Modelling the human blood brain barrier in Huntington Disease.

by

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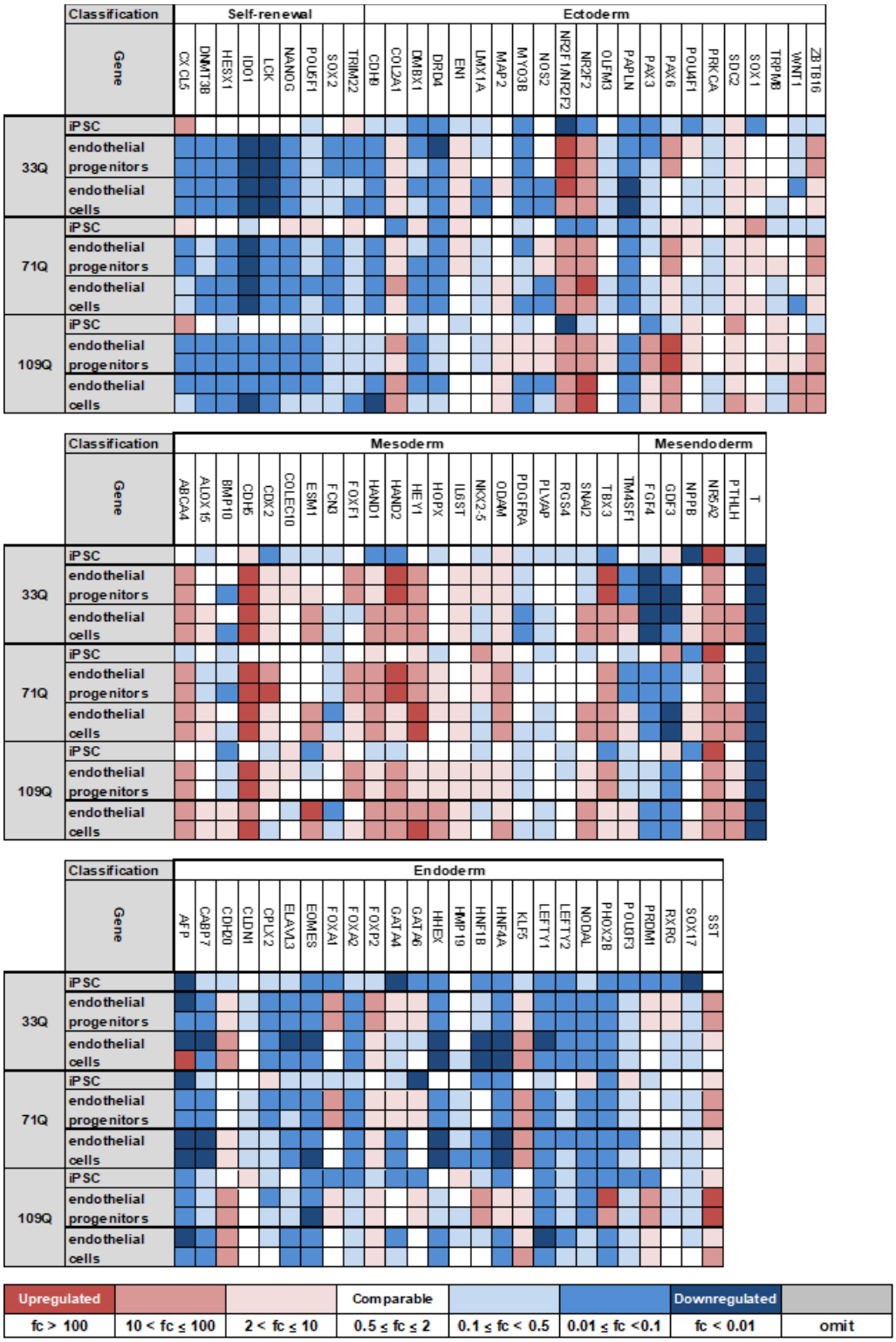

Figure S1. Characterization of human iPSCs. The pluripotency of the clones as well as their self-renewal ability were confirmed by pluripotency score card analysis. Colours indicate the fold change in expression relative to the undifferentiated reference set for each gene.

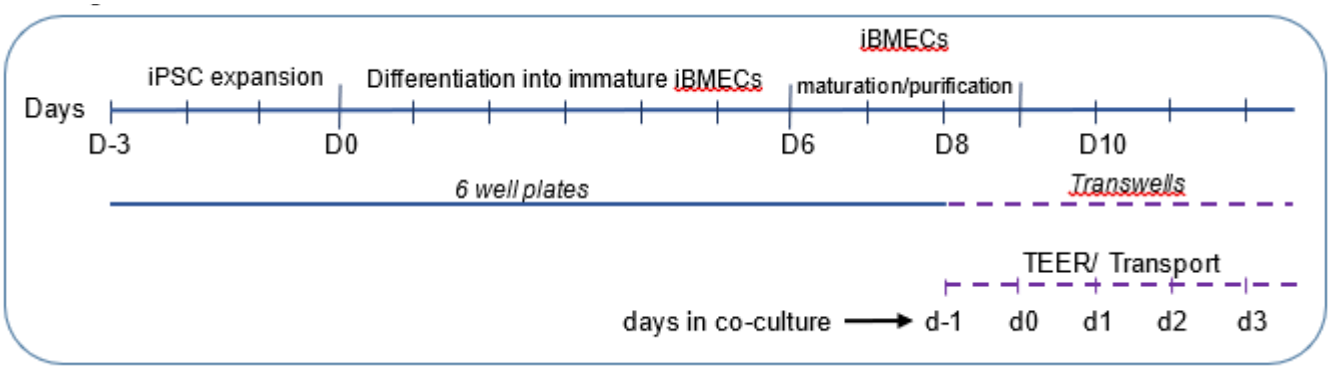

Figure S2: Generation and selection of iBMECs. Scheme illustrating the timeline and the cell culture steps.

Table S1: Differentially expressed genes between HD-iBMECs and healthy iBMEC. More than 3 fold up-regulated and down-regulated genes (statistical difference using Student's t-test set at $p<0.05$).

Gene (in use alias)	iBMEC_71 vs 33		iBMEC_109 vs 33		HD	Other neurological disorders
	FC	Log_2 FC	FC	Log_2 FC		
HLA-C	**1548.8**	**10.6**	**1477.0**	**10.5**	-	-
UNC5D	**366.0**	**8.5**	**1232.1**	**10.3**	**[79]**	Psychiatric illness [80]
COL22A1	**763.4**	**9.6**	**678.4**	**9.4**	[81,82]	Behavioral psychopathologies[83][a]; fragile X syndrome [84][a]
CTSF	**22.4**	**4.5**	**364.3**	**8.5**	-	adult-onset neuronal ceroid lipofuscinosis [85]
SP8	**18.5**	**4.2**	**239.6**	**7.9**	-	-
CDH6	**7.0**	**2.8**	**239.4**	**7.9**	-	AD [86]
C5orf38	**167.7**	**7.4**	**142.9**	**7.2**	-	-
LOC100128252 * (ZNF667-AS1)	**>39.4**	**>5.3**	**>5**	**>2.3**	-	Frontotemporal dementia diseases [87]; cerebral ischemia [88][a]
KCNQ2	**15.3**	**3.9**	**28.5**	**4.8**	**[89,90]**	Epilepsy [91]; epileptic encephalopathy [92]; Linked to CALM3 in neurological disorders [93][a]
C10orf57 (TMEM254)	**21.5**	**4.4**	**24.0**	**4.6**	-	Linked to STX1A and SYT1 in neurological disorders [93][a]
HIST1H3C	**150.2**	**7.2**	**23.7**	**4.6**	[94]	-
ZBTB16	**3.5**	**1.8**	**20.7**	**4.4**	**[95]**	-
IRX2*	**>19.6**	**>4.3**	**>15.9**	**>4.0**	-	PD [96]
HLA-A	**5.8**	**2.5**	**17.9**	**4.2**	[97]	Neurologicals disorders [98]
POU5F1	**5.5**	**2.4**	**17.4**	**4.1**	**[99]**	-
GABRB3	**6.2**	**2.6**	**17.3**	**4.1**	-	Epileptic encephalopathy [100]; neurodevelopment [101]; Febrile seizure [102]
NEFL	**3.1**	**1.6**	**15.9**	**4.0**	**[103-106]**	Charcot-Marie-Tooth disease [107]; PD [108]
CDH4*	**>6.3**	**2.7**	**>12.4**	**>3.6**	-	-
GAP43	**6.0**	**2.6**	**11.1**	**3.5**	-	AD and PD [109]
LIX1	**4.7**	**2.2**	**10.9**	**3.4**	-	-
ARSE	**5.3**	**2.4**	**10.1**	**3.3**	-	-
PMP22	**3.9**	**2.0**	**7.7**	**2.9**	-	Charcot-Marie-Tooth disease [110]
PCDHA11	**3.8**	**1.9**	**6.9**	**2.8**	**[111]**	Protocadherins in neural circuit formation [112][a]; psychosis [113][a]
DPPA4	**3.3**	**1.7**	**6.9**	**2.8**	-	-
THY1	**3.7**	**1.9**	**6.8**	**2.8**	-	-
PAX6	**3.9**	**2.0**	**6.6**	**2.7**	**[114]**	Autism [115][a]; neurodegeneration [116][a]

RGL1	**3.4**	**1.8**	**6.0**	**2.6**	-	-
DPYSL5	**3.2**	**1.7**	**5.6**	**2.5**	**[79,117]**	Age-related [118][a]; X-linked brain disease [119]
SOBP	**4.6**	**2.2**	**5.5**	**2.5**	-	Trisomy 18 [120][c]
EFNA2	**3.9**	**2.0**	**5.4**	**2.4**	-	PD [121]
COL9A3	**5.8**	**2.5**	**4.3**	**2.1**	**[122]**	Ring chromosome 20 [123]; Behavioral psychopathologies [83]
PCDHB5	**23.1**	**4.5**	**4.2**	**2.1**	[124[a]]	-
KCTD12	**3.7**	**1.9**	**3.8**	**1.9**	-	Bipolar I disorder [125]; schizophrenia [126]; depression [127]
CENPM	**4.1**	**2.0**	**3.7**	**1.9**	-	-
KIAA0922 (TMEM131L)	**3.5**	**1.8**	**3.6**	**1.9**	-	-
SEPT3 (SEPTIN3)	**3.8**	**1.9**	**3.5**	**1.8**	-	AD [128]
EEF1A2	**3.1**	**1.6**	**3.4**	**1.8**	**[129]** *(KO induces HTT aggregation)*	Degenerative epileptic-dyskinetic encephalopathy [130]; epilectic autistic patient [131]
CDC45	**3.1**	**1.6**	**3.2**	**1.7**	-	Schizophrenia [132]
ADAMTS5	**0.3**	**-1.8**	**0.3**	**-1.8**	**[133]**	AD [134,135]; Cerebral cavernous malformation [136]
MXRA5	**0.3**	**-1.6**	**0.3**	**-1.9**	-	Heart failure [137]
KCNJ2-AS1	**0.3**	**-1.8**	**0.3**	**-1.9**	[138][a]	-
NAALADL2	**0.3**	**-1.7**	**0.3**	**-1.9**	-	-
CEBPA	**0.3**	**-1.9**	**0.2**	**-2.2**	**[139,140]**	Migraine [141][c]
STAC	**0.3**	**-1.6**	**0.2**	**-2.4**	**[142]**	-
CDH20	**0.1**	**-2.8**	**0.2**	**-2.5**	-	Glioblastoma [143]
WNT9B	**0.2**	**-2.3**	**0.2**	**-2.5**	**[144,145]**	Hunter syndrome [146] https://dx.doi.org/10.3390%2Fijms18051072
FAM20A	**0.2**	**-2.1**	**0.2**	**-2.6**	-	-
ST6GALNAC2	**0.3**	**-1.9**	**0.2**	**-2.6**	**[147]**	-
TNNT3	**0.2**	**-2.2**	**0.2**	**-2.6**	**[148]**	-
ESRRG	**0.2**	**-2.4**	**0.2**	**-2.6**	**[148]**	Common neurodegenerative hub [149]; AD [150][c]
PLAGL1 (Zac1)	**0.2**	**-2.2**	**0.2**	**-2.7**	**[151][c]**	AD [152]
CA10	**0.1**	**-3.0**	**0.1**	**-2.8**	-	Glioma [153]
SLC16A10	**0.3**	**-1.7**	**0.1**	**-3.3**	-	-
SNCG	**0.2**	**-2.4**	**0.1**	**-3.6**	-	PD [139,154[b]]
NPR3	**0.1**	**-2.8**	**0.1**	**-4.2**	-	AD [155][a]
MRPS21	**0.2**	**-2.6**	**0.1**	**-4.2**	-	-
DSCR6 (RIPPLY3)	**0.2**	**-2.4**	**0.0**	**-4.4**	-	-
LOC100134868	**0.3**	**-1.6**	**0.0**	**-5.8**	-	-

a: not a strong or direct evidence,
b: absence of correlation or discorrelation
c: opposite effect observed

Table S2: Excel file transcriptome results

Table S2_selected transcriptome results.xlsx

Table S3: The most expressed SLC transporters is reported.

Gene (protein)	iBMEC			FC (iBMEC_109 vs 33)	p value (Student's t-test)	Role	Disease
	33Q	71Q	109Q			(IUPHAR)	(Hu. 2020)
SLC2A3 (GLUT3)	3473	3504	3118	0.9	0.246	Brain/neuron glucose transporter	
SLC7A5 (LAT1)	1210	824	817	0.7	0.132	Large neutral aa subunit	Autism secptrum disorder (glioma in rodent)
SLC25A3 (MPCP)	1101	776	1000	0.9	0.234	Mitochondrial phosphate carrier	(11 of the- 25 family are linked to brain disorders)
SLC25A6 (ANT3)	633	582	501	0.8	**0.023**	Mitochondrial adenine nucleotide translocator 3	(11 of the- 25 family are linked to brain disorders)
SLC2A1 (GLUT1)	588	360	491	0.8	0.168	Erythrocyte /brain glucose transporter	Glucose transport type 1 deficiency syndrome. intractable infantile seizure. complex motor disorder. intellectual impairment. hypoglycorrhachia. microcephaly. (epilepsy and metabolic dysfunction in redent)
SLC44A2 (CTL2)	454	374	349	0.8	**0.005**	Chloline transporter-like 2	
SLC25A5 (ANT2)	412	467	425	1.0	0.729	Mitochondrial adenine nucleotide translocator 2	Intellectual disability
NPC2	386	321	318	0.8	**0.014**	NPC intracellular cholesterol transporter 2	Niemann-Pick disease, type C
SLC39A1 (ZIP1)	311	273	253	0.8	0.082	Zinc transporrter-1	
SLC38A2 (SNAT2)	294	310	286	1.0	0.840	Amino acid transporter 2	
SLC39A7 (RING5)	279	202	224	0.8	0.096	Zinc transporrter-7	
SLC3A2 (4F2hc)	264	265	249	0.9	0.153	Heterodimerize with SLC7 family members (dibasic and neutral aa)	
SLC25A8 (UCP2)	258	208	123	0.5	**0.003**	mitochondrial uncoupling protein 2	
SLC16A1 (MCT1)	233	327	333	1.4	0.103	Transport of the product of cellular metabolism	
SLC25A1 (CIC)	222	197	214	1.0	0.709	Mitochondrial citrate transporter	
SLC5A6 (SMVT)	190	207	195	1.0	0.740	Multivitamin transporter (apical membrane enterocytes and colonocytes (biotin. pantothenic acid)	
SLC25A39 (CIG69)	189	149	174	0.9	0.521	Mitochondrial aa transporter subfamily	Childhood absence epilepsy
SLC35A4 (MGC2541)	184	179	167	0.9	0.465	For nucleotide-conjugated sugars within Golgi for glycoprotein formation	
SLC16A10 (TAT1)	178	56	18	0.1	**0.001**	Aromatic aa (tryptophane. phenylalanine. tyrosine. L-DOPA)	
SLC9A3R1	168	128	174	1.0	0.829	(SLC9A3: sodium hydrogen exchanger)	
SLC64A1 (TMEM165)	166	135	131	0.8	**0.032**	Golgi Ca^{2+}/H^{+} exchangers	

SLC56A1 (SFXN1)	148	147	140	0.9	0.663	Mitochondrial serine transporte	
SLC25A50 (MTCH2)	141	139	135	1.0	0.557	Mitochondrial Carrier 2	
SLC53A1 (XPR1)	133	136	108	0.8	0.163	Xenotropic And Polytropic Retrovirus Receptor 1	Brain calcification
SLC2A4RG	129	113	105	0.8	**0.020**	(SLC2A4: insulin-responsive glucose transporter. GLUT4)	
SLC58A2 (TUSC3)	129	121	128	1.0	0.951	Tumor Suppressor Candidate 3	
SLC11A2 (DMT1)	113	64	66	0.6	**0.020**	Divalent cations across endosomal membranes	Parkinson's disease in rodent
SLC25A23 (APC2)	105	112	99	0.9	0.616	Mitochondrial phosphate carrier 2	
SLC35B1 (UGTREL1)	103	92	91	0.9	0.264	Galactose transporter	
SLC1A5 (ASCT2)	99	115	138	1.4	**0.012**	Neutral aa transporter (alanine. serine. cysteine) (unlike EAATs same SLC1 family. donot counter transport K+)	Schizophrenia in rodents
SLC54A2 (MPC2)	96	96	95	1.0	0.931	Mitochondrial Pyruvate Carrier 2	
SLC7A1 (CAT1)	96	99	115	1.2	**0.046**	Y+ basic aa (arginine. lysine. histidine. ornithine)	
SLC66A5 (MPDU1)	94	79	65	0.7	**0.011**	Mannose-P-Dolichol Utilization Defect 1	
SLC25A4 (ANT1)	92	102	94	1.0	0.684	Mitochondrial adenine nucleotide translocator 1	Bipolar disorder in rodent

Table S4: *In vitro-in vivo* correlation. Table showing values used for correlation shown in **Figure 9** and references for in vivo $K_{p,uu,CSF}$.

Compound	**Human $K_{p,uu,CSF}$**	**References**
arginine	0.28	[156]
atenolol	0.18	[157]
bupropion	1.11	[158]
caffeine	1.00	[159]
carbamazepine	0.24	[160]
citalopram	1.77	[161]
digoxin	0.31	[162]
gabapentin	0.16	[157]
glucose	0.65	[161]
IgG (MEM189)	0.002	[161]
indomethacin	0.27	[157]
KYNA	0.024	[164]
L-DOPA	0.49	[158]
leucine	0.12	[156]
methotrexate	0.02	[165]
phenylalanine	0.28	[156]
phenytoin	0.19	[166]
propranolol	0.42	[157]
verapamil	1.13	[157]

Table S5: Antibodies used in this study.

Target epitope	Species	Type	Label	RRID*	Vendor	Cat n	Dilution
Claudin-5	rabbit	polyclonal		AB_2533157	Thermo Fisher	34-1600	1:25
Claudin-1	rabbit	polyclonal		AB_2533977	Thermo Fisher	71-500	1:25
Actin	mouse	monoclonal		AB_2533147	Thermo Fisher	33-9100	1:200
ACE2	rabbit	polyclonal			Abcam	Ab15384	1:500
LDLR	rabbit	polyclonal			Abcam	Ab133127	1:1000
EGFR	rabbit	monoclonal			Abcam	Ab52894	1:1000
LRP1	rabbit	polyclonal			Origene	AP21130PU-N	1:500
HAP1	mouse	monoclonal			Origene	TA309681	1:500
TFR1	rabbit	polyclonal			Origene	TA324761	1:1000
Human Oct-4A	mouse IgG2A	monoclonal			ReD System	MAB17591	10 µl x 10^6 cells
Human Von Willebrand Factor	rabbit	polyclonal		AB_2315602	Dako/Agilent	A008202-5	1:100
Von Willebrand Factor	mouse IgG1 Kappa	monoclonal	Alexa Fluor 488		Novusbio	NBP2-34510AF488	5µL x 10^6 cells
Isotype Control APC-conjugated Antibody Clone # 20102	mouse IgG2A	monoclonal			ReD System	IC003A	10µl x 10^6 cells
Isotype Control (11711)	mouse IgG1		Alexa Fluor 488		ReD System	IC002G	5µL x 10^6 cells
ZO1 tigh junction protein	mouse	monoclonal		AB_2533147	Thermo Fisher	339100	1:100
CD31/PECAM-1	rabbit	polyclonal			Thermo Fisher	RB-10333-P1	1:25 MEOH
LDLR	rabbit	polyclonal			Invitrogen	PA5-22976	1:1000
Anti-rabbit IgG (H+L) Highly Cross-Adsorbed	goat	polyclonal	Alexa Fluor 488	AB_2576217	Thermo Fisher	A-11034	1:3000
Anti-rabbit IgG (H+L) Highly Cross-Adsorbed	goat	polyclonal	Alexa Fluor 594	AB_2534095	Thermo Fisher	A-11037	1:3000
Anti-Mouse IgG (H+L) Highly Cross-Adsorbed	goat	polyclonal	Alexa Fluor Plus 488	AB_2633275	Thermo Fisher	A32723	1:3000
Anti-Mouse IgG (H+L) Highly Cross-Adsorbed	goat	polyclonal	Alexa Fluor Plus 594	AB_2534091	Thermo Fisher	A-11032	1:3000

*: Research resource identifier.

References

79. Ring, K.L.; An, M.C.; Zhang, N.; O'Brien, R.N.; Ramos, E.M.; Gao, F.; Atwood, R.; Bailus, B.J.; Melov, S.; Mooney, S.D.; et al. Genomic Analysis Reveals Disruption of Striatal Neuronal Development and Therapeutic Targets in Human Huntington's Disease Neural Stem Cells. *Stem Cell Rep.* **2015**, *5*, 1023–1038, https://doi.org/10.1016/j.stemcr.2015.11.005.
80. Srikanth, P.; Lagomarsino, V.N.; Pearse, R.; Liao, M.; Ghosh, S.; Nehme, R.; Seyfried, N.; Eggan, K.; Young-Pearse, T.L. Convergence of independent DISC1 mutations on impaired neurite growth via decreased UNC5D expression. *Transl. Psychiatry* **2018**, *8*, 245, https://doi.org/10.1038/s41398-018-0281-9.
81. Agus, F.; Crespo, D.; Myers, R.H.; Labadorf, A. The caudate nucleus undergoes dramatic and unique transcriptional changes in human prodromal Huntington's disease brain. *BMC Med Genom.* **2019**, *12*, 1–17, https://doi.org/10.1186/s12920-019-0581-9.
82. Mehta, S.R.; Tom, C.M.; Wang, Y.; Bresee, C.; Rushton, D.; Mathkar, P.P.; Tang, J.; Mattis, V.B. Human Huntington's Disease iPSC-Derived Cortical Neurons Display Altered Transcriptomics, Morphology, and Maturation. *Cell Rep.* **2018**, *25*, 1081–1096.e6, https://doi.org/10.1016/j.celrep.2018.09.076.
83. Smagin, D.; Galyamina, A.G.; Kovalenko, I.L.; Babenko, V.; Kudryavtseva, N.N. Aberrant Expression of Collagen Gene Family in the Brain Regions of Male Mice with Behavioral Psychopathologies Induced by Chronic Agonistic Interactions. *BioMed Res. Int.* **2019**, *2019*, 1–13, https://doi.org/10.1155/2019/7276389.
84. Boland, M.J.; Nazor, K.L.; Tran, H.T.; Szücs, A.; Lynch, C.L.; Paredes, R.; Tassone, F.; Sanna, P.P.; Hagerman, R.J.; Loring, J.F. Molecular analyses of neurogenic defects in a human pluripotent stem cell model of fragile X syndrome.. *Brain* **2017**, *140*, 582–598, https://doi.org/10.1093/brain/aww357.
85. van der Zee, J.; Mariën, P.; Crols, R.; Van Mossevelde, S.; Dillen, L.; Perrone, F.; Engelborghs, S.; Verhoeven, J.; D'Aes, T.; Groote, C.C.-D.; et al. Mutated*CTSF*in adult-onset neuronal ceroid lipofuscinosis and FTD. *Neurol. Genet.* **2016**, *2*, e102, https://doi.org/10.1212/nxg.0000000000000102.
86. Ahmad, S.; Milan, M.D.C.; Hansson, O.; Demirkan, A.; Agustin, R.; Sáez, M.E.; Giagtzoglou, N.; Cabrera-Socorro, A.; Bakker, M.H.M.; Ramirez, A.; et al. CDH6 and HAGH protein levels in plasma associate with Alzheimer's disease in APOE ε4 carriers. *Sci. Rep.* **2020**, *10*, 1–13, https://doi.org/10.1038/s41598-020-65038-5.
87. Ehrlich, M.; Hallmann, A.-L.; Reinhardt, P.; Araúzo-Bravo, M.J.; Korr, S.; Röpke, A.; Psathaki, O.E.; Ehling, P.; Meuth, S.G.; Oblak, A.L.; et al. Distinct Neurodegenerative Changes in an Induced Pluripotent Stem Cell Model of Frontotemporal Dementia Linked to Mutant TAU Protein. *Stem Cell Rep.* **2015**, *5*, 83–96, https://doi.org/10.1016/j.stemcr.2015.06.001.
88. Yuan, D.; Huang, J.; Yuan, X.; Zhao, J.; Jiang, W. Zinc finger protein 667 expression is upregulated by cerebral ischemic preconditioning and protects cells from oxidative stress. *Biomed. Rep.* **2013**, *1*, 534–538, https://doi.org/10.3892/br.2013.124.

89. Cao, Y.; Bartolomé-Martín, D.; Rotem, N.; Rozas, C.; Dellal, S.S.; Chacon, M.A.; Kadriu, B.; Gulinello, M.; Khodakhah, K.; Faber, D.S. Rescue of homeostatic regulation of striatal excitability and locomotor activity in a mouse model of Huntington's disease. *Proc. Natl. Acad. Sci.* **2015**, *112*, 2239–2244, https://doi.org/10.1073/pnas.1405748112.
90. Mucha, M.; Ooi, L.; Linley, J.E.; Mordaka, P.; Dalle, C.; Robertson, B.; Gamper, N.; Wood, I.C. Transcriptional Control of KCNQ Channel Genes and the Regulation of Neuronal Excitability. *J. Neurosci.* **2010**, *30*, 13235–13245, https://doi.org/10.1523/JNEUROSCI.1981-10.2010.
91. Amadori, E.; Brolatti, N.; Scala, M.; Marchese, F.; Vari, M.S.; Ramenghi, L.A.; Madia, F.; Minetti, C.; Striano, P. Precision medicine in early-onset epilepsy: The KCNQ2 paradigm. *J. Transl. Genet. Genom.* **2020**, https://doi.org/10.20517/jtgg.2020.36.
92. Weckhuysen, S.; Ivanovic, V.; Hendrickx, R.; Van Coster, R.; Hjalgrim, H.; Møller, R.S.; Grønborg, S.; Schoonjans, A.-S.; Ceulemans, B.; Heavin, S.B.; et al. Extending the KCNQ2 encephalopathy spectrum: Clinical and neuroimaging findings in 17 patients. *Neurology* **2013**, *81*, 1697–1703, https://doi.org/10.1212/01.wnl.0000435296.72400.a1.
93. Zhang, Y.; Zhao, Y.; Song, X.; Luo, H.; Sun, J.; Han, C.; Gu, X.; Li, J.; Cai, G.; Zhu, Y.; et al. Modulation of Stem Cells as Therapeutics for Severe Mental Disorders and Cognitive Impairments. *Front. Psychiatry* **2020**, *11*, https://doi.org/10.3389/fpsyt.2020.00080.
94. Świtońska, K.; Szlachcic, W.J.; Handschuh, L.; Wojciechowski, P.; Marczak, .; Stelmaszczuk, M.; Figlerowicz, M.; Figiel, M. Identification of Altered Developmental Pathways in Human Juvenile HD iPSC With 71Q and 109Q Using Transcriptome Profiling. *Front. Cell. Neurosci.* **2019**, *12*, https://doi.org/10.3389/fncel.2018.00528.
95. Zhang, T.; Dong, K.; Liang, W.; Xu, D.; Xia, H.; Geng, J.; Najafov, A.; Liu, M.; Li, Y.; Han, X.; et al. G-protein-coupled receptors regulate autophagy by ZBTB16-mediated ubiquitination and proteasomal degradation of Atg14L. *eLife* **2015**, *4*, e06734–e06734, https://doi.org/10.7554/elife.06734.
96. Sim, H.; Lee, J.-E.; Yoo, H.M.; Cho, S.; Lee, H.; Baek, A.; Kim, J.; Seo, H.; Kweon, M.-N.; Kim, H.G.; et al. Iroquois Homeobox Protein 2 Identified as a Potential Biomarker for Parkinson's Disease. *Int. J. Mol. Sci.* **2020**, *21*, 3455, https://doi.org/10.3390/ijms21103455.
97. Madsen, H.; Nielsen, L.S.; A Sorensen, S. An association study of Huntington's disease and HLA.. *J. Med Genet.* **1982**, *19*, 452–454, https://doi.org/10.1136/jmg.19.6.452.
98. Misra, M.; Damotte, V.; Hollenbach, J.A. The immunogenetics of neurological disease. *Immunology* **2017**, *153*, 399–414, https://doi.org/10.1111/imm.12869.
99. Smith-Geater, C.; Hernandez, S.J.; Lim, R.; Adam, M.; Wu, J.; Stocksdale, J.T.; Wassie, B.T.; Gold, M.P.; Wang, K.Q.; Miramontes, R.; et al. Aberrant Development Corrected in Adult-Onset Huntington's Disease iPSC-Derived Neuronal Cultures via WNT Signaling Modulation. *Stem Cell Rep.* **2020**, *14*, 406–419, https://doi.org/10.1016/j.stemcr.2020.01.015.
100. Papandreou, A.; McTague, A.; Trump, N.; Ambegaonkar, G.; Ngoh, A.; Meyer, E.; Scott, R.H.; A Kurian, M. *GABRB3*mutations: A new and emerging cause of early infantile epileptic encephalopathy. *Dev. Med. Child Neurol.* **2015**, *58*, 416–420, https://doi.org/10.1111/dmcn.12976.
101. Tanaka, M.; DeLorey, T.M.; Delgado-Escueta, A.V.; Olsen, R.W. GABRB3, Epilepsy, and Neurodevelopment. **2012**, 887–899, https://doi.org/10.1093/med/9780199746545.003.0070.
102. Møller, R.S.; Wuttke, T.V.; Helbig, I.; Marini, C.; Johannesen, K.M.; Brilstra, E.H.; Vaher, U.; Borggraefe, I.; Talvik, I.; Talvik, T.; et al. Mutations in *GABRB3*. *Neurology* **2017**, *88*, 483–492, https://doi.org/10.1212/wnl.0000000000003565.
103. Byrne, L.M.; Rodrigues, F.B.; Blennow, K.; Durr, A.; Leavitt, B.R.; Roos, R.A.C.; I Scahill, R.; Tabrizi, S.J.; Zetterberg, H.; Langbehn, D.; et al. Neurofilament light protein in blood as a potential biomarker of neurodegeneration in Huntington's disease: A retrospective cohort analysis. *Lancet Neurol.* **2017**, *16*, 601–609, https://doi.org/10.1016/s1474-4422(17)30124-2.
104. Johnson, E.B.; Byrne, L.M.; Gregory, S.; Rodrigues, F.B.; Blennow, K.; Durr, A.; Leavitt, B.; Roos, R.A.; Zetterberg, H.; Tabrizi, S.J.; et al. Neurofilament light protein in blood predicts regional atrophy in Huntington disease. *Neurology* **2018**, *90*, e717–e723, https://doi.org/10.1212/wnl.0000000000005005.
105. Rodrigues, F.B., Byrne, L.M., Tortelli, R., Johnson, E.B., Wijeratne, P.A., Arridge, M., de Vita, E., Ghazaleh, N., Houghton, R., Furby, H., Alexander, D.C., Tabrizi, S.J., Schobel, S., Scahill, R.I., Heslegrave, A., Zetterberg, H., & Wild, E.J. (2020). Longitudinal dynamics of mutant huntingtin and neurofilament light in Huntington's disease: The prospective HD-CSF study. In medRxiv. https://doi.org/10.1101/2020.03.31.20045260.
106. Soylu-Kucharz, R.; Sandelius, .; Sjögren, M.; Blennow, K.; Wild, E.J.; Zetterberg, H.; Björkqvist, M. Neurofilament light protein in CSF and blood is associated with neurodegeneration and disease severity in Huntington's disease R6/2 mice. *Sci. Rep.* **2017**, *7*, 1–8, https://doi.org/10.1038/s41598-017-14179-1.
107. Jordanova, A.; De Jonghe, P.; Boerkoel, C.F.; Takashima, H.; De Vriendt, E.; Ceuterick, C.; Martin, J.-J.; Butler, I.J.; Mancias, P.; Ch Papasozomenos, S.; et al. Mutations in the neurofilament light chain gene (NEFL) cause early onset severe Charcot-Marie-Tooth disease. *Brain* **2003**, *126*, 590–597, https://doi.org/10.1093/brain/awg059.
108. Bäckström, D.; Linder, J.; Mo, S.J.; Riklund, K.; Zetterberg, H.; Blennow, K.; Forsgren, L.; Lenfeldt, N. NfL as a biomarker for neurodegeneration and survival in Parkinson disease. *Neurology* **2020**, *95*, e827–e838, https://doi.org/10.1212/wnl.0000000000010084.
109. Chung, D.; Shum, A.; Caraveo, G. GAP-43 and BASP1 in Axon Regeneration: Implications for the Treatment of Neurodegenerative Diseases. *Front. Cell Dev. Biol.* **2020**, *8*, https://doi.org/10.3389/fcell.2020.567537.
110. Boutary, S.; Echaniz-Laguna, A.; Adams, D.; Loisel-Duwattez, J.; Schumacher, M.; Massaad, C.; Massaad-Massade, L. Treating PMP22 gene duplication-related Charcot-Marie-Tooth disease: The past, the present and the future. *Transl. Res.* **2020**, *227*, 100–111, https://doi.org/10.1016/j.trsl.2020.07.006.

111. Langfelder, P.; Cantle, J.P.; Chatzopoulou, D.; Wang, N.; Gao, F.; Al-Ramahi, I.; Lu, X.-H.; Ramos, E.M.; El-Zein, K.; Zhao, Y.; et al. Integrated genomics and proteomics define huntingtin CAG length–dependent networks in mice. *Nat. Neurosci.* **2016**, *19*, 623–633, https://doi.org/10.1038/nn.4256.
112. Peek, S.L.; Mah, K.M.; Weiner, J.A. Regulation of neural circuit formation by protocadherins. *Experientia* **2017**, *74*, 4133–4157, https://doi.org/10.1007/s00018-017-2572-3.
113. Melka, M.G.; A Castellani, C.; Rajakumar, N.; O'Reilly, R.; Singh, S.M. Olanzapine-induced methylation alters cadherin gene families and associated pathways implicated in psychosis. *BMC Neurosci.* **2014**, *15*, 112, https://doi.org/10.1186/1471-2202-15-112.
114. Ament, