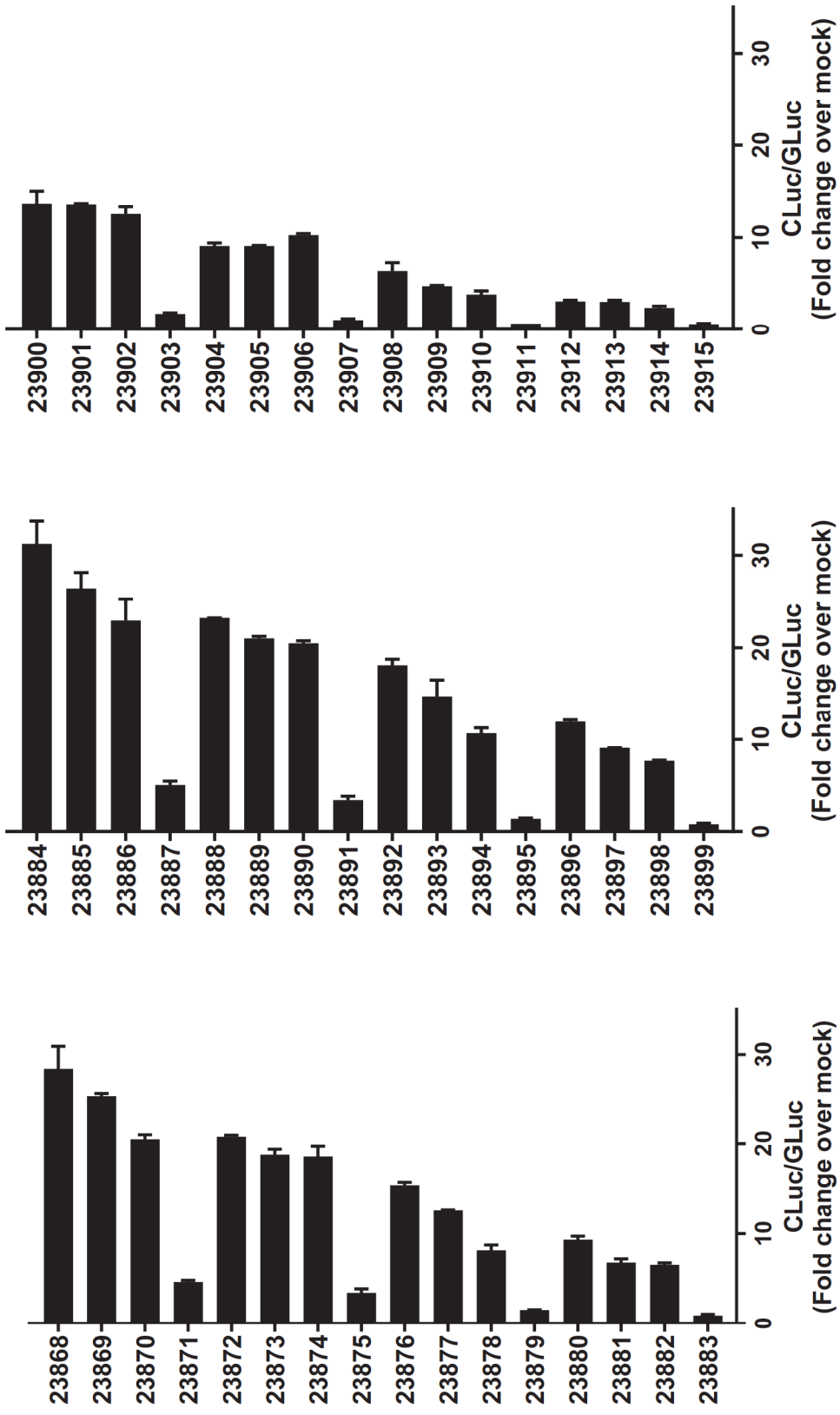

20733
22259
22260
22261
22262
22263
22264
22265
22266
22267
22268
22269
22270
22271
22272
22273
0
10
20
30
CLuc/GLuc
(Fold change over mock)
22290
22291
22292
22293
22294
22295
22296
22297
22298
22299
22300
22301
22302
22303
22304
22305
0
10
20
30
CLuc/GLuc
(Fold change over mock)
22306
22307
22308
22309
22310
22311
22312
22313
22314
22315
22316
22317
22318
22319
22320
22321
0
10
20
30
CLuc/GLuc
(Fold change over mock)

(a)

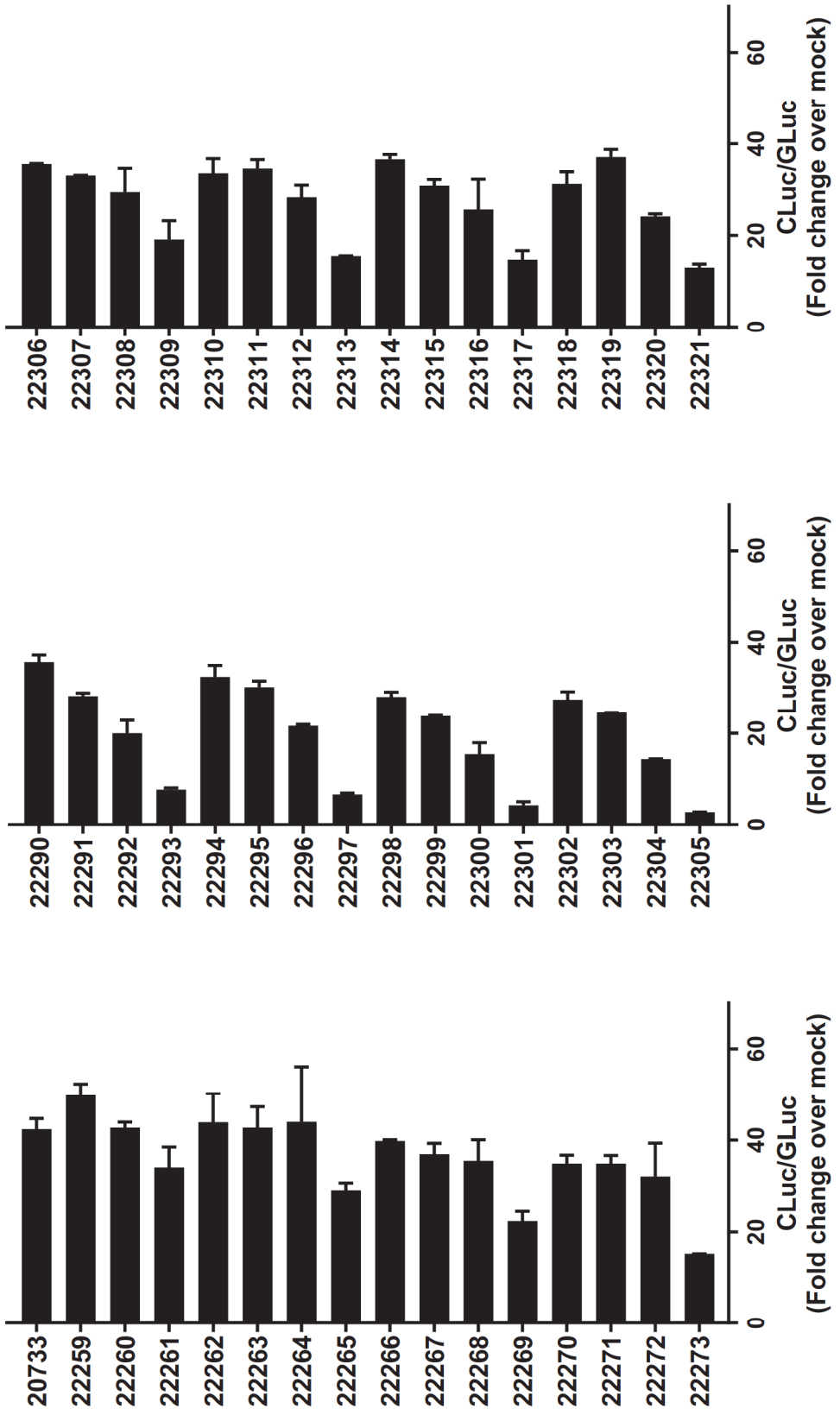
FIG. 5



(a) (Continued)
FIG. 5

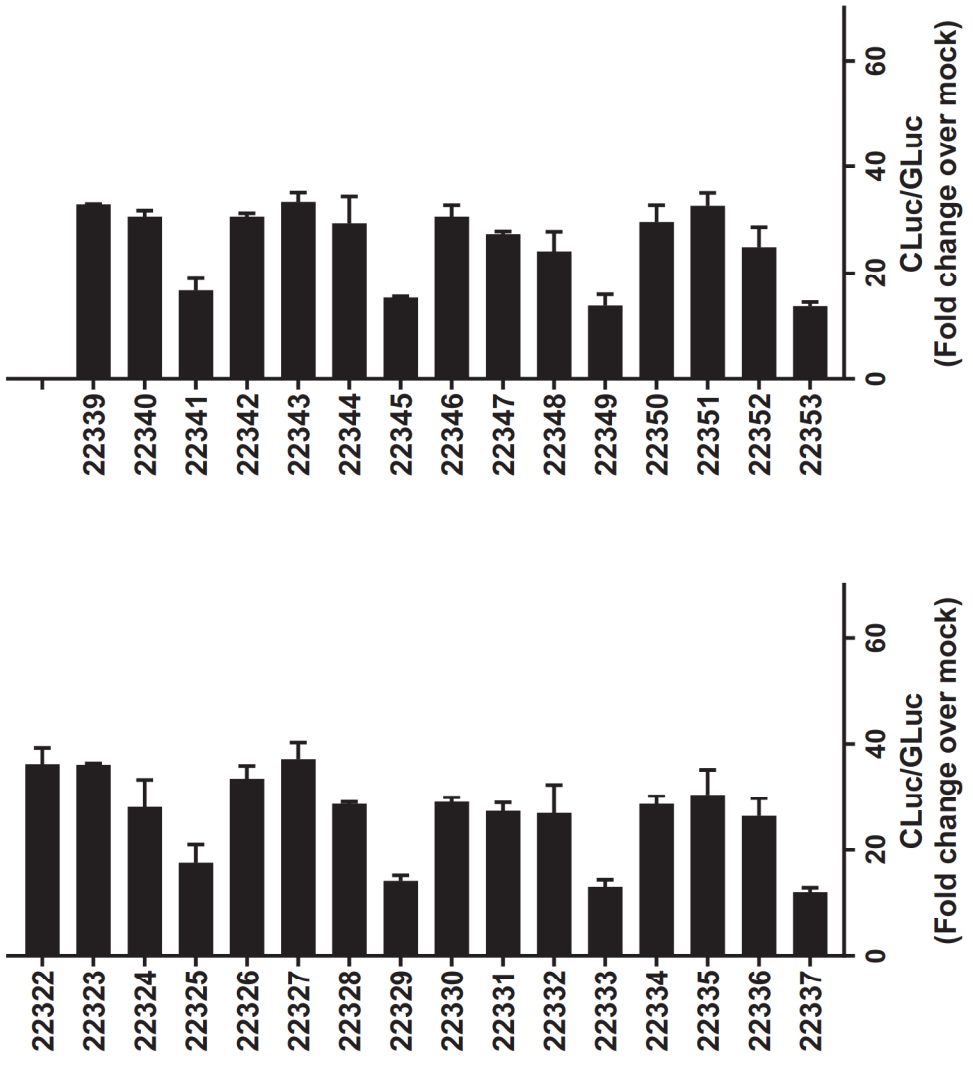

23868
23869
23870
23871
23872
23873
23874
23875
23876
23877
23878
23879
23880
23881
23882
23883
0
10
20
30
CLuc/GLuc
(Fold change over mock)
23884
23885
23886
23887
23888
23889
23890
23891
23892
23893
23894
23895
23896
23897
23898
23899
0
10
20
30
CLuc/GLuc
(Fold change over mock)
23900
23901
23902
23903
23904
23905
23906
23907
23908
23909
23910
23911
23912
23913
23914
23915
0
10
20
30
CLuc/GLuc
(Fold change over mock)

(b)
FIG. 5

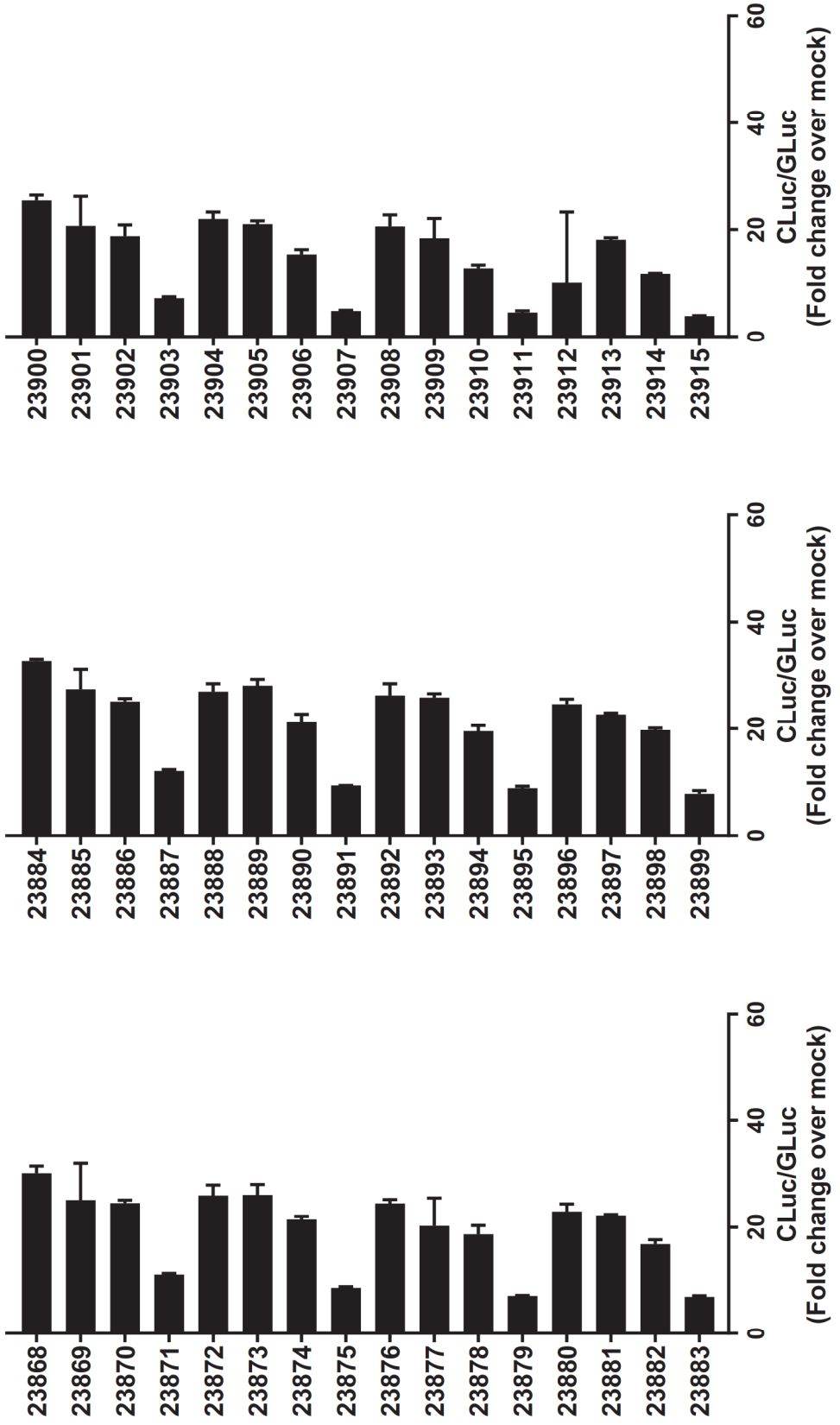

20733
22259
22260
22261
22262
22263
22264
22265
22266
22267
22268
22269
22270
22271
22272
22273
0
20
40
60
CLuc/GLuc
(Fold change over mock)
22290
22291
22292
22293
22294
22295
22296
22297
22298
22299
22300
22301
22302
22303
22304
22305
0
20
40
60
CLuc/GLuc
(Fold change over mock)
22306
22307
22308
22309
22310
22311
22312
22313
22314
22315
22316
22317
22318
22319
22320
22321
0
20
40
60
CLuc/GLuc
(Fold change over mock)

(c)

FIG. 5



(c) (Continued)
FIG. 5


23868
23869
23870
23871
23872
23873
23874
23875
23876
23877
23878
23879
23880
23881
23882
23883
0
20
40
60
CLuc/GLuc
(Fold change over mock)
23884
23885
23886
23887
23888
23889
23890
23891
23892
23893
23894
23895
23896
23897
23898
23899
0
20
40
60
CLuc/GLuc
(Fold change over mock)
23900
23901
23902
23903
23904
23905
23906
23907
23908
23909
23910
23911
23912
23913
23914
23915
0
20
40
60
CLuc/GLuc
(Fold change over mock)

(d)

FIG. 5

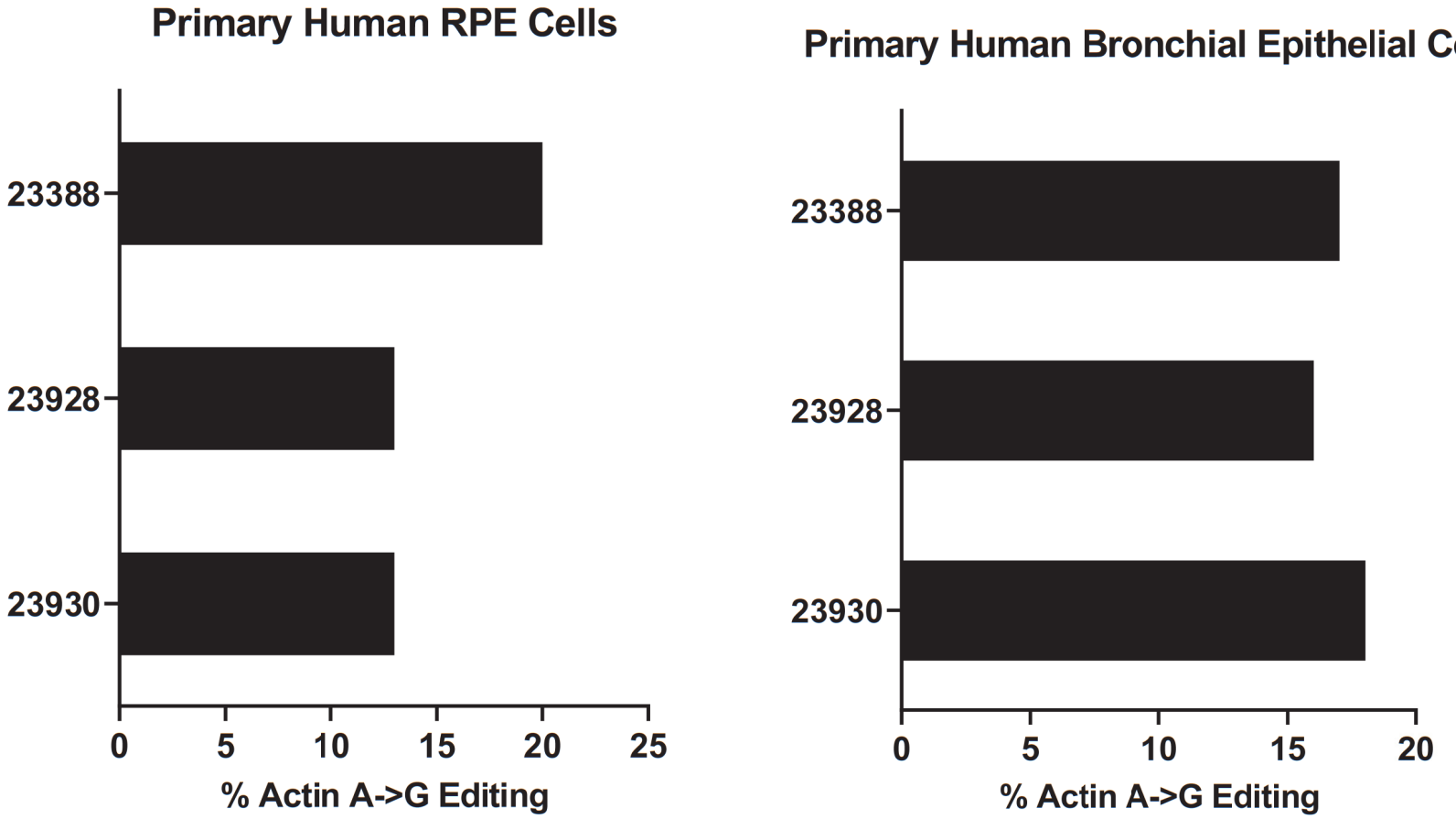

Primary Human RPE Cells
23388
23928
23930
0
5
10
15
20
25
% Actin A->G Editing
Primary Human Bronchial Epithelial Cells
23388
23928
23930
0
5
10
15
20
% Actin A->G Editing

FIG. 6

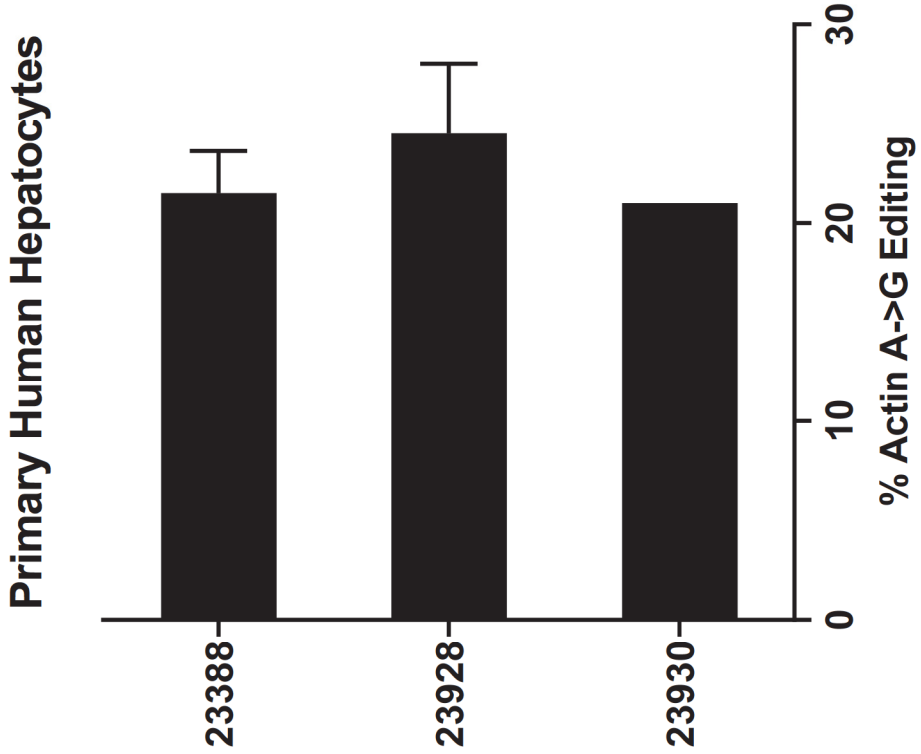


FIG. 6 (Continued)

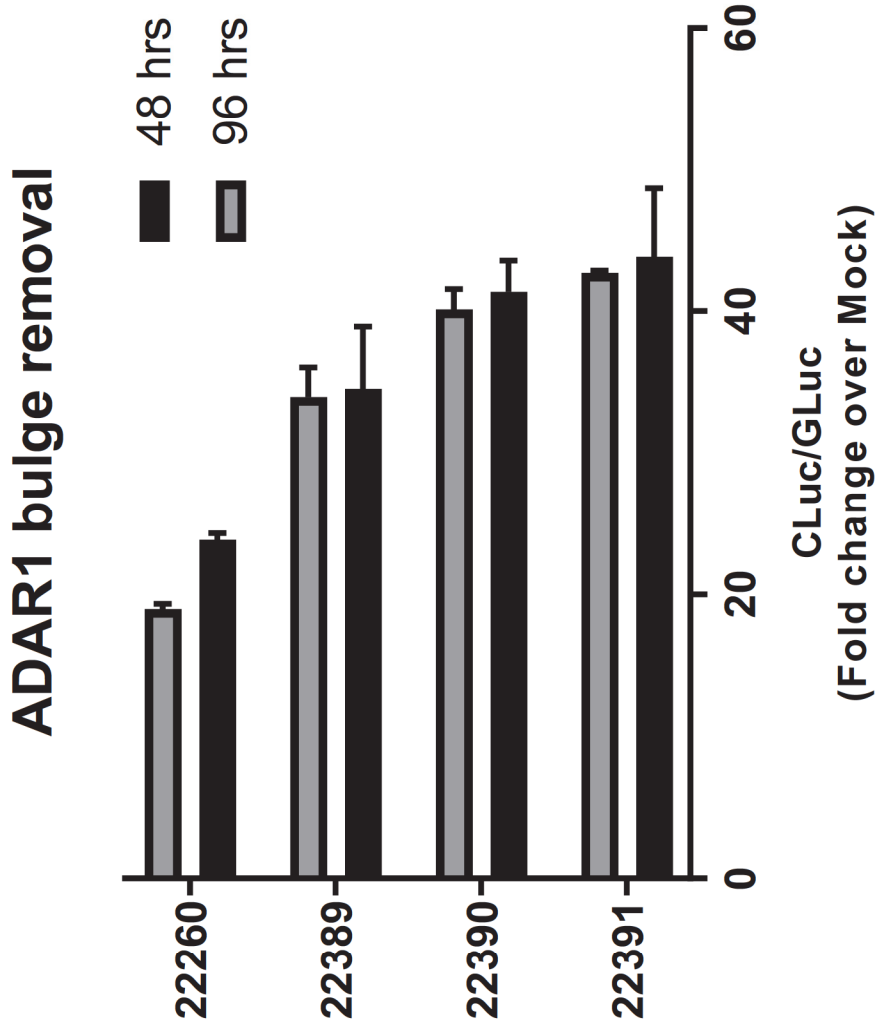

ADAR1 bulge removal
48 hrs
96 hrs
22260
22389
22390
22391
0
20
40
60
CLuc/GLuc
(Fold change over Mock)

FIG. 7

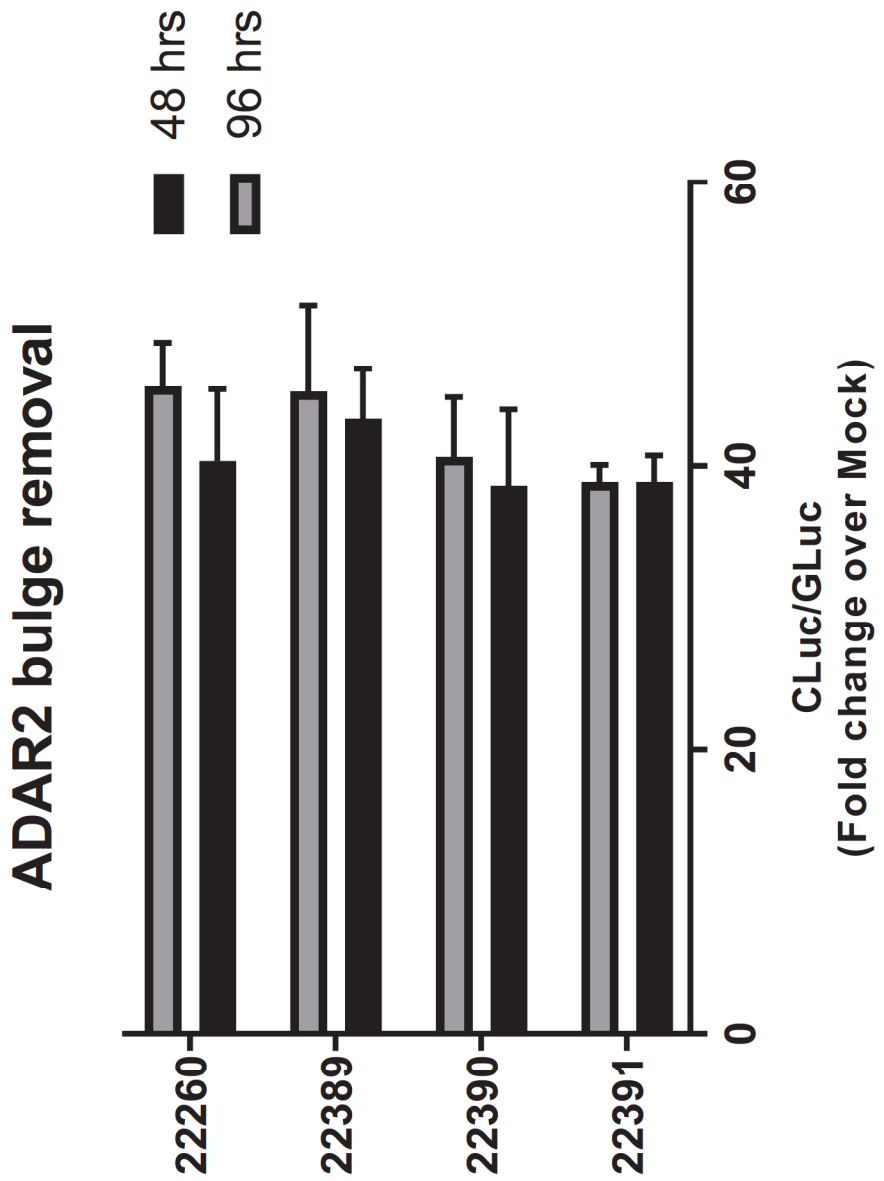


FIG. 7 (Continued)

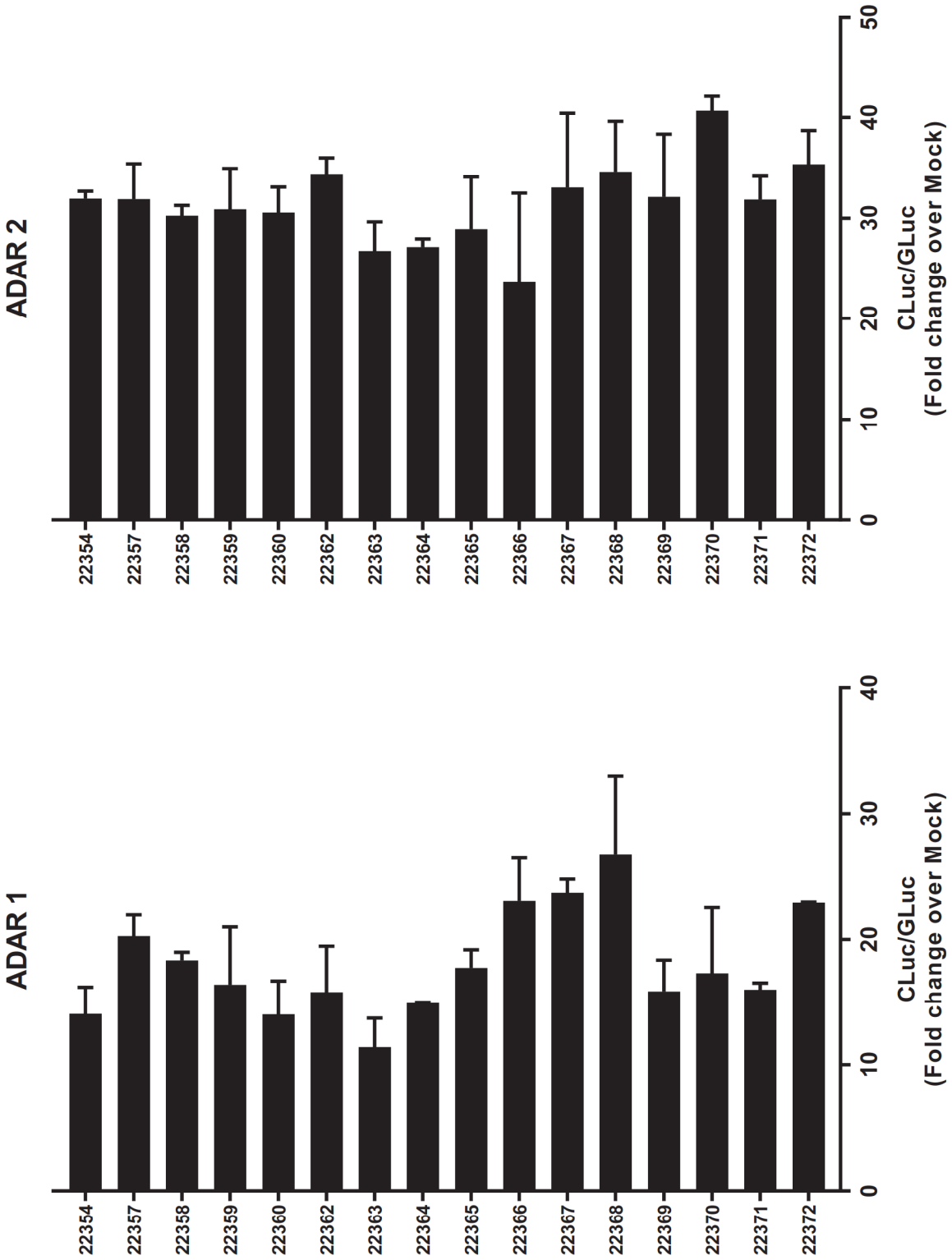

ADAR 1
CLuc/GLuc
(Fold change over Mock)
0
10
20
30
40
22354
22357
22358
22359
22360
22362
22363
22364
22365
22366
22367
22368
22369
22370
22371
22372
ADAR 2
CLuc/GLuc
(Fold change over Mock)
0
10
20
30
40
50
22354
22357
22358
22359
22360
22362
22363
22364
22365
22366
22367
22368
22369
22370
22371
22372

FIG. 8

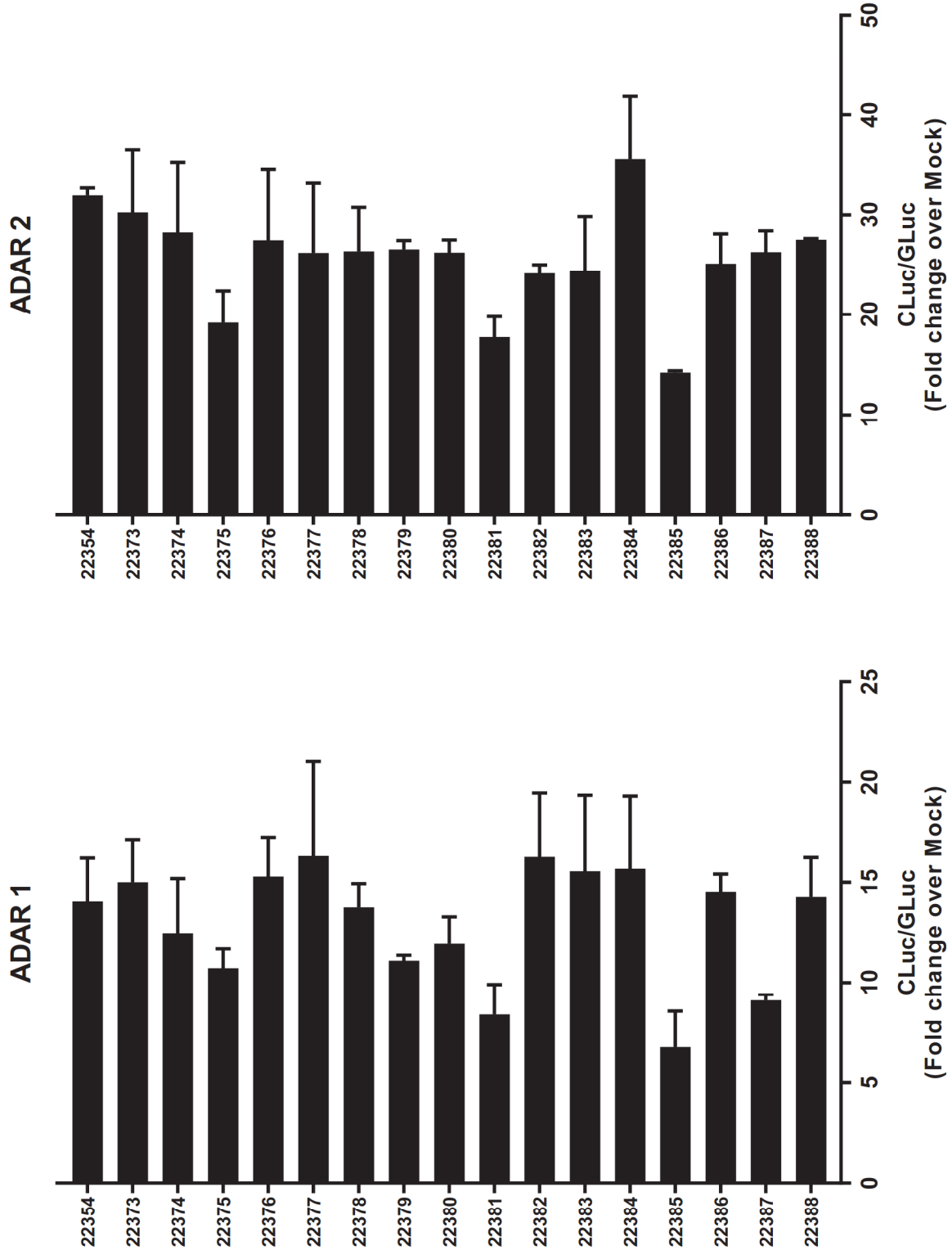

ADAR 1
CLuc/GLuc
(Fold change over Mock)
0
5
10
15
20
25
22354
22373
22374
22375
22376
22377
22378
22379
22380
22381
22382
22383
22384
22385
22386
22387
22388
ADAR 2
CLuc/GLuc
(Fold change over Mock)
0
10
20
30
40
50
22354
22373
22374
22375
22376
22377
22378
22379
22380
22381
22382
22383
22384
22385
22386
22387
22388

