

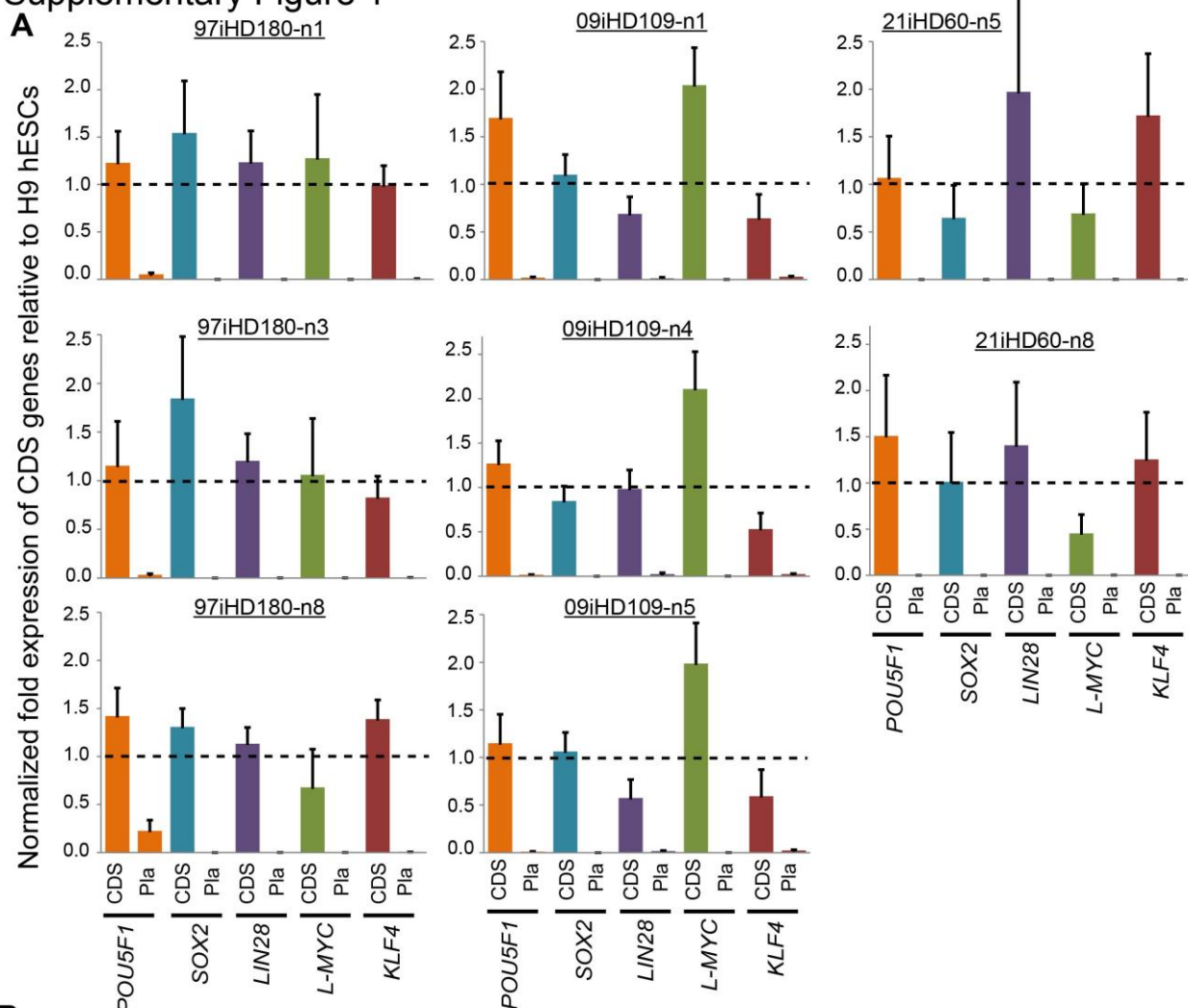
Supplementary Figure 1. Characterization of allelic non-integrating Huntington's Disease-iPSCs and spontaneous differentiation. **(A)** Quantitative RT-PCR analyses of POU5F1 (OCT4), SOX2, LIN28, L-MYC, and KLF4 expression in all clonal HD-iPSCs normalized using $2^{-\Delta\Delta CT}$ method relative to coding genes expressed in H9 hESCs (shown by horizontal dotted line at 1-fold). "CDS" indicates that primers designed for the coding sequence measured expression of the total endogenous gene expression only, whereas "Pla" indicates that primers designed for the plasmid transgene expression, were insignificant or undetectable. Expression of transcripts amplified episomal plasmid-specific primers of a gene is normalized relative to the CDS expression of the same gene. Data are represented as mean \pm SEM. **(B)** Spontaneous *in vitro* EB differentiation of all non-integrating HD-iPSC lines illustrating iPSC (TDGF) and germ-layer (NCAM1, HAND1, MSX1, EOMES and AFP) specific gene expression. GAPDH was used as a loading control. Note: only the 97iHD180 line was deficient in generating expression of endoderm-specific genes (EOMES and AFP). This observation was also confirmed by TaqMan hPSC Scorecard analysis (not shown).

Supplementary Figure 2. HD iPSC-derived striatal-like cultures do not significantly differ in the expression of adult neural/ glial genes or proliferative markers. qRTPCR data at days 42-56 of differentiation does not display a significant difference in expression of the glial/ neuronal genes **(A)** GFAP, **(B)** MAP2, **(C)** DARPP32. **(D)** HD iPSC-derived striatal-like cultures at day 42 of differentiation does not increased proliferation over controls, as displayed by a similar percentage of Ki67 positive nuclei to controls.

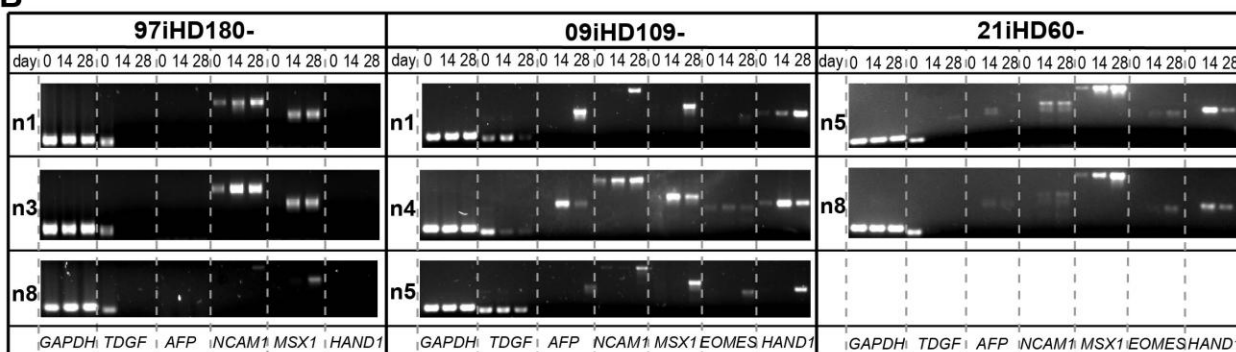
Supplementary Figure 3. TrkB Receptor agonist antibody activates TrkB and reverses phenotypes. **(A)** Phospho-TrkB is upregulated after differentiated HD iPSCs (42 days) were treated with either 20 ng/ml BDNF or 300 nM TrkB activating antibody for 15 min after 48 hrs of BDNF withdrawal. **(B)** Downstream signaling molecules of TrkB, Phospho-Akt and Phospho-Erk are upregulated after differentiated HD iPSCs (42 days) were treated with either 20 ng/ml BDNF or 300 nM TrkB activating antibody for 15 min after 48 hrs of BDNF withdrawal.

Supplementary Figure 4. Representative images of stereologically counted cells. **(A)** Representative images nestin-expressing cells in iPSC-derived striatal cultures after 24 hours of + or – BDNF. **(B)** Representative images of the adult medium spiny neuron marker DARPP32, **(C)** a pan-neural marker TUJ1 or **(D)** a glial marker GFAP that were not decreased in HD cultures upon BDNF withdrawal. **(E)** Neural progenitors from the HD (BACHD) and control mouse hippocampus prior to the exposure of BDNF had similar percentages of Nestin+ cells. **(F)** Representative images after one week in BDNF-containing media, the HD cultures had significantly more Nestin+ cells and this population was lost after acute BDNF withdrawal. **(G)** Representative images of TUNEL+ (green) nuclei (blue) after the acute withdrawal with or without small molecules inhibitors of glutamate signaling.

Supplementary Figure 1

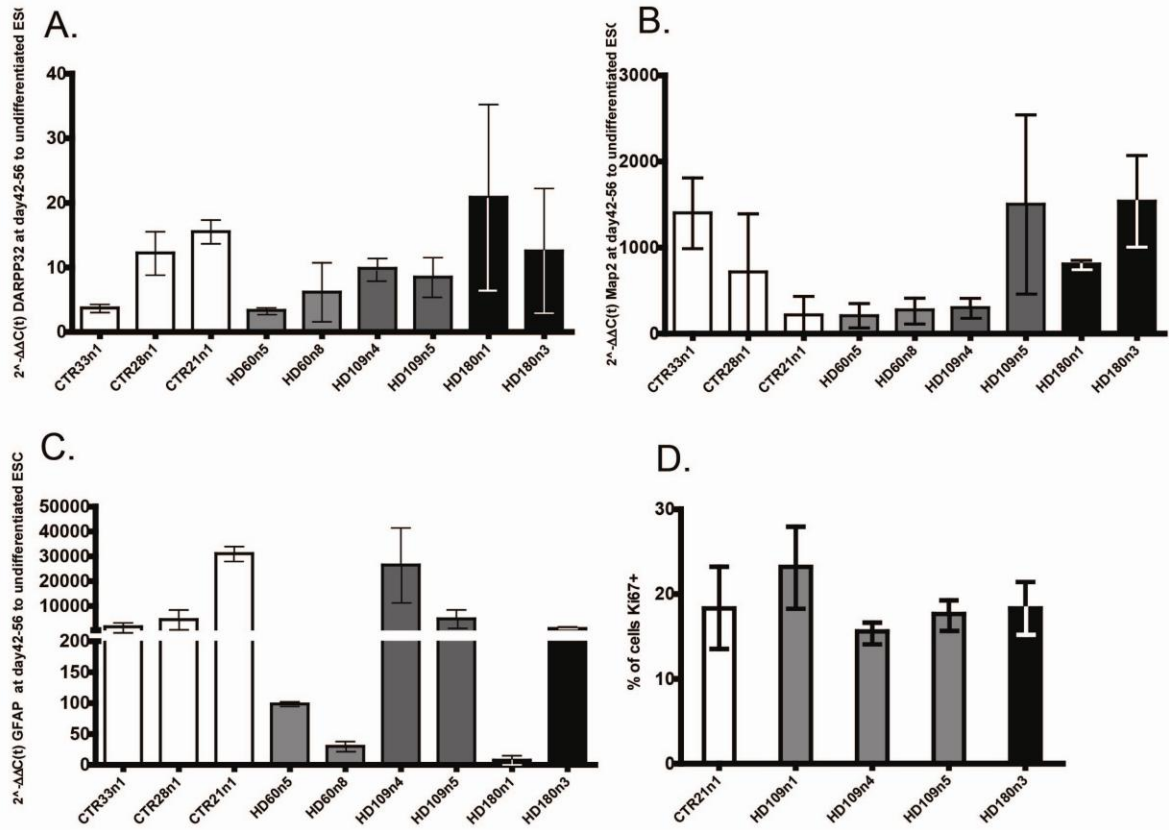


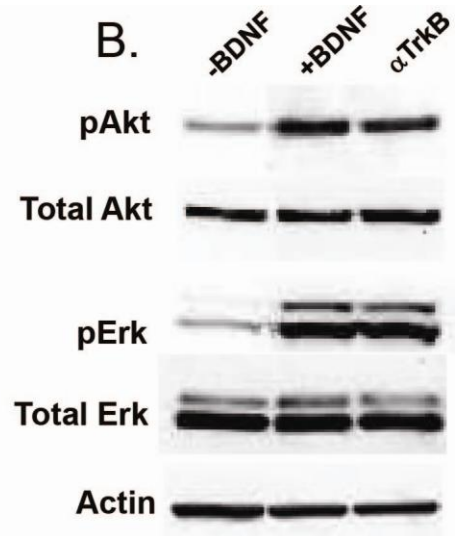
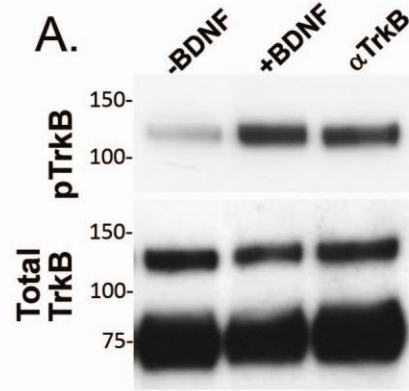
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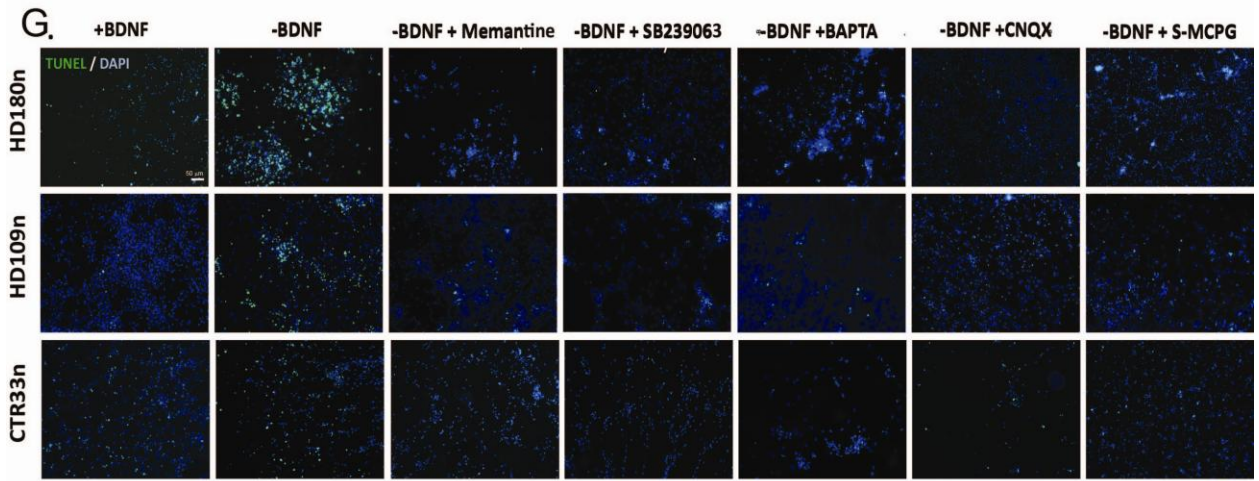
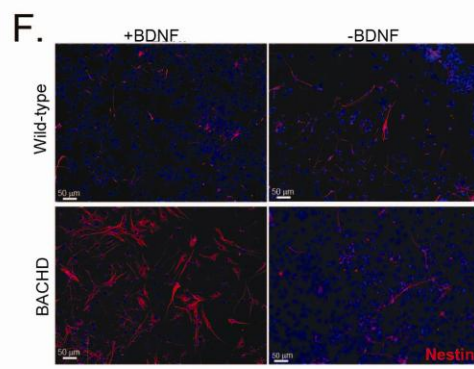
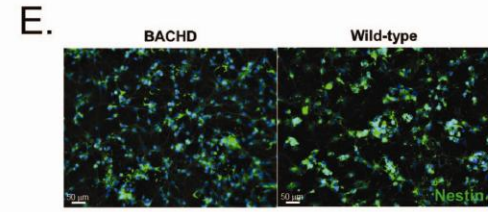
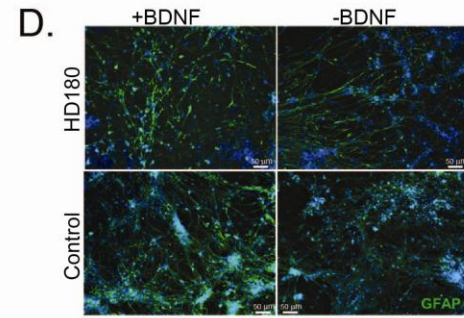
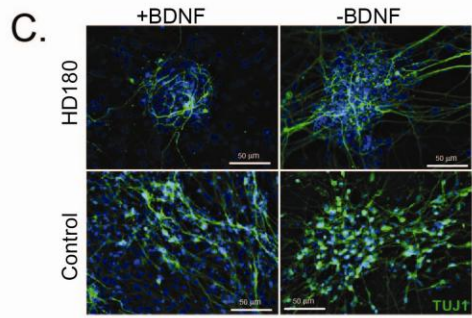
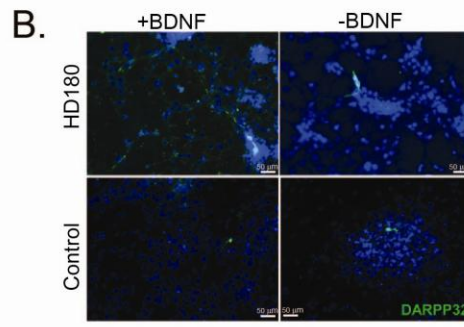
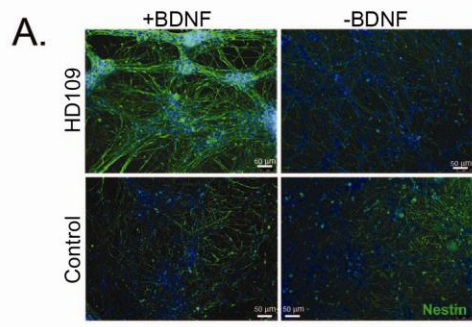


Housekeeping: *GAPDH*
 Pluripotency: *TDGF*
 Endoderm: *AFP*, *EOMES*
 Ectoderm: *NCAM1*
 Mesoderm: *MSX1*, *HAND1*

day 0: iPSC stage
 day 14: spontaneous embryoid body differentiation (-FGF2) for 14 days
 day 28: spontaneous embryoid body differentiation (-FGF2) for 28 days







Supplementary Table 1. Lines used for this study

iPSC lines	iPSC abbreviated	CAG repeat number	Original Coriell fibroblast	Clone numbers used
CS97iHD180n	HD180	180/18	GM09197	1, 2, 3
CS09iHD109n	HD109	109/19	ND39258	1, 4, 5
CS21iHD60n	HD60	60/18	GM03621	5, 8
CS83iCTR33n	CTR33	33/18	GM02183	1, 2
CS14iCTR28n	CTR28	28/18	GM03814	5, 6
CS00iCTR21n	CTR21	21/18	GM05400	1, 2

Supplementary Table 2. Oligo sequences:

ASO	Sequence¹
ASO1	5'-ATTGT ^m CAT ^m CA ^m C ^m CAGA
ASO2	5'-ATAAATTGT ^m CAT ^m CA ^m C ^m C
ASO3	5'-ATAAATTGT ^m CAT ^m CA ^m C ^m CA

¹: Black nucleotides = 2'-deoxynucleotides, orange = MOE and blue = cEt. ^mC denotes 5-methyl cytosine.