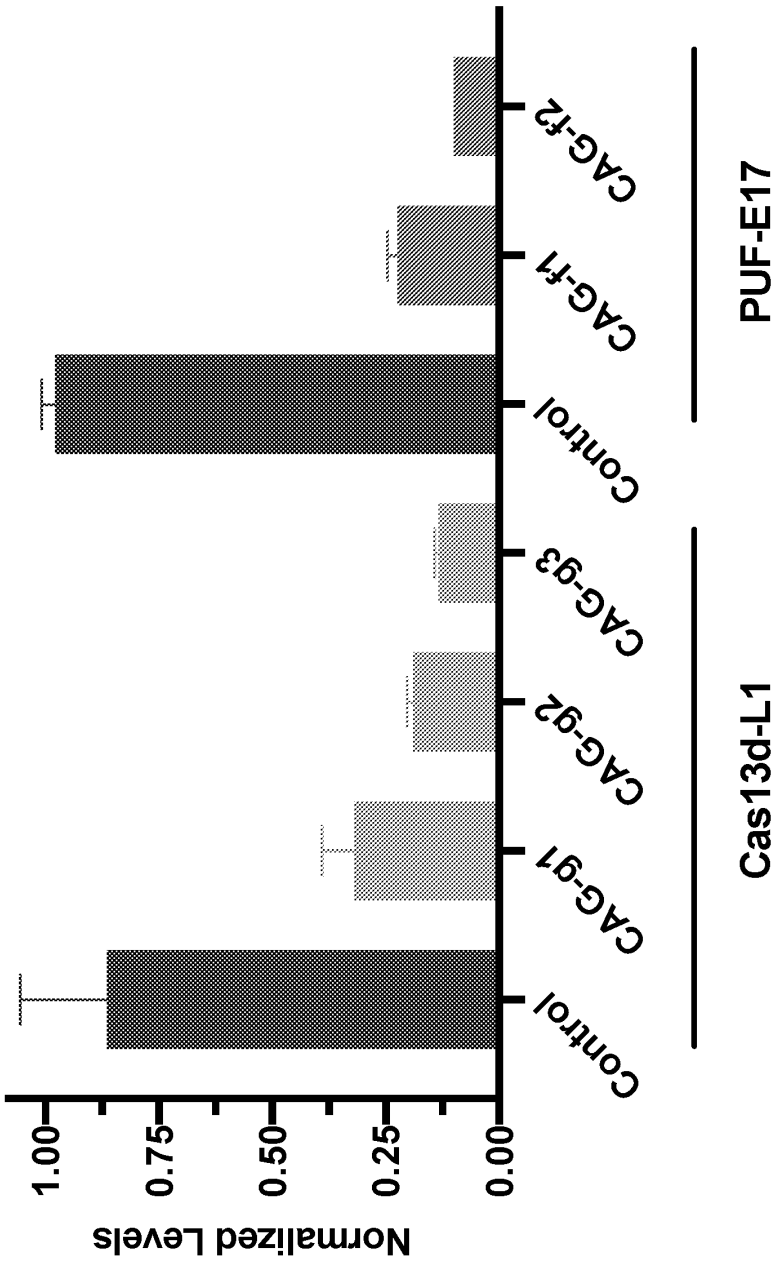
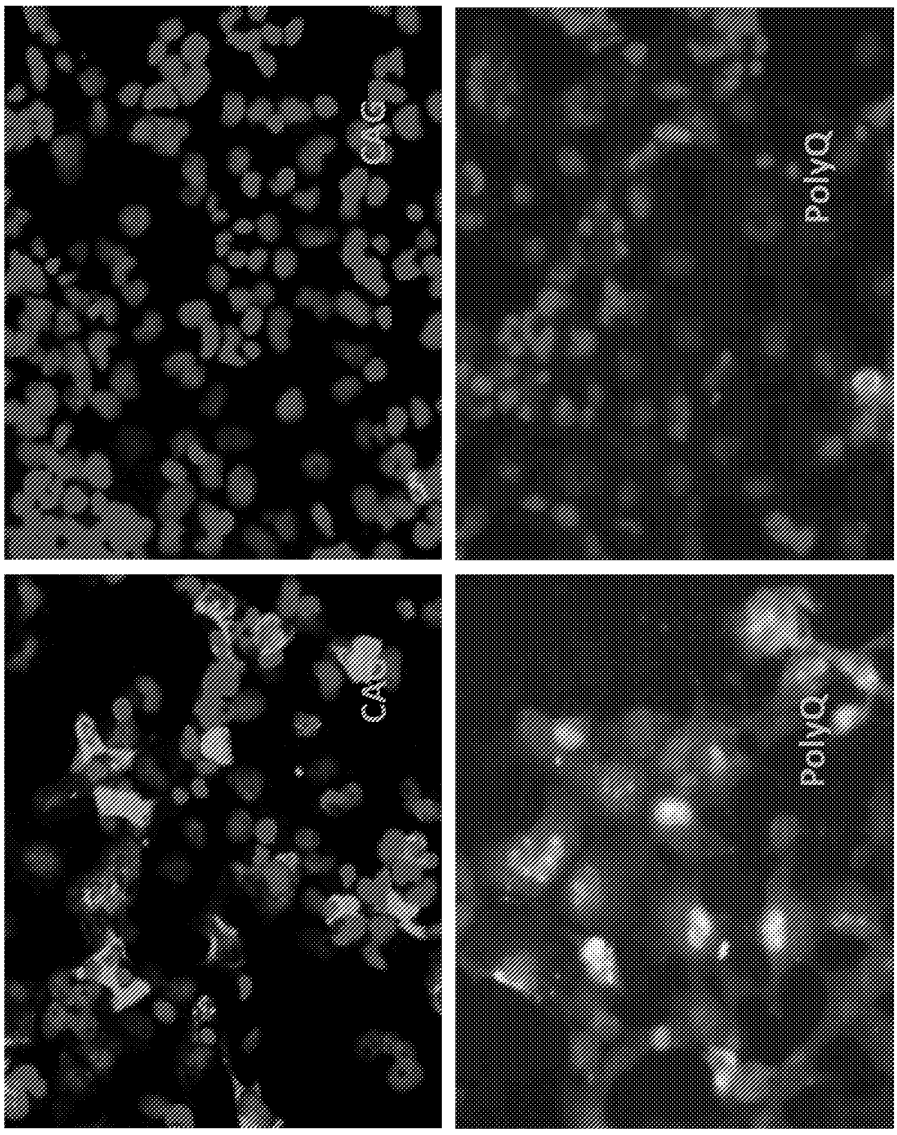

Normalized Levels
1.00
0.75
0.50
0.25
0.00
Control
CAG-g1
CAG-g2
CAG-g3
Control
CAG-f1
CAG-f2
Cas13d-L1
PUF-E17
CAG80 qPCR Assay

FIG. 1



FISH Assay

FIG. 2

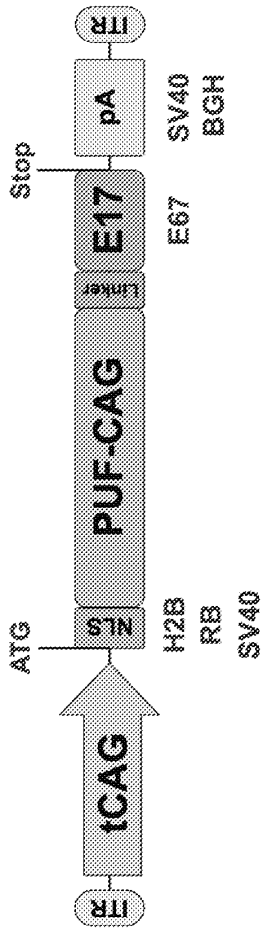


FIG. 3A

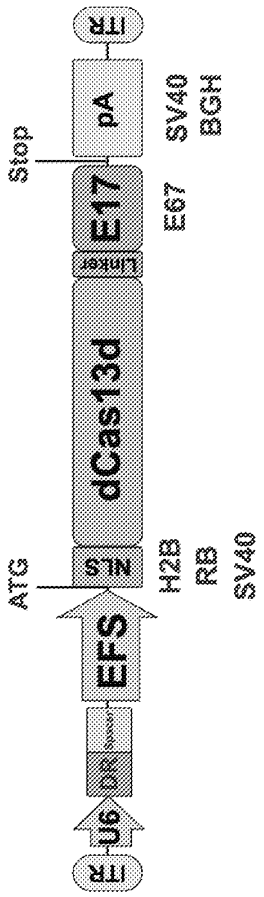


FIG. 3B

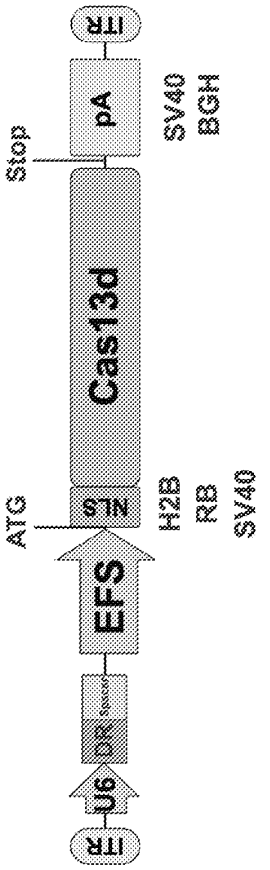


FIG. 3C

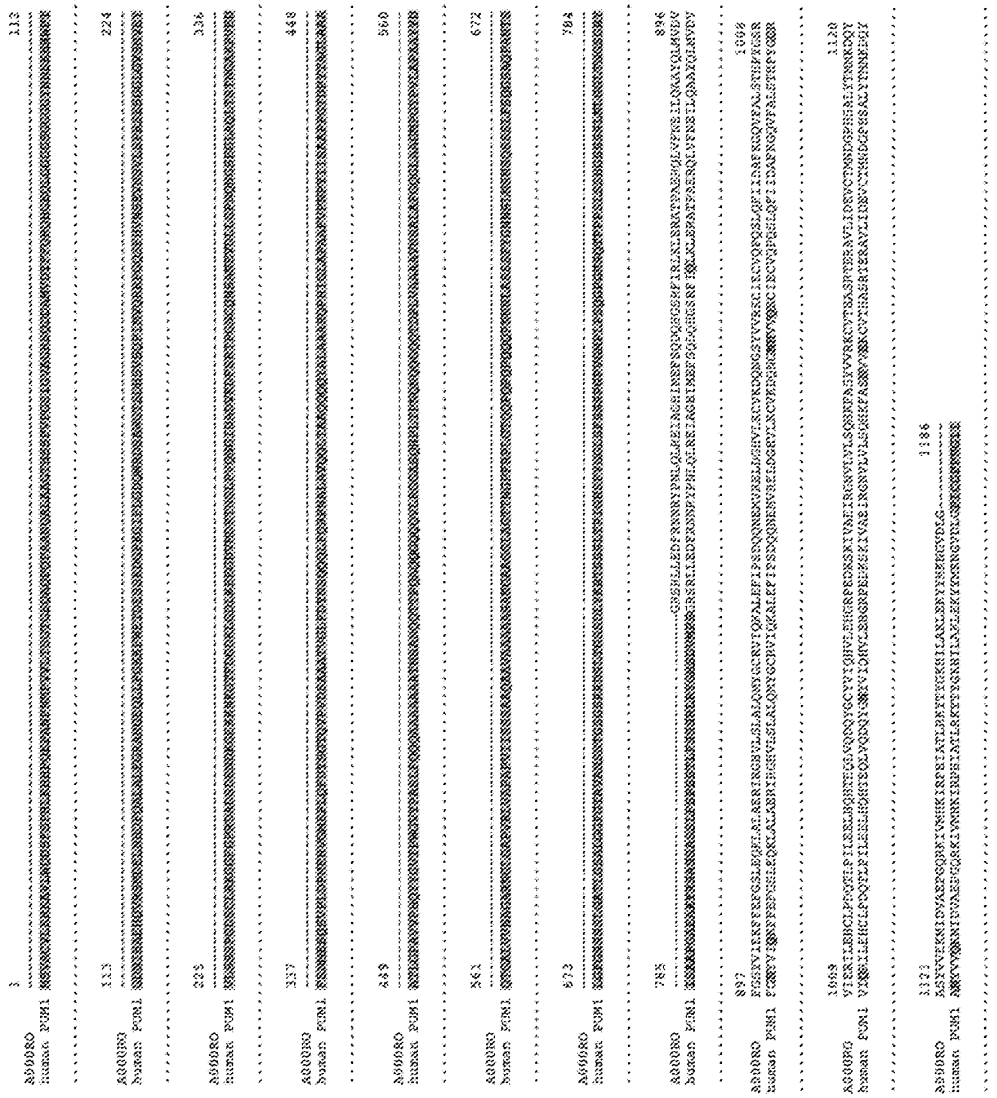


FIG. 4

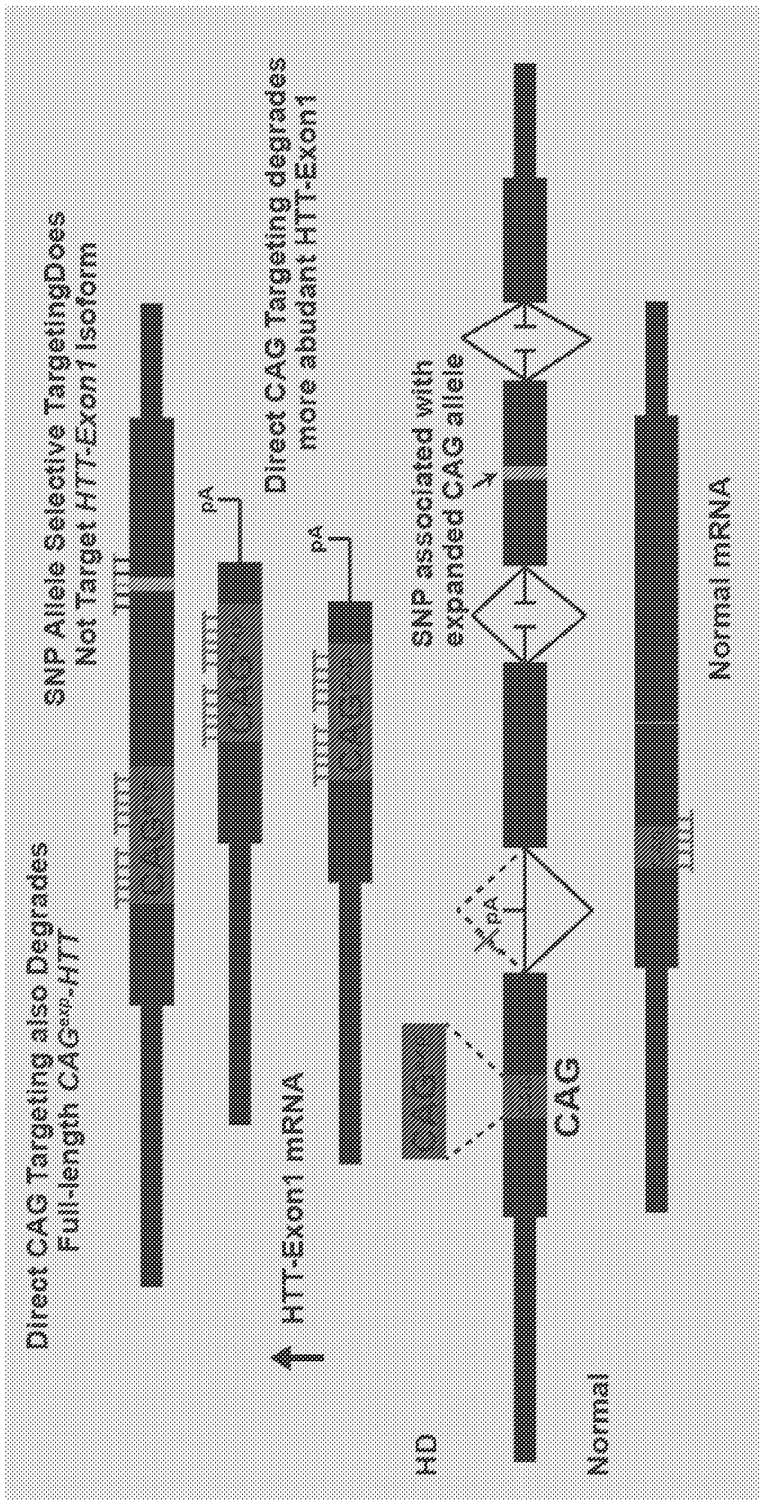

Direct CAG Targeting also Degrades
Full-length CAG^exp-HTT
SNP Allele Selective TargetingDoes
Not Target HTT-Exon1 Isoform
pA
Direct CAG Targeting degrades
more abudant HTT-Exon1
pA
HTT-Exon1 mRNA
SNP associated with
expanded CAG allele
pA
CAG
HD
Normal
Normal mRNA

FIG. 5

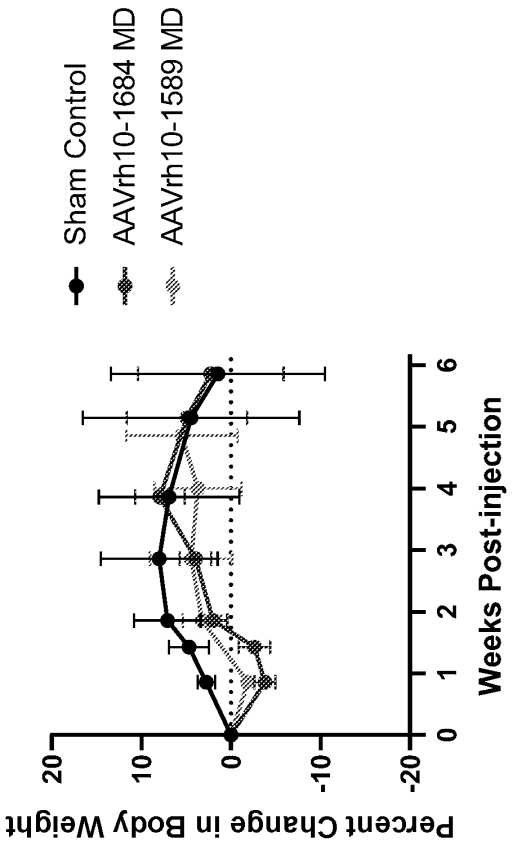


FIG. 6A

Component	AAVrh10-1684	AAVrh10-1589
Promoter	EFS/UBB	EFS/UBB
RBP	**PUF(CAG)**	NA
Endonuclease	NA	**E17**

FIG. 6B

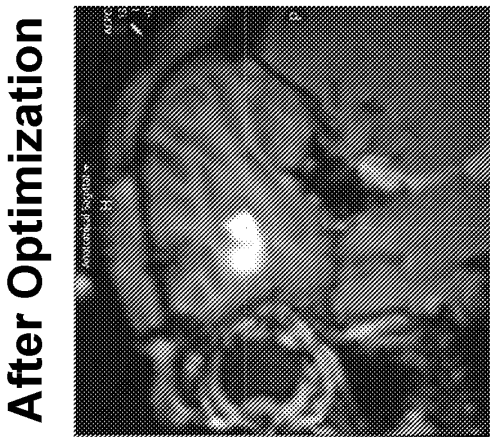


FIG. 7B

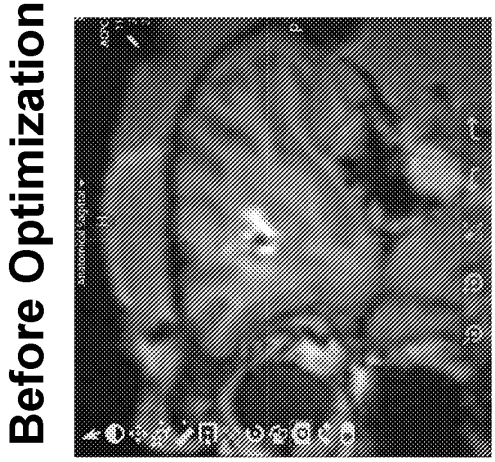


FIG. 7A

Destroy RNA
Reductions in mutant HTT protein

FIG. 8A

Block/Weakly cleave RNA
Translation prevented
Reductions in mutant HTT protein

FIG. 8B

Study	Group	Test Substance
HD08	1	One Hemi: AAV9-RCas9-PIN + NT guide (AAV9-1475)
		Other Hemi: AAV9-RCas9-PIN + CAG guide (AAV9-1347)
HD08b	2	AAV9-RCas9-PIN + CAG guide (AAV9-1347)
	3	AAV9-RCas9-PIN + NT guide (AAV9-1475)

FIG. 9A

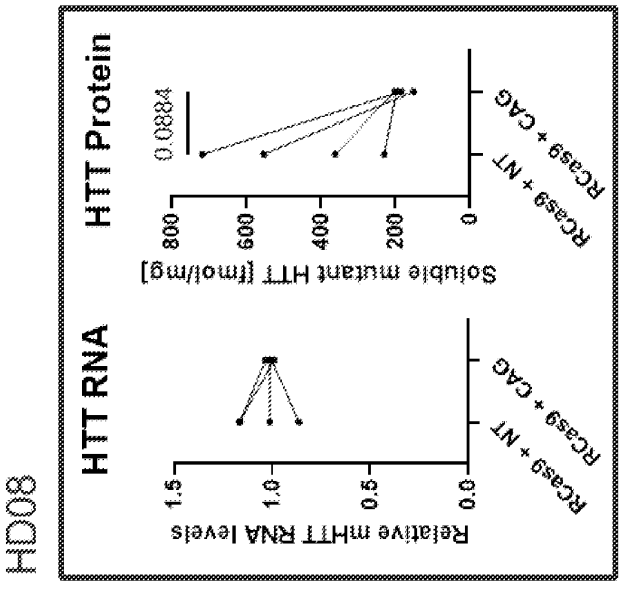


FIG. 9B

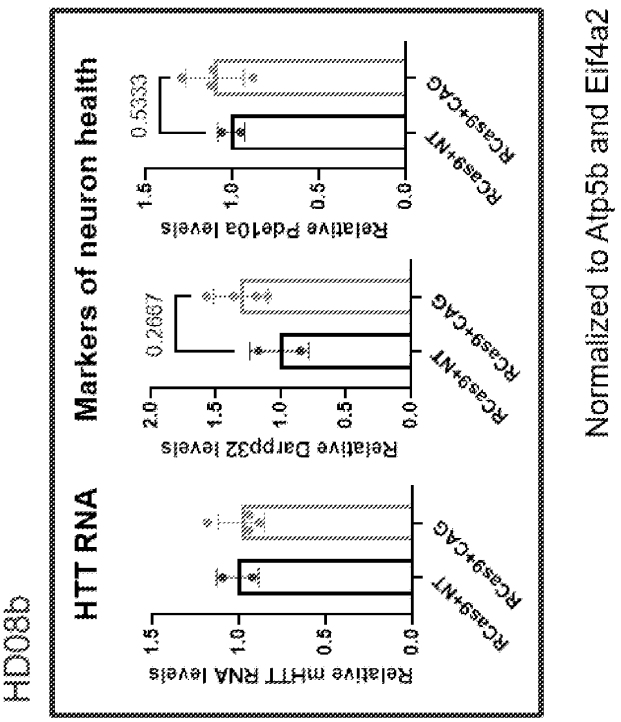
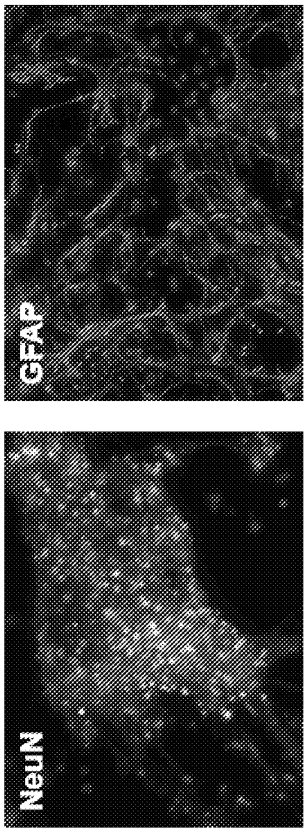
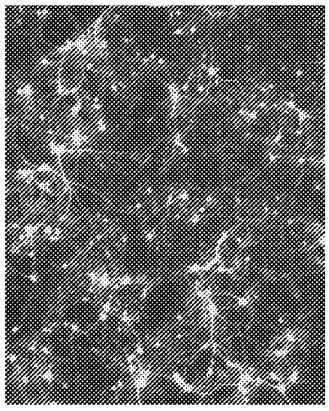


FIG. 9C



Cultures contain both neurons and astrocytes

FIG. 10A



AAVrh.10-GFP

FIG. 10B

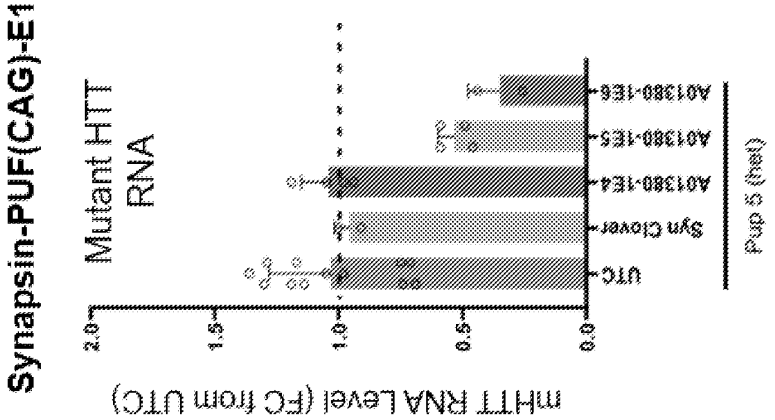


FIG. 10C

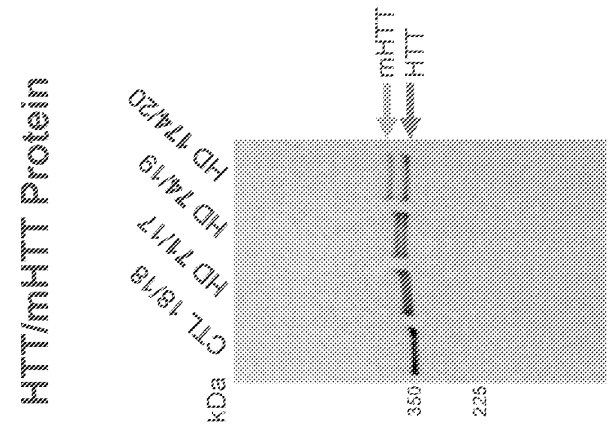


FIG. 11B

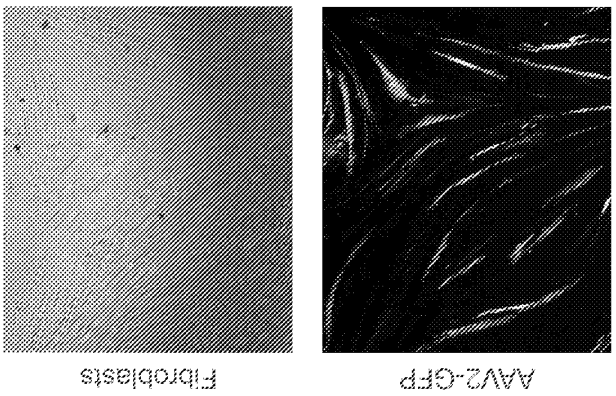


FIG. 11A

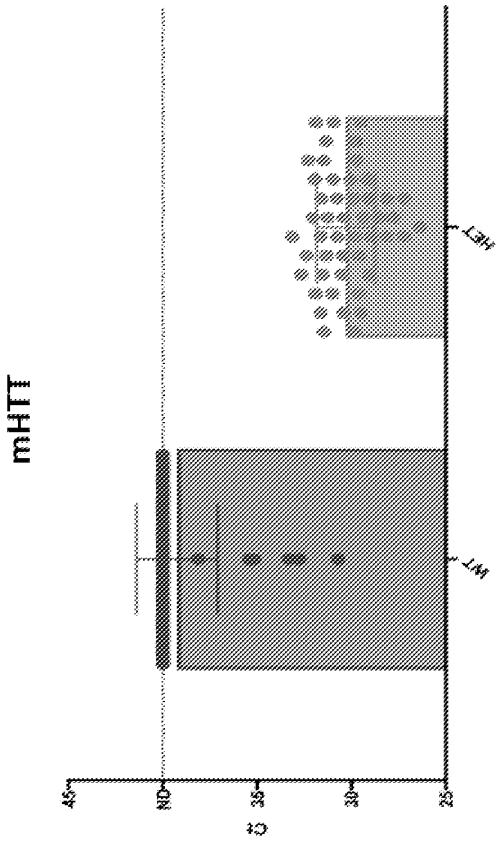


FIG. 12

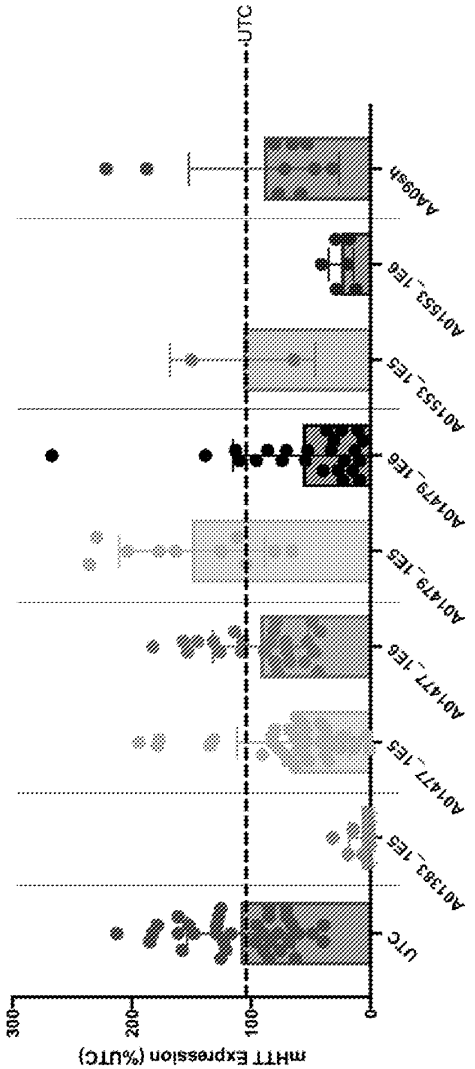


FIG. 13A

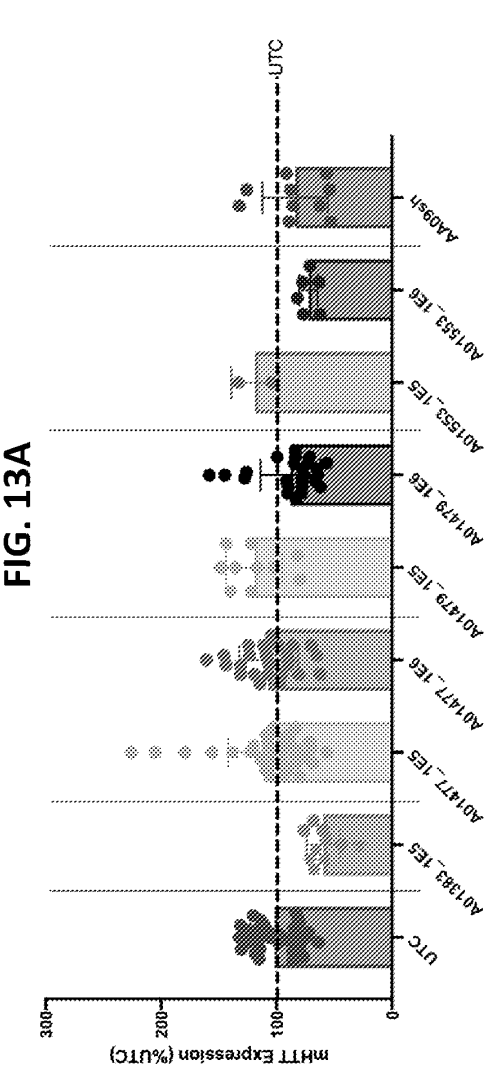


FIG. 13B

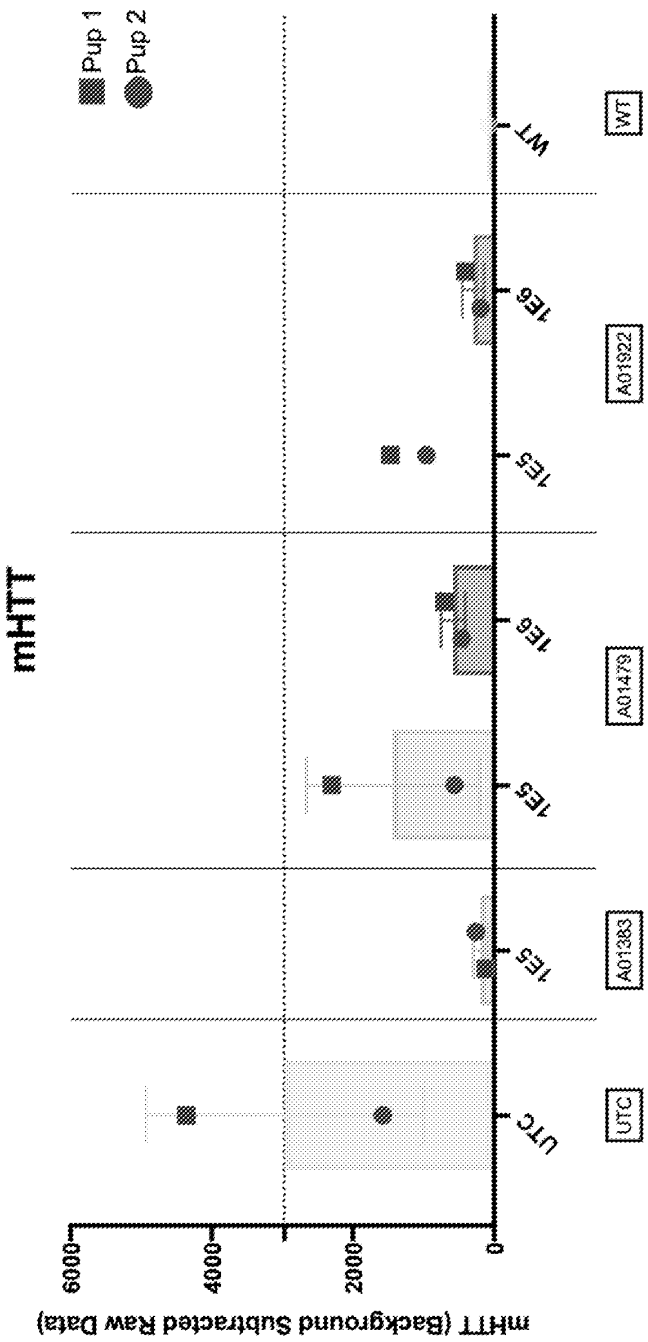

mHTT
Pup 1
Pup 2
mHTT (Background Subtracted Raw Data)
6000
4000
2000
0
UTC
WT
1E5
1E6
A01383
A01479
A01922
WT

FIG. 14A

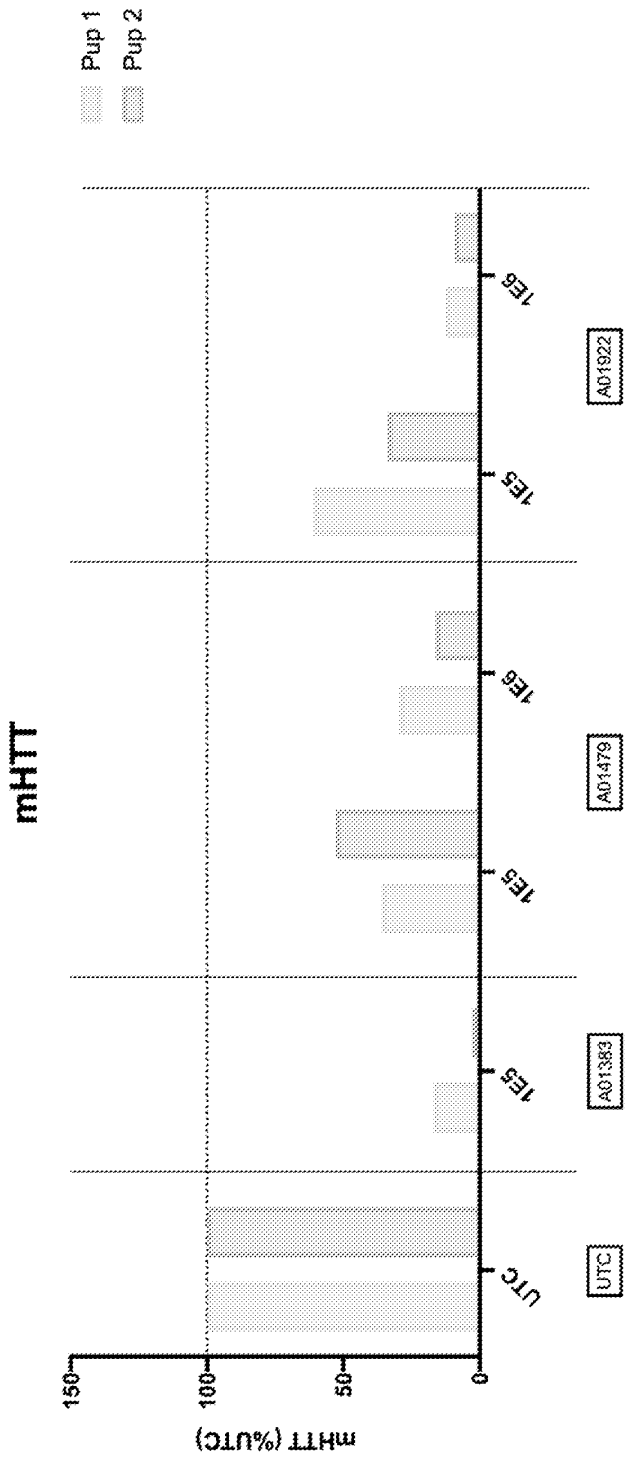

Pup 1
Pup 2
mHTT
mHTT (%UTC)
150
100
50
0
UTC
1E5
A01383
1E5
A01479
1E5
A01922
1E5

FIG. 14B

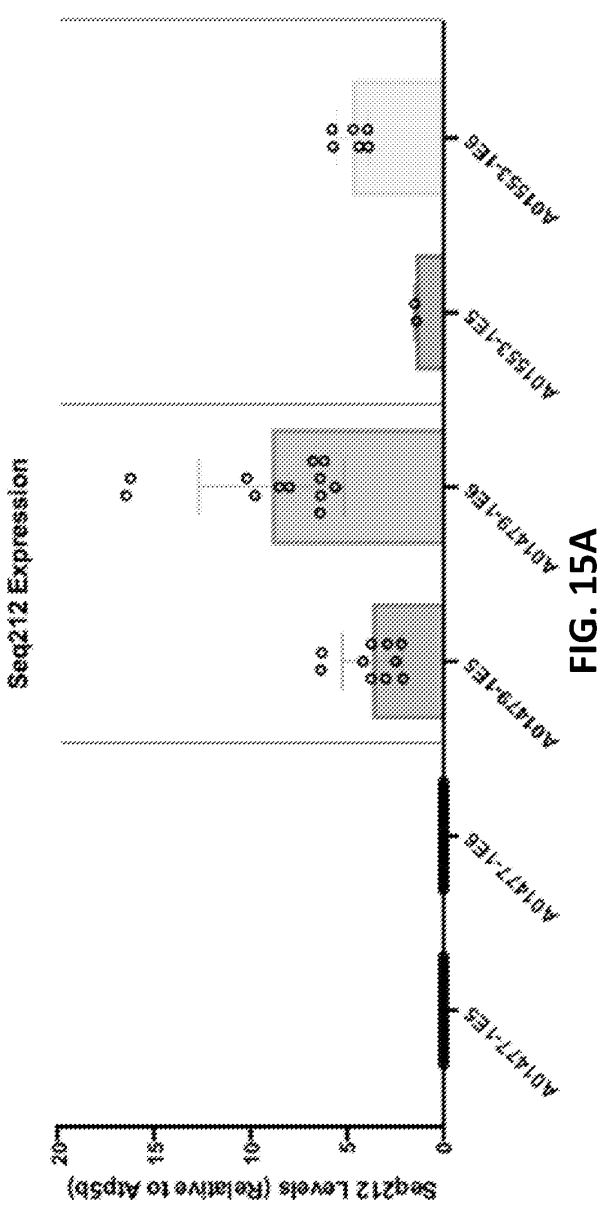


FIG. 15A

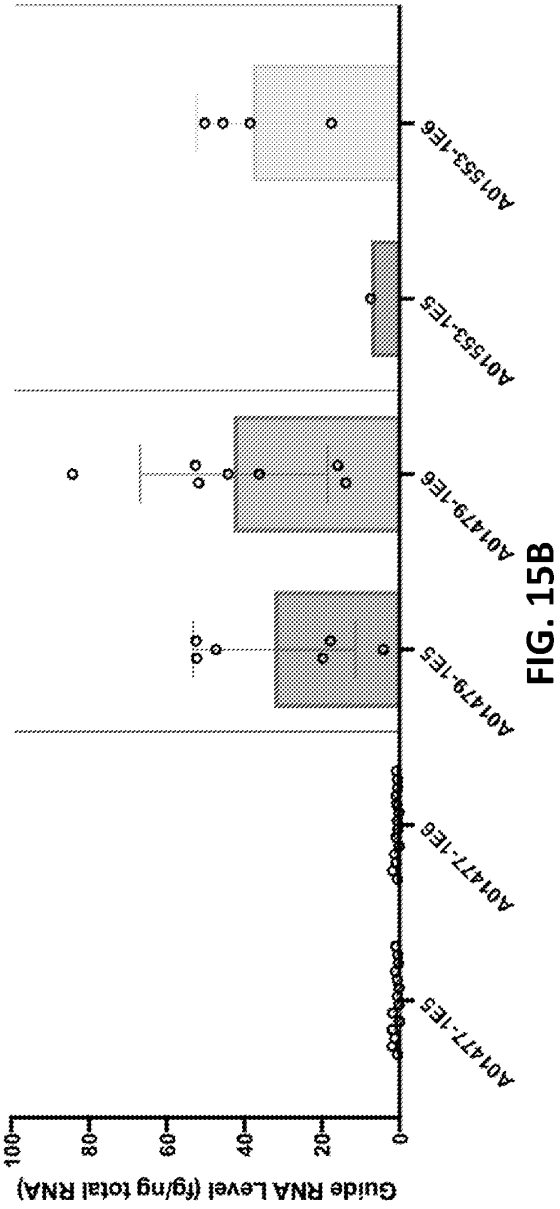


FIG. 15B

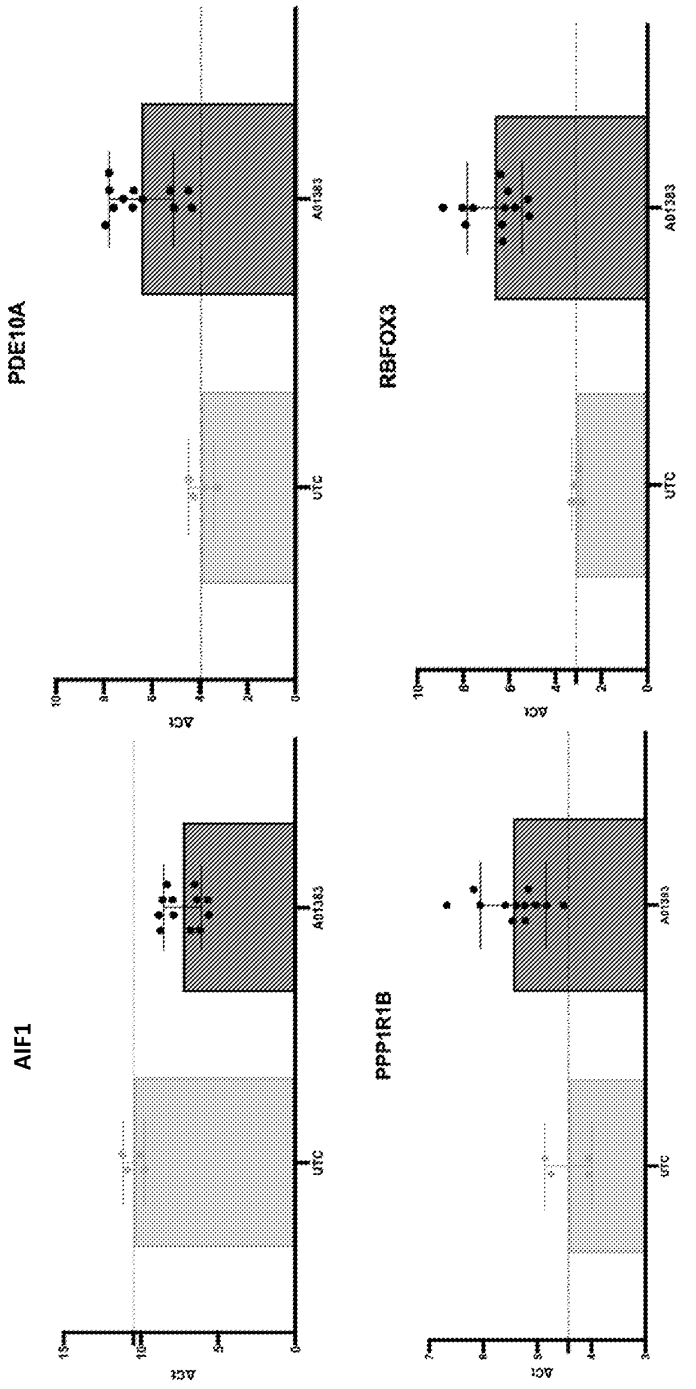


FIG. 16A

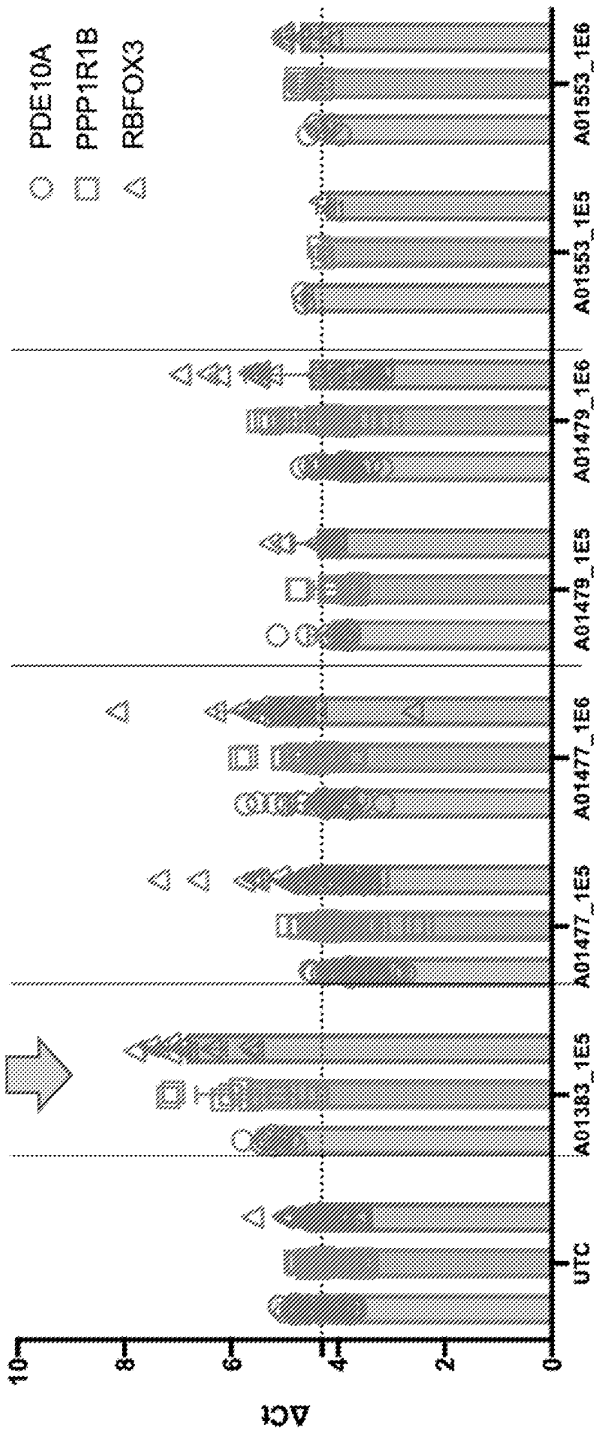

PDE10A
PPP1R1B
RBFOX3
ΔCt
10
8
6
4
2
0
UTC
A01383_1E5
A01477_1E5
A01477_1E6
A01479_1E5
A01479_1E6
A01553_1E5
A01553_1E6

FIG. 16B

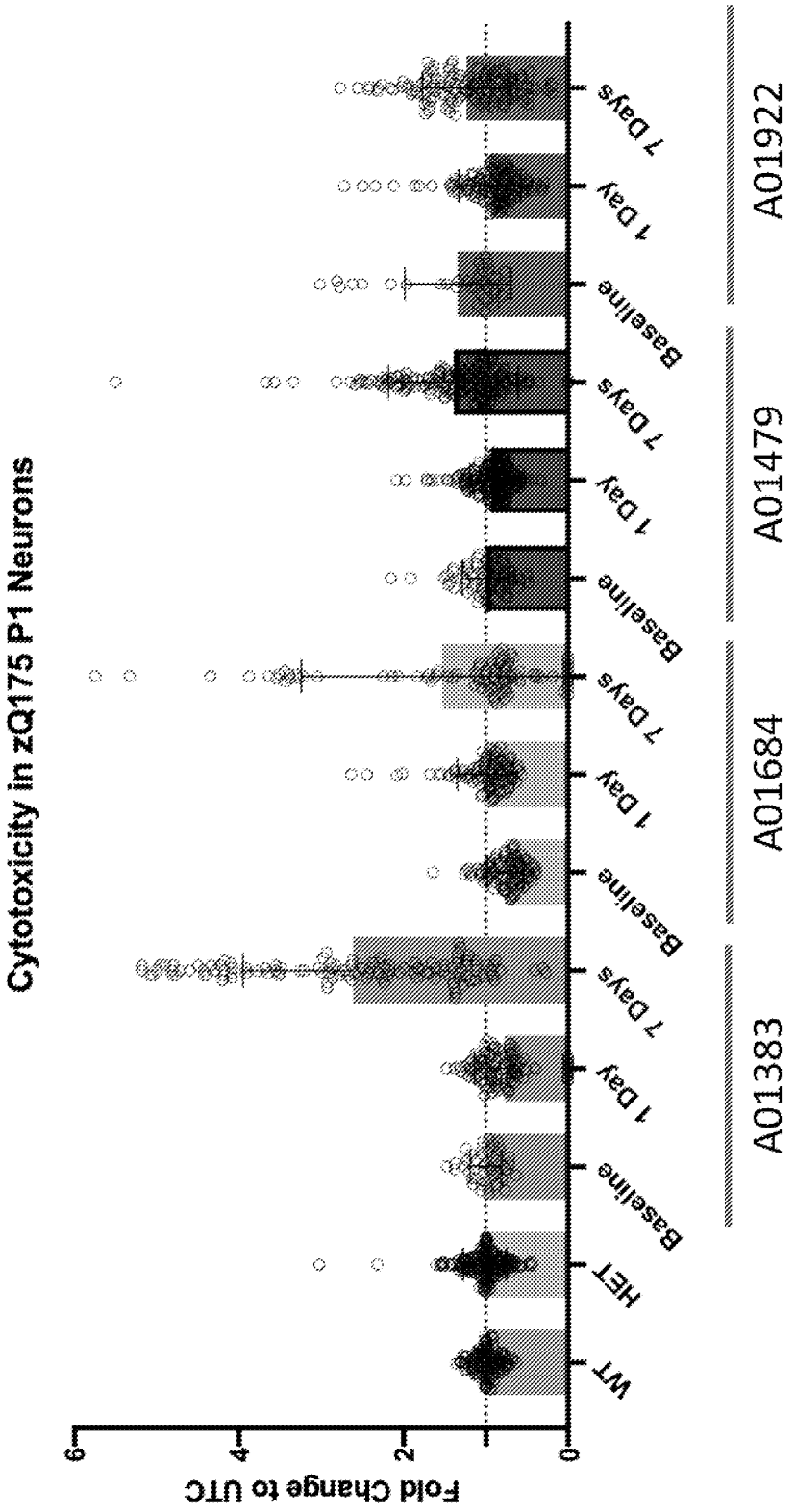

Cytotoxicity in zQ175 P1 Neurons
Fold Change to UTC
0
2
4
6
WT
HET
Baseline
1 Day
7 Days
A01383
A01684
A01479
A01922

FIG. 17

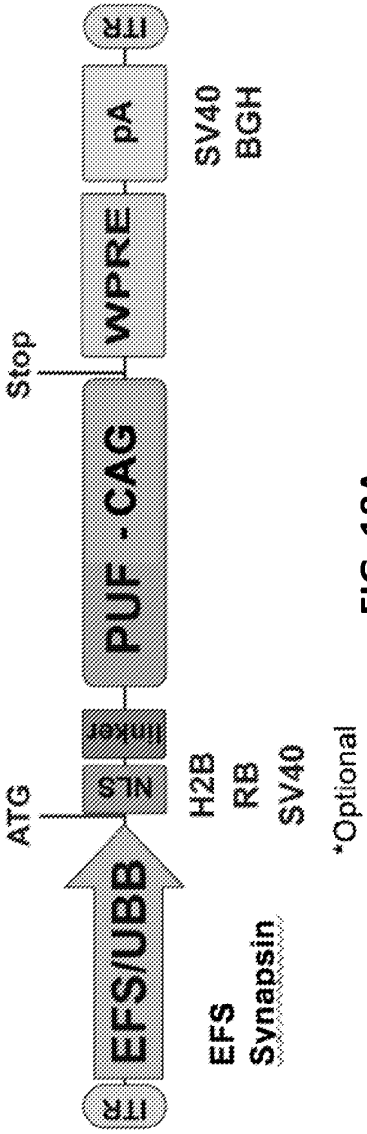


FIG. 18A

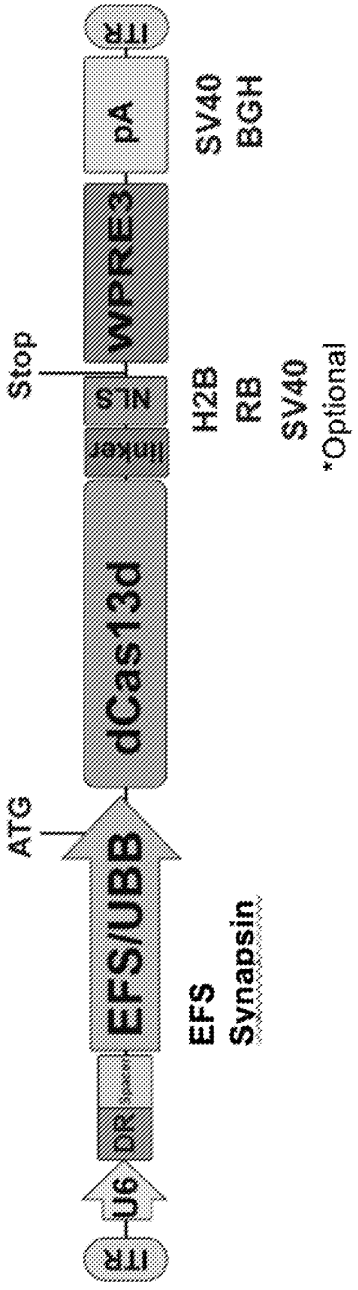
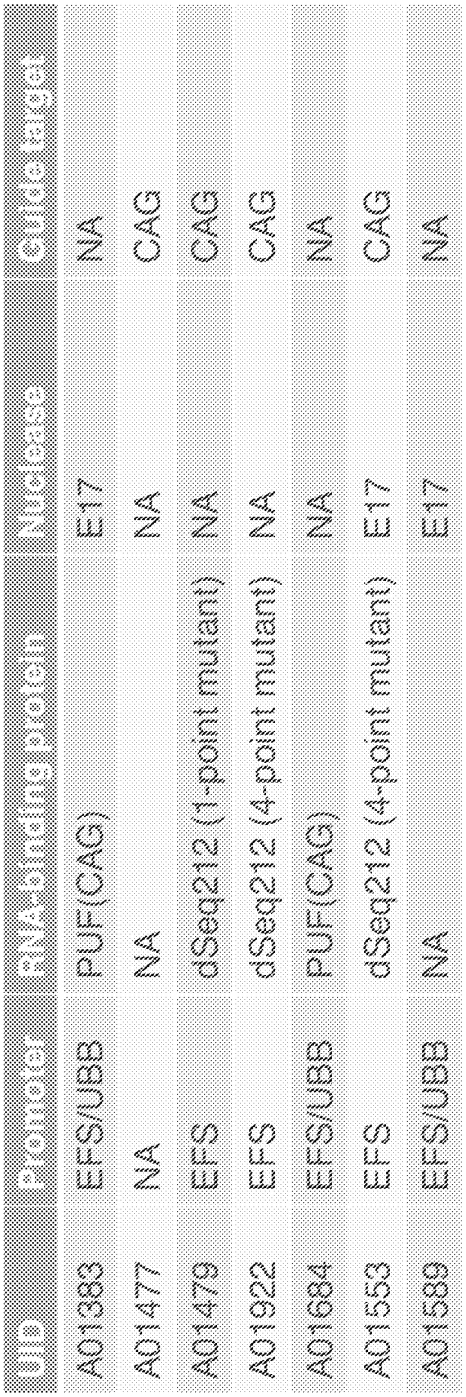


FIG. 18B



UIB	Promoter	RNA binding protein	Nuclease	Guide target
A01383	EFS/UBB	PUF(CAG)	E17	NA
A01477	NA	NA	NA	CAG
A01479	EFS	dSeq212 (1-point mutant)	NA	CAG
A01922	EFS	dSeq212 (4-point mutant)	NA	CAG
A01684	EFS/UBB	PUF(CAG)	NA	NA
A01553	EFS	dSeq212 (4-point mutant)	E17	CAG
A01589	EFS/UBB	NA	E17	NA

FIG. 19