FIG. 9

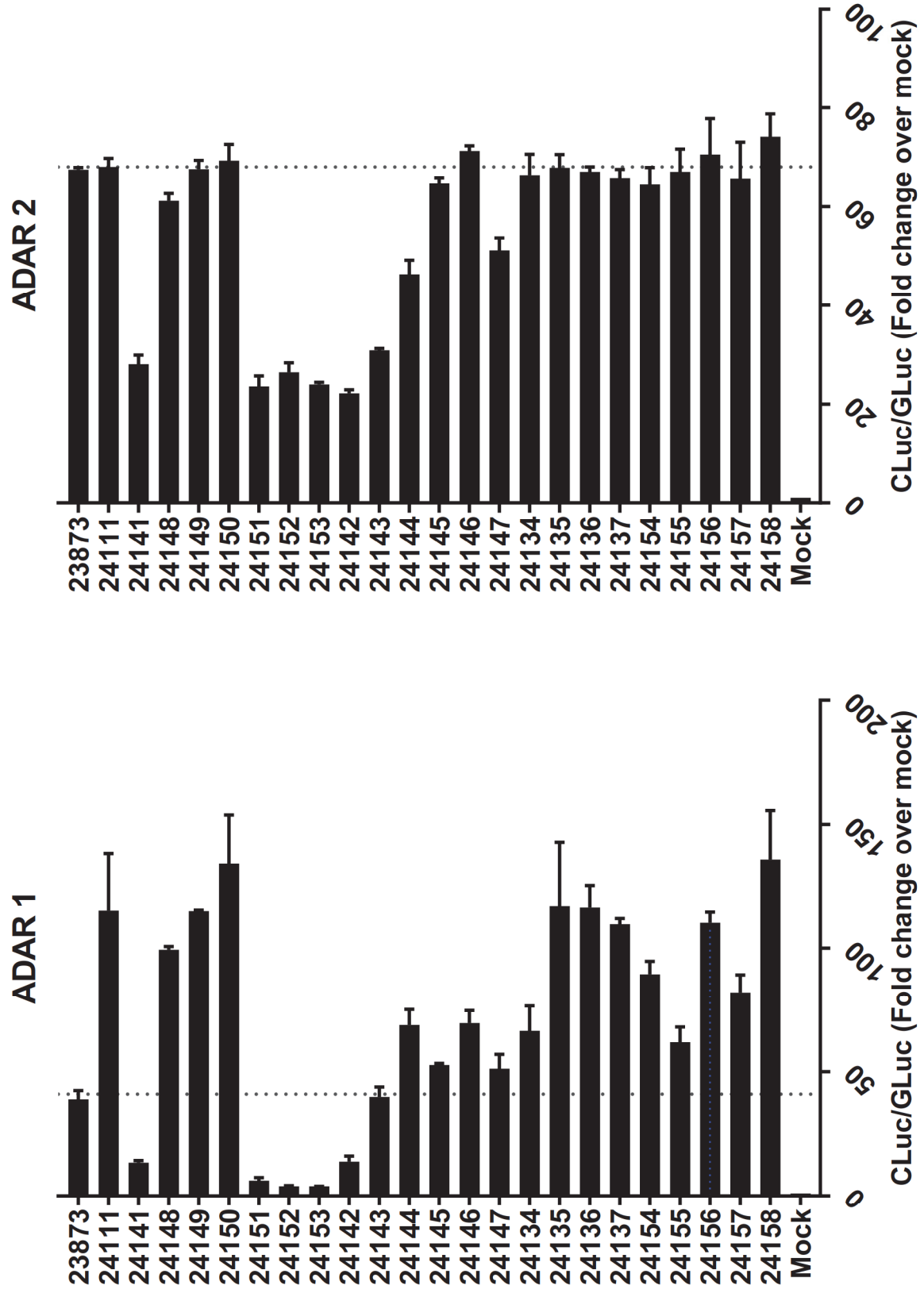

ADAR 1
CLuc/GLuc (Fold change over mock)
0
50
100
150
200
23873
24111
24141
24148
24149
24150
24151
24152
24153
24142
24143
24144
24145
24146
24147
24134
24135
24136
24137
24154
24155
24156
24157
24158
Mock
ADAR 2
CLuc/GLuc (Fold change over mock)
0
20
40
60
80
100
23873
24111
24141
24148
24149
24150
24151
24152
24153
24142
24143
24144
24145
24146
24147
24134
24135
24136
24137
24154
24155
24156
24157
24158
Mock

FIG. 10

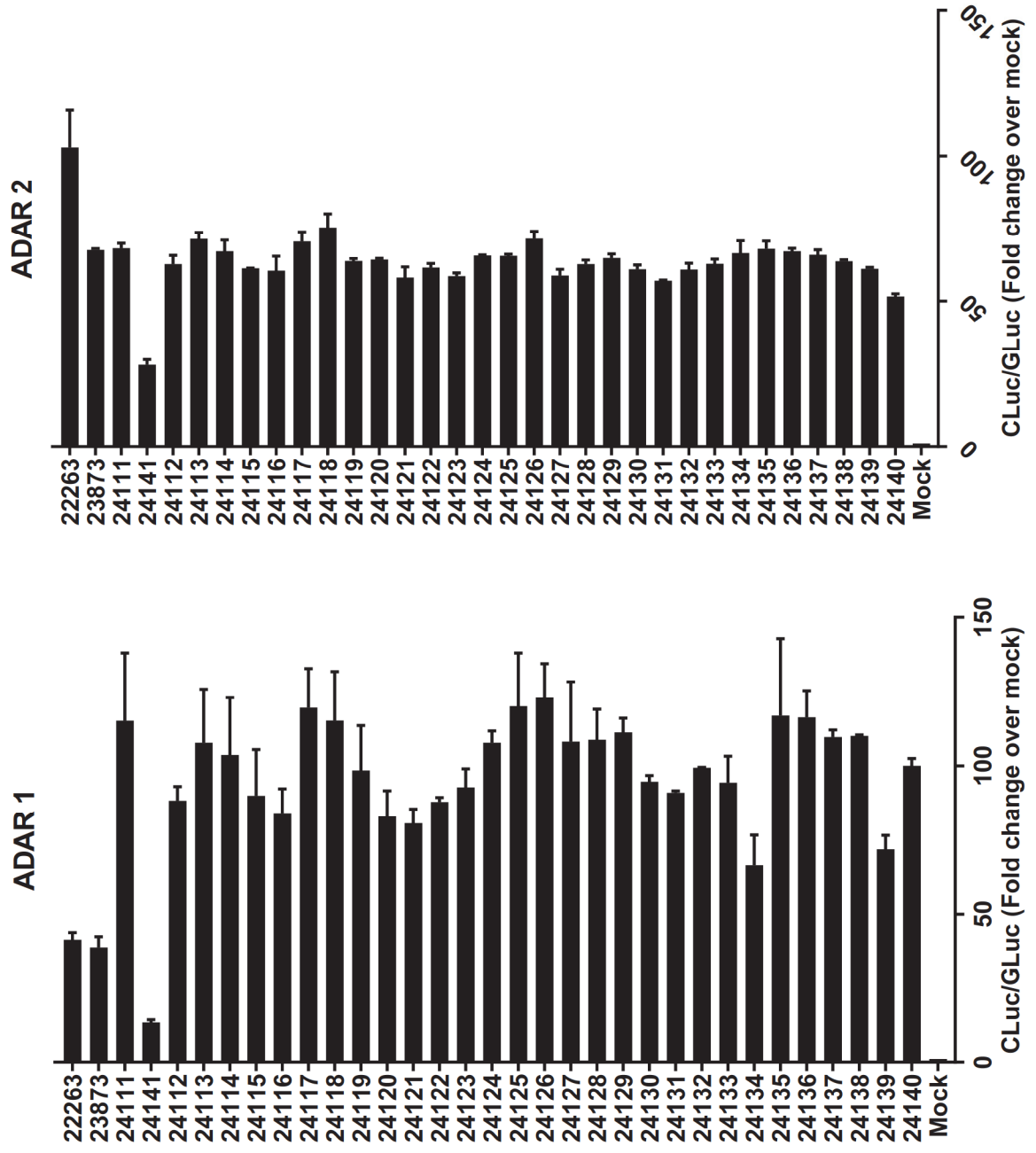


FIG. 10 (Continued)

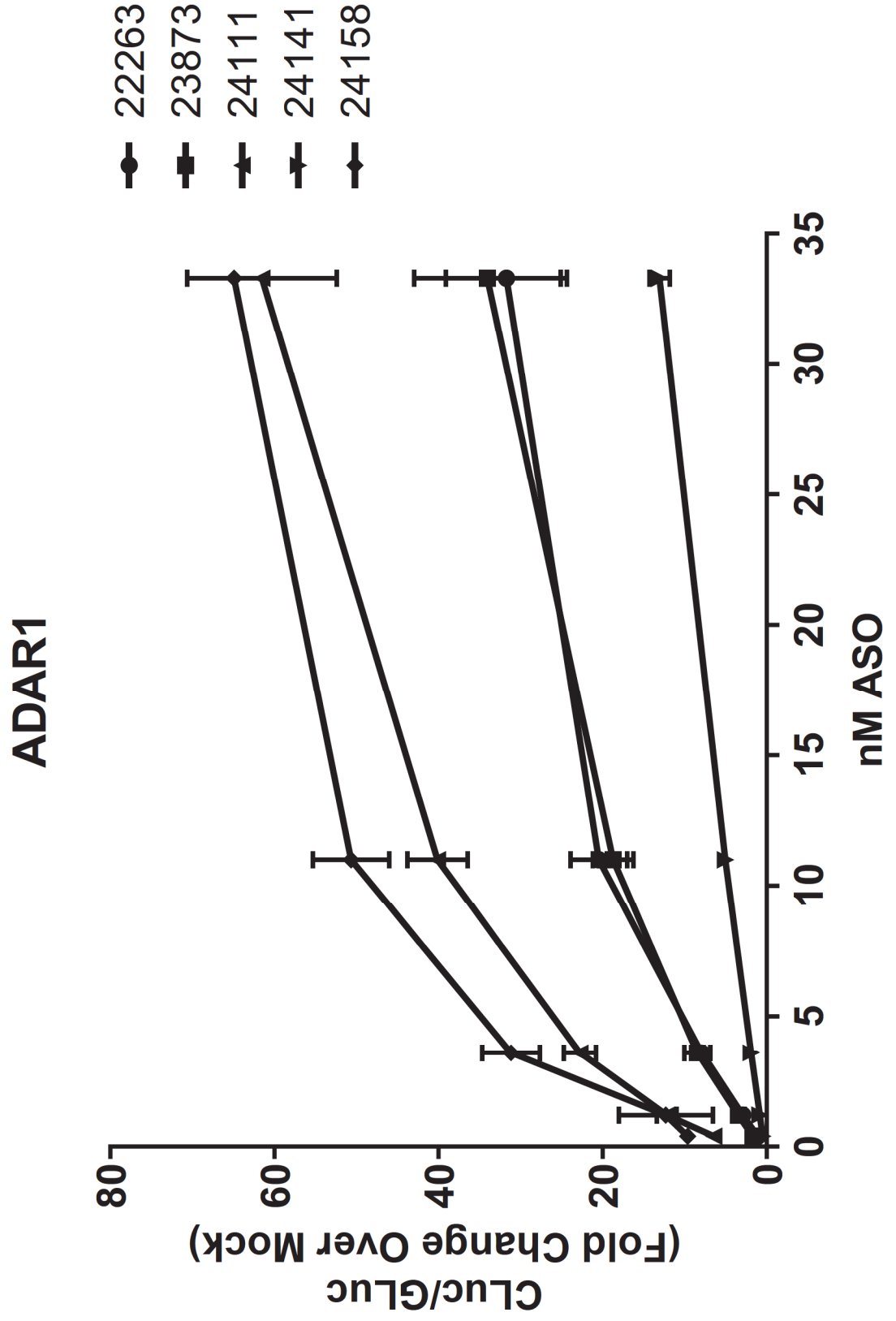

ADAR1
22263
23873
24111
24141
24158
CLuc/GLuc
(Fold Change Over Mock)
0
20
40
60
80
0
5
10
15
20
25
30
35
nM ASO

FIG. 11

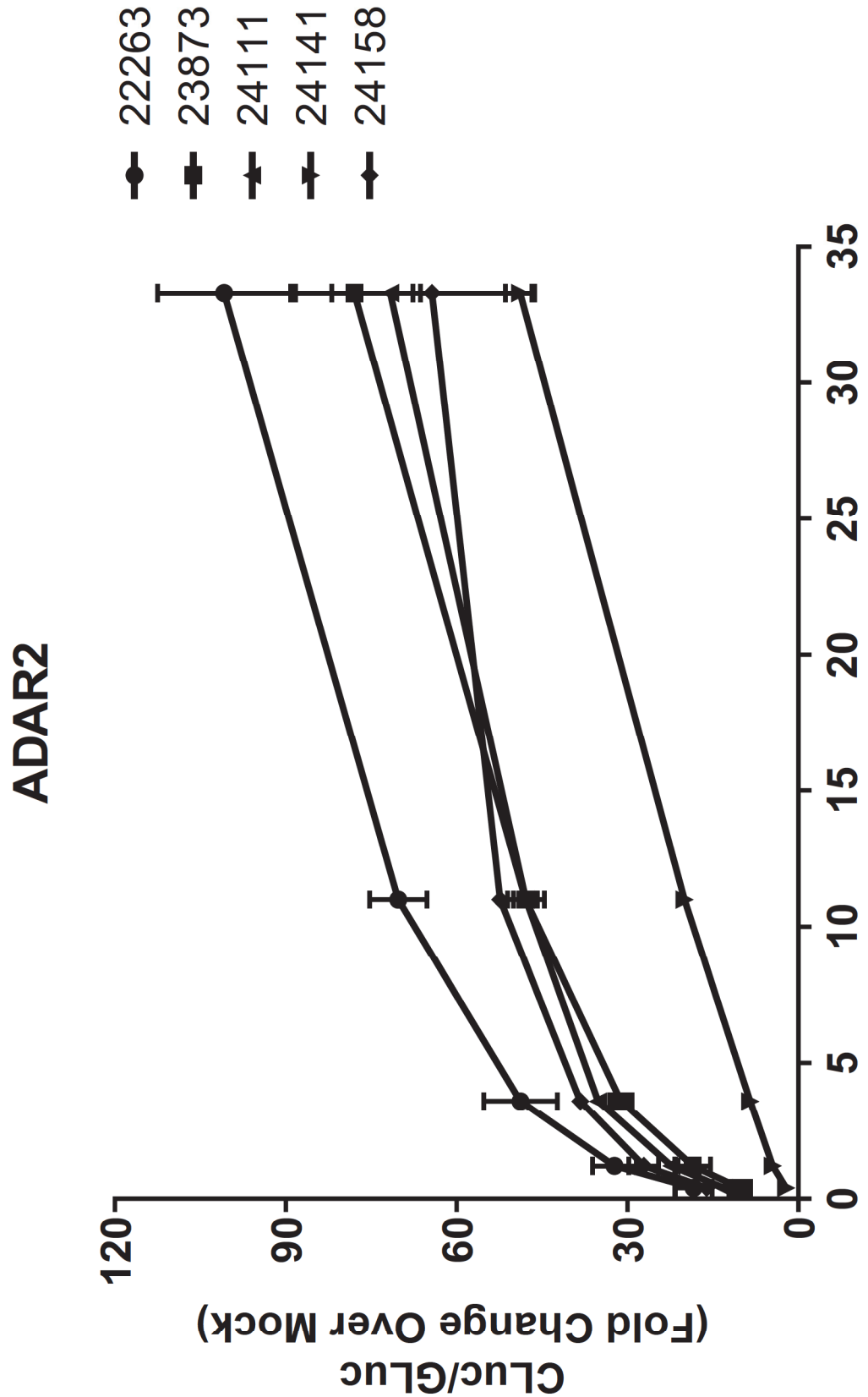


FIG. 11 (Continued)

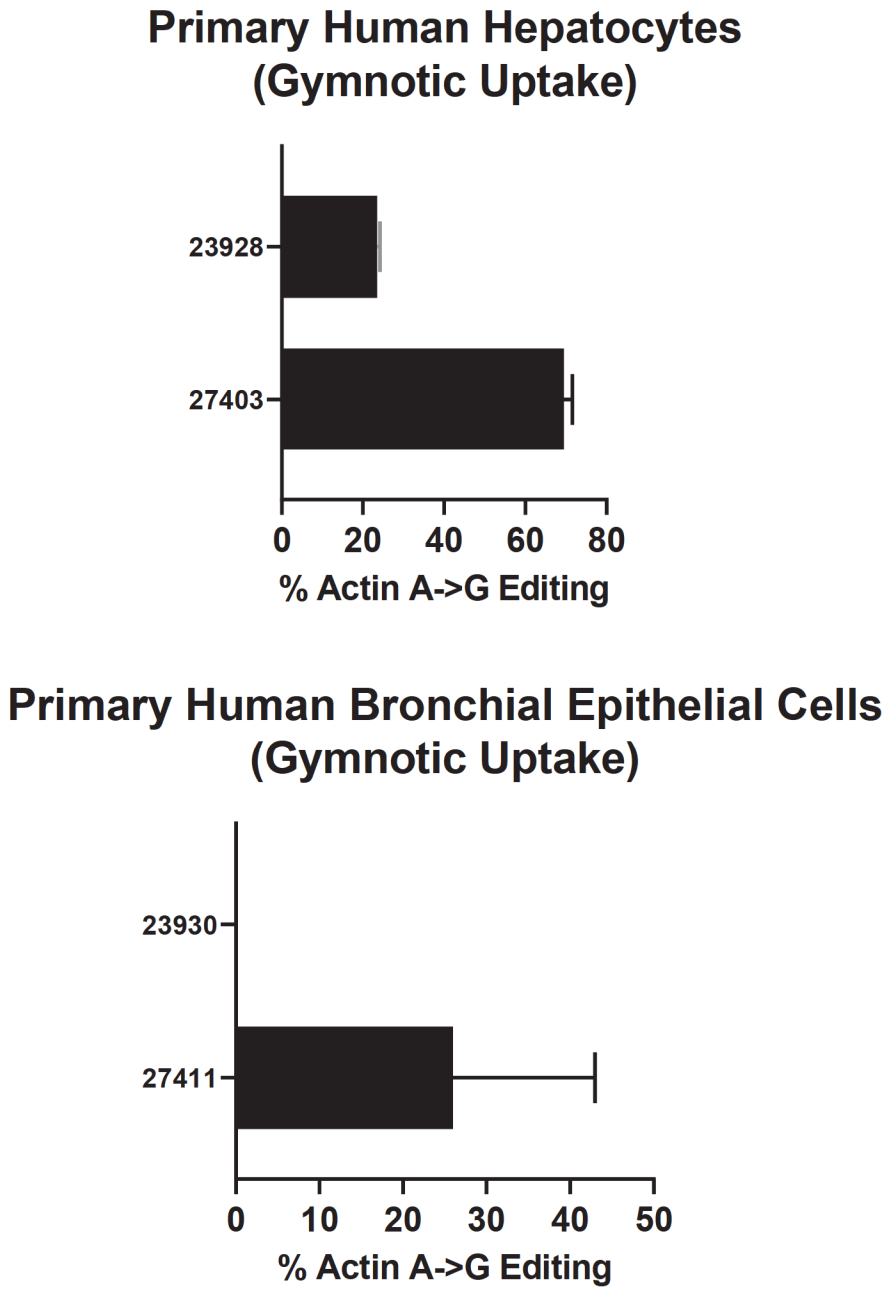

Primary Human Hepatocytes
(Gymnotic Uptake)
23928
27403
0
20
40
60
80
% Actin A->G Editing
Primary Human Bronchial Epithelial Cells
(Gymnotic Uptake)
23930
27411
0
10
20
30
40
50
% Actin A->G Editing

FIG. 12.

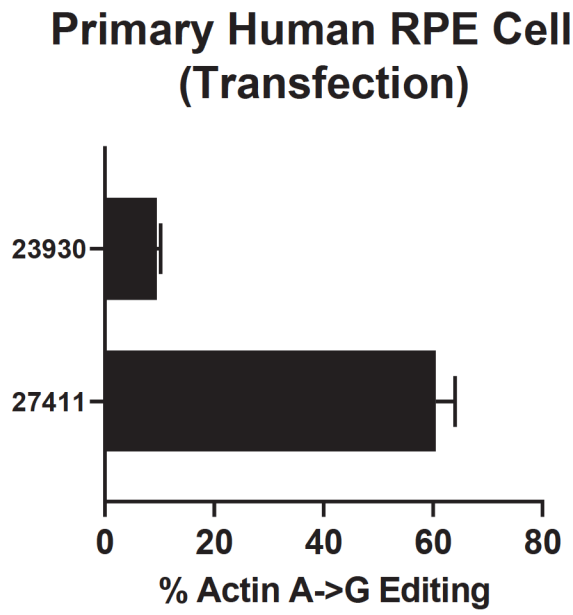


FIG. 12 (Continued)

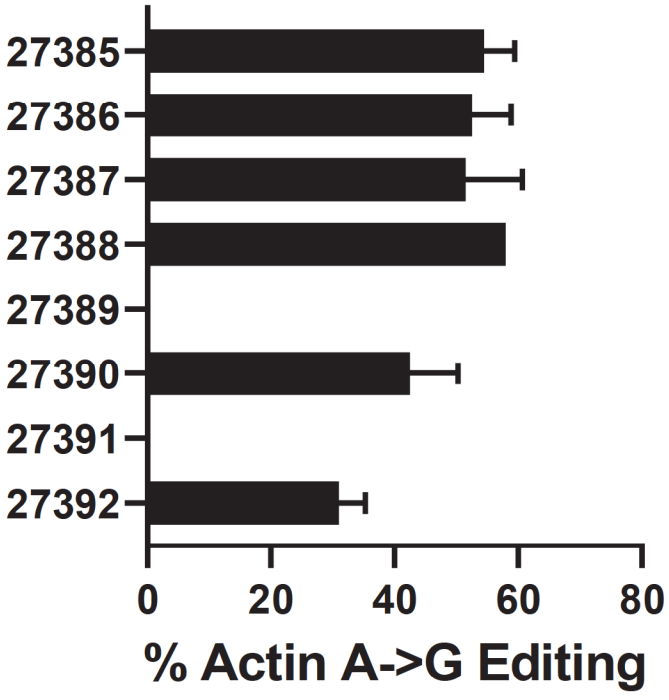
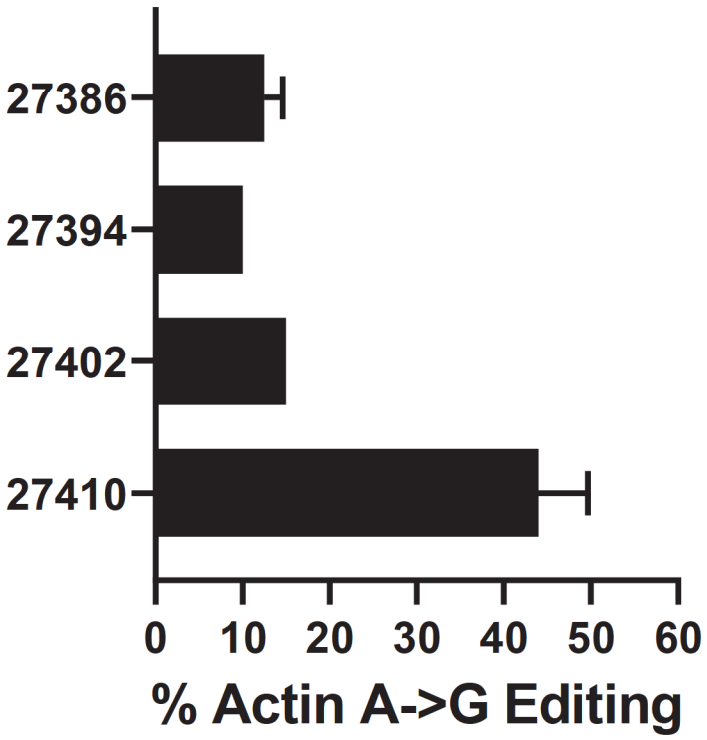


FIG. 13

Primary human bronchial epithelial cells (Gymnotic uptake)



Primary retinal pigmented epithelial cells (Transfection)

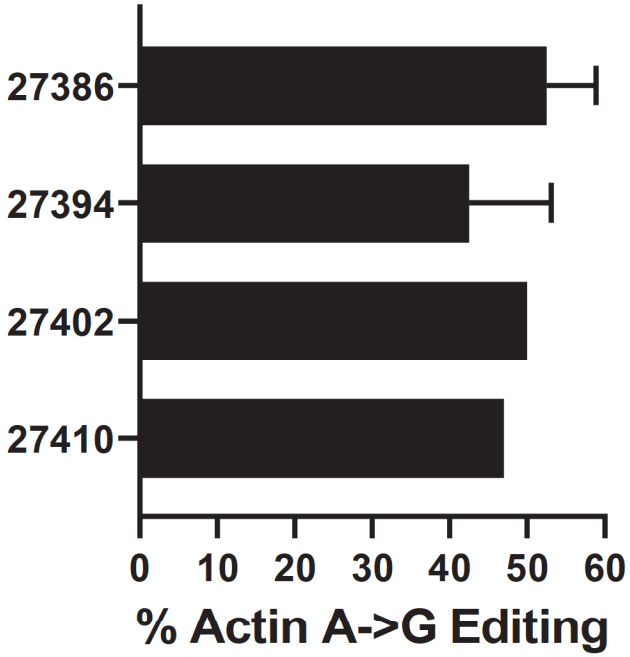


FIG. 14

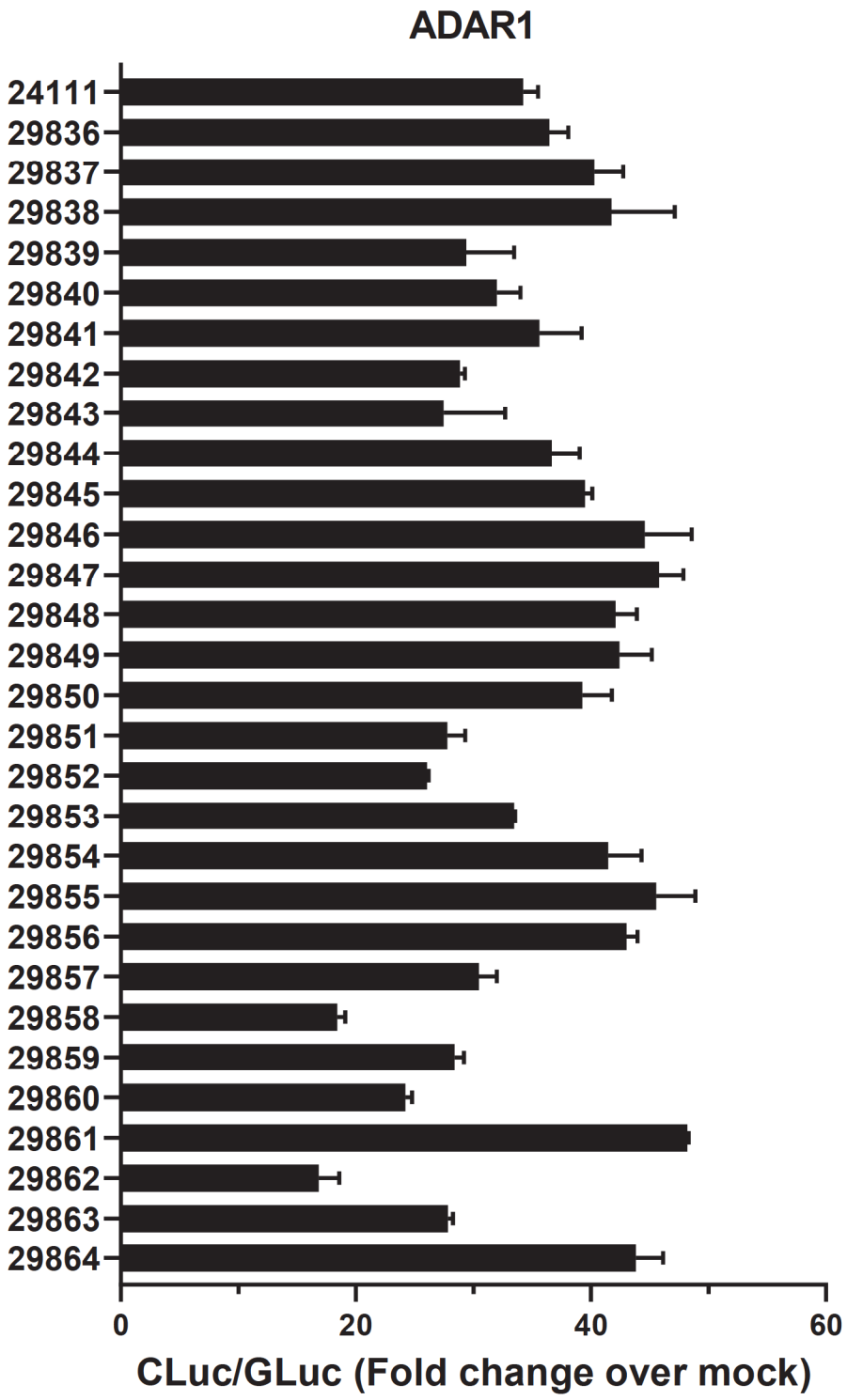

ADAR1
24111
29836
29837
29838
29839
29840
29841
29842
29843
29844
29845
29846
29847
29848
29849
29850
29851
29852
29853
29854
29855
29856
29857
29858
29859
29860
29861
29862
29863
29864
0
20
40
60
CLuc/GLuc (Fold change over mock)

FIG. 15

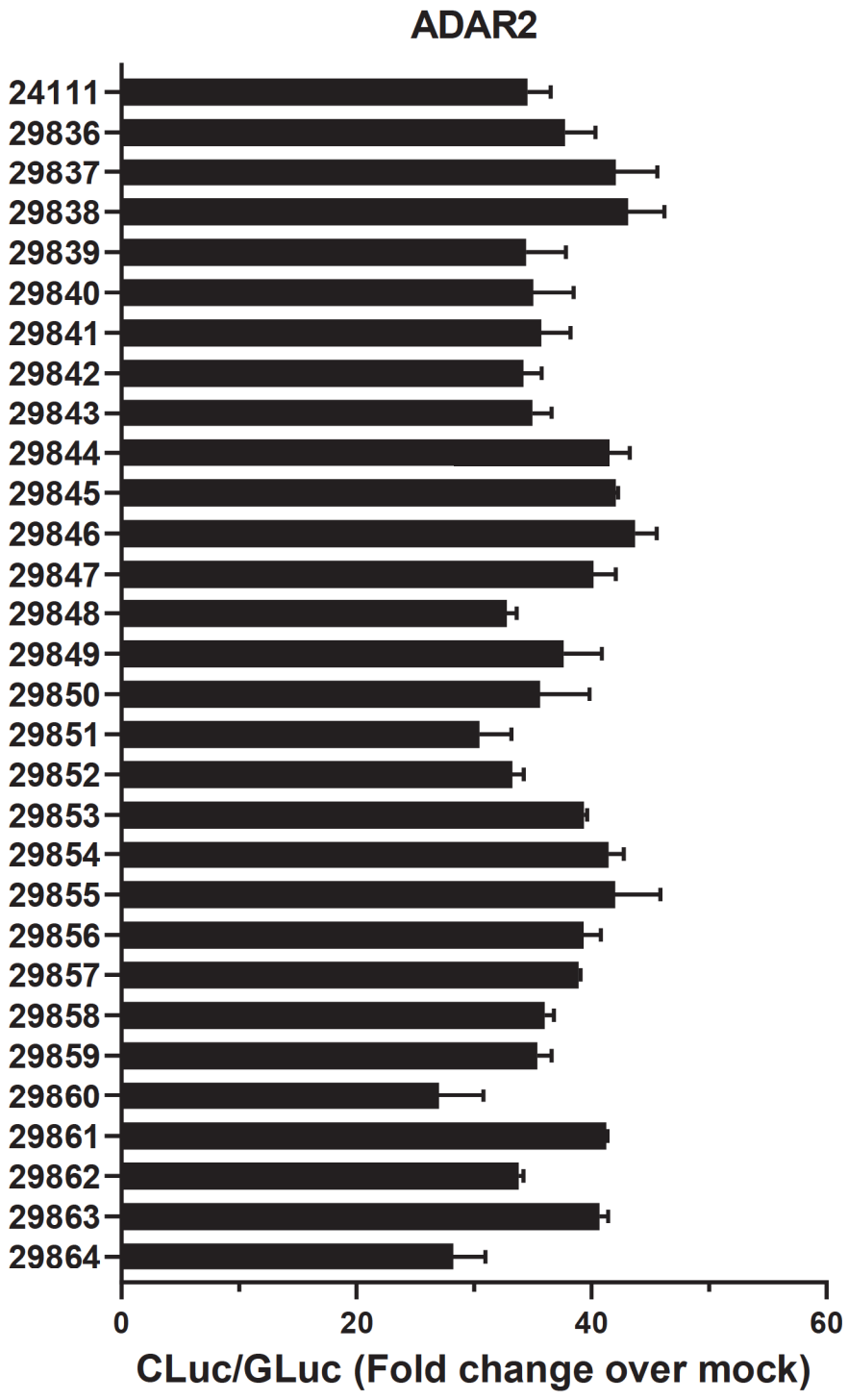


FIG. 15 (Continued)

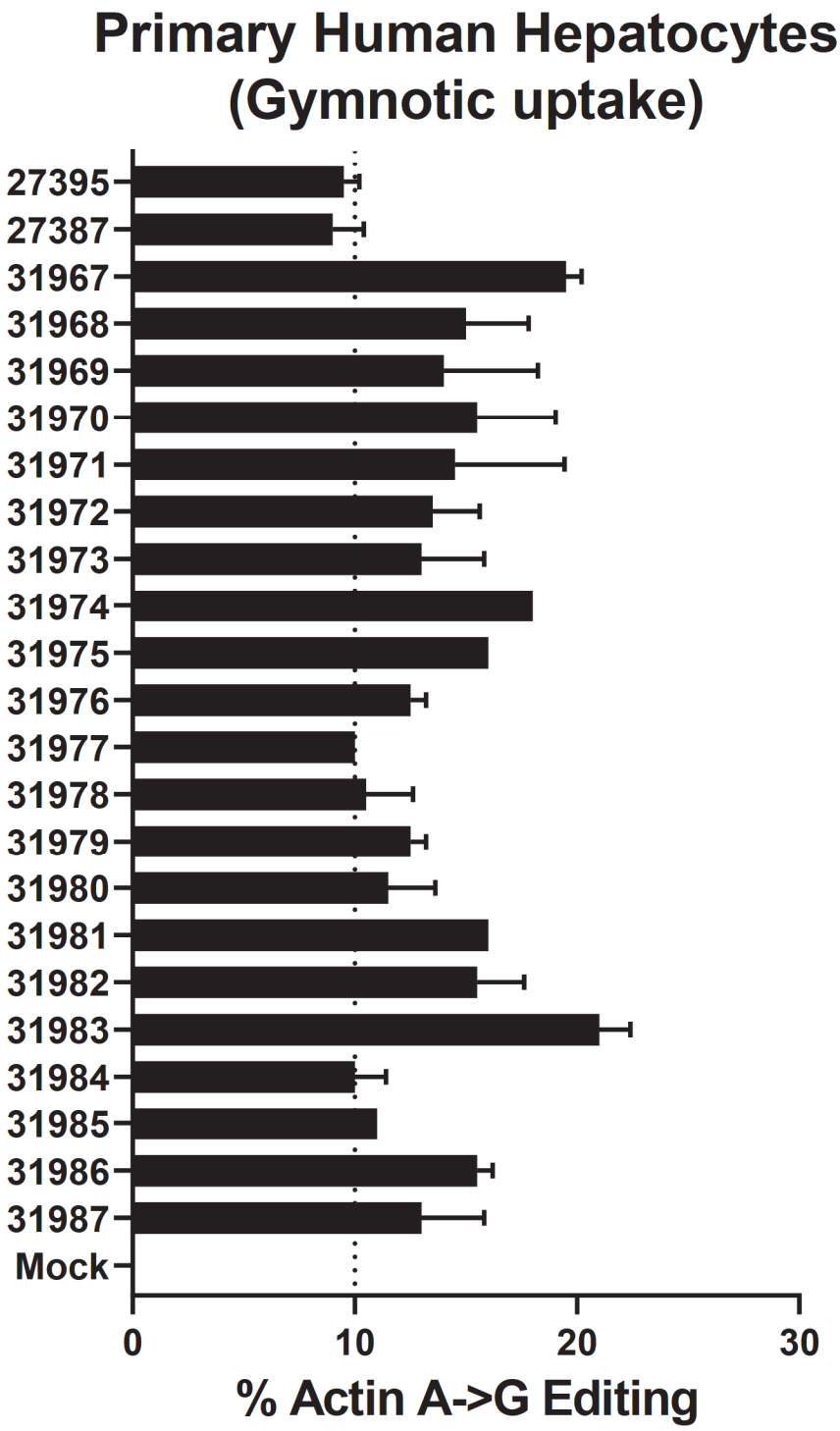

Primary Human Hepatocytes
(Gymnotic uptake)
27395
27387
31967
31968
31969
31970
31971
31972
31973
31974
31975
31976
31977
31978
31979
31980
31981
31982
31983
31984
31985
31986
31987
Mock
0
10
20
30
% Actin A->G Editing

FIG. 16

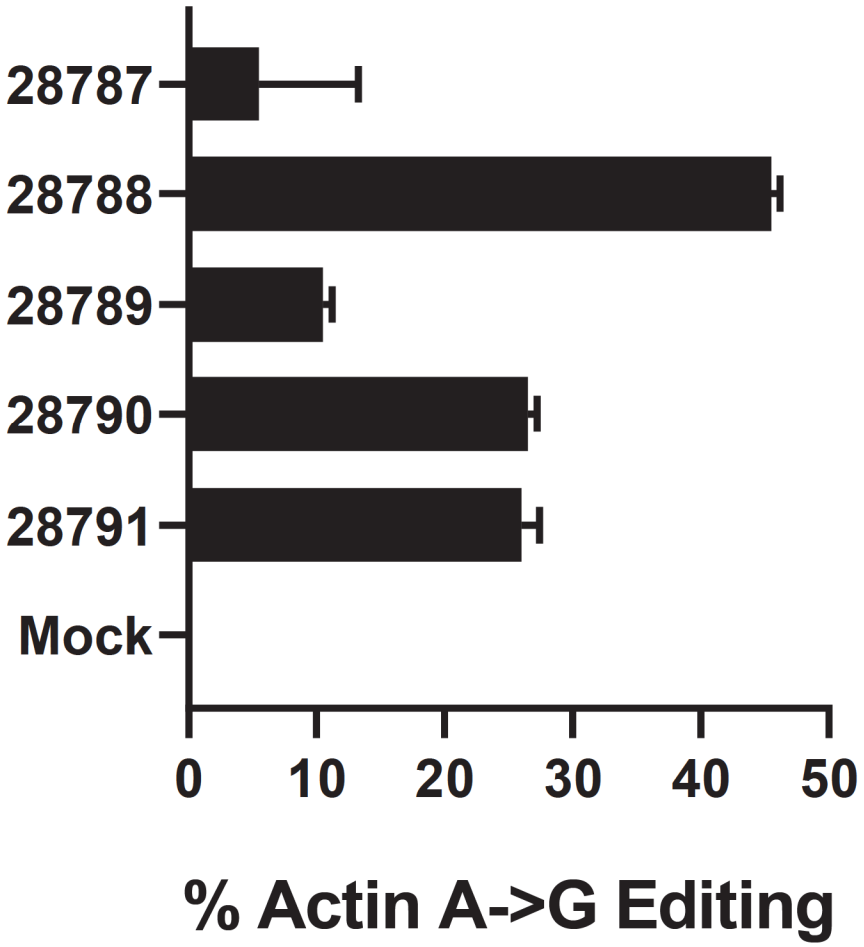
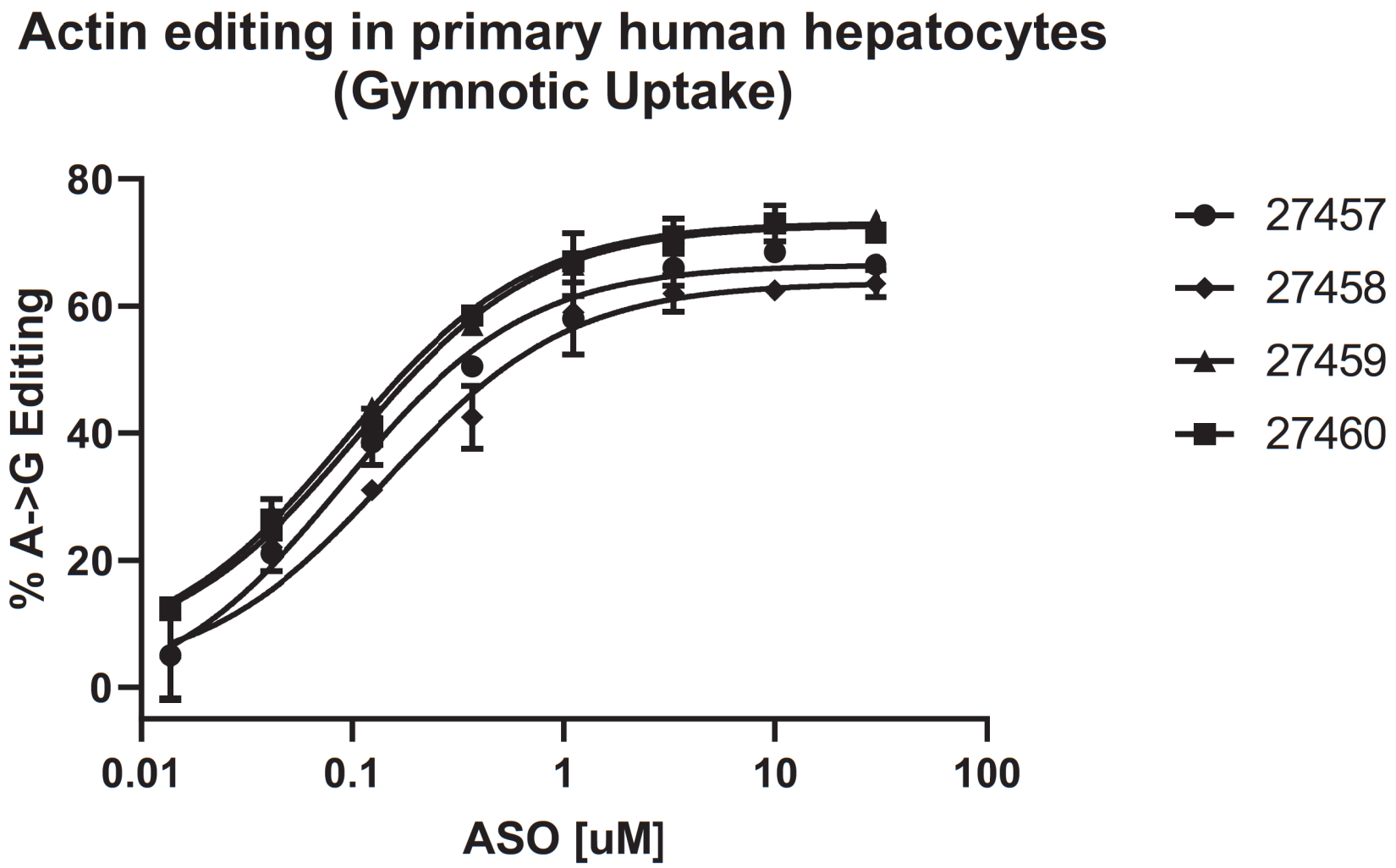
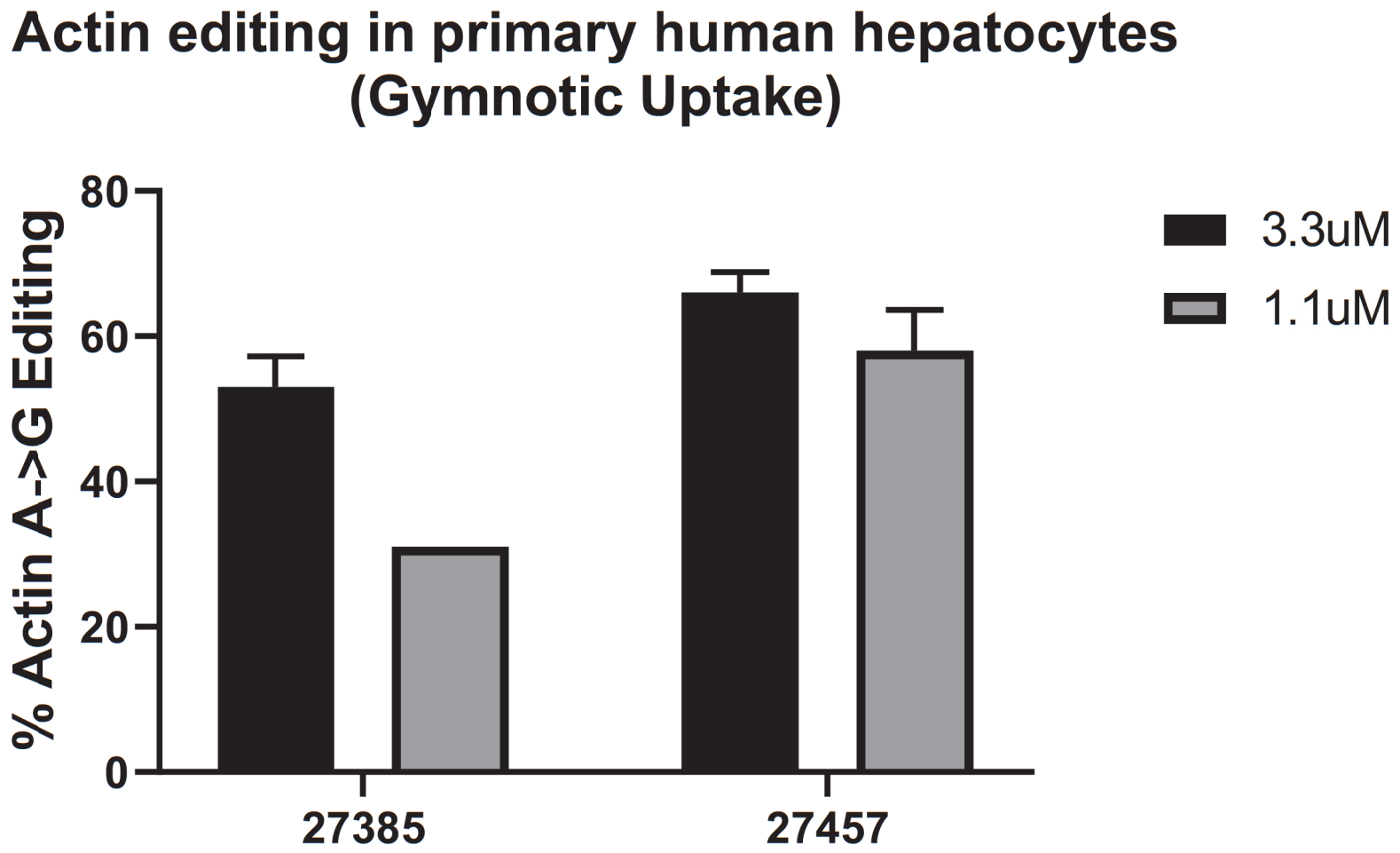

28787
28788
28789
28790
28791
Mock
0
10
20
30
40
50
% Actin A->G Editing

FIG. 17


Actin editing in primary human hepatocytes
(Gymnotic Uptake)
% A->G Editing
80
60
40
20
0
0.01
0.1
1
10
100
ASO [uM]
27457
27458
27459
27460

(a)

FIG. 18


Actin editing in primary human hepatocytes
(Gymnotic Uptake)
% Actin A->G Editing
80
60
40
20
0
27385
27457
3.3uM
1.1uM

(b)

FIG. 18

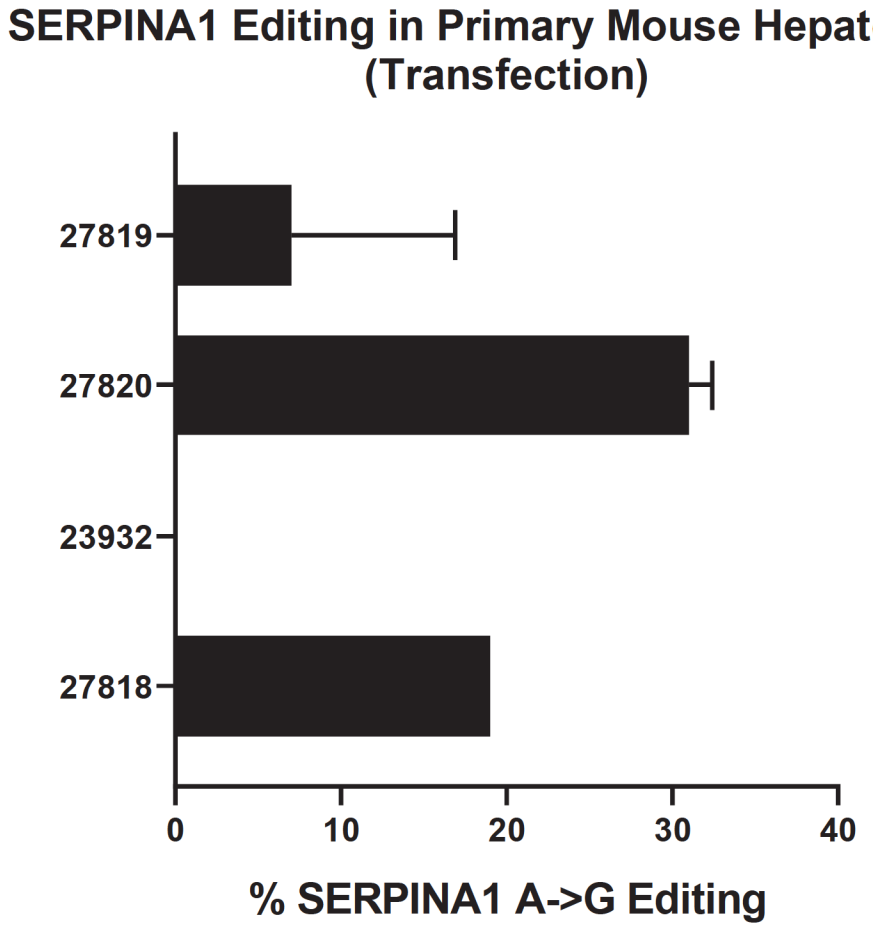

SERPINA1 Editing in Primary Mouse Hepatocytes
(Transfection)
27819
27820
23932
27818
0
10
20
30
40
% SERPINA1 A->G Editing

FIG. 19

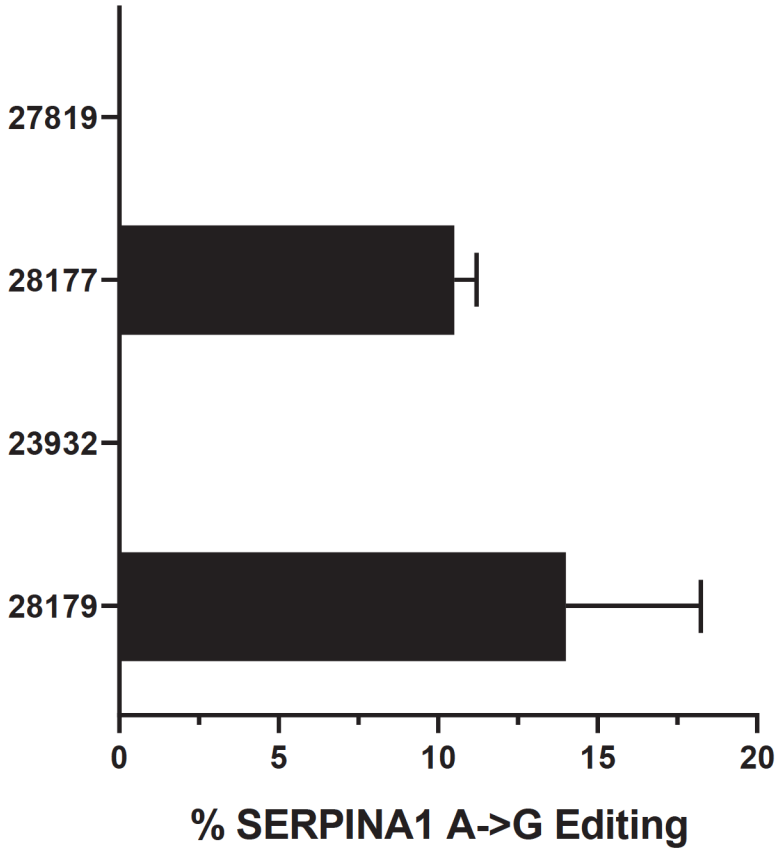


FIG. 20

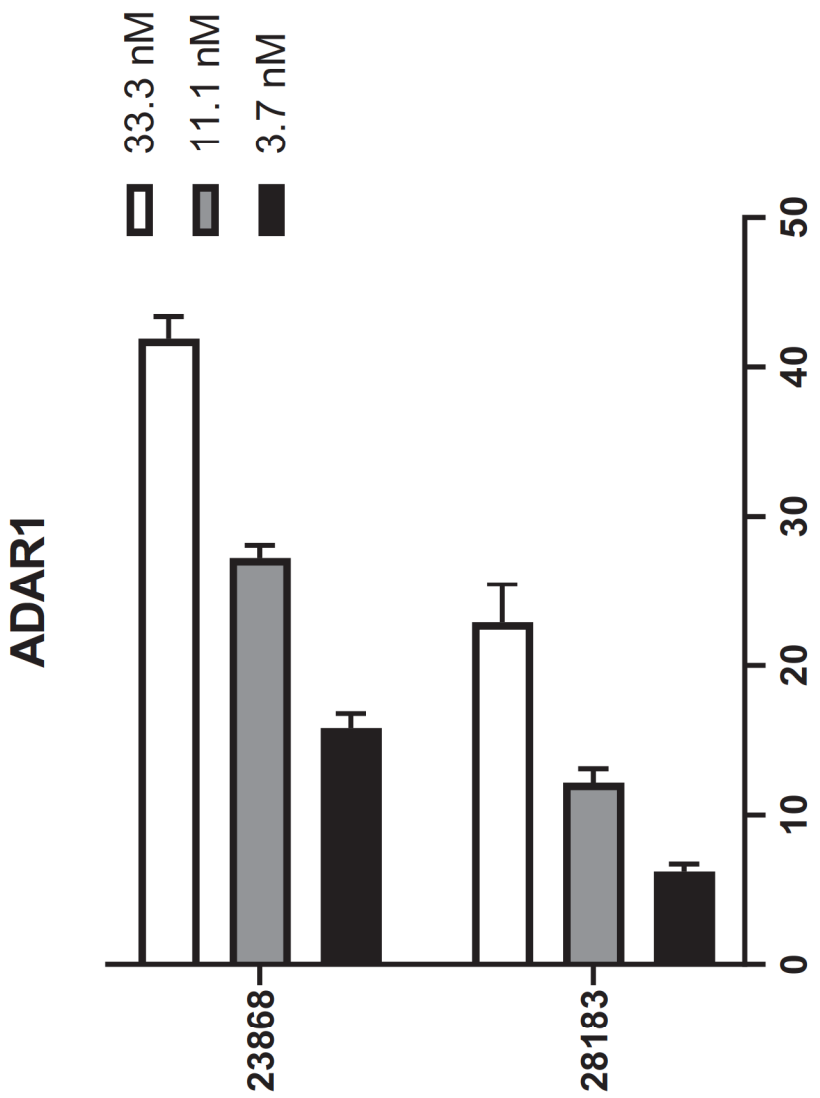


FIG. 21

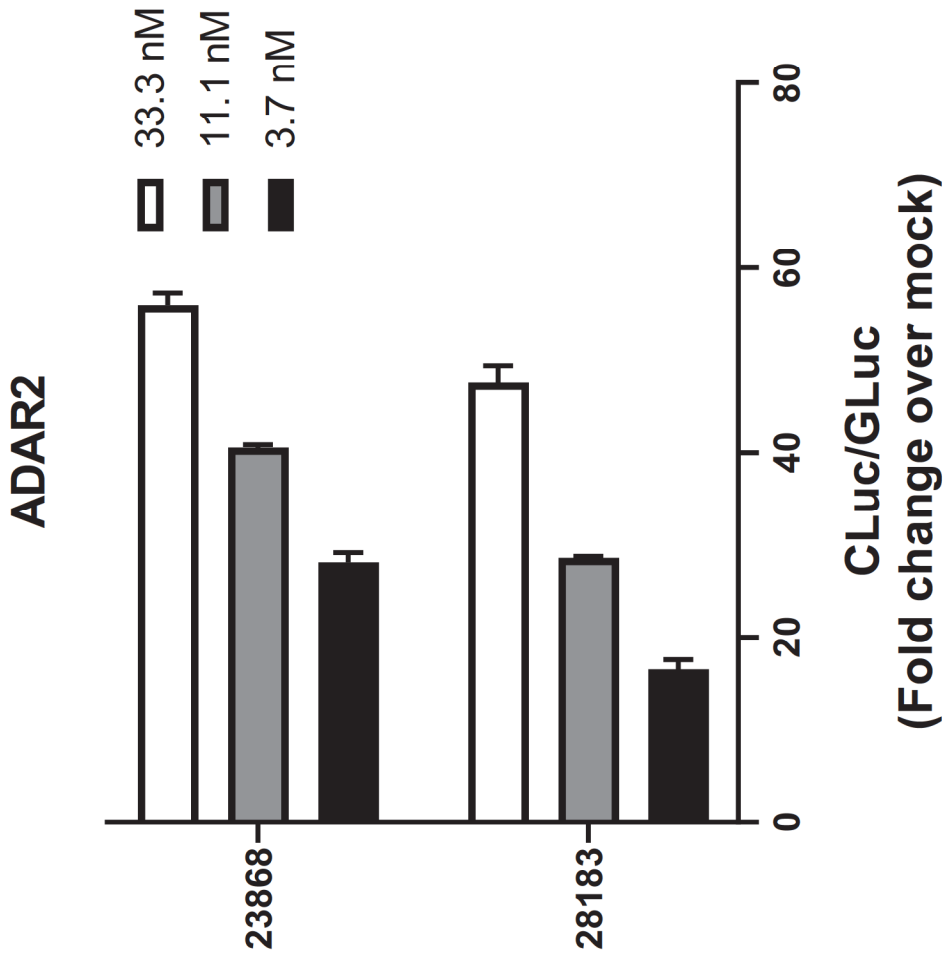


FIG. 21 (Continued)

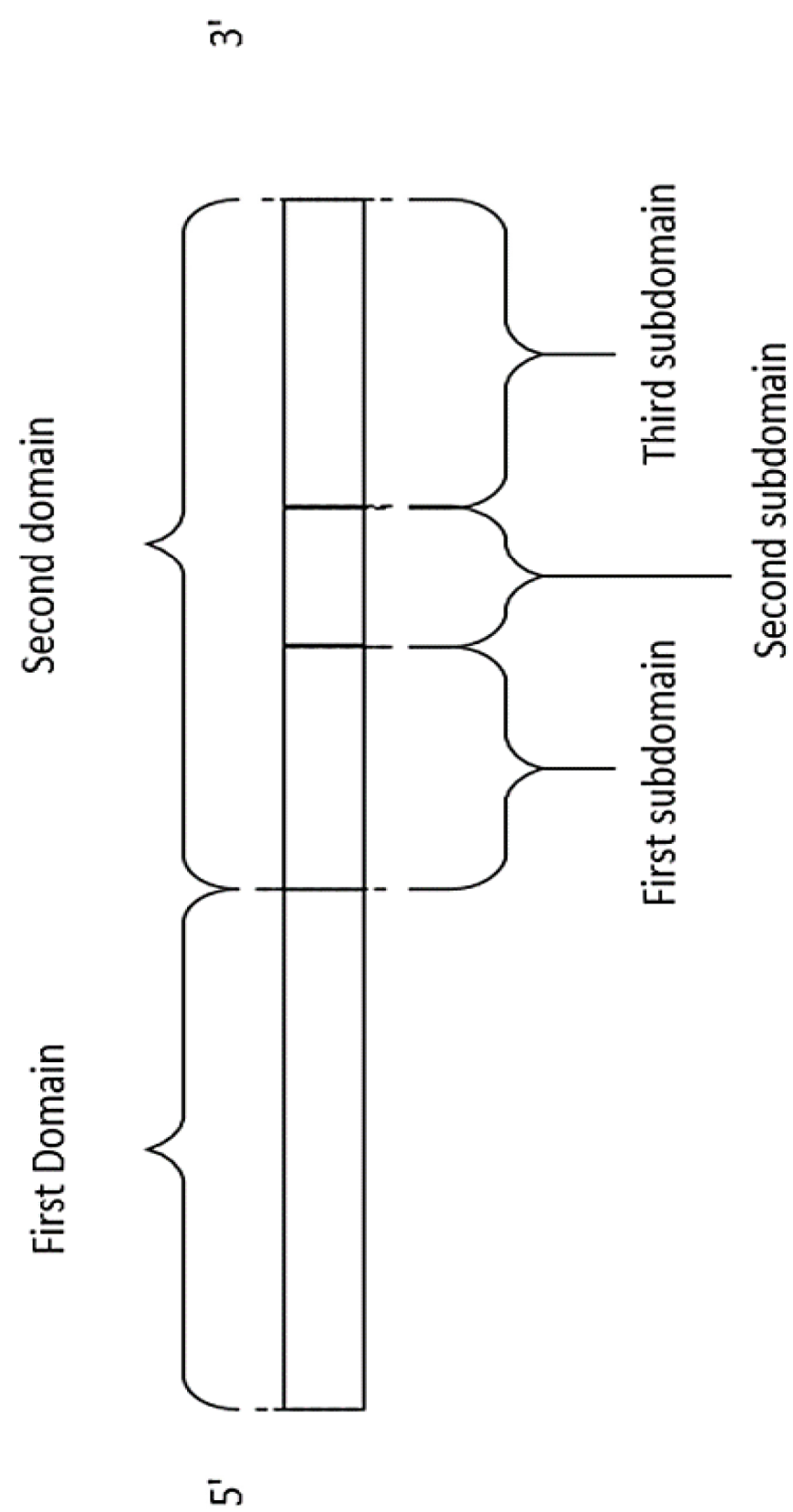

5'
First Domain
Second domain
3'
First subdomain
Second subdomain
Third subdomain

FIG. 22

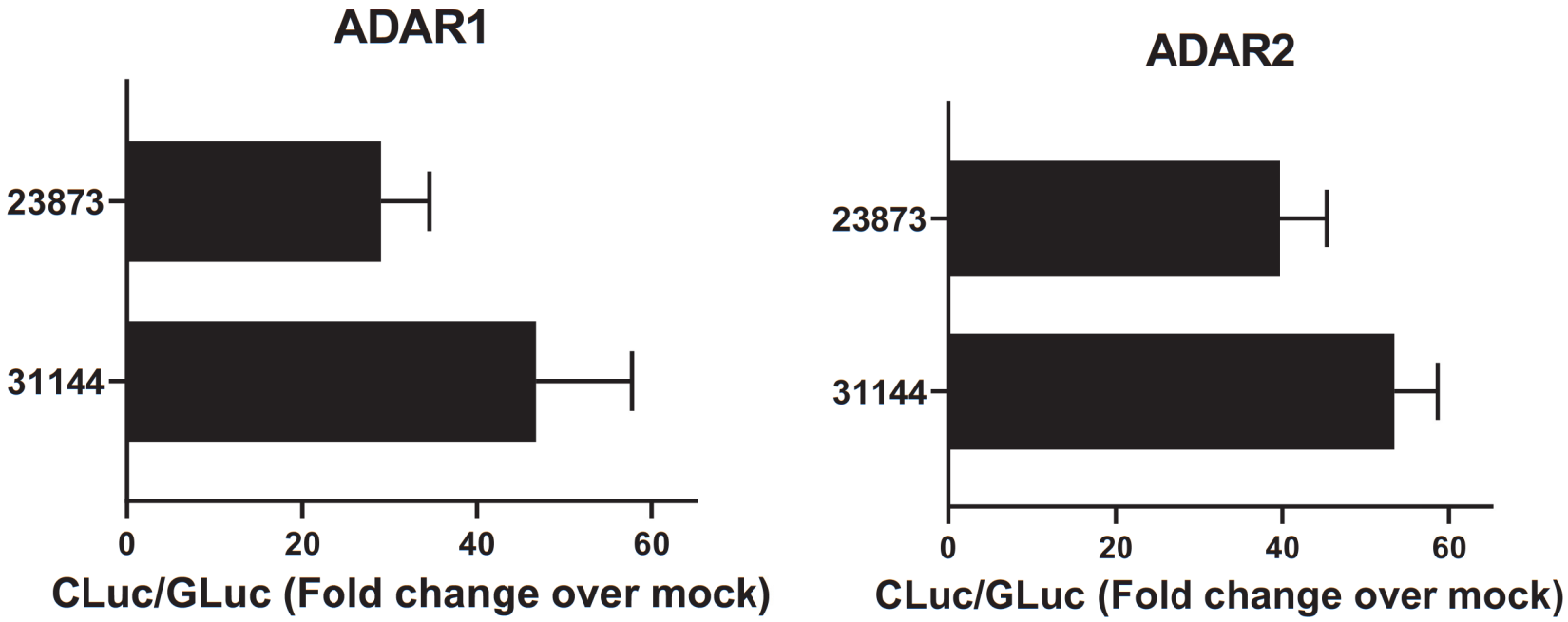

ADAR1
23873
31144
0
20
40
60
CLuc/GLuc (Fold change over mock)
ADAR2
23873
31144
0
20
40
60
CLuc/GLuc (Fold change over mock)

FIG. 23

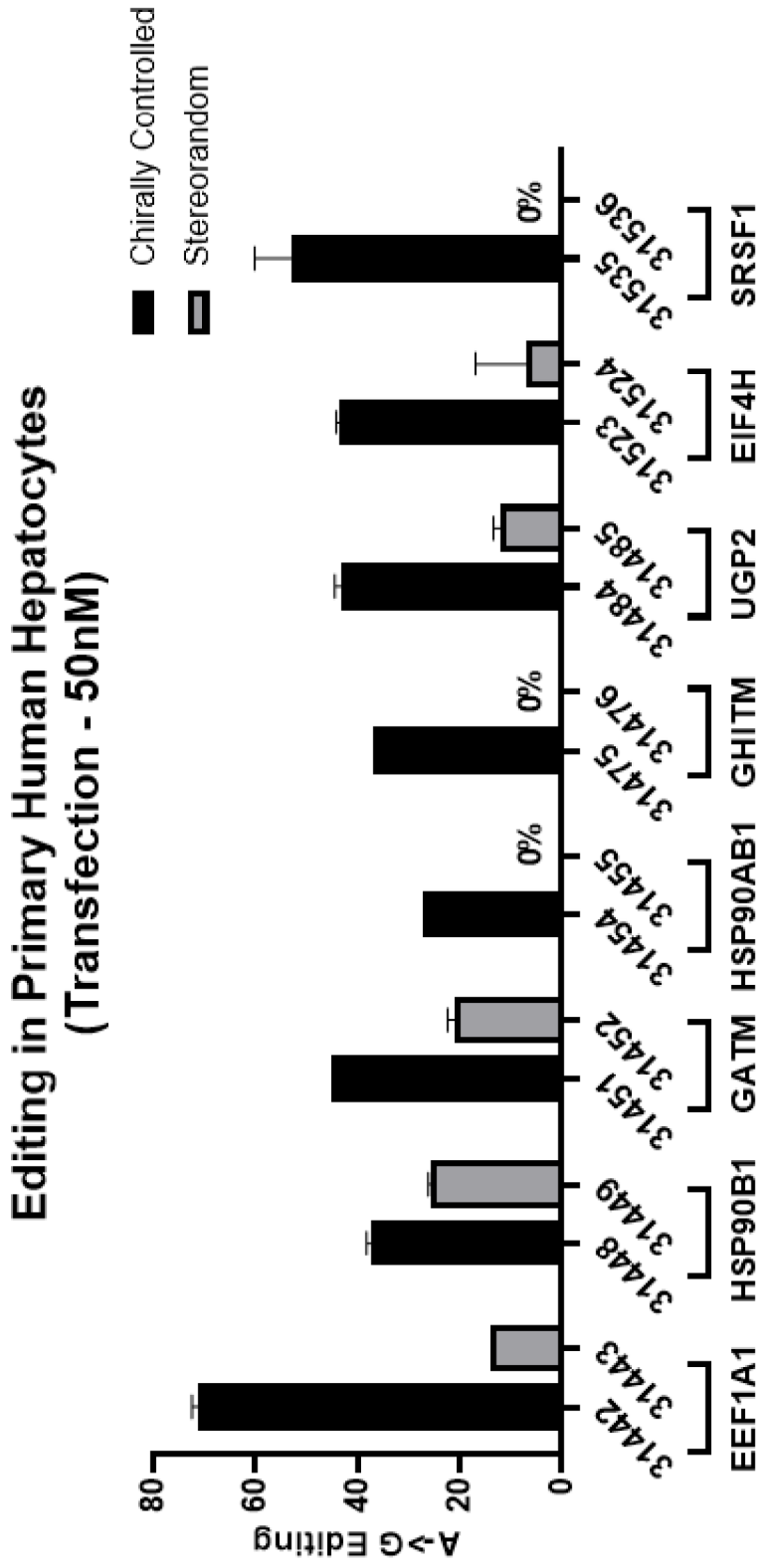

Editing in Primary Human Hepatocytes
(Transfection - 50nM)
Chirally Controlled
Stereorandom
A->G Editing
0
20
40
60
80
3142
3143
3148
3149
3151
3152
3154
3155
3175
3176
3184
3185
3223
3224
3235
3236
0%
0%
0%
EEF1A1
HSP90B1
GATM
HSP90AB1
GHITM
UGP2
EIF4H
SRSF1

FIG. 24

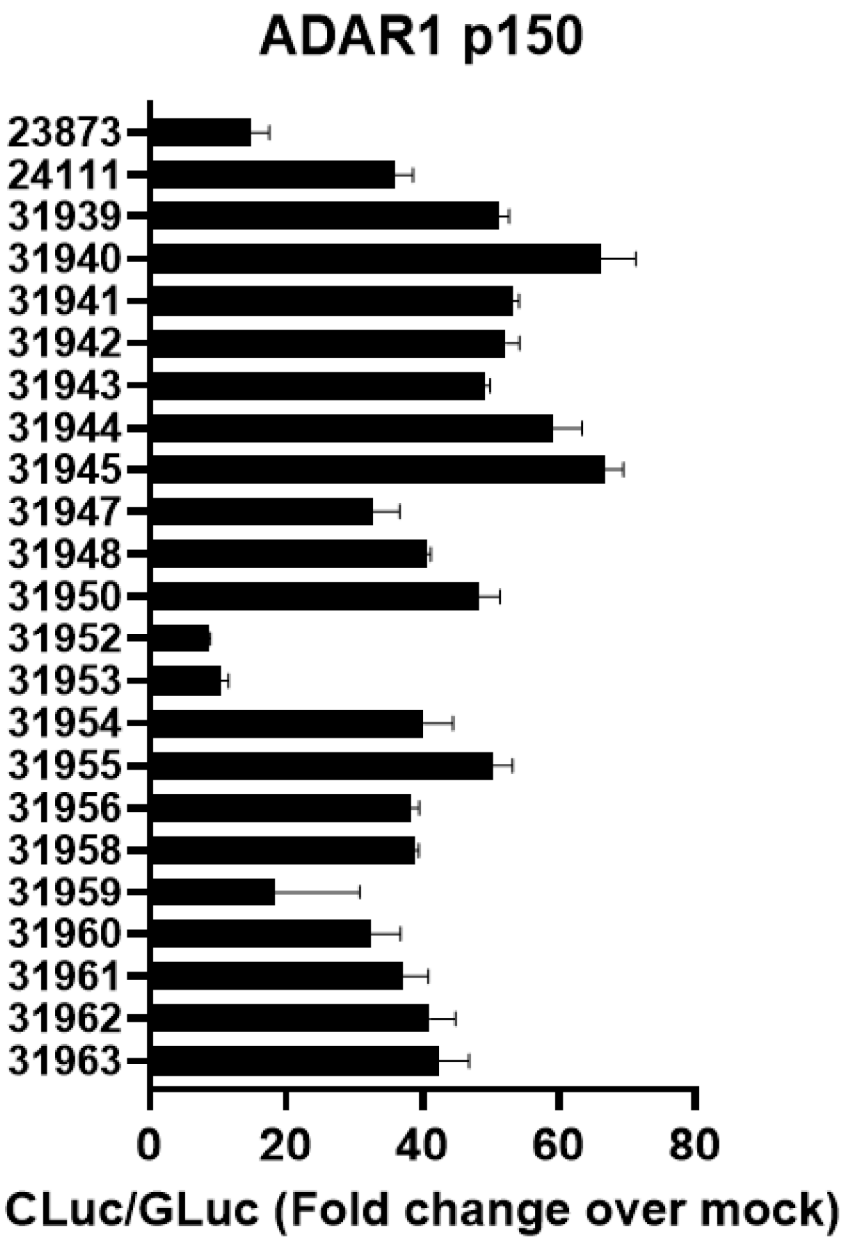

ADAR1 p150
23873
24111
31939
31940
31941
31942
31943
31944
31945
31947
31948
31950
31952
31953
31954
31955
31956
31958
31959
31960
31961
31962
31963
0
20
40
60
80
CLuc/GLuc (Fold change over mock)

FIG. 25

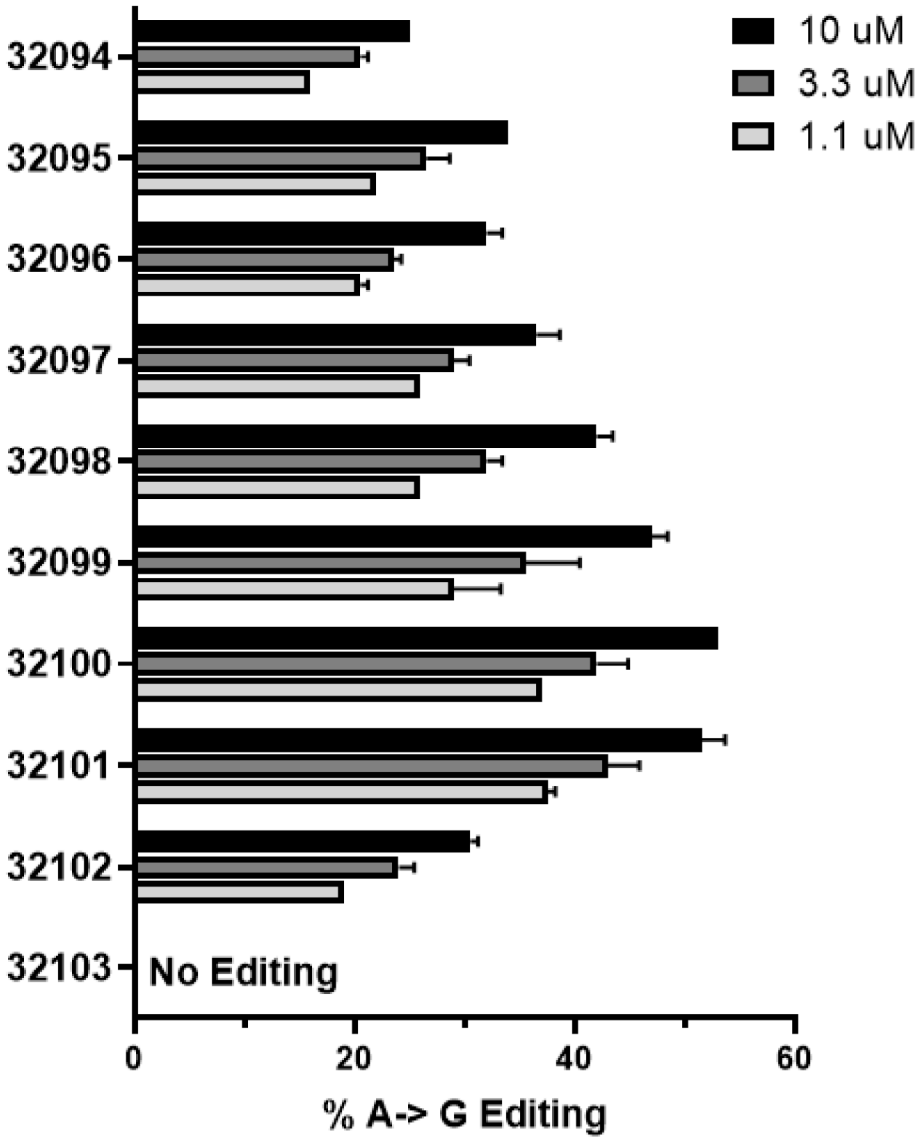

10 uM
3.3 uM
1.1 uM
32094
32095
32096
32097
32098
32099
32100
32101
32102
32103
No Editing
0
20
40
60
% A-> G Editing

FIG. 26

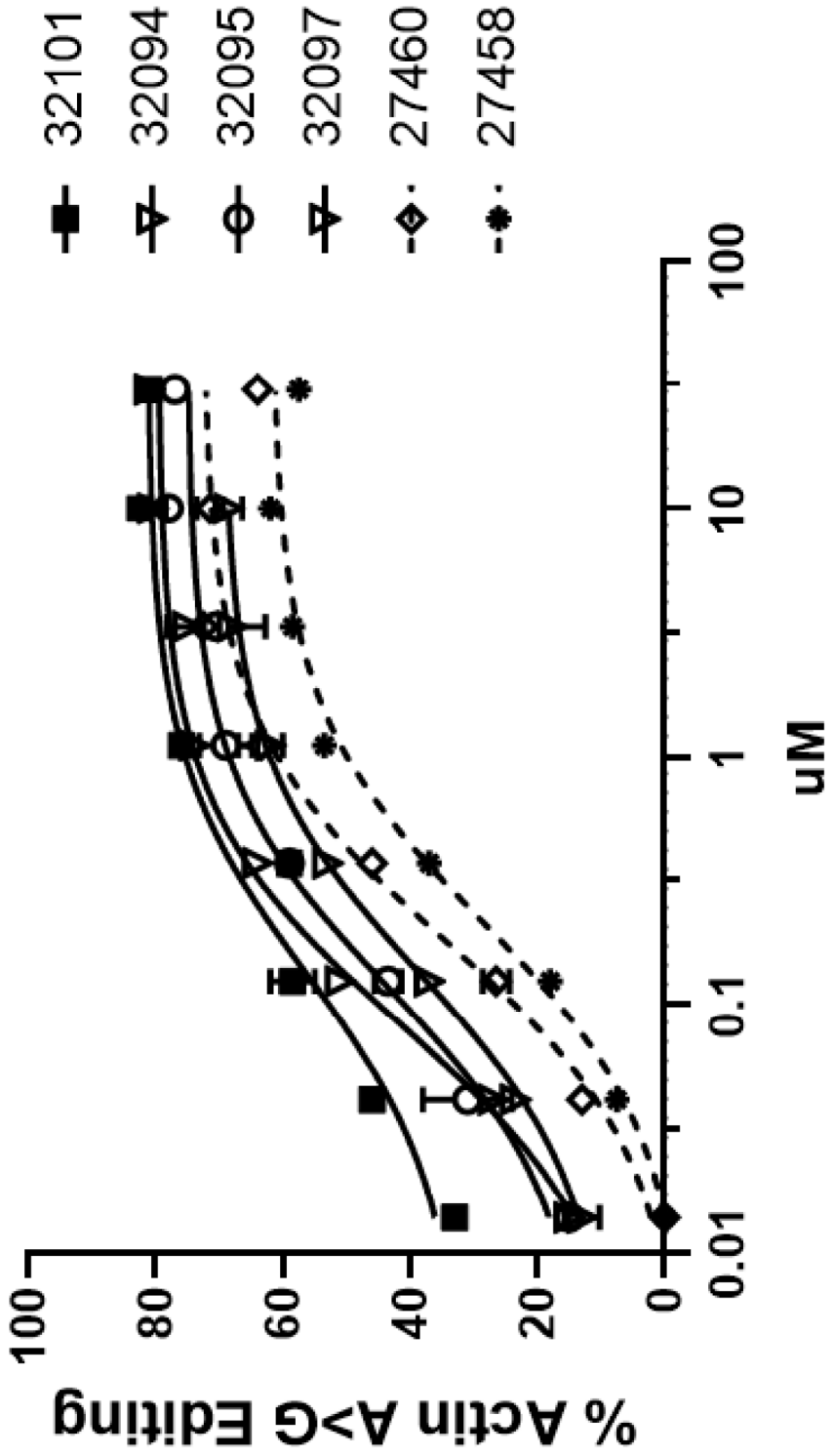

% Actin A>G Editing
100
80
60
40
20
0
0.01
0.1
1
10
100
uM
32101
32094
32095
32097
27460
27458

FIG. 27

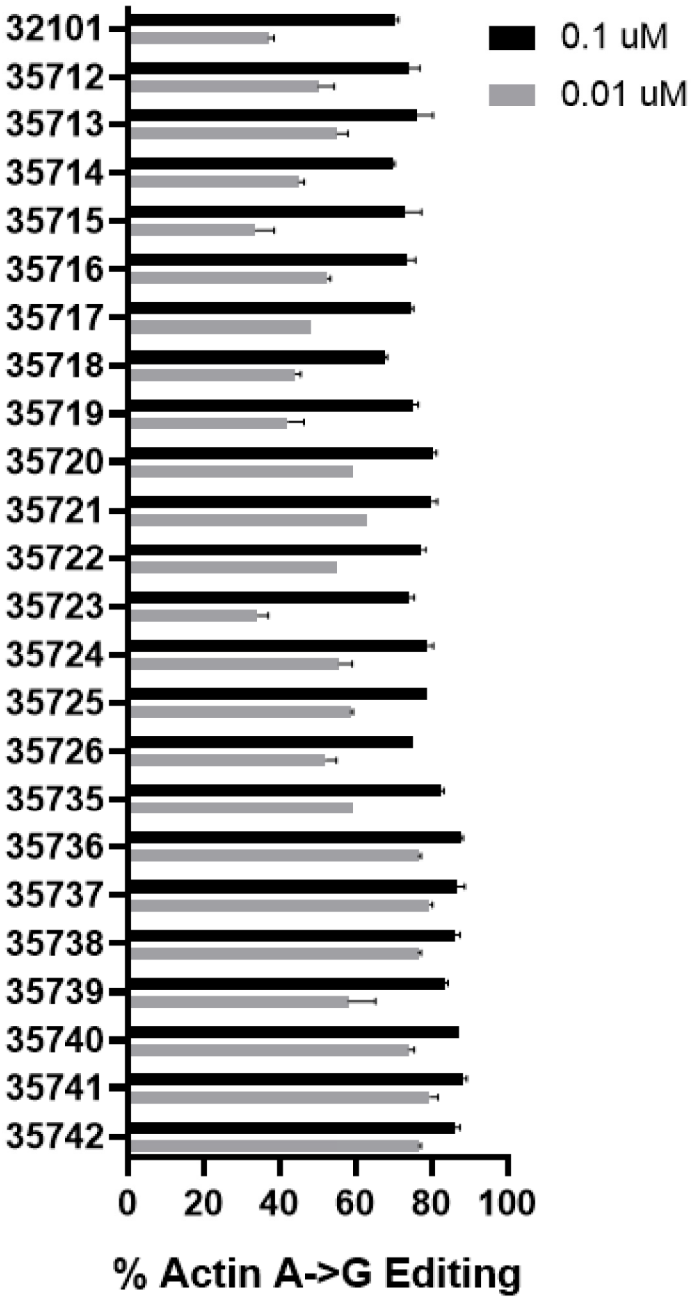

32101
35712
35713
35714
35715
35716
35717
35718
35719
35720
35721
35722
35723
35724
35725
35726
35735
35736
35737
35738
35739
35740
35741
35742
0.1 uM
0.01 uM
0
20
40
60
80
100
% Actin A->G Editing

FIG. 28

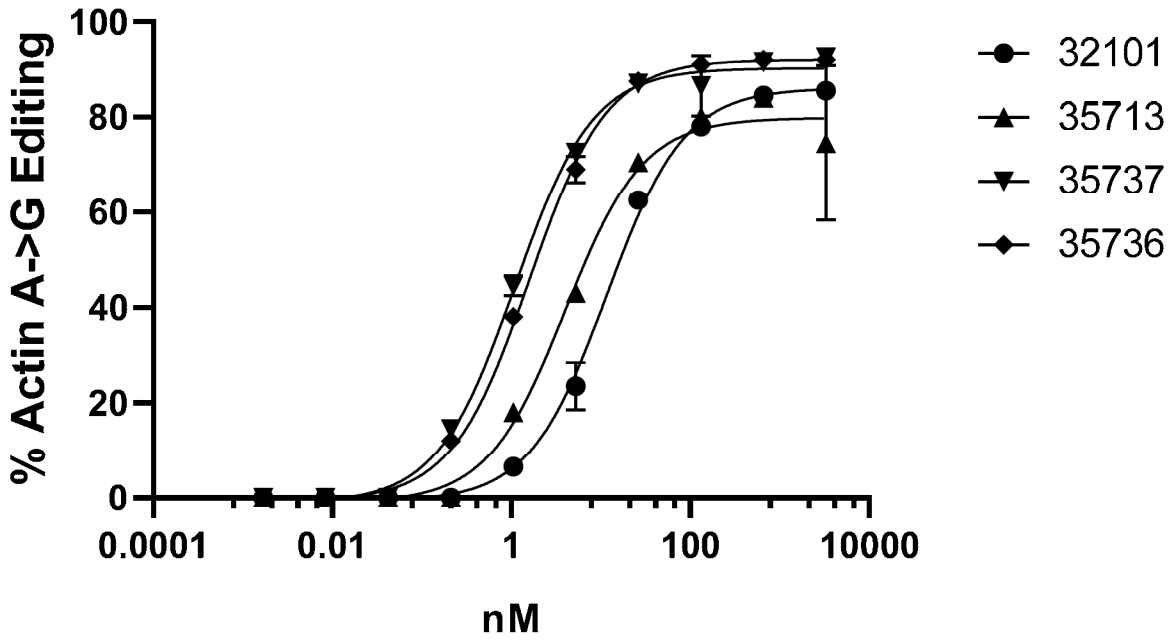
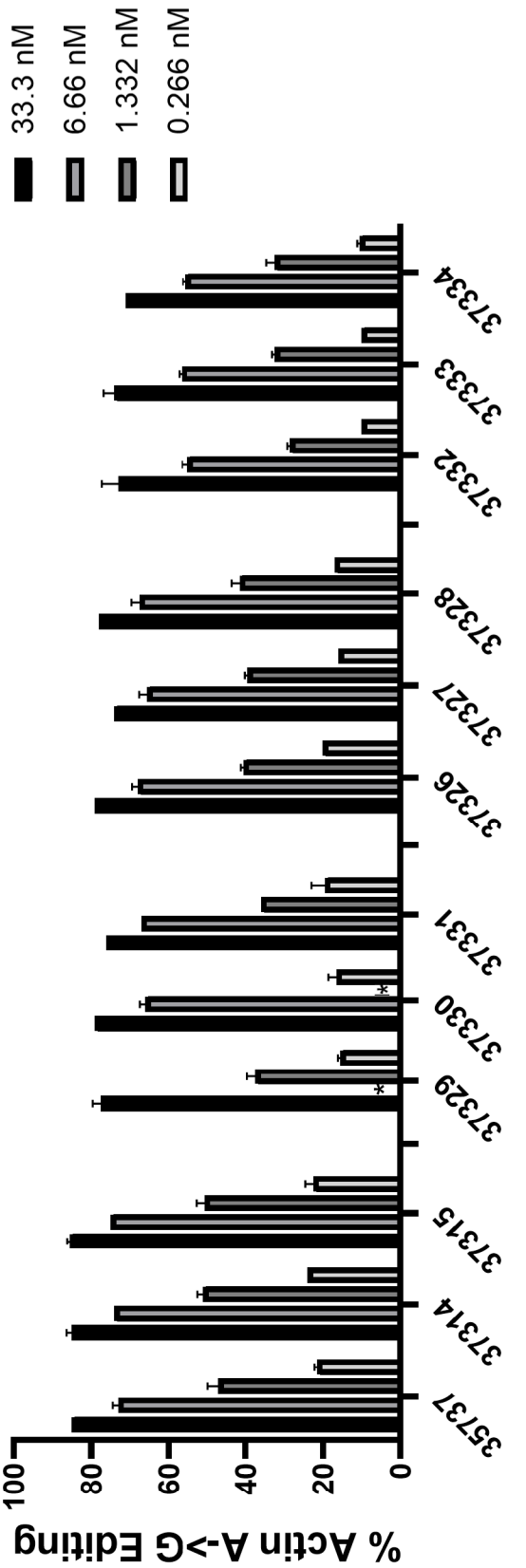
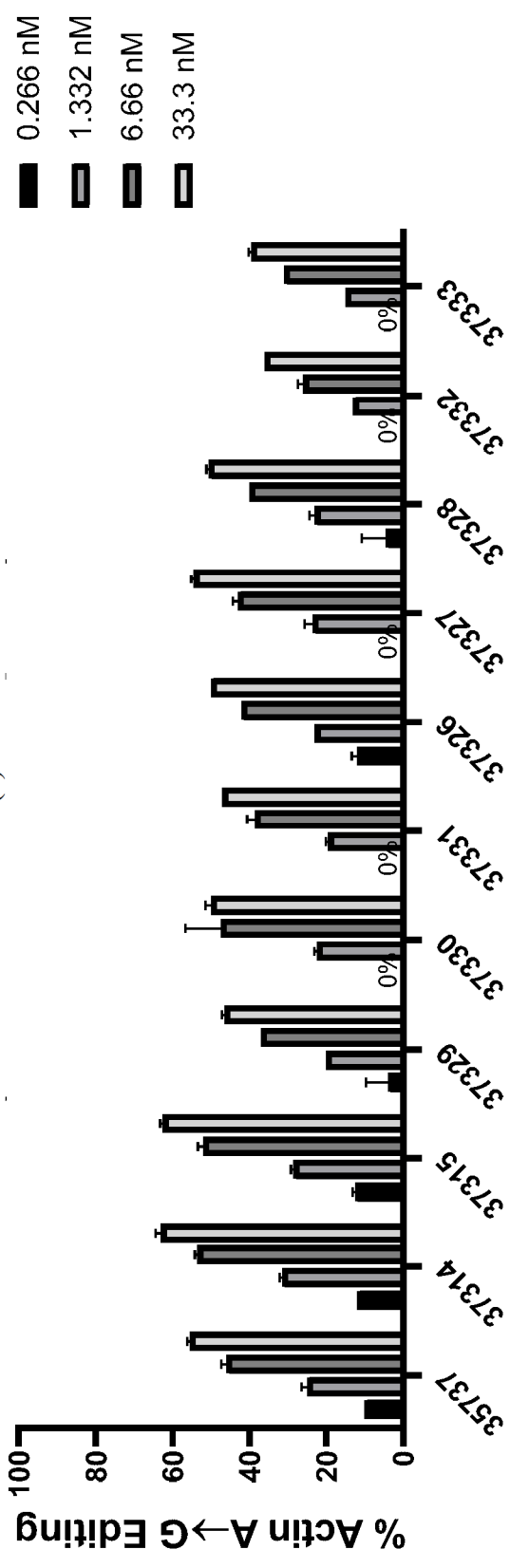

% Actin A->G Editing
100
80
60
40
20
0
0.0001
0.01
1
100
10000
nM
32101
35713
35737
35736

FIG. 29


33.3 nM
6.66 nM
1.332 nM
0.266 nM
% Actin A->G Editing
100
80
60
40
20
0
35737
37314
37315
37329
37330
37331
37326
37321
37328
37332
37333
37334
*
*

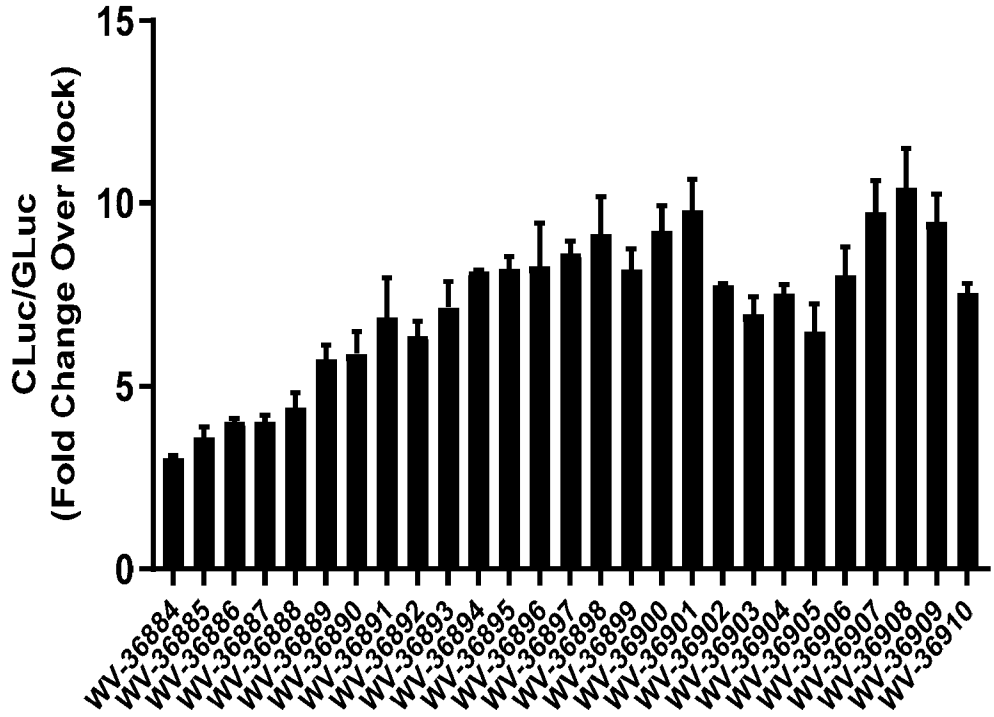
(a)


0.266 nM
1.332 nM
6.66 nM
33.3 nM
% Actin A→G Editing
100
80
60
40
20
0
35737
37314
37315
37329
37330
37331
37326
37321
37328
37332
37333
0%
0%
0%
0%
0%
0%

(b)

FIG. 30

ADAR1-p110



ADAR1-p150

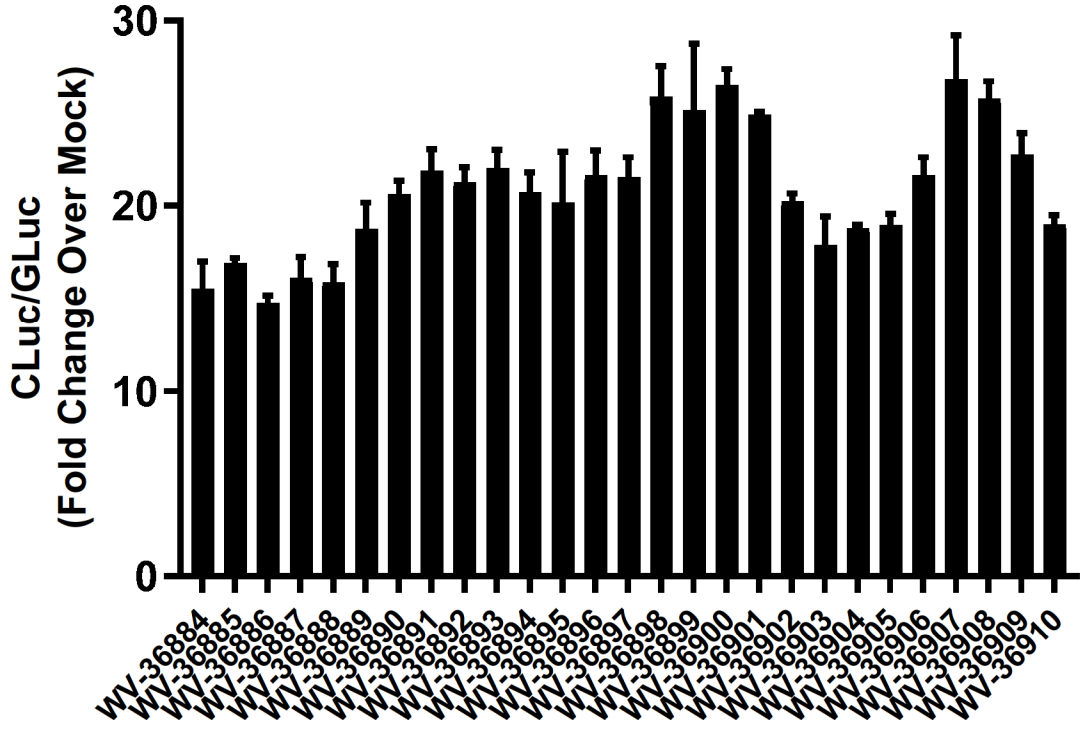
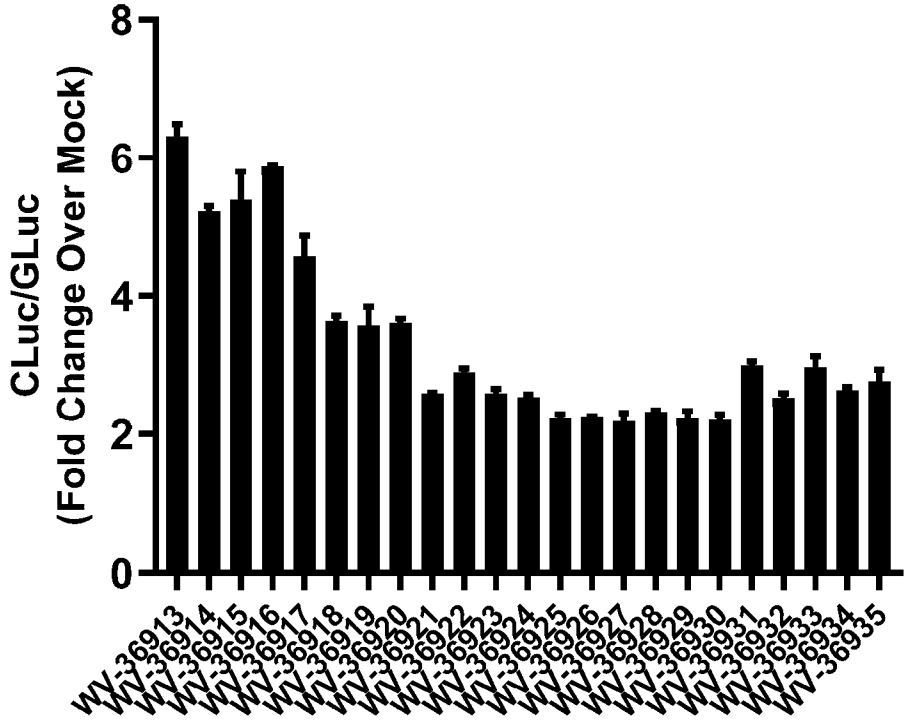


FIG. 31

ADAR1-p110



ADAR1-p150

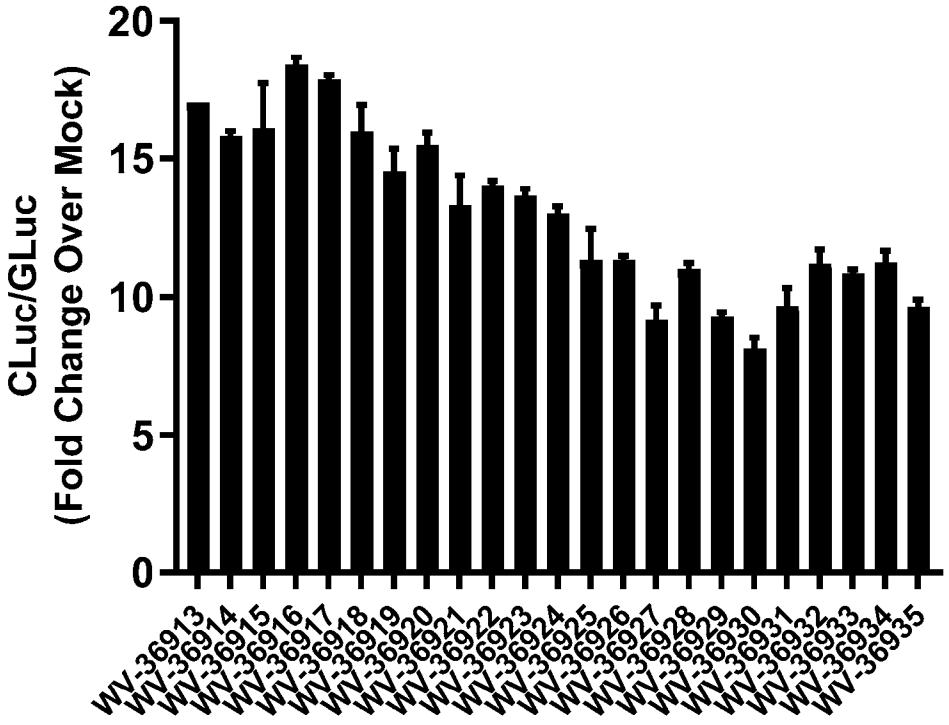
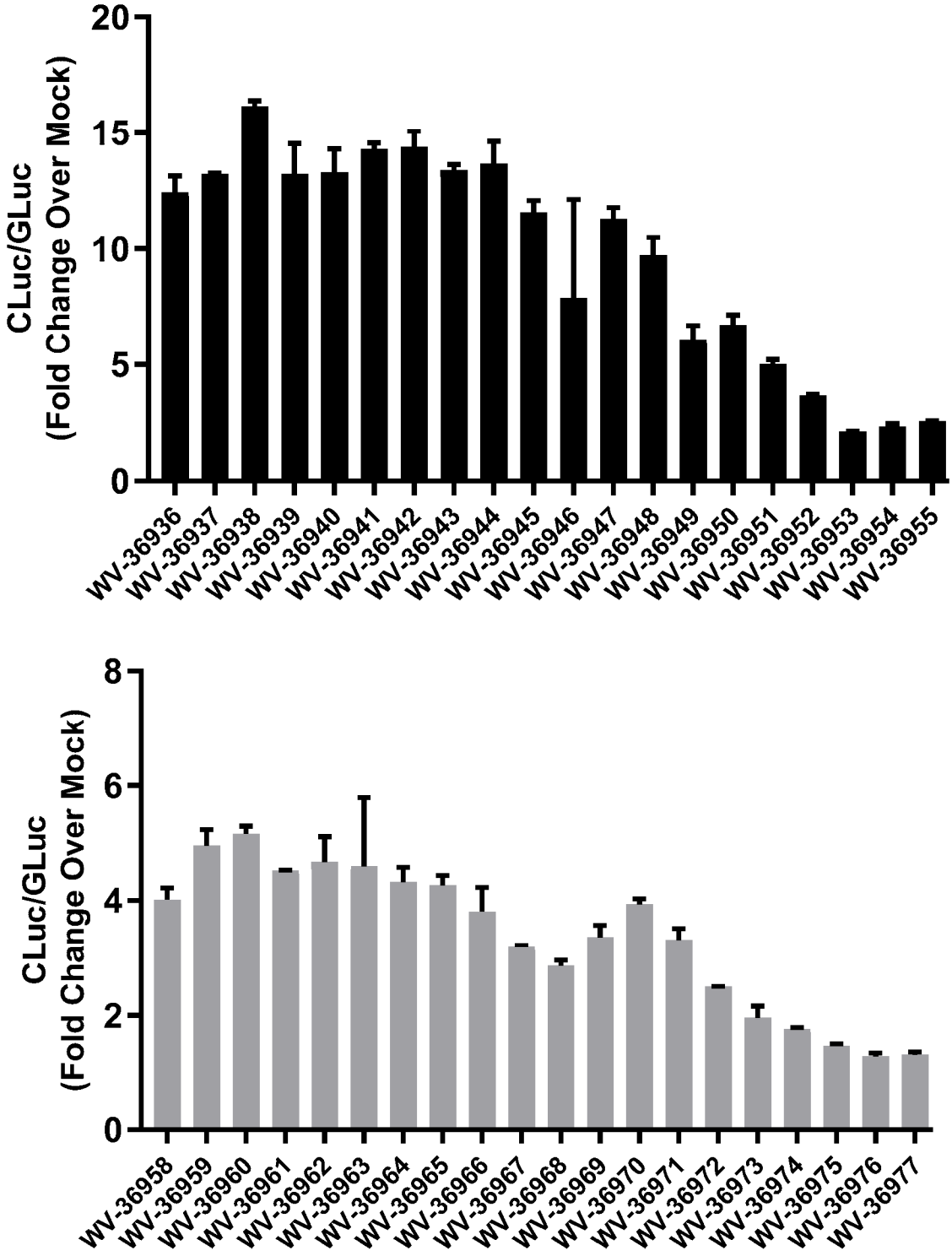


FIG. 32

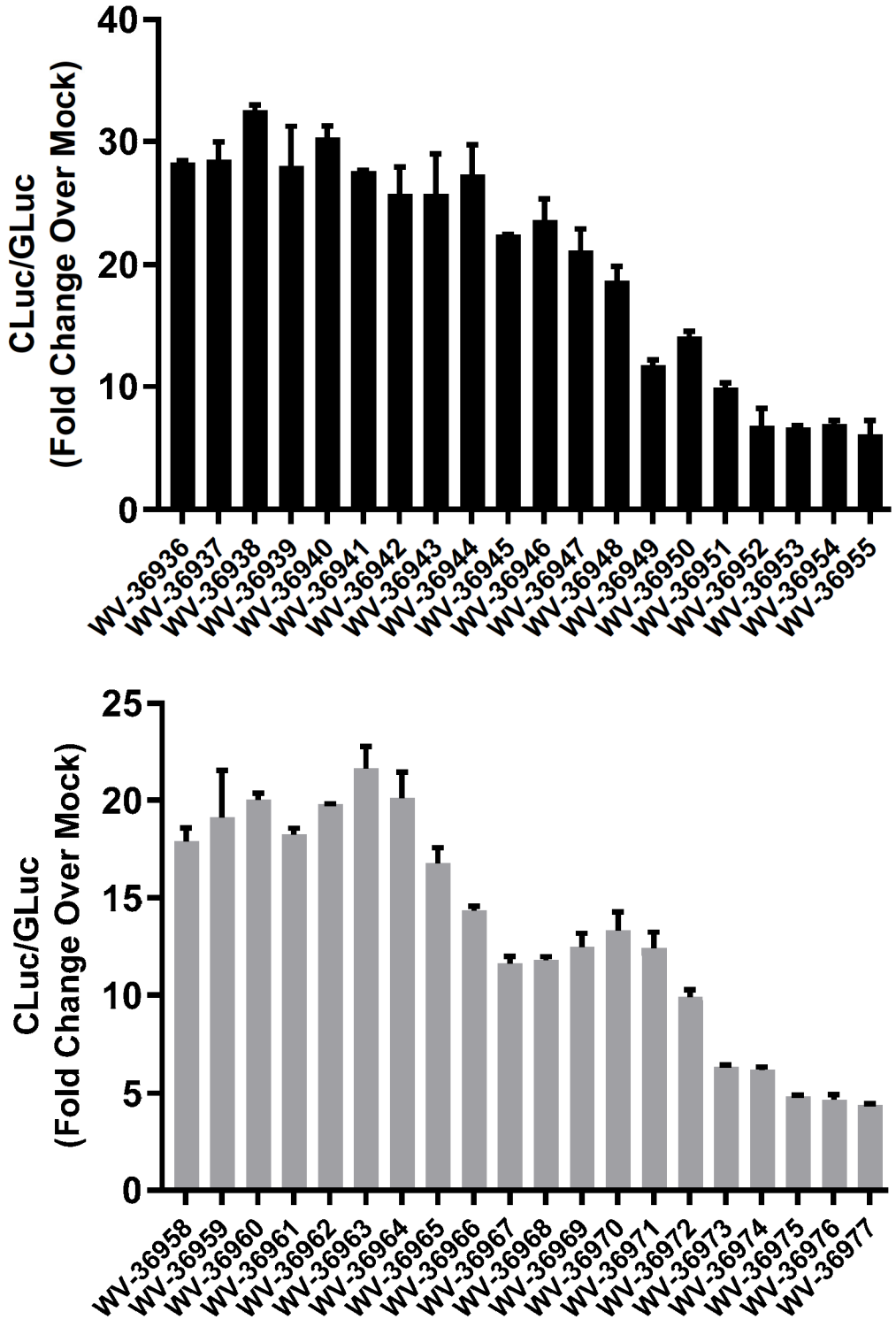
ADAR1-p110



(a)

FIG. 33

ADAR1-p150



(b)

FIG. 33

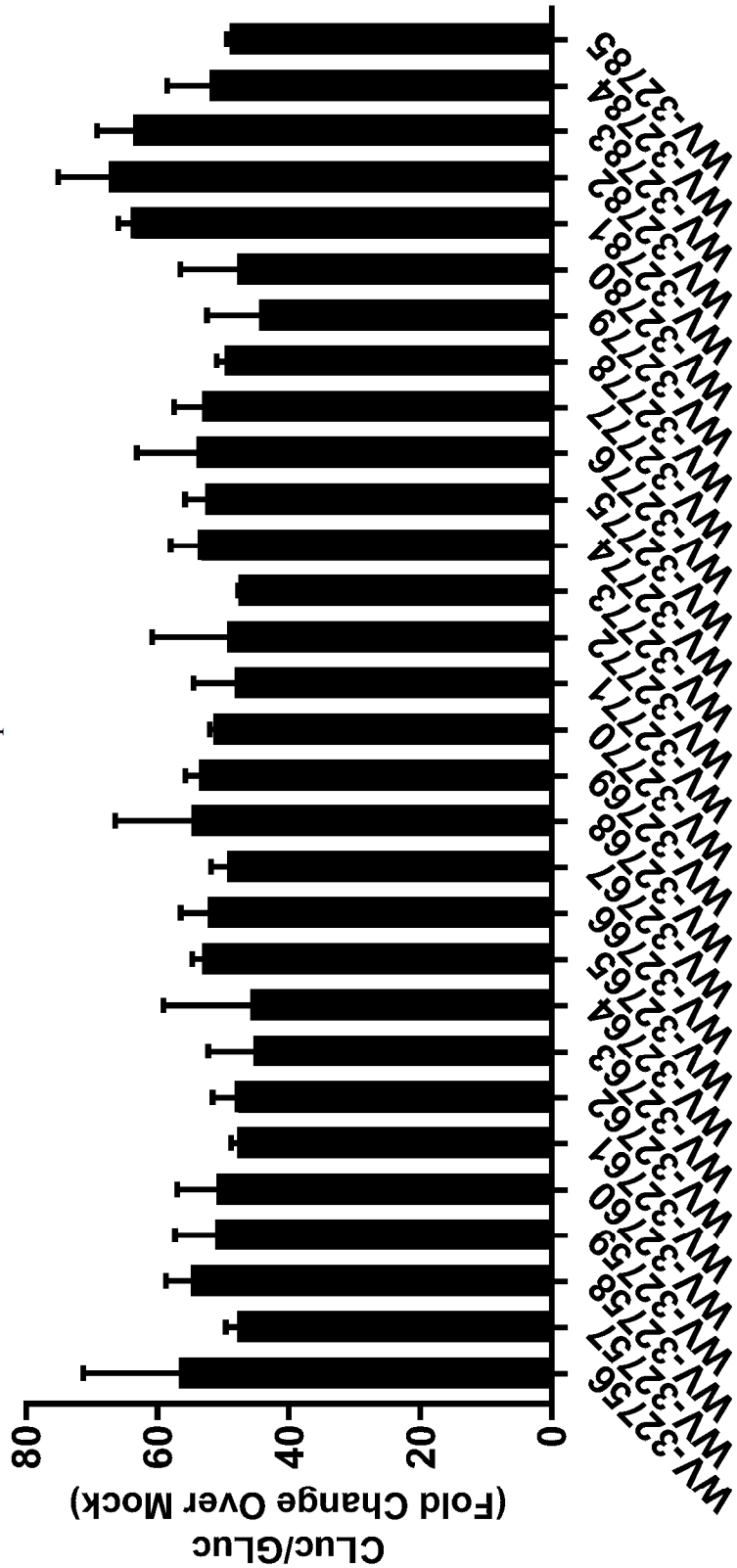

ADAR1-p150
CLuc/GLuc
(Fold Change Over Mock)
0
20
40
60
80
WV-321756
WV-321757
WV-321758
WV-321759
WV-321760
WV-321761
WV-321762
WV-321763
WV-321764
WV-321765
WV-321766
WV-321767
WV-321768
WV-321769
WV-321770
WV-321771
WV-321772
WV-321773
WV-321774
WV-321775
WV-321776
WV-321777
WV-321778
WV-321779
WV-321780
WV-321781
WV-321782
WV-321783
WV-321784
WV-321785

FIG. 34

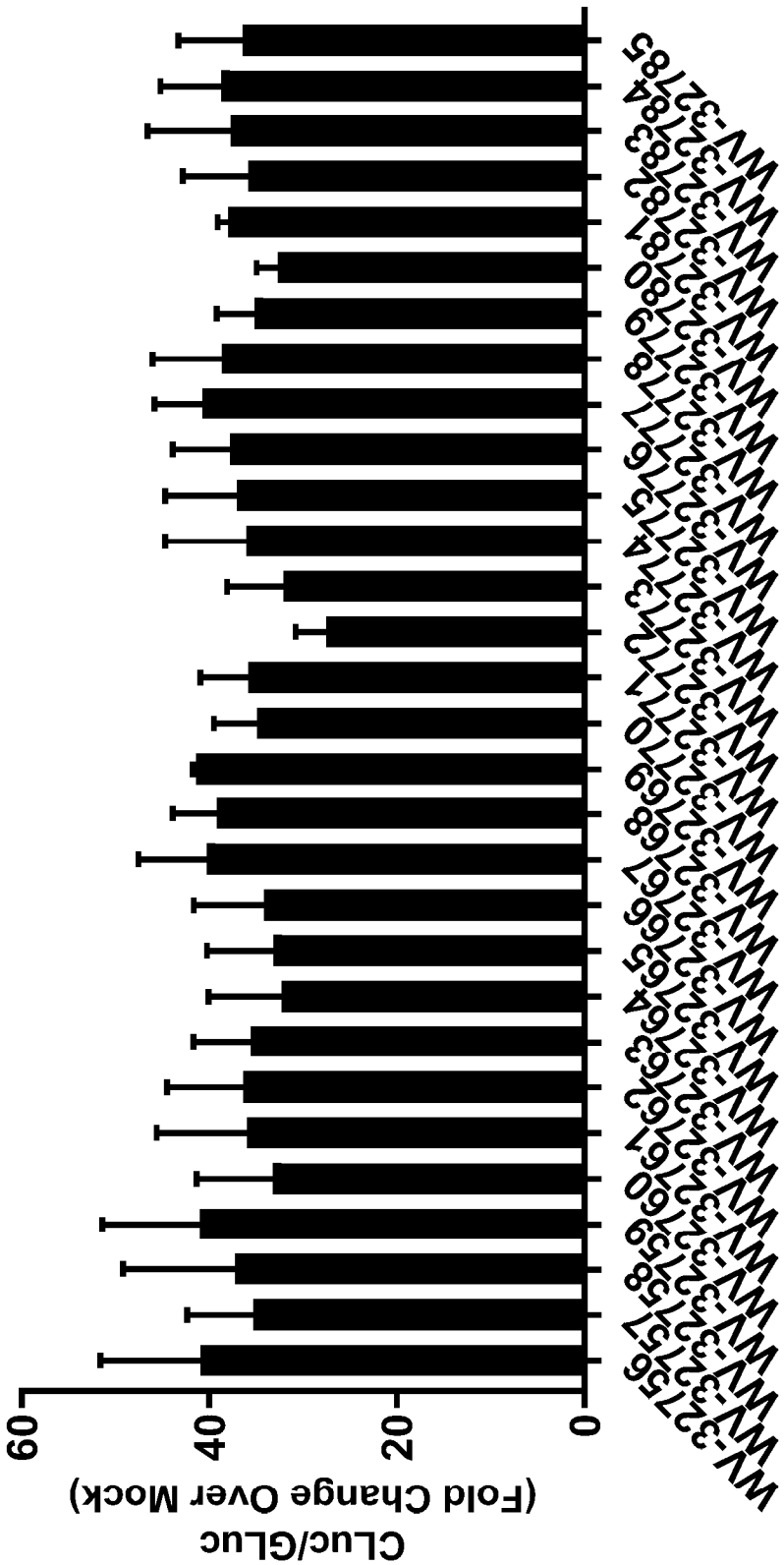


FIG. 34 (CONTINUED)

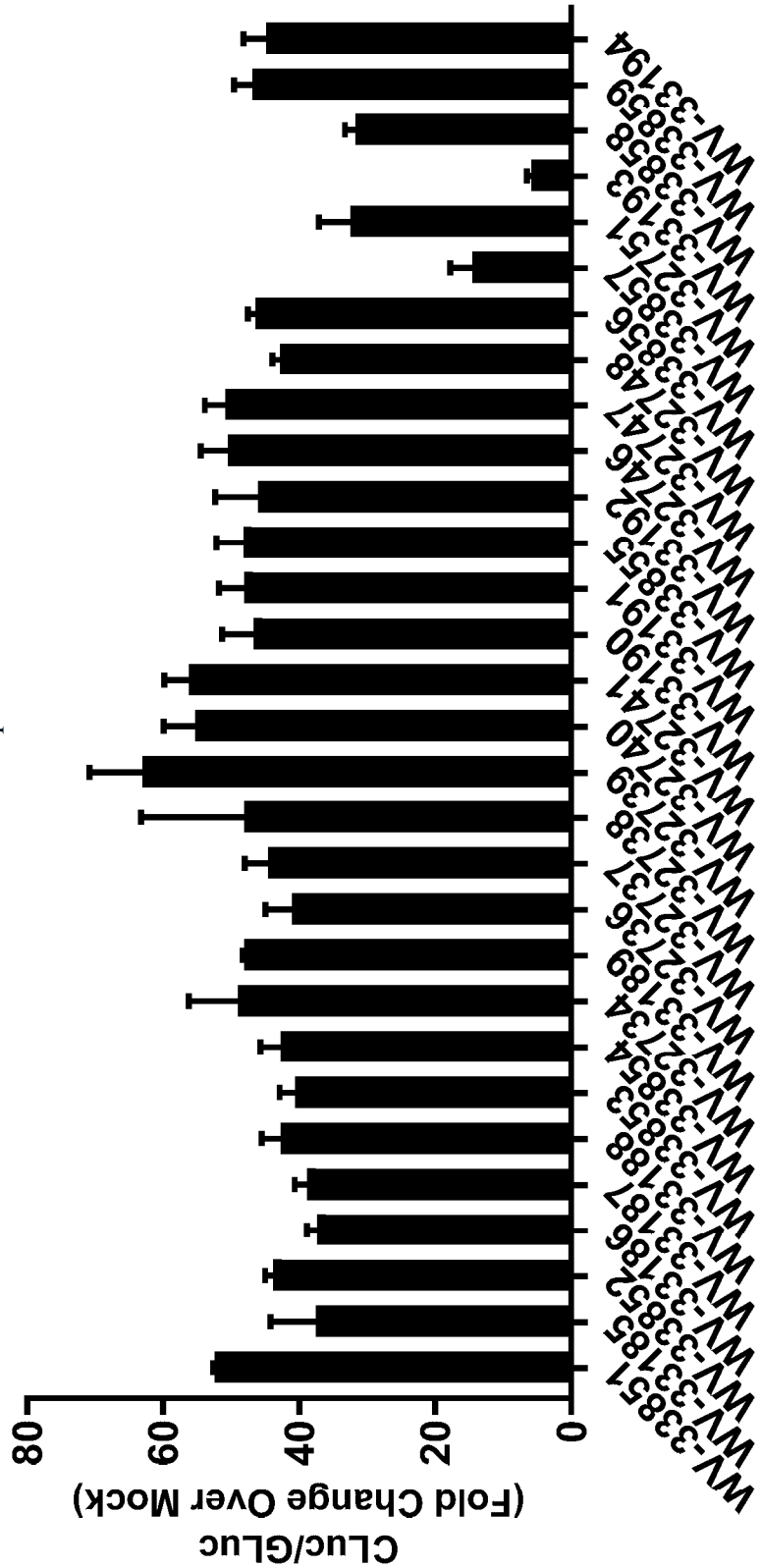


FIG. 35

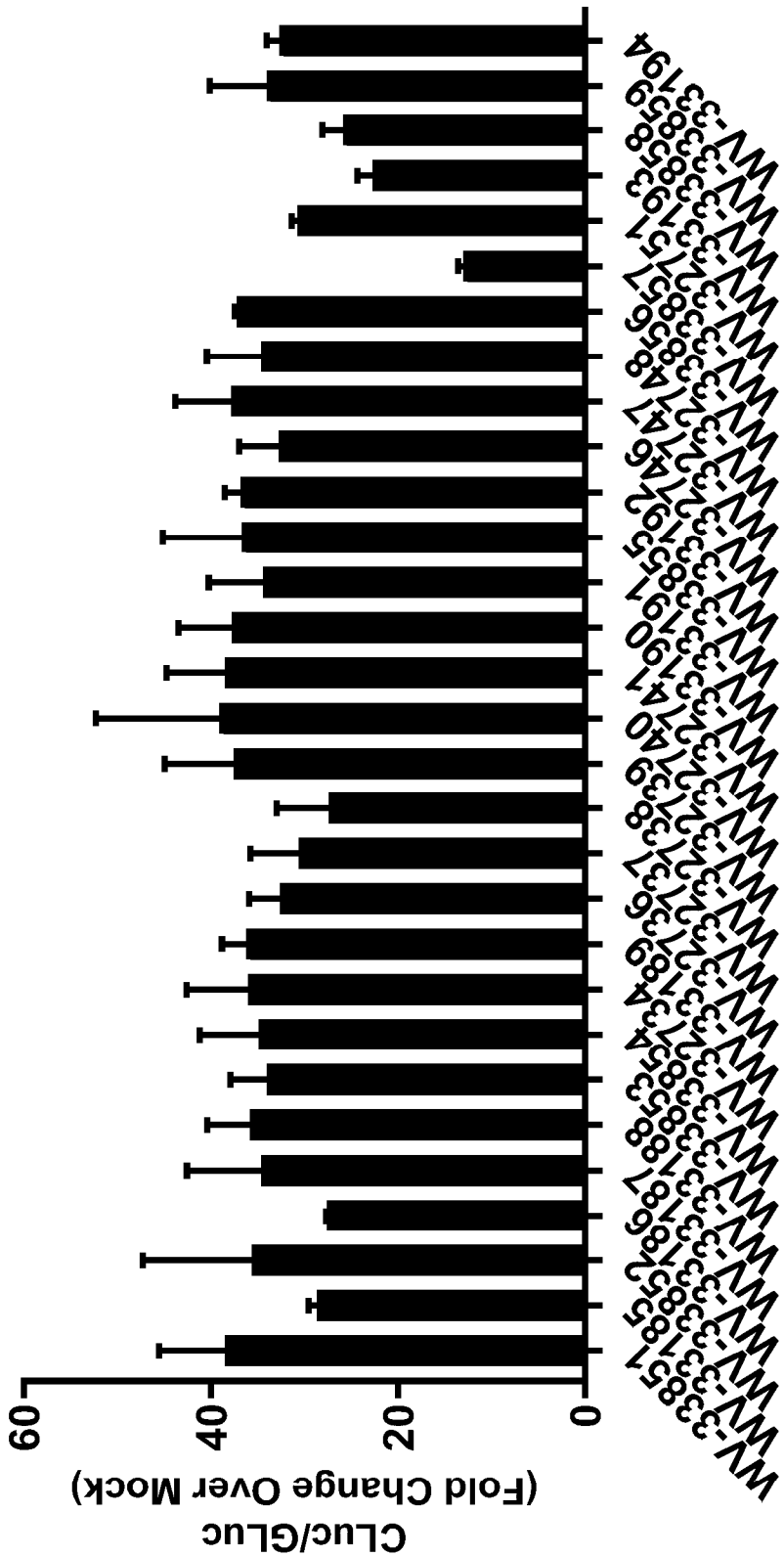
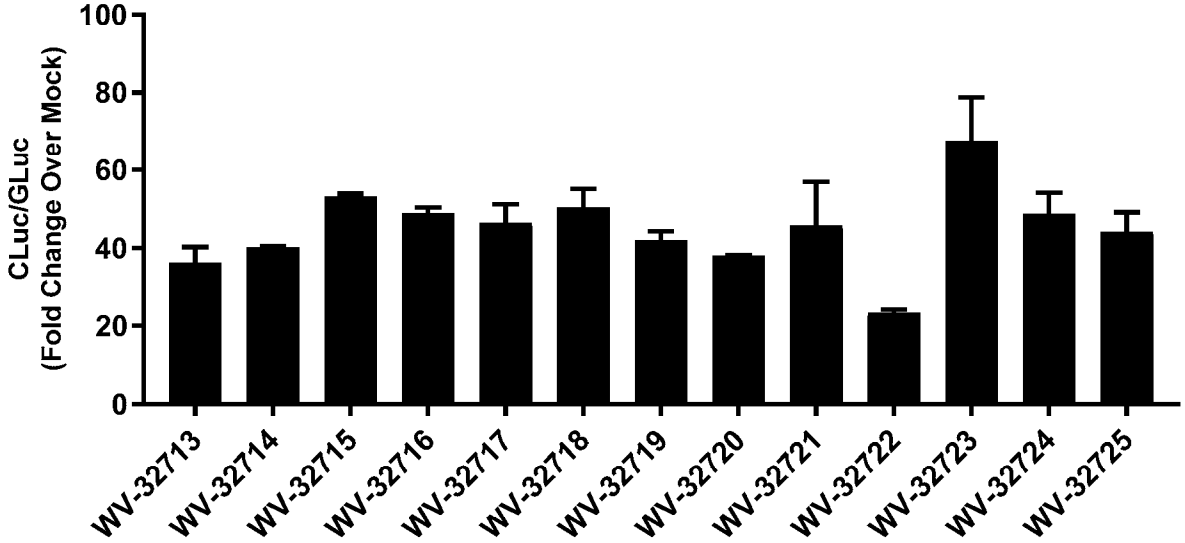
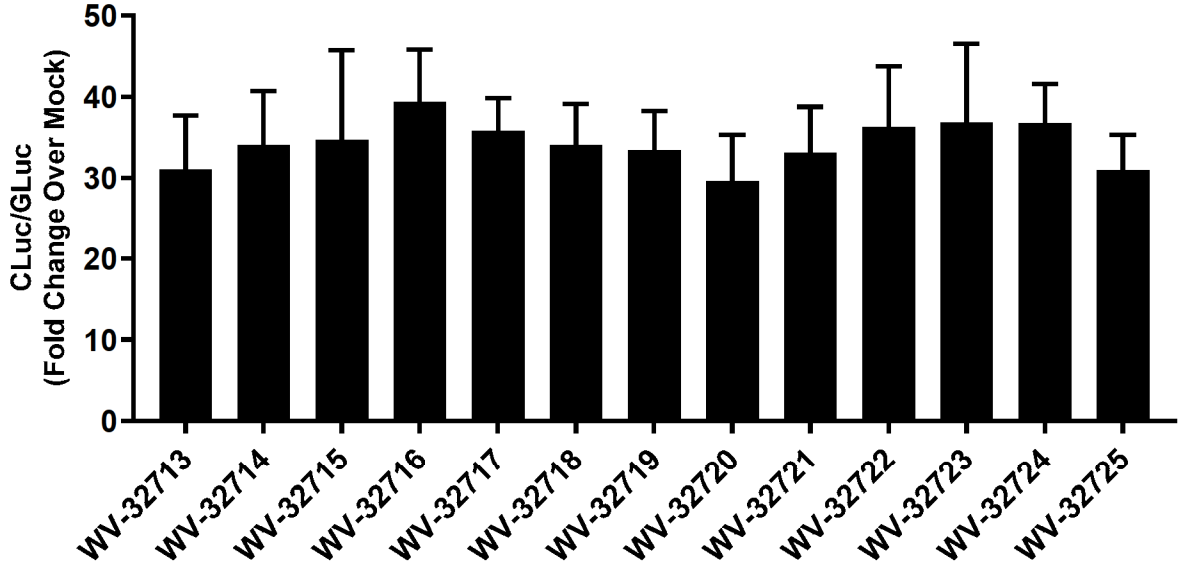


FIG. 35 (CONTINUED)

ADAR1-p150

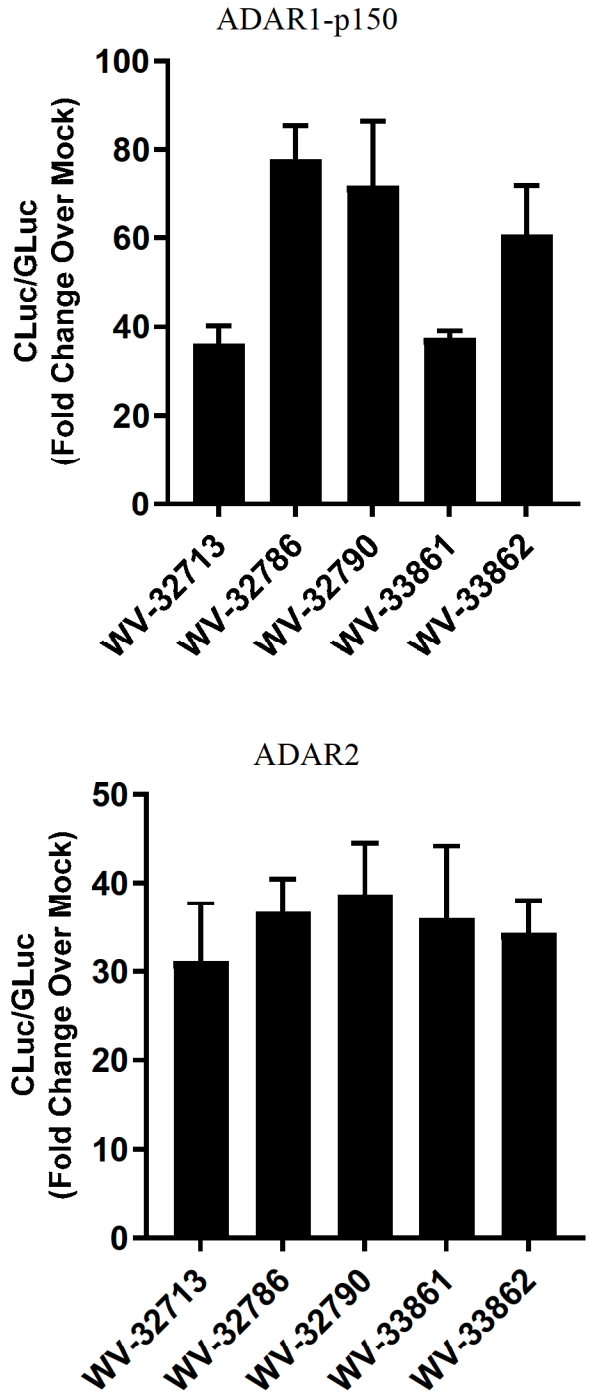


ADAR2



(a)

FIG. 36


ADAR1-p150
CLuc/GLuc
(Fold Change Over Mock)
100
80
60
40
20
0
WV-32713
WV-32786
WV-32790
WV-33861
WV-33862
ADAR2
CLuc/GLuc
(Fold Change Over Mock)
50
40
30
20
10
0
WV-32713
WV-32786
WV-32790
WV-33861
WV-33862

(b)

FIG. 36

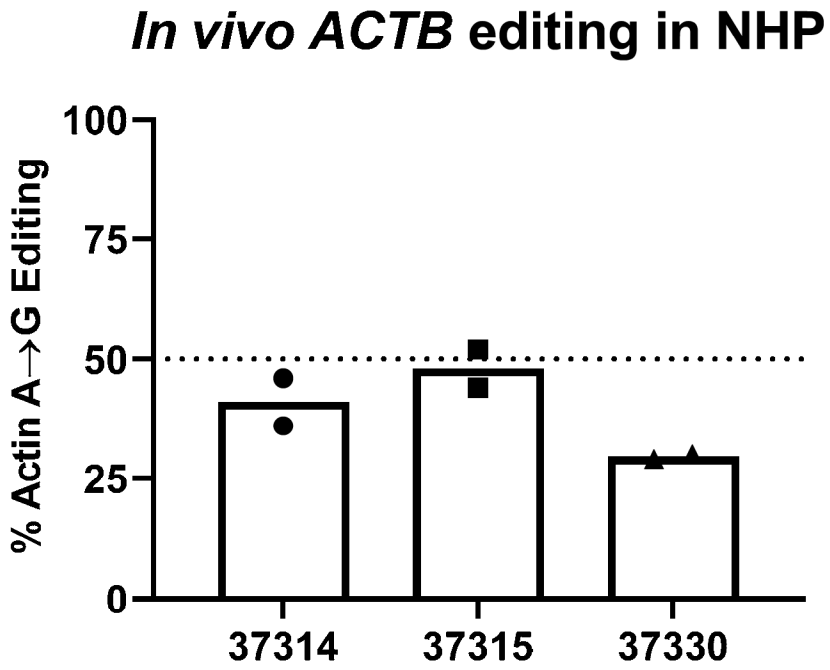
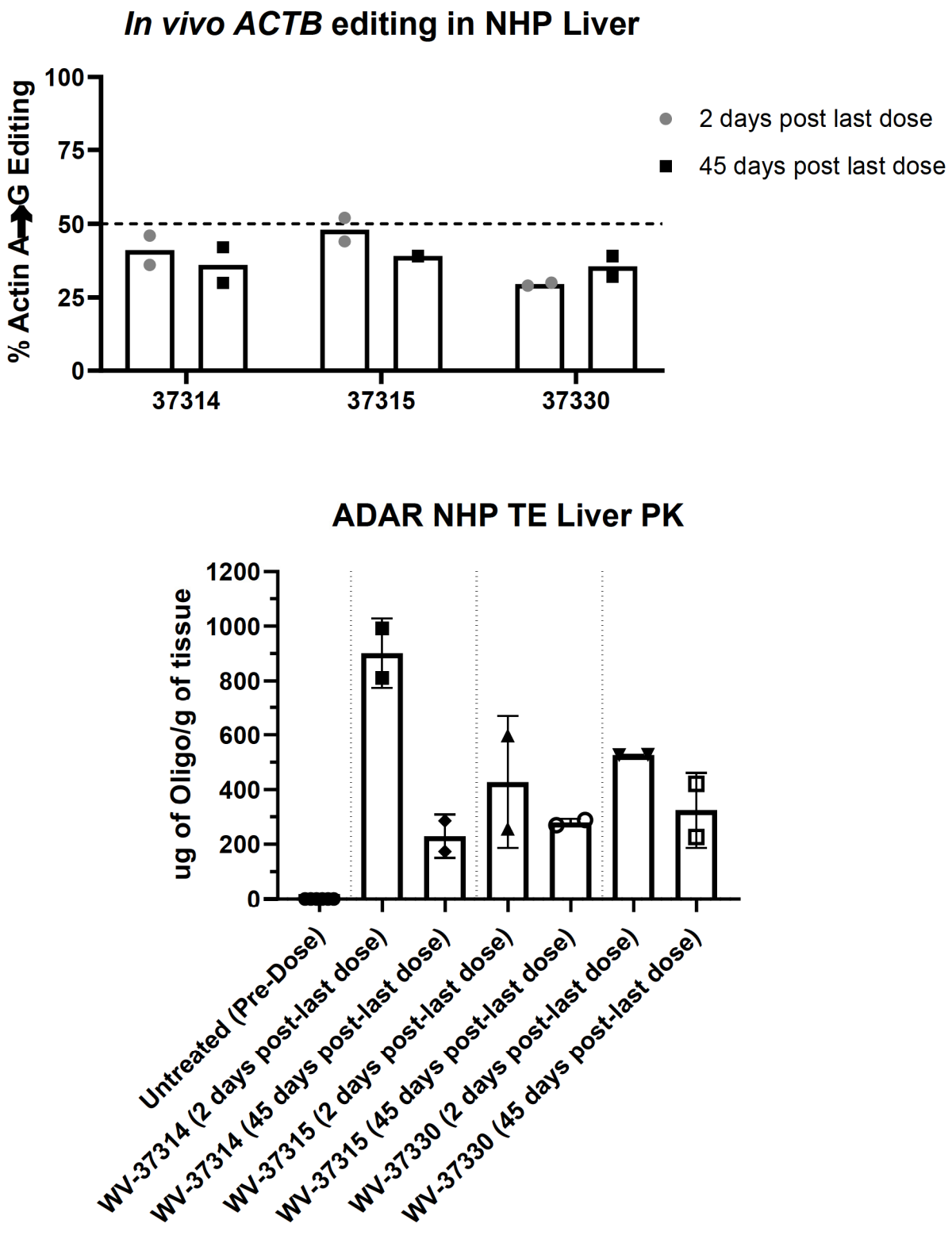
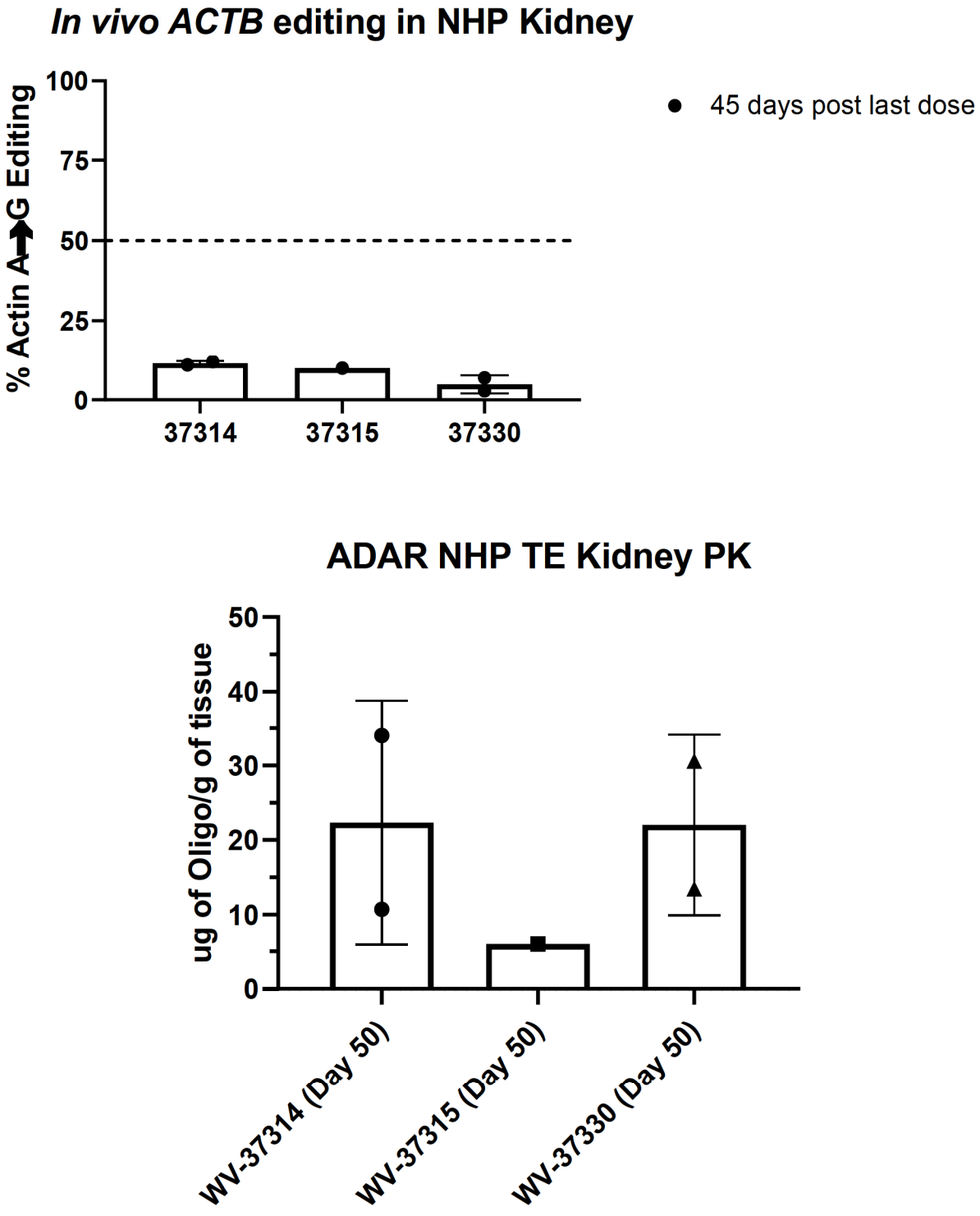

In vivo ACTB editing in NHP
% Actin A→G Editing
100
75
50
25
0
37314
37315
37330

FIG. 37


In vivo ACTB editing in NHP Liver
% Actin A→G Editing
100
75
50
25
0
37314
37315
37330
2 days post last dose
45 days post last dose
ADAR NHP TE Liver PK
ug of Oligo/g of tissue
1200
1000
800
600
400
200
0
Untreated (Pre-Dose)
WV-37314 (2 days post-last dose)
WV-37314 (45 days post-last dose)
WV-37315 (2 days post-last dose)
WV-37315 (45 days post-last dose)
WV-37330 (2 days post-last dose)
WV-37330 (45 days post-last dose)

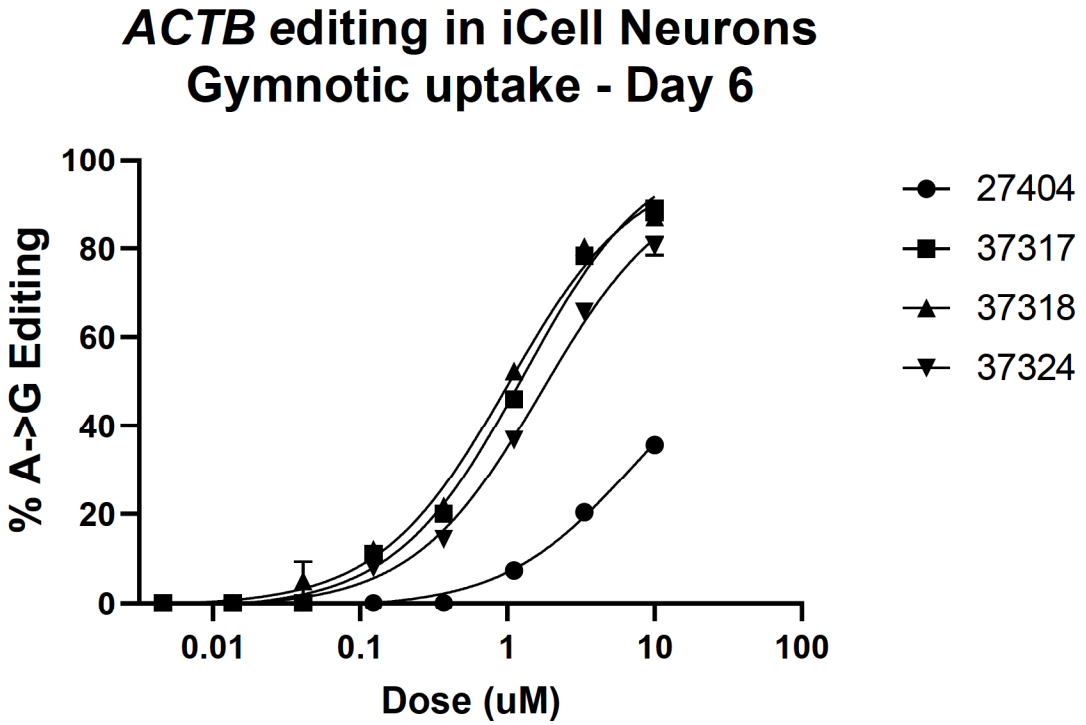
(a)

FIG. 38

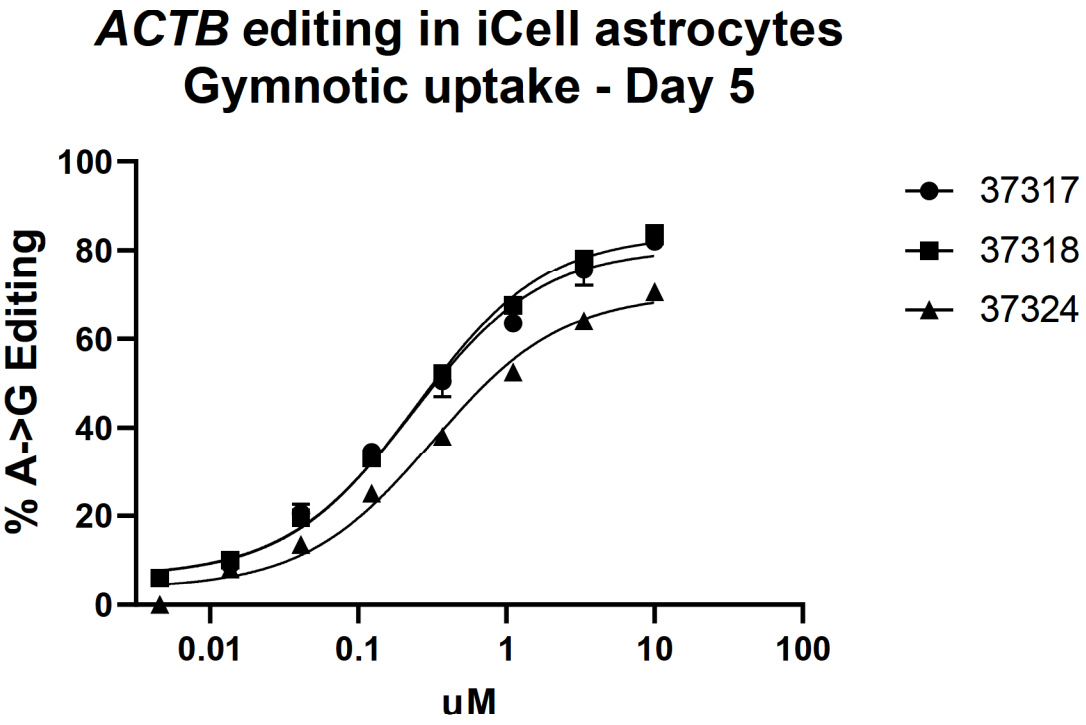


(b)

FIG. 38 (CONTINUED)

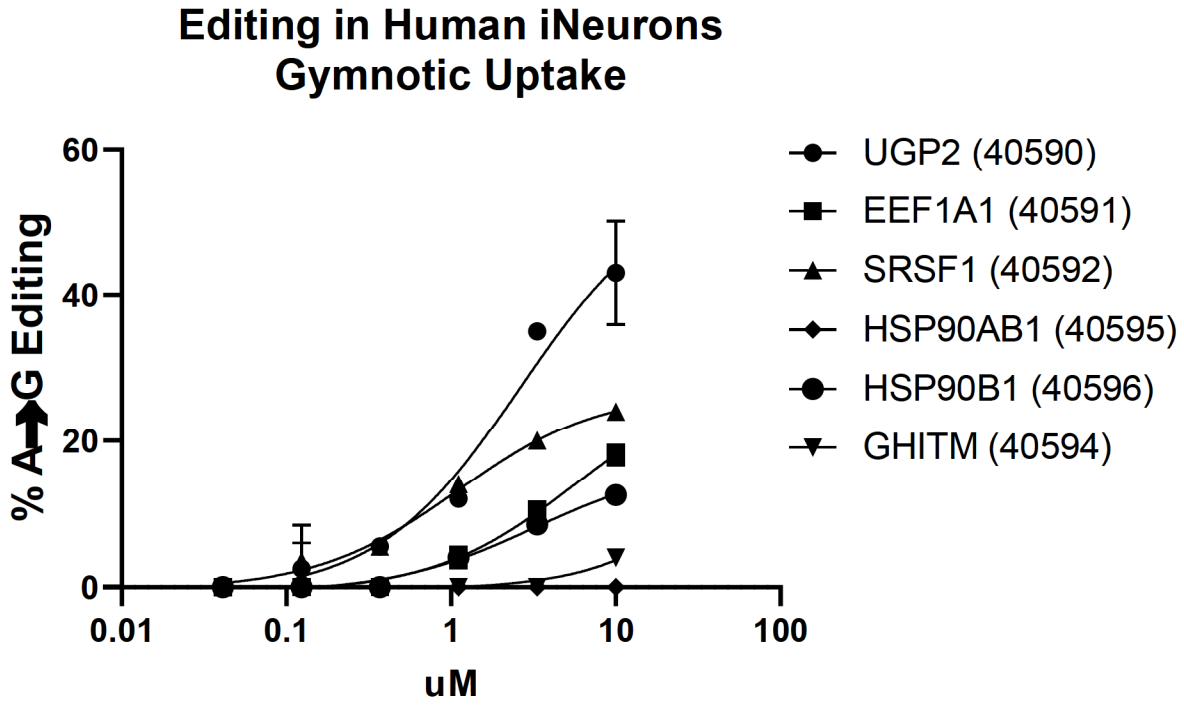

ACTB editing in iCell Neurons
Gymnotic uptake - Day 6
% A->G Editing
100
80
60
40
20
0
0.01
0.1
1
10
100
Dose (uM)
27404
37317
37318
37324

(a)

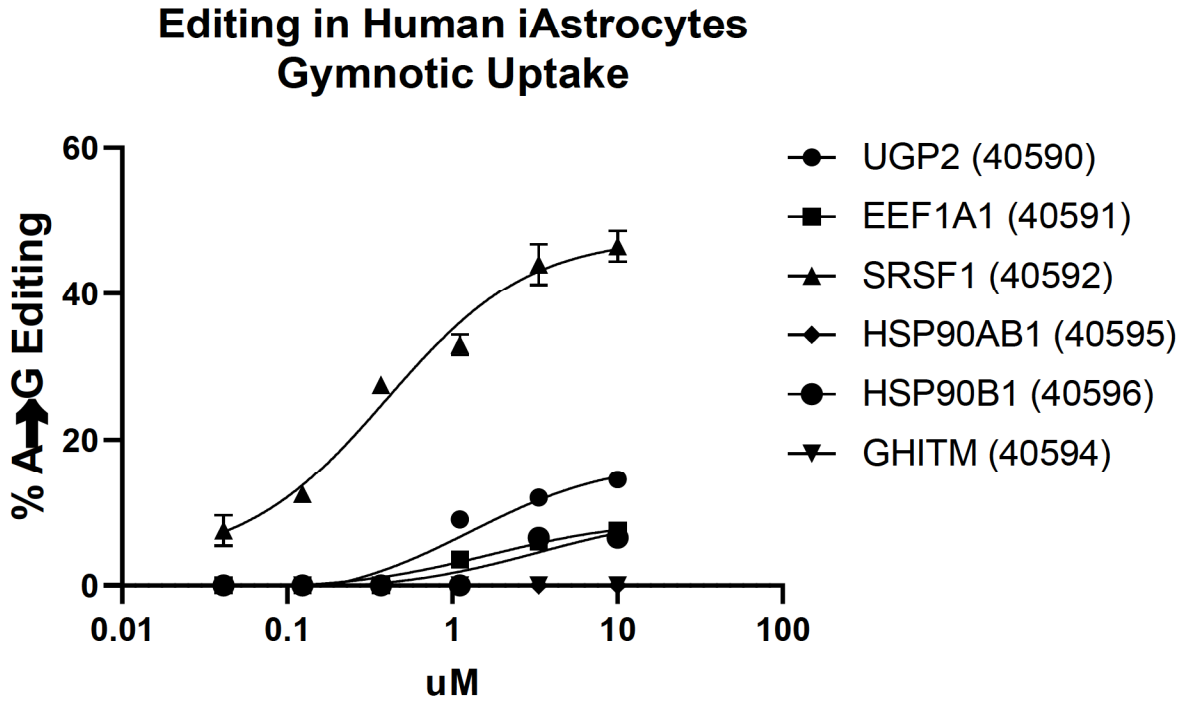

ACTB editing in iCell astrocytes
Gymnotic uptake - Day 5
% A->G Editing
100
80
60
40
20
0
0.01
0.1
1
10
100
uM
37317
37318
37324

(b)

FIG. 39

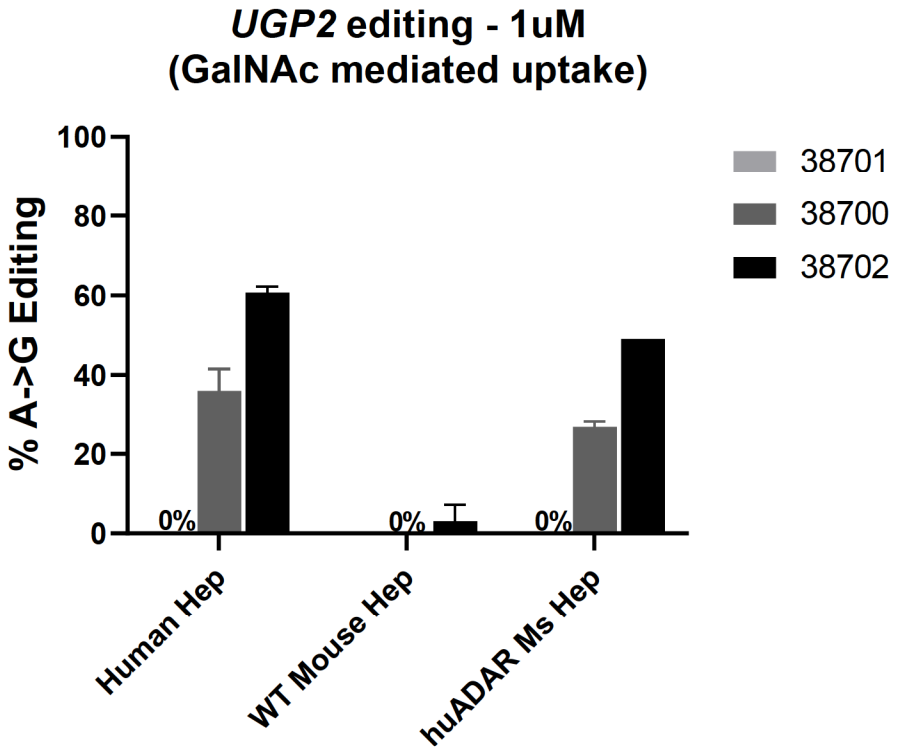


(c)

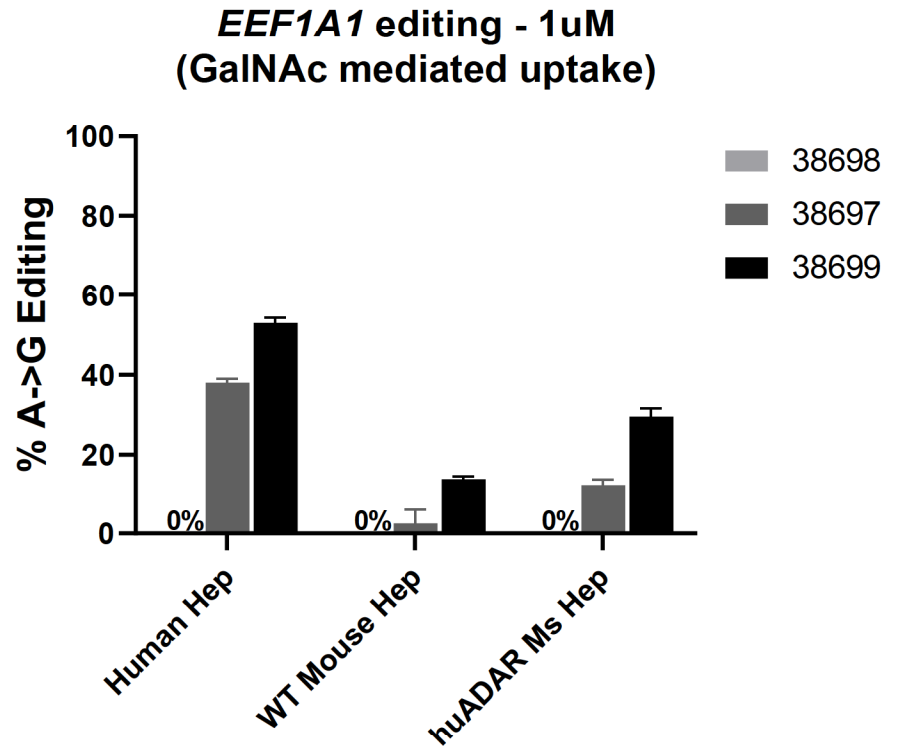


(d)

FIG. 39 (CONTINUED)

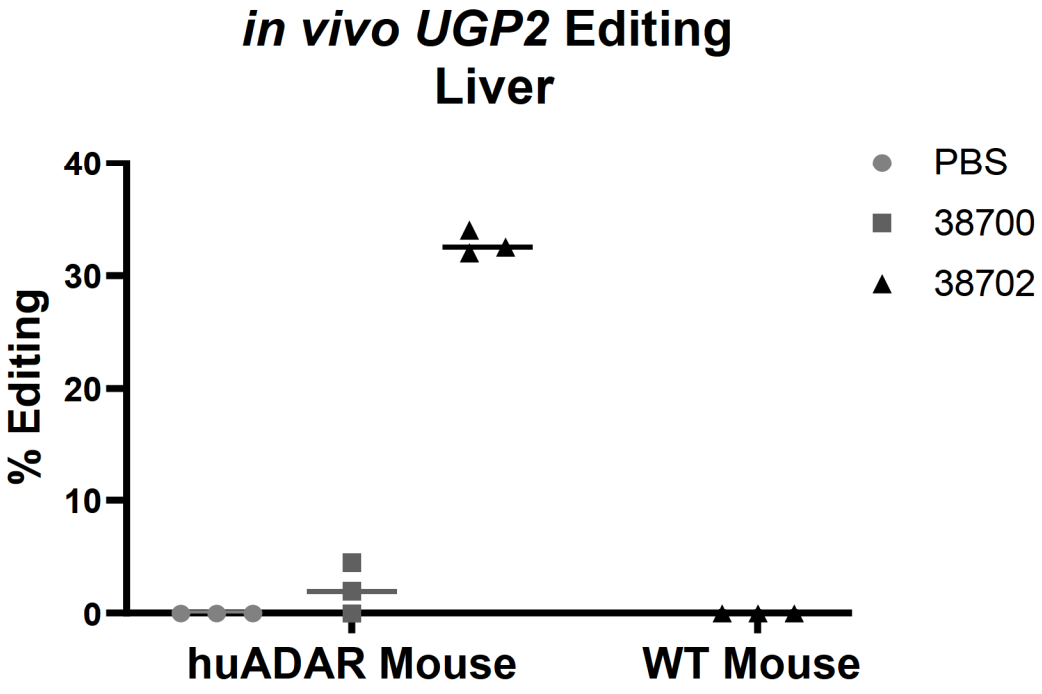

UGP2 editing - 1uM
(GalNAc mediated uptake)
% A->G Editing
100
80
60
40
20
0
0%
0%
0%
Human Hep
WT Mouse Hep
huADAR Ms Hep
38701
38700
38702

(a)

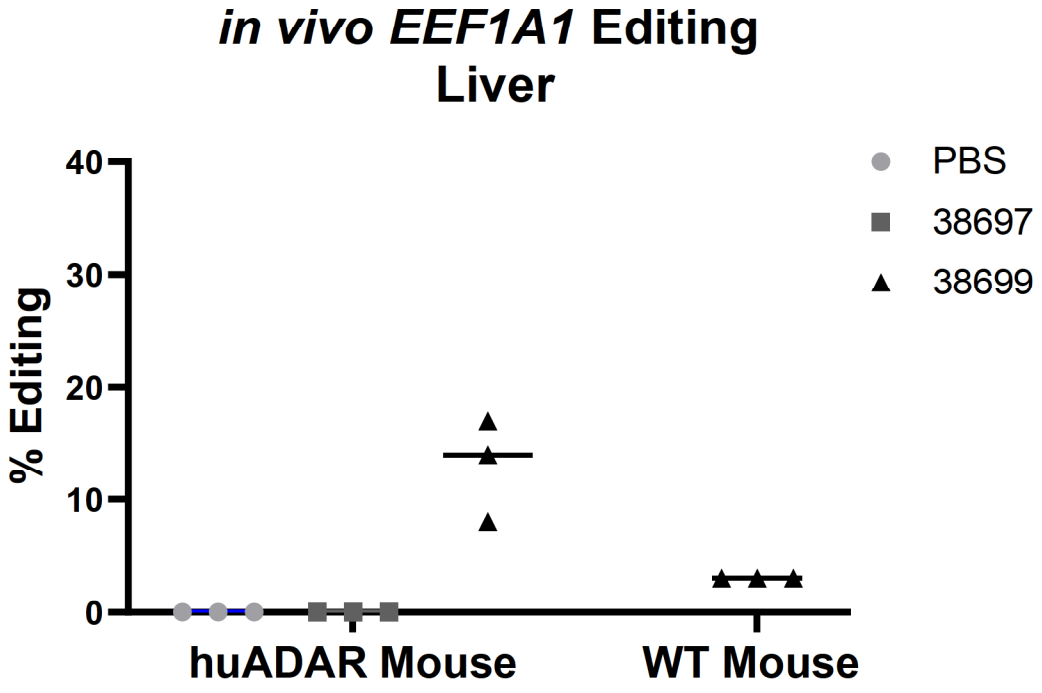

EEF1A1 editing - 1uM
(GalNAc mediated uptake)
% A->G Editing
100
80
60
40
20
0
0%
0%
0%
Human Hep
WT Mouse Hep
huADAR Ms Hep
38698
38697
38699

(b)

FIG. 40

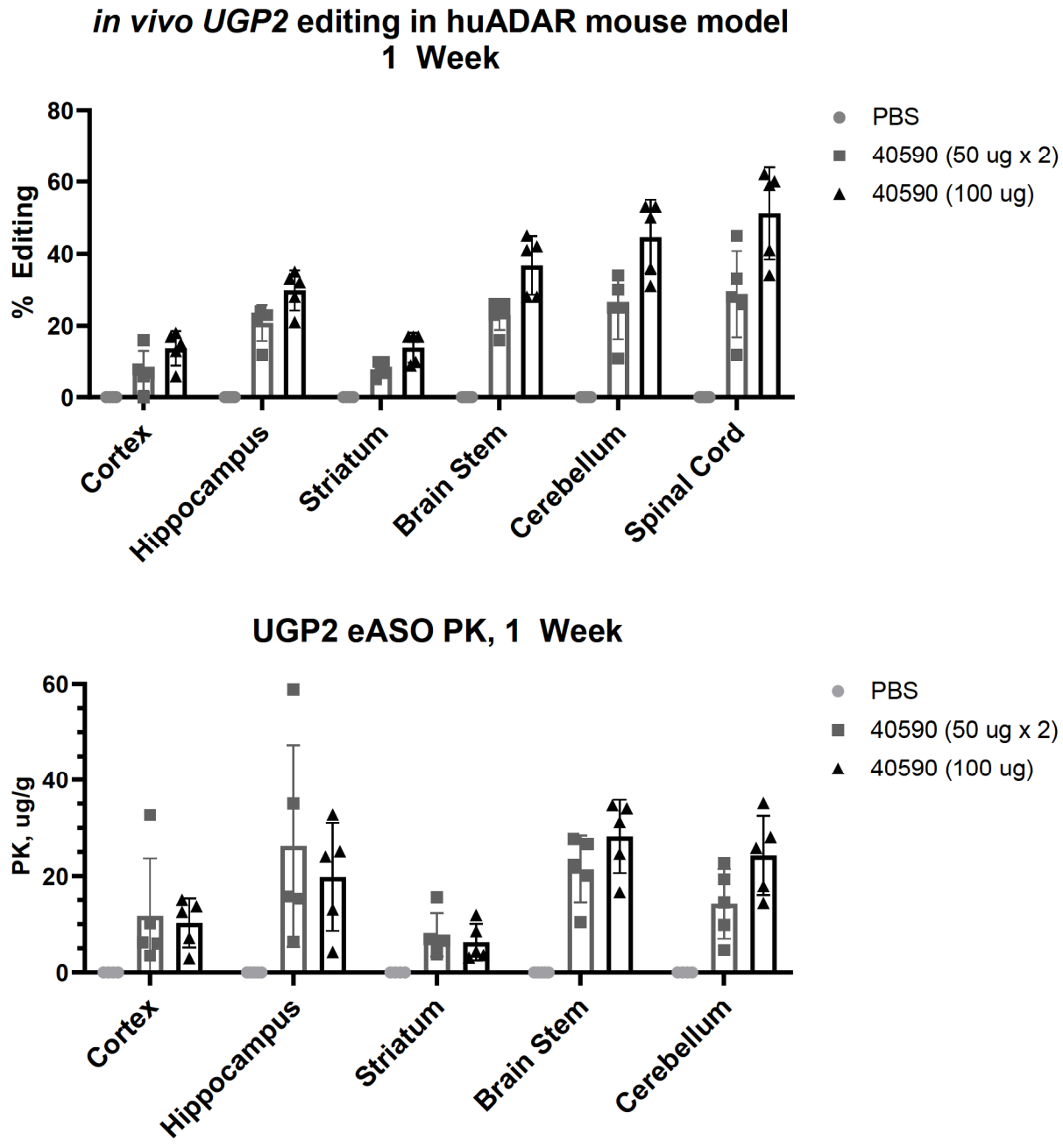

in vivo UGP2 Editing
Liver
% Editing
40
30
20
10
0
huADAR Mouse
WT Mouse
PBS
38700
38702

(a)


in vivo EEF1A1 Editing
Liver
% Editing
40
30
20
10
0
huADAR Mouse
WT Mouse
PBS
38697
38699

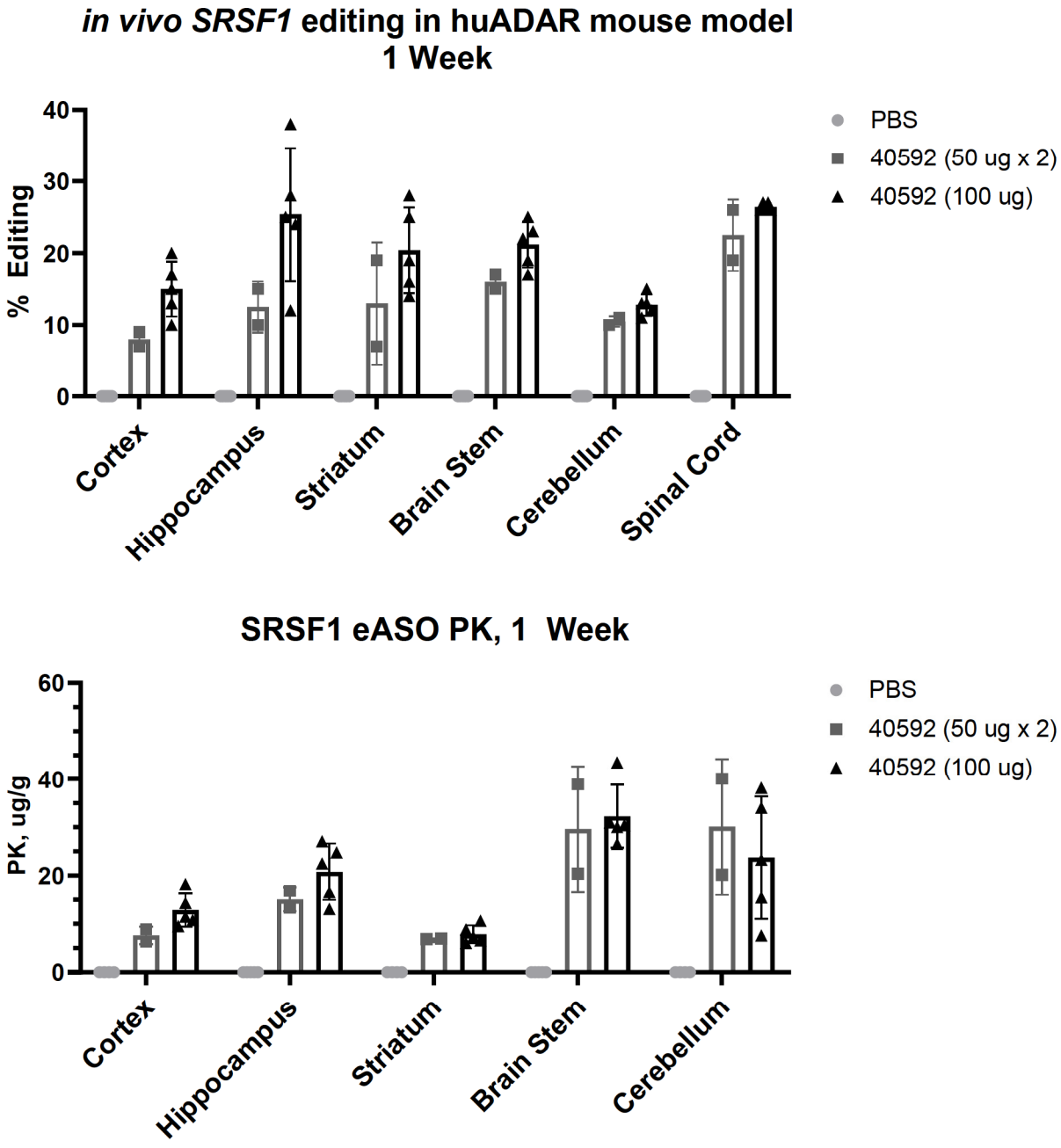
(b)

FIG. 41


in vivo UGP2 editing in huADAR mouse model
1 Week
% Editing
80
60
40
20
0
Cortex
Hippocampus
Striatum
Brain Stem
Cerebellum
Spinal Cord
PBS
40590 (50 ug x 2)
40590 (100 ug)
UGP2 eASO PK, 1 Week
PK, ug/g
60
40
20
0
Cortex
Hippocampus
Striatum
Brain Stem
Cerebellum
PBS
40590 (50 ug x 2)
40590 (100 ug)

(a)

FIG. 42



(b)

FIG. 42 (CONTINUED)

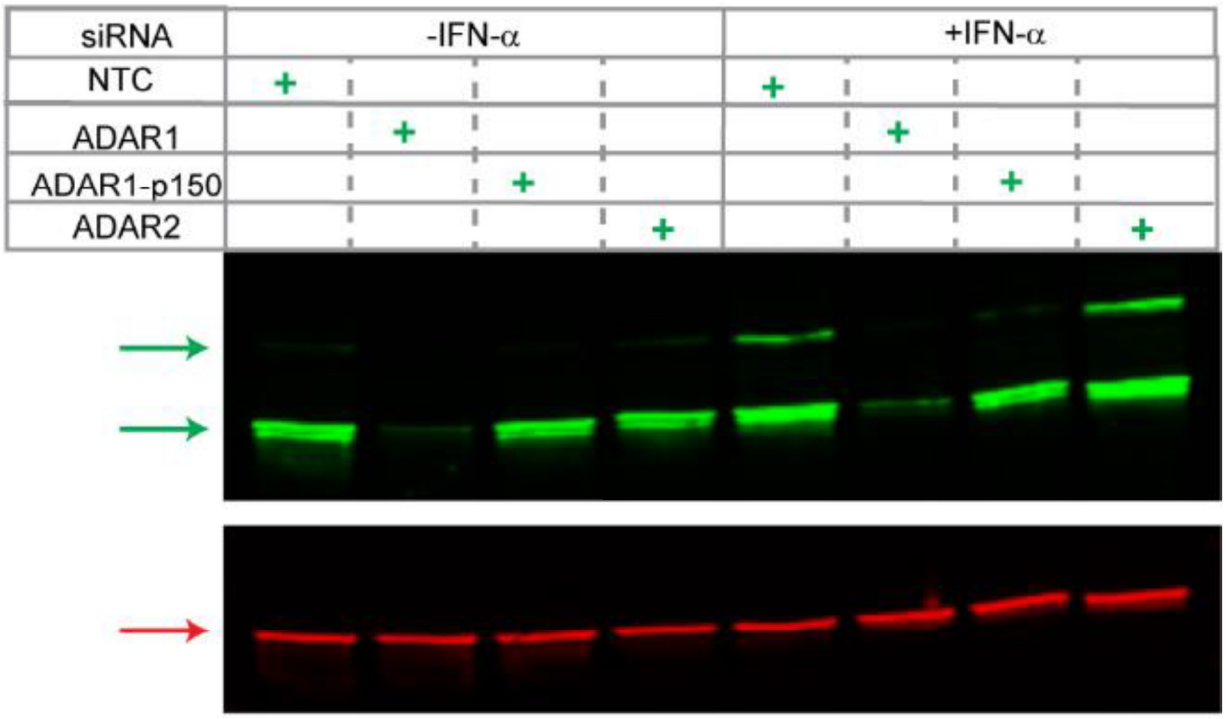

siRNA
-IFN-α
+IFN-α
NTC
ADAR1
ADAR1-p150
ADAR2

FIG. 43

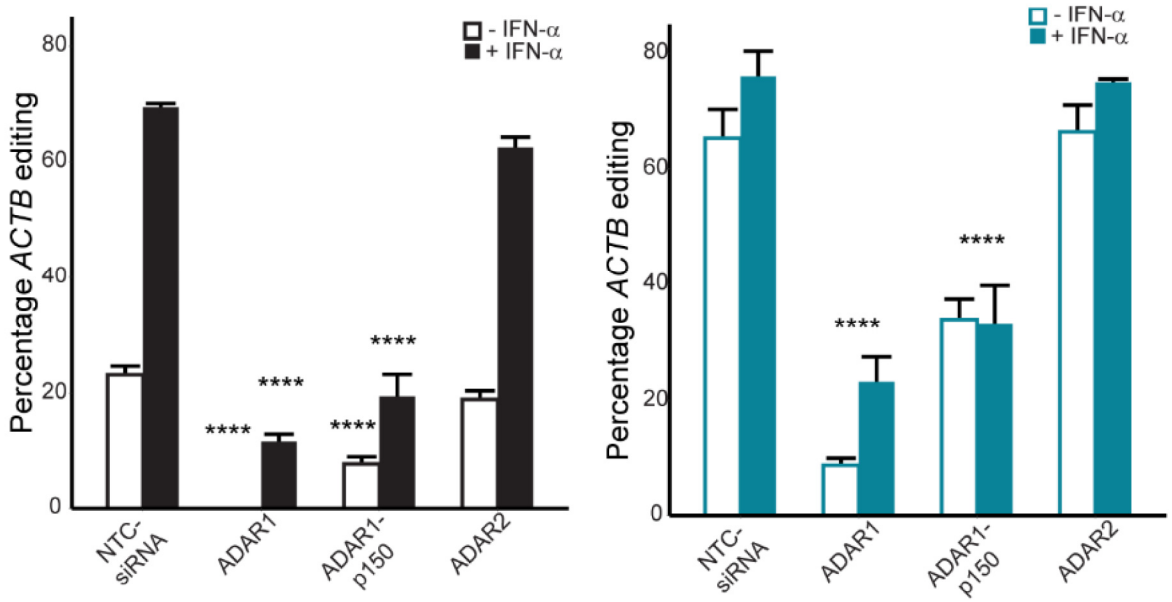
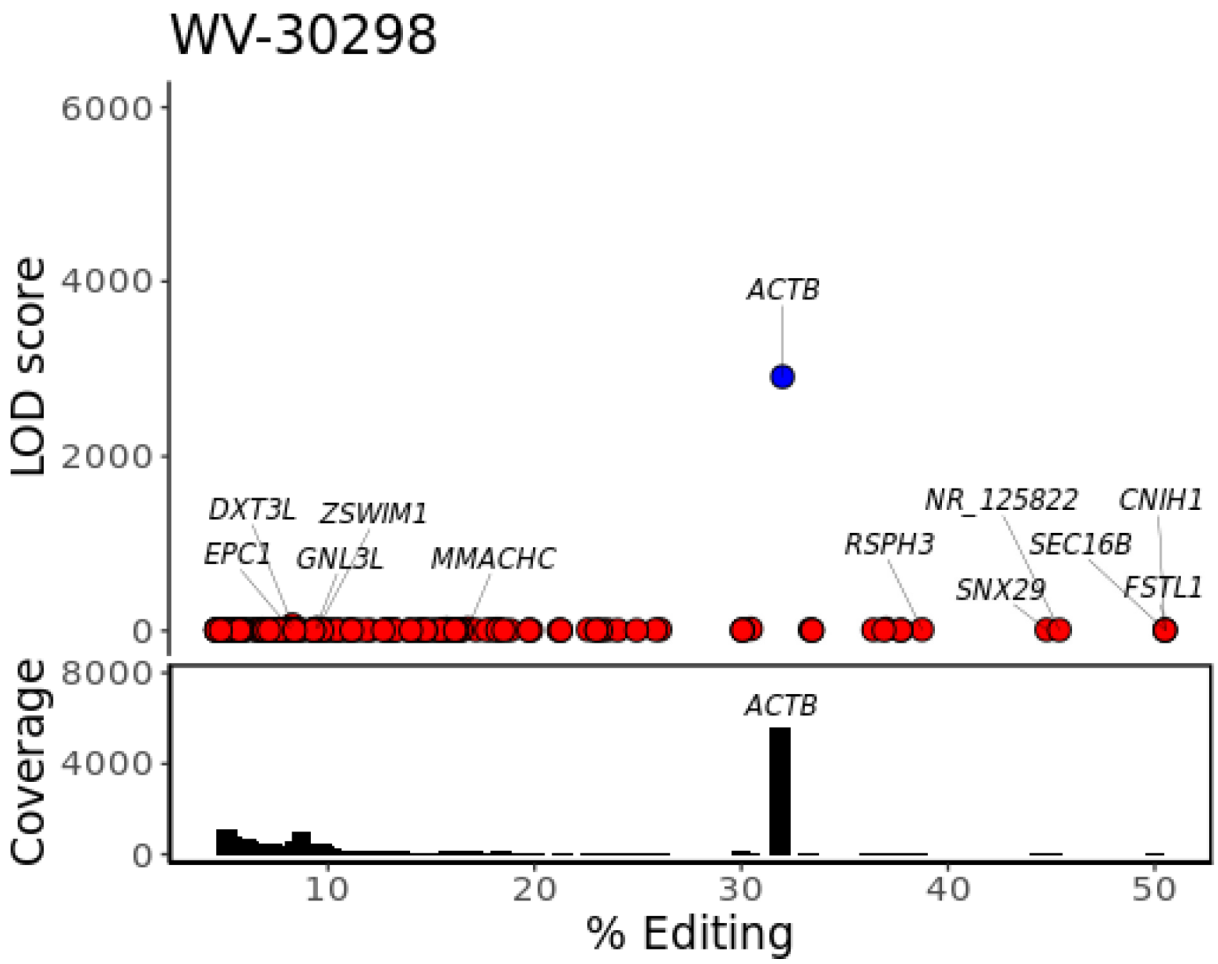
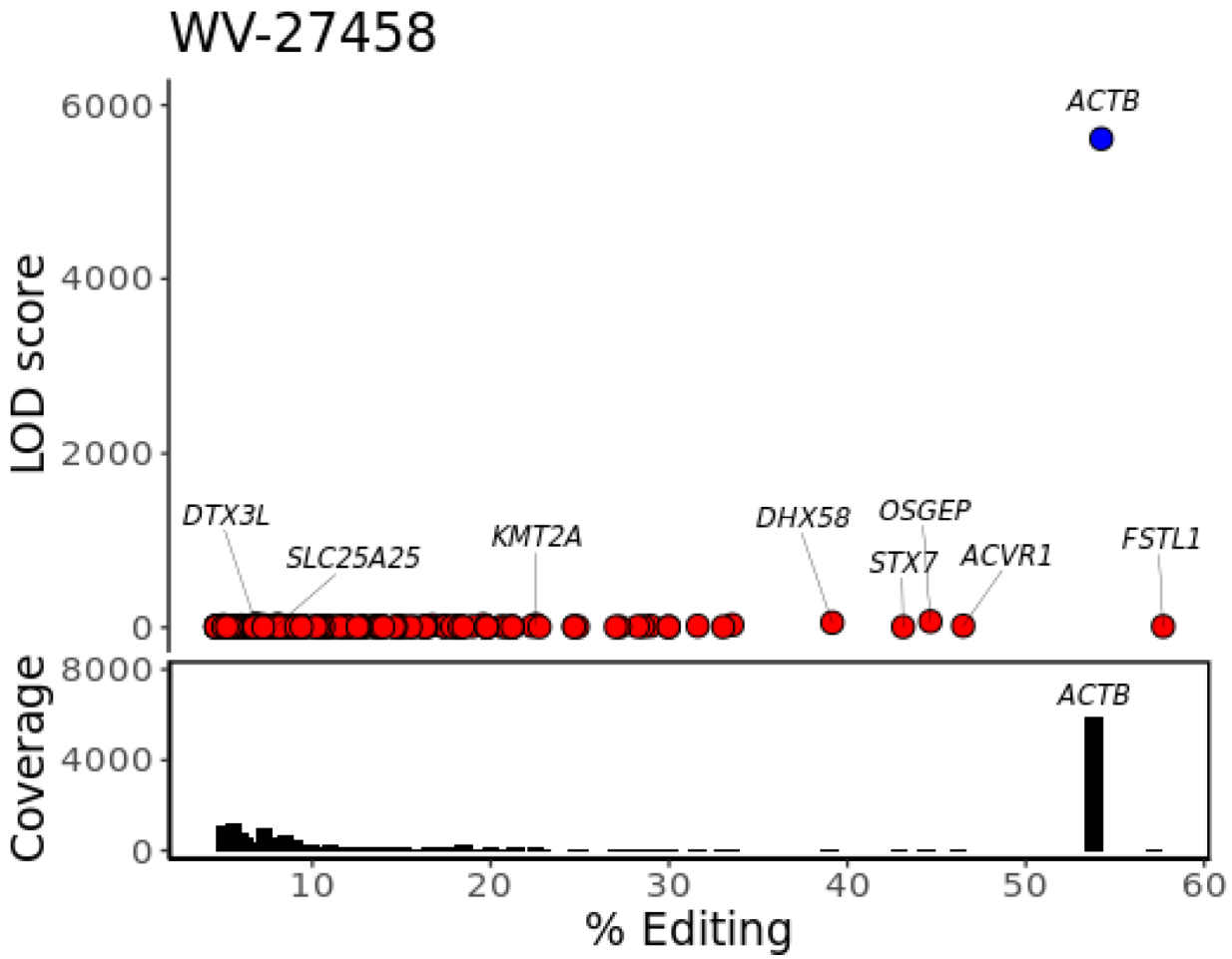

- IFN-α
+ IFN-α
Percentage ACTB editing
0
20
40
60
80
****
NTC-siRNA
ADAR1
ADAR1-p150
ADAR2

FIG. 44


WV-30298
LOD score
6000
4000
2000
0
ACTB
DXT3L
ZSWIM1
EPC1
GNL3L
MMACHC
NR_125822
CNIH1
RSPH3
SEC16B
SNX29
FSTL1
Coverage
8000
4000
0
ACTB
10
20
30
40
50
% Editing

(a)

FIG. 45



(b)

FIG. 45 (CONTINUED)

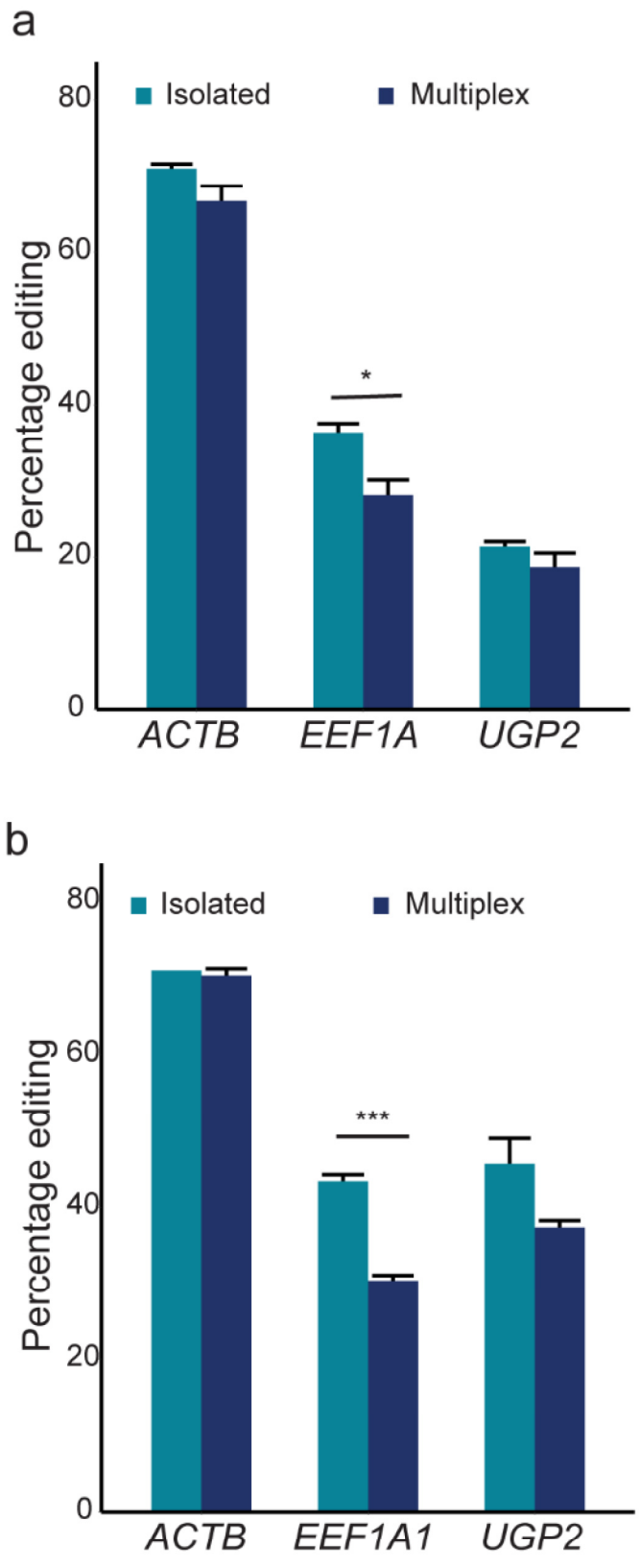
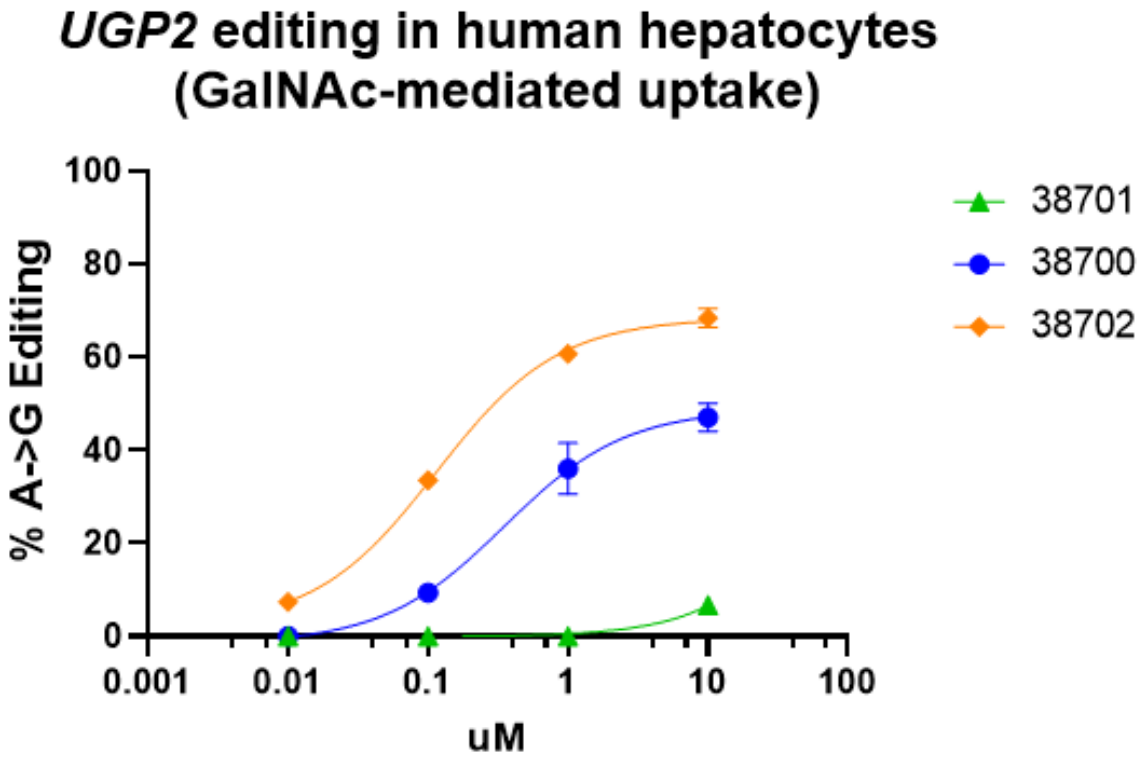
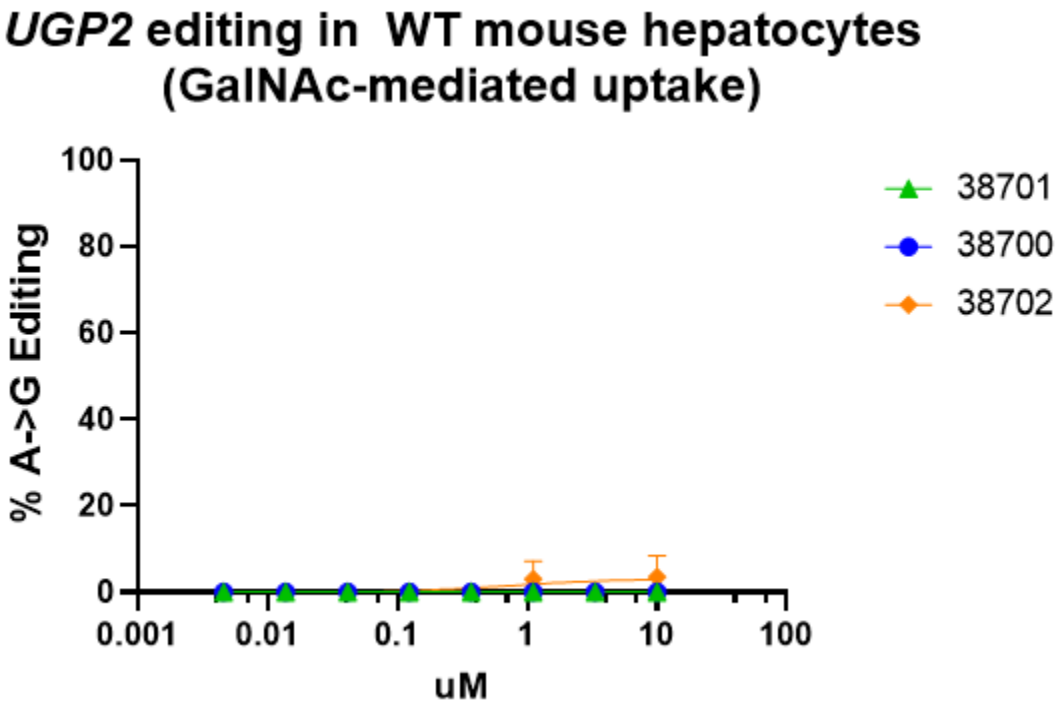

a
Isolated
Multiplex
Percentage editing
80
60
40
20
0
*
ACTB
EEF1A
UGP2
b
Isolated
Multiplex
Percentage editing
80
60
40
20
0
***
ACTB
EEF1A1
UGP2

FIG. 46

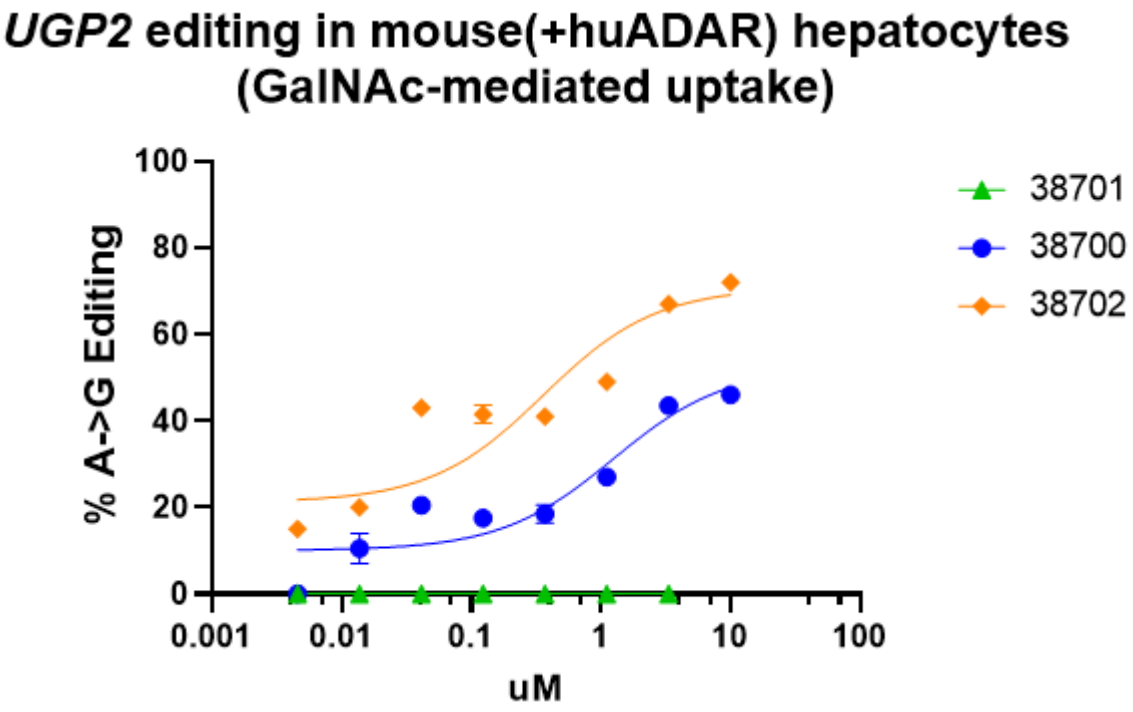

UGP2 editing in human hepatocytes
(GalNAc-mediated uptake)
% A->G Editing
100
80
60
40
20
0
0.001
0.01
0.1
1
10
100
uM
38701
38700
38702

(a)

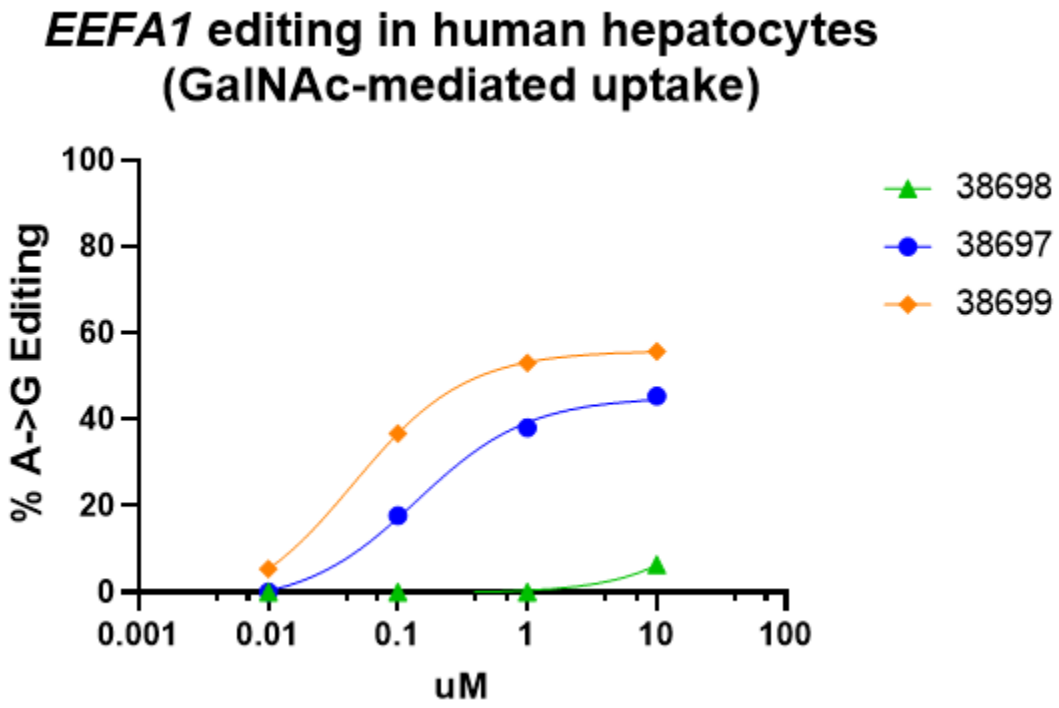

UGP2 editing in WT mouse hepatocytes
(GalNAc-mediated uptake)
% A->G Editing
100
80
60
40
20
0
0.001
0.01
0.1
1
10
100
uM
38701
38700
38702

(b)

FIG. 47

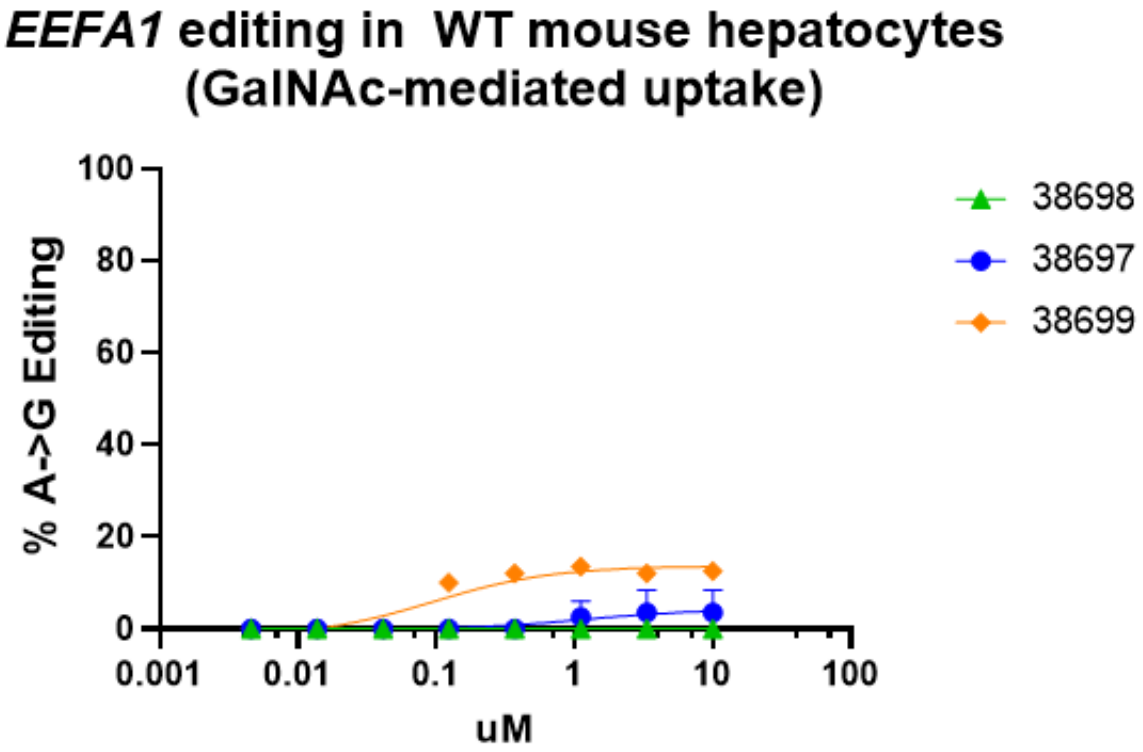


(c)

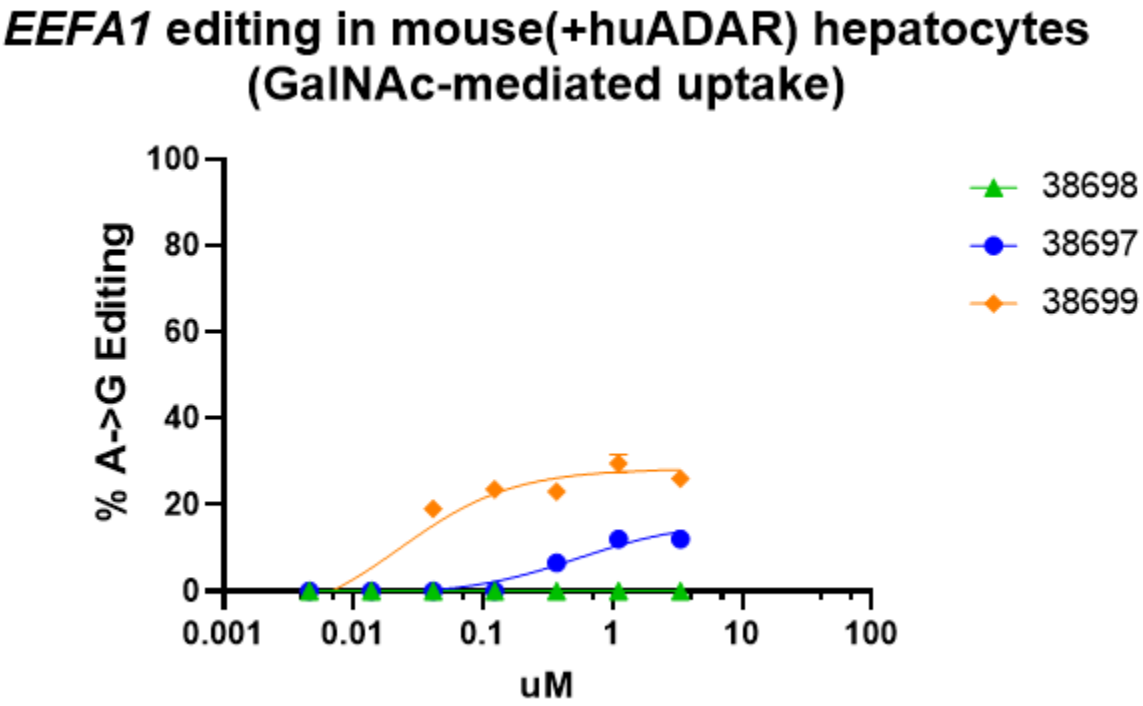


(d)

FIG. 47 (CONTINUED)



(e)



(f)

FIG. 47 (CONTINUED)

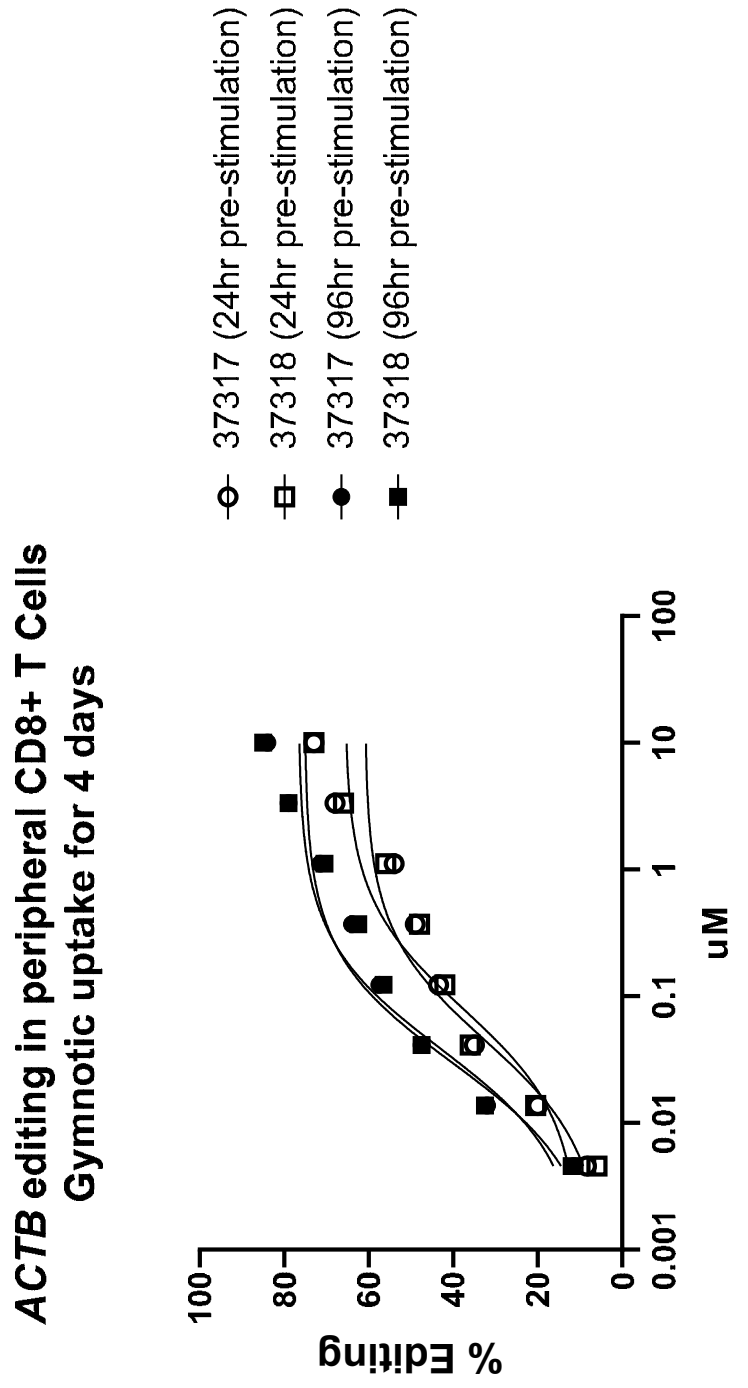

ACTB editing in peripheral CD8+ T Cells
Gymnotic uptake for 4 days
% Editing
100
80
60
40
20
0
0.001
0.01
0.1
1
10
100
uM
37317 (24hr pre-stimulation)
37318 (24hr pre-stimulation)
37317 (96hr pre-stimulation)
37318 (96hr pre-stimulation)

FIG. 48

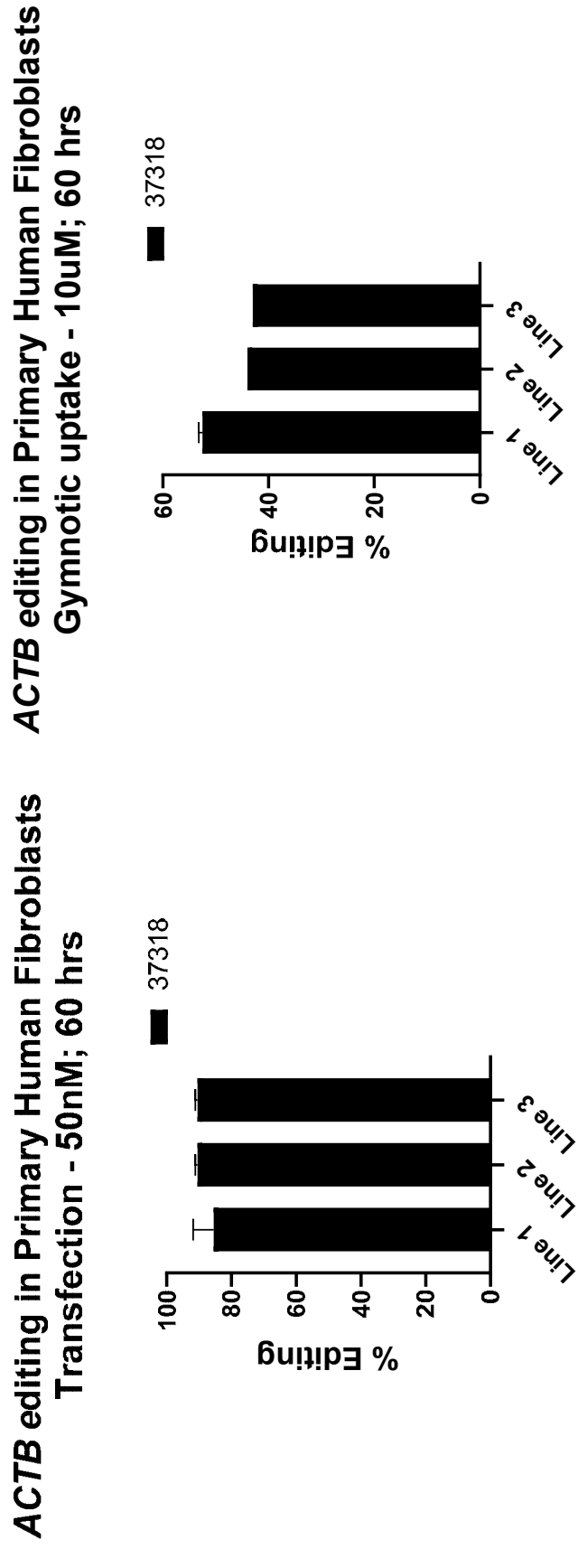
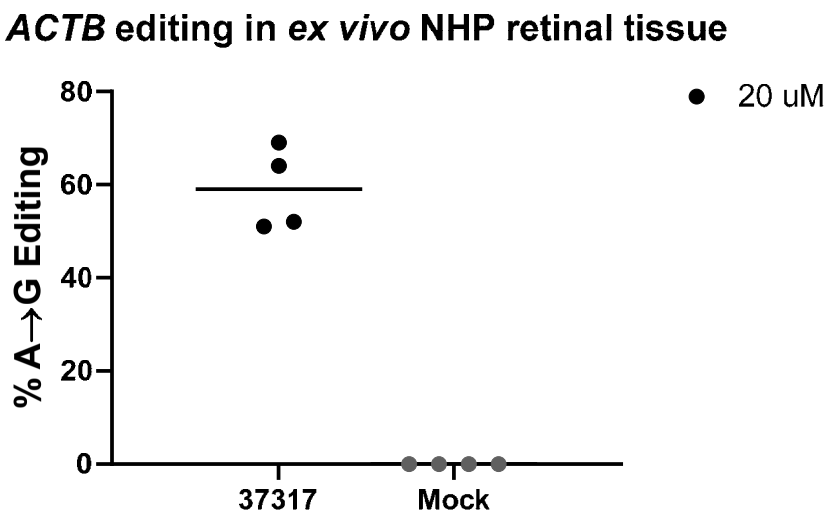

ACTB editing in Primary Human Fibroblasts
Transfection - 50nM; 60 hrs
37318
% Editing
0
20
40
60
80
100
Line 1
Line 2
Line 3
ACTB editing in Primary Human Fibroblasts
Gymnotic uptake - 10uM; 60 hrs
37318
% Editing
0
20
40
60
Line 1
Line 2
Line 3

FIG. 49


ACTB editing in *ex vivo* NHP retinal tissue
% A→G Editing
80
60
40
20
0
37317
Mock
20 uM

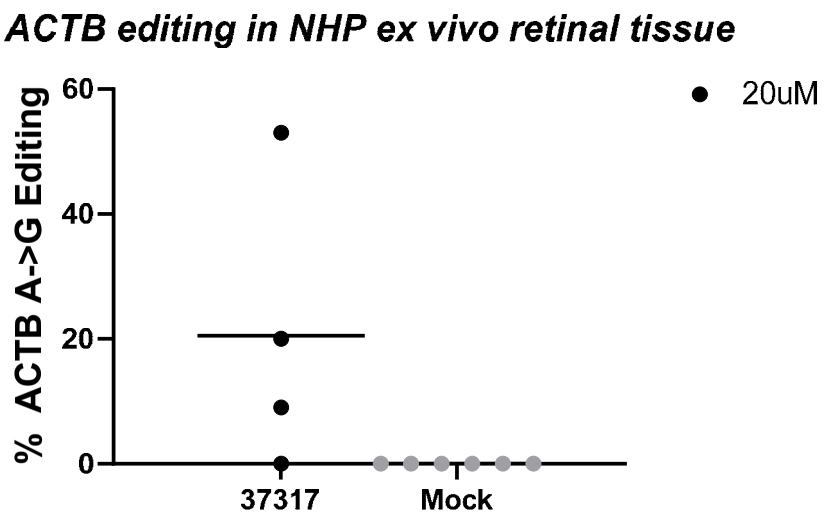

ACTB editing in NHP ex vivo retinal tissue
% ACTB A->G Editing
60
40
20
0
37317
Mock
20uM

FIG. 50

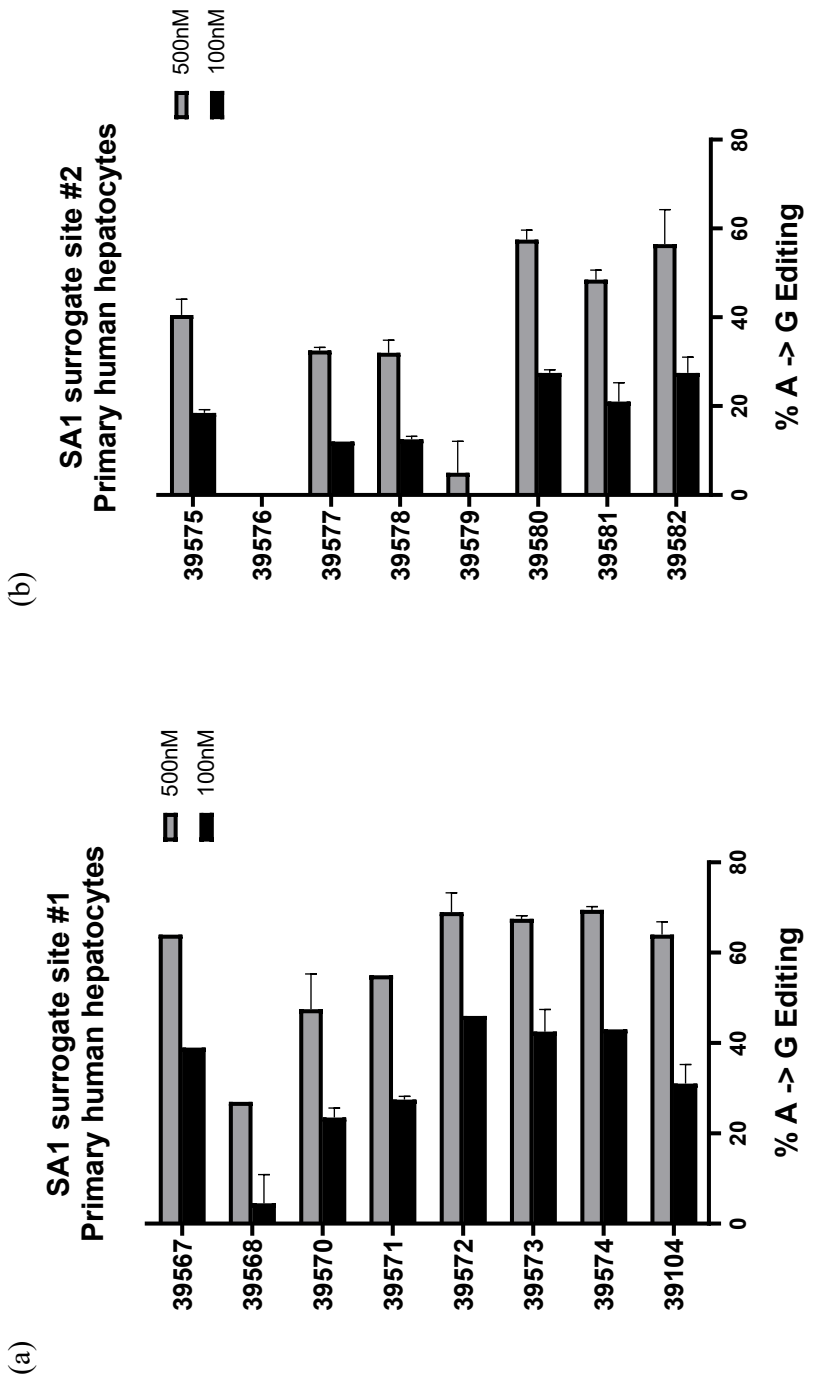

(a)
SA1 surrogate site #1
Primary human hepatocytes
500nM
100nM
% A -> G Editing
0
20
40
60
80
39567
39568
39570
39571
39572
39573
39574
39104
(b)
SA1 surrogate site #2
Primary human hepatocytes
500nM
100nM
% A -> G Editing
0
20
40
60
80
39575
39576
39577
39578
39579
39580
39581
39582

FIG. 51

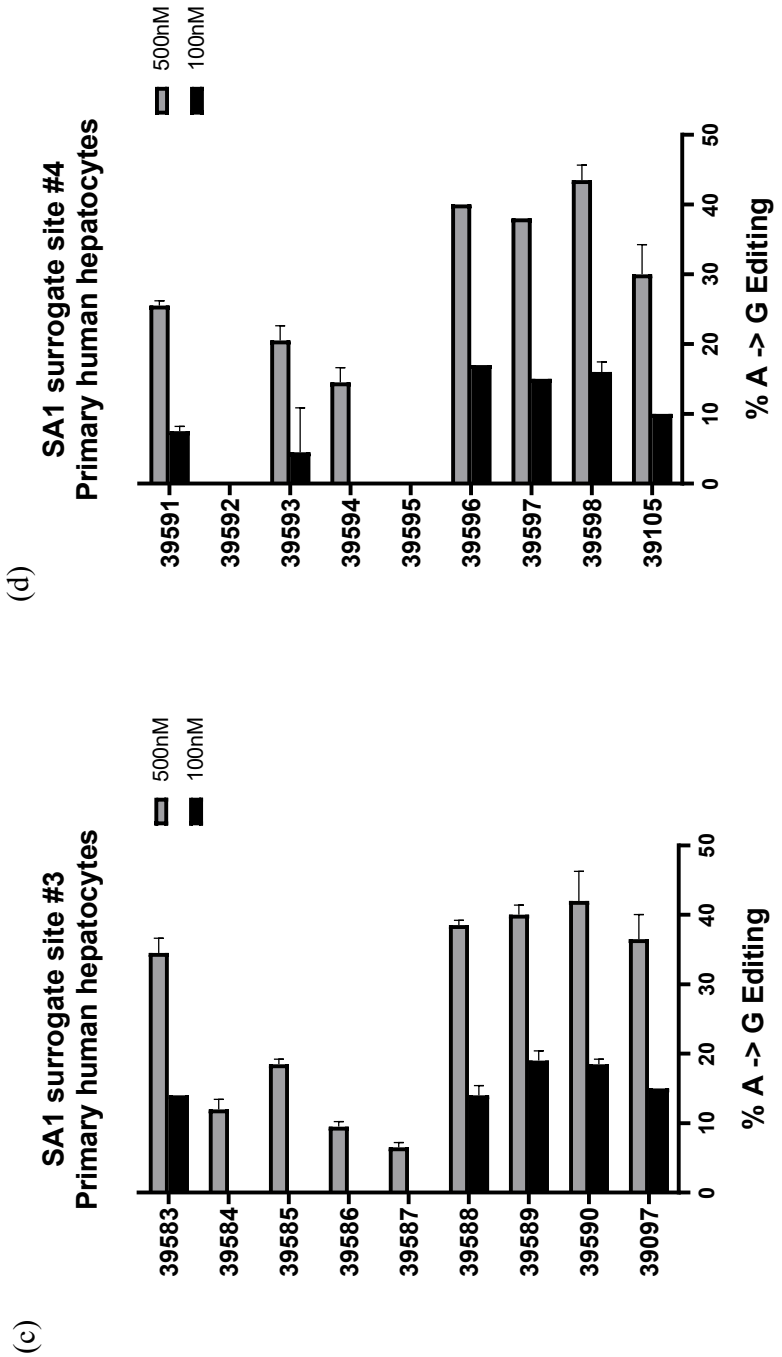


FIG. 51 (CONTINUED)

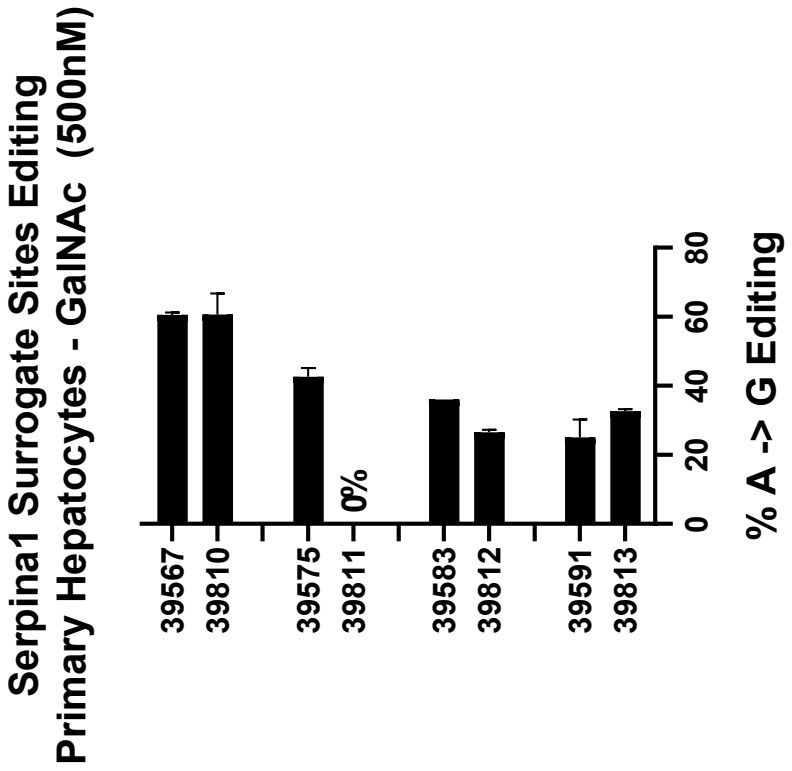

Serpina1 Surrogate Sites Editing
Primary Hepatocytes - GalNAc (500nM)
39567
39810
39575
39811
0%
39583
39812
39591
39813
0
20
40
60
80
% A -> G Editing

FIG. 52

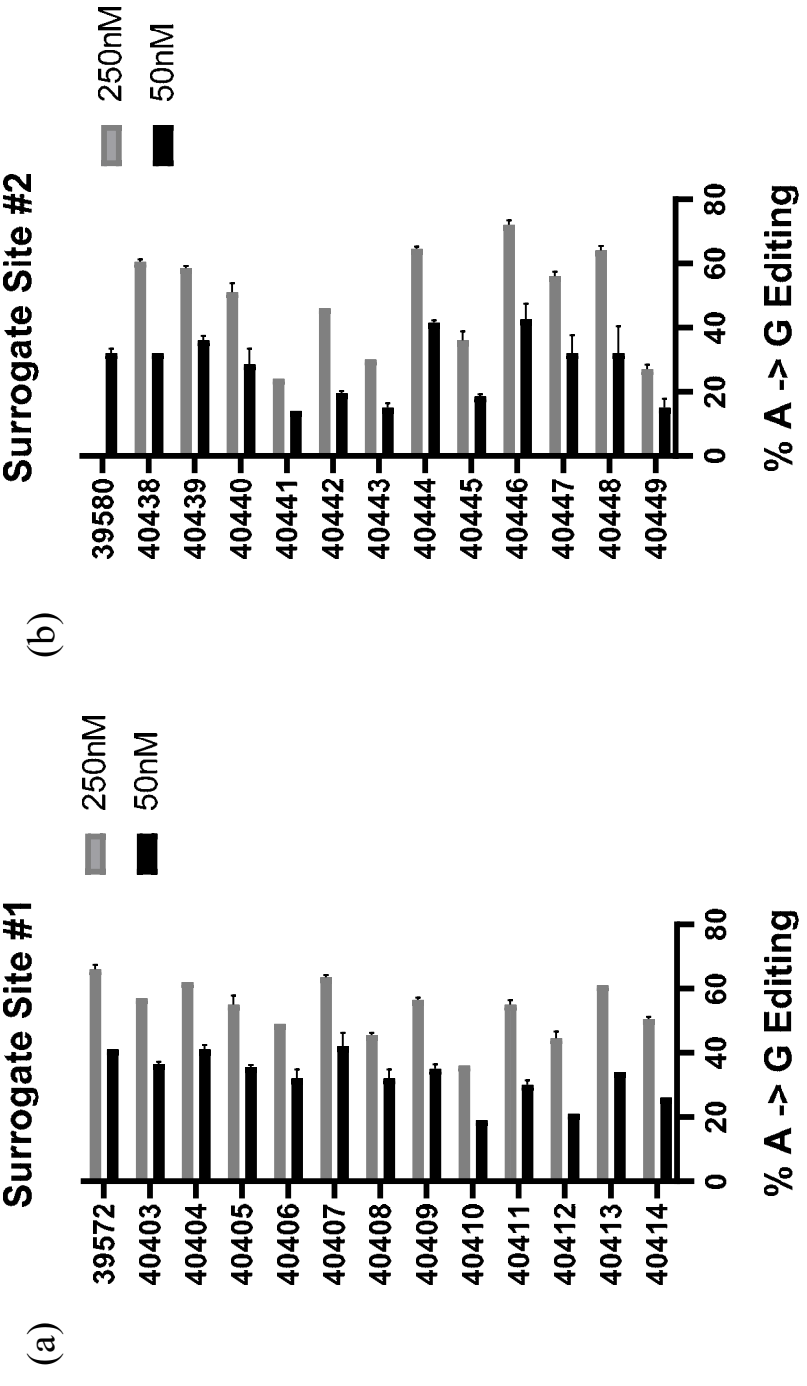

(a)
Surrogate Site #1
250nM
50nM
39572
40403
40404
40405
40406
40407
40408
40409
40410
40411
40412
40413
40414
0
20
40
60
80
% A -> G Editing
(b)
Surrogate Site #2
250nM
50nM
39580
40438
40439
40440
40441
40442
40443
40444
40445
40446
40447
40448
40449
0
20
40
60
80
% A -> G Editing

FIG. 53

(c)

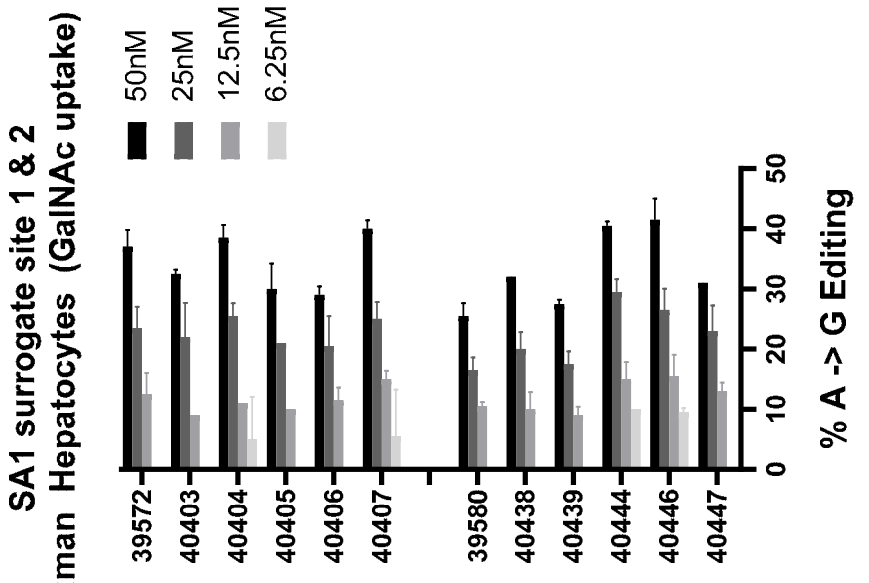


Fig. 53 (CONTINUED)

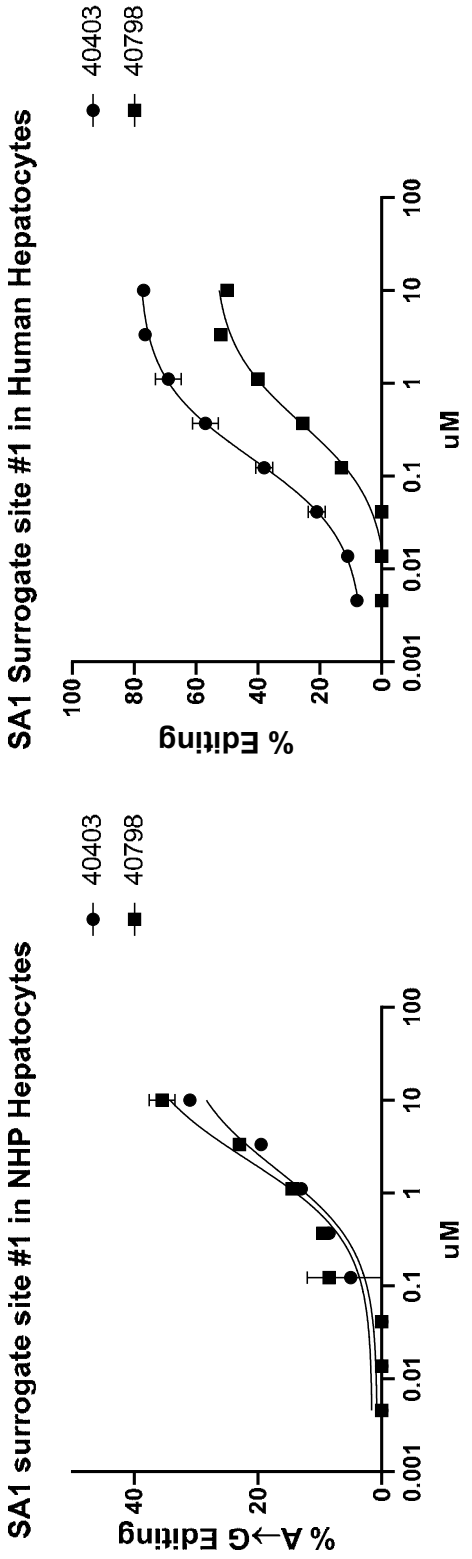
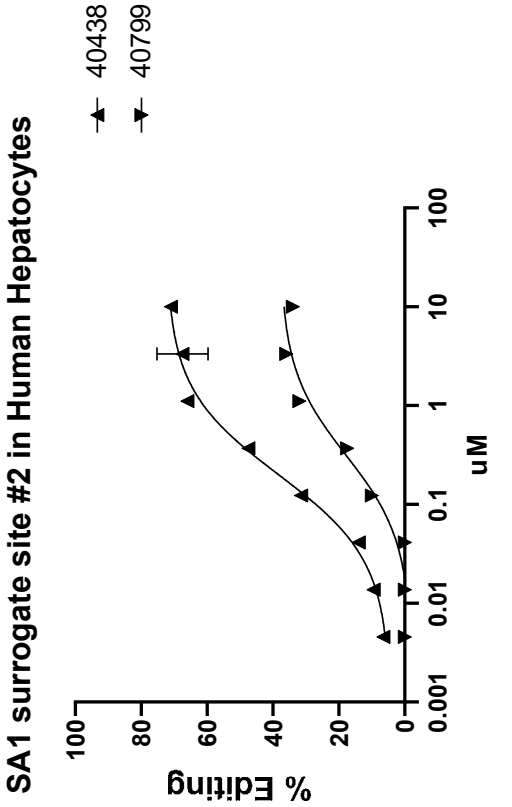

SA1 surrogate site #1 in NHP Hepatocytes
% A→G Editing
0
20
40
0.001
0.01
0.1
1
10
100
uM
40403
40798
SA1 Surrogate site #1 in Human Hepatocytes
% Editing
0
20
40
60
80
100
0.001
0.01
0.1
1
10
100
uM
40403
40798

FIG. 54



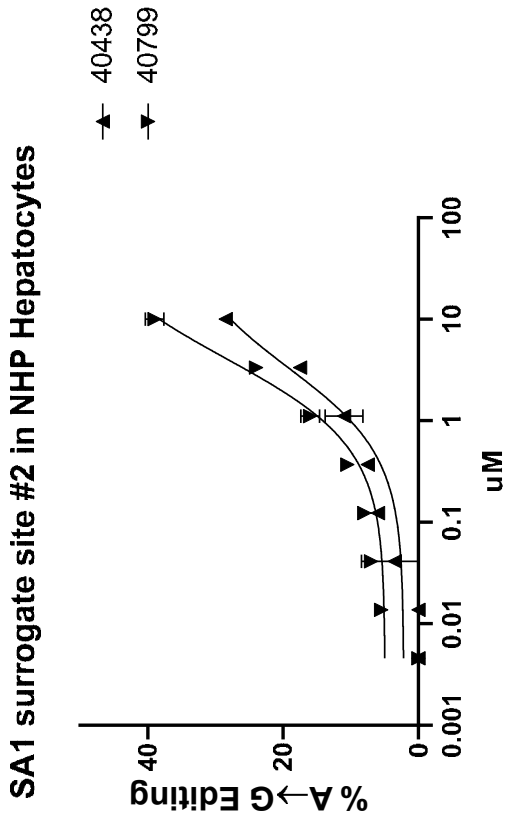


FIG. 54 (CONTINUED)

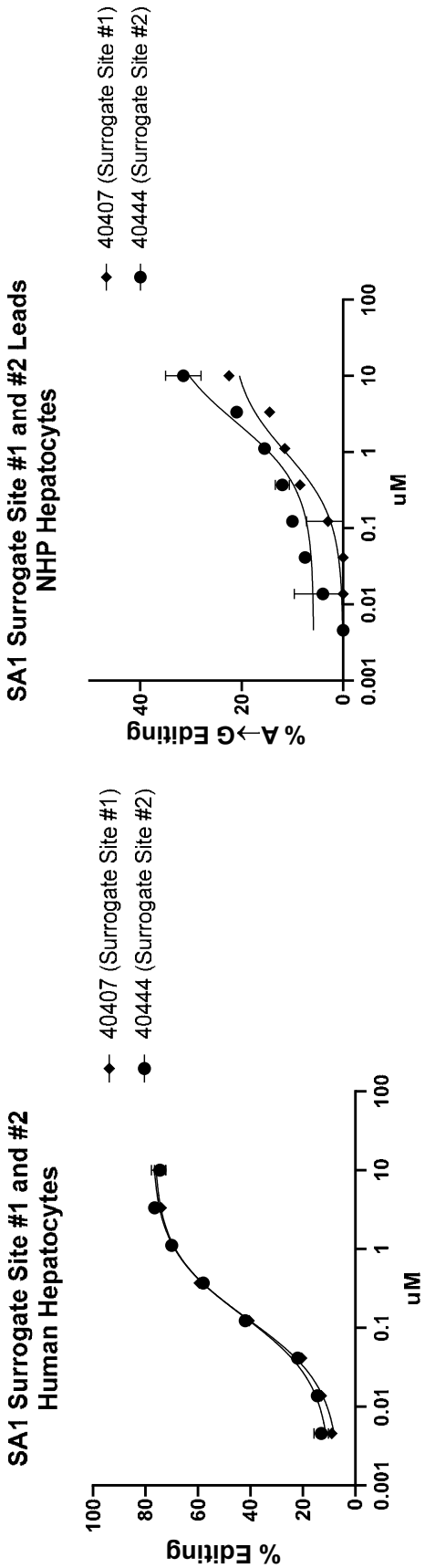

SA1 Surrogate Site #1 and #2 Leads
NHP Hepatocytes
40407 (Surrogate Site #1)
40444 (Surrogate Site #2)
% A→G Editing
0
20
40
0.001
0.01
0.1
1
10
100
uM
SA1 Surrogate Site #1 and #2
Human Hepatocytes
40407 (Surrogate Site #1)
40444 (Surrogate Site #2)
% Editing
0
20
40
60
80
100
0.001
0.01
0.1
1
10
100
uM

FIG. 55

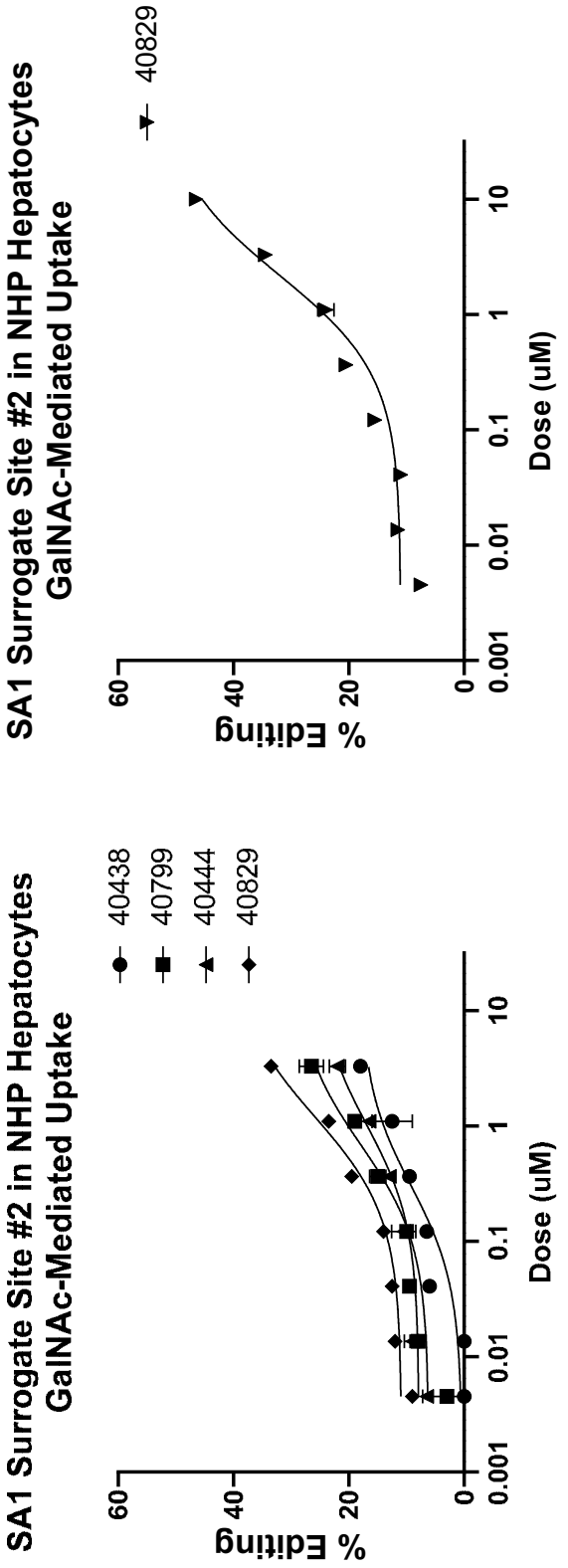

SA1 Surrogate Site #2 in NHP Hepatocytes
GalNAc-Mediated Uptake
% Editing
Dose (uM)
40438
40799
40444
40829
SA1 Surrogate Site #2 in NHP Hepatocytes
GalNAc-Mediated Uptake
% Editing
Dose (uM)
40829

FIG. 56

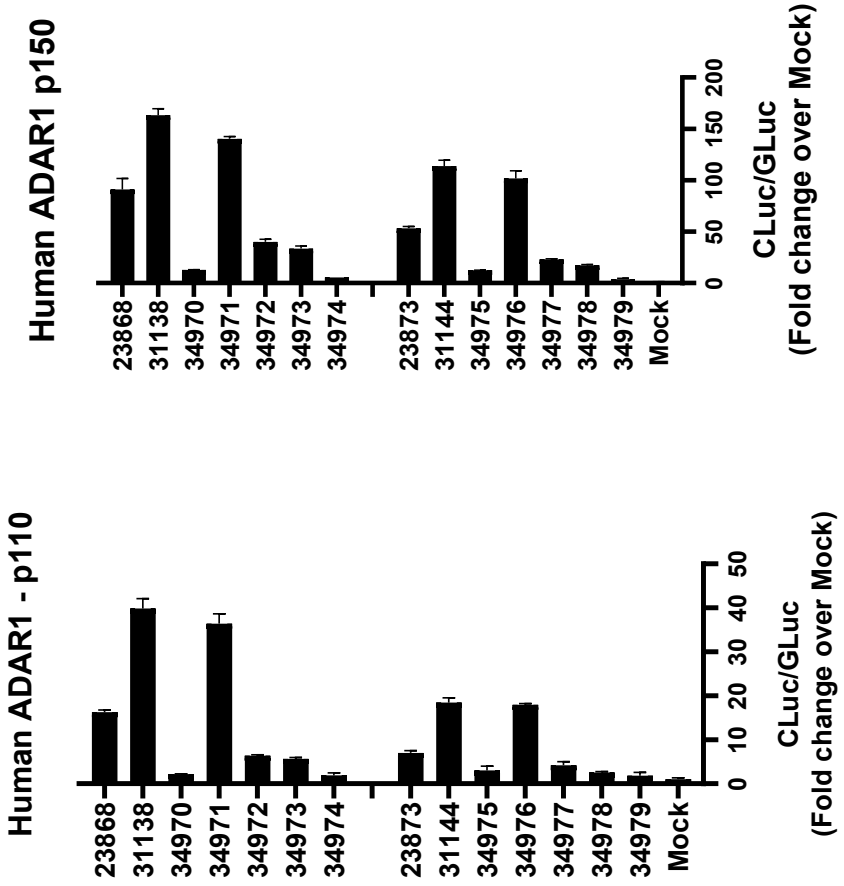

Human ADAR1 p150
23868
31138
34970
34971
34972
34973
34974
23873
31144
34975
34976
34977
34978
34979
Mock
0 50 100 150 200
CLuc/GLuc
(Fold change over Mock)
Human ADAR1 - p110
23868
31138
34970
34971
34972
34973
34974
23873
31144
34975
34976
34977
34978
34979
Mock
0 10 20 30 40 50
CLuc/GLuc
(Fold change over Mock)

FIG. 57

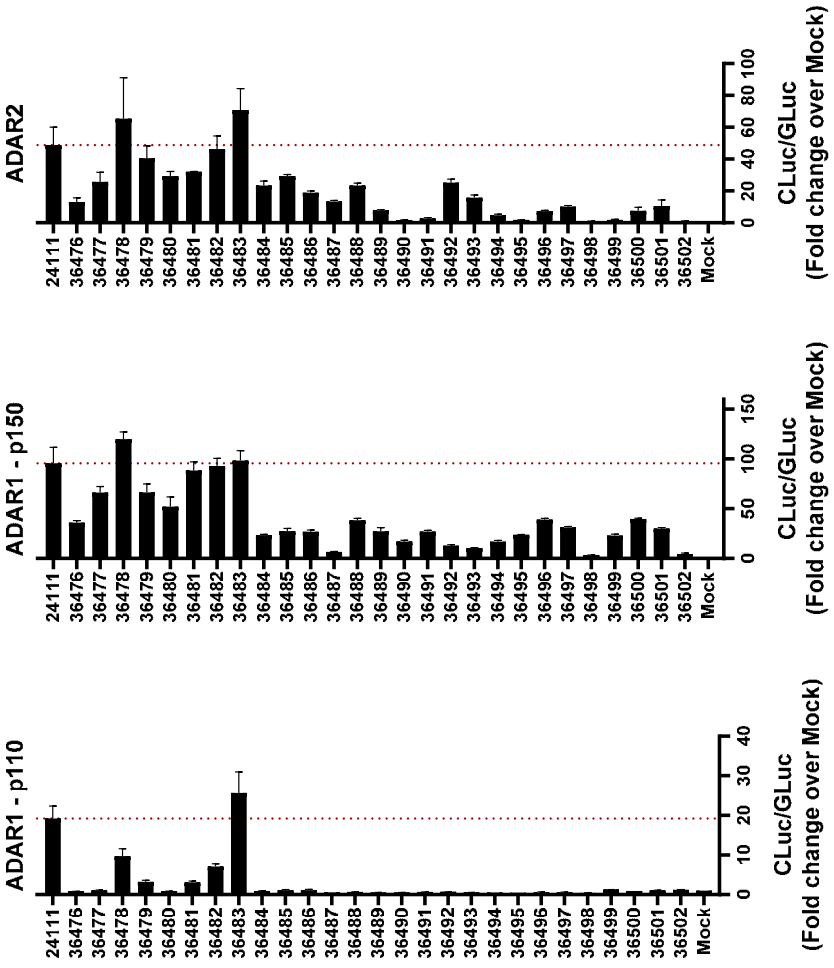

ADAR2
ADAR1 - p150
ADAR1 - p110
24111
36476
36477
36478
36479
36480
36481
36482
36483
36484
36485
36486
36487
36488
36489
36490
36491
36492
36493
36494
36495
36496
36497
36498
36499
36500
36501
36502
Mock
CLuc/GLuc
(Fold change over Mock)
0
20
40
60
80
100
50
150
10
30

FIG. 58

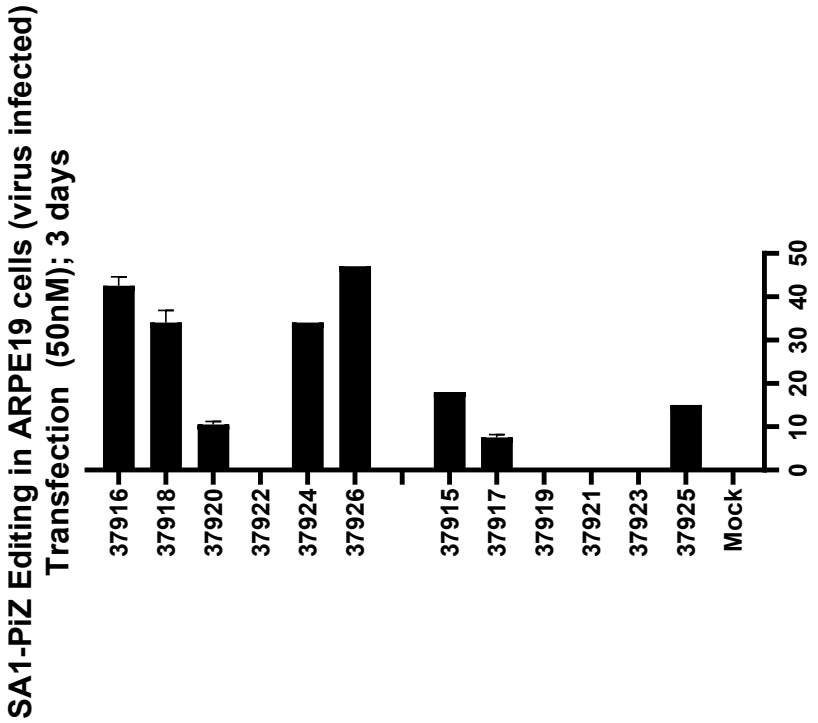

SA1-PiZ Editing in ARPE19 cells (virus infected)
Transfection (50nM); 3 days
37916
37918
37920
37922
37924
37926
37915
37917
37919
37921
37923
37925
Mock
0
10
20
30
40
50
% Editing

FIG. 59

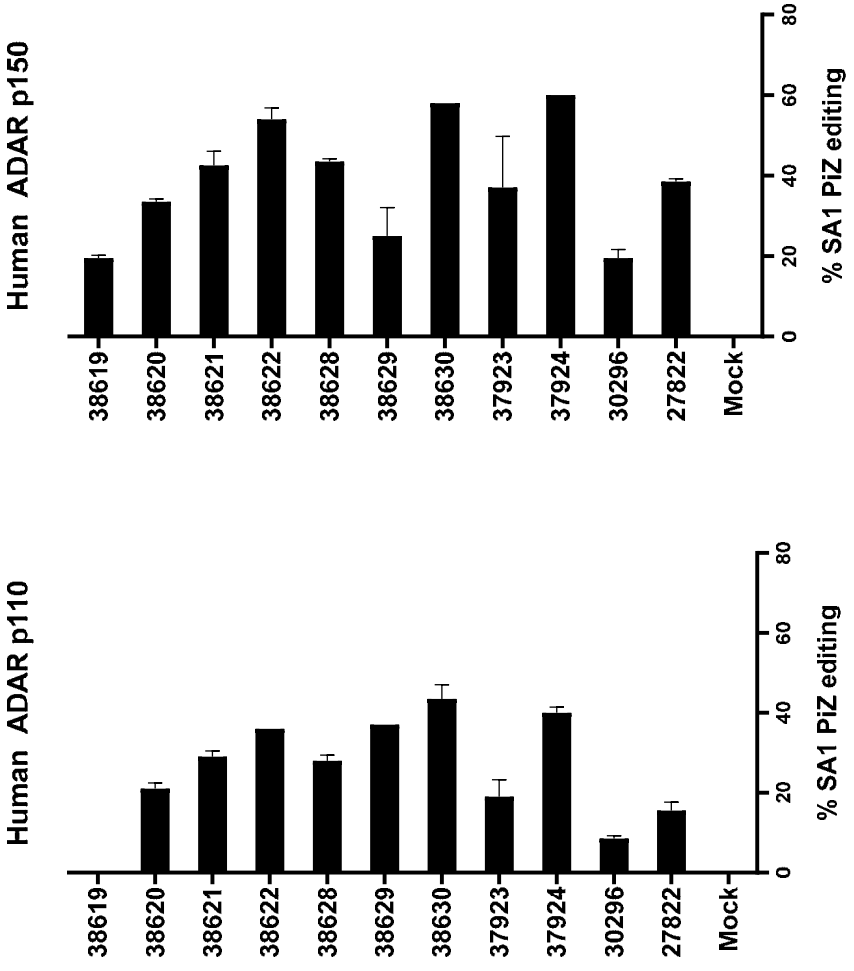

Human ADAR p150
% SA1 PiZ editing
0
20
40
60
80
38619
38620
38621
38622
38628
38629
38630
37923
37924
30296
27822
Mock
Human ADAR p110
% SA1 PiZ editing
0
20
40
60
80
38619
38620
38621
38622
38628
38629
38630
37923
37924
30296
27822
Mock

FIG. 60

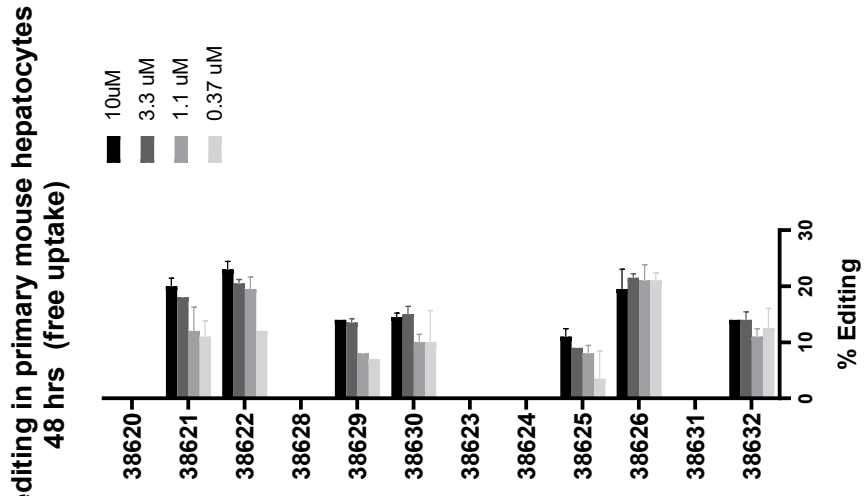

SA1-PiZ editing in primary mouse hepatocytes
48 hrs (free uptake)
10uM
3.3 uM
1.1 uM
0.37 uM
38620
38621
38622
38628
38629
38630
38623
38624
38625
38626
38631
38632
0
10
20
30
% Editing

FIG. 61

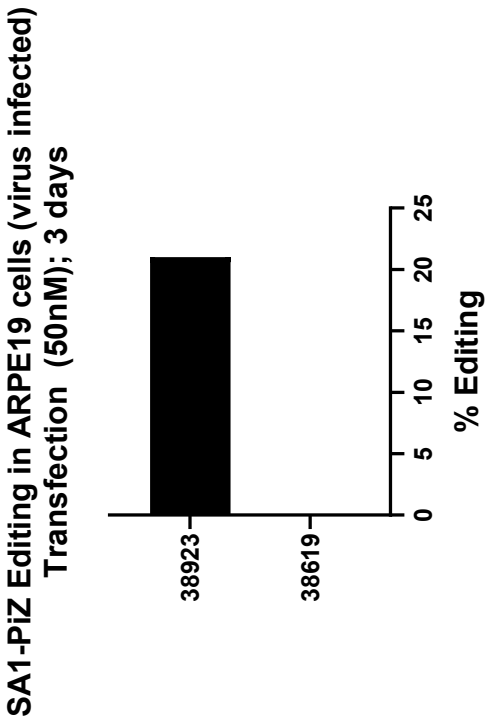

SA1-PiZ Editing in ARPE19 cells (virus infected)
Transfection (50nM); 3 days
38923
38619
0
5
10
15
20
25
% Editing

FIG. 62

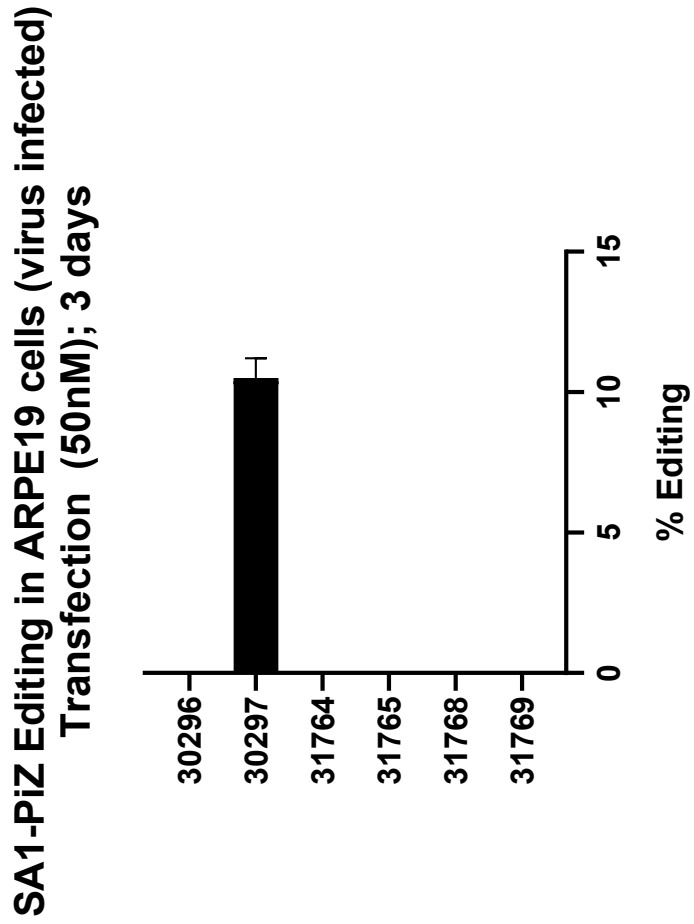

SA1-PiZ Editing in ARPE19 cells (virus infected)
Transfection (50nM); 3 days
30296
30297
31764
31765
31768
31769
0
5
10
15
% Editing

FIG. 63

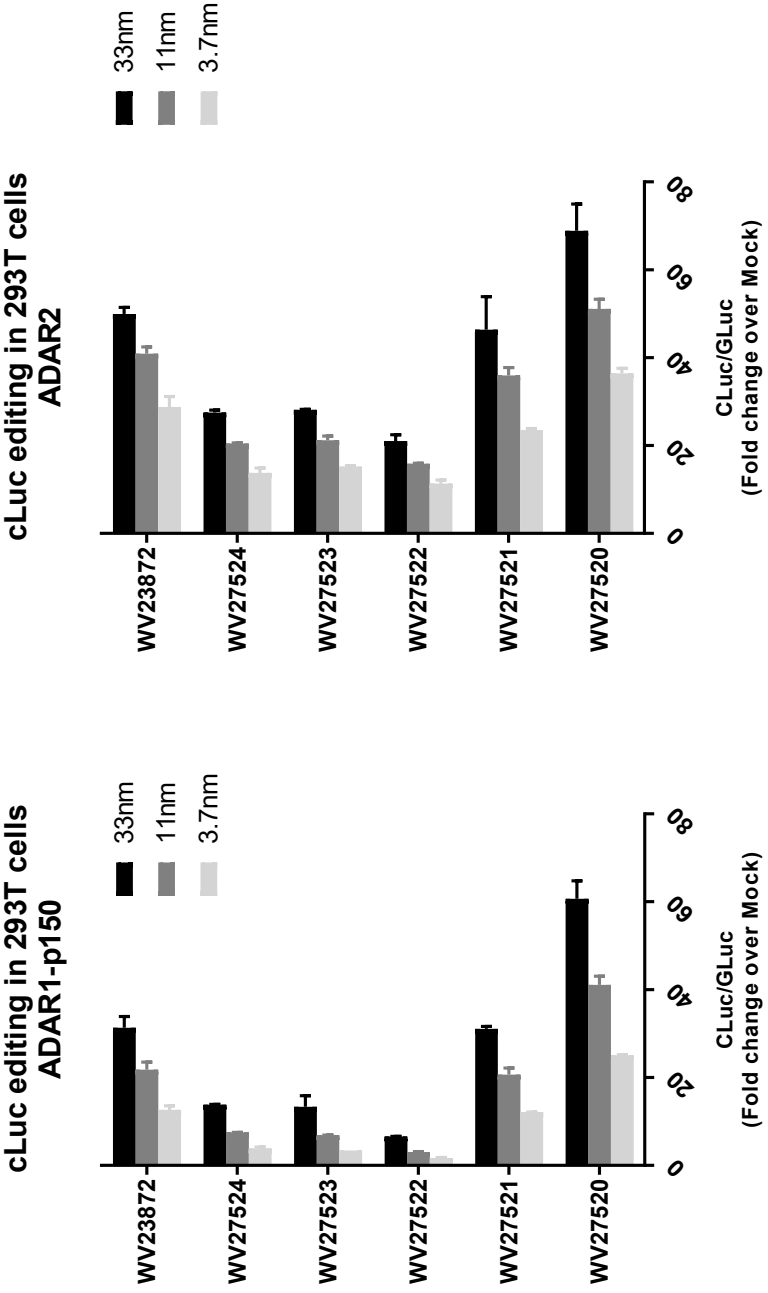

cLuc editing in 293T cells
ADAR2
33nm
11nm
3.7nm
WV23872
WV27524
WV27523
WV27522
WV27521
WV27520
0
20
40
60
80
CLuc/GLuc
(Fold change over Mock)
cLuc editing in 293T cells
ADAR1-p150
33nm
11nm
3.7nm
WV23872
WV27524
WV27523
WV27522
WV27521
WV27520
0
20
40
60
80
CLuc/GLuc
(Fold change over Mock)

FIG. 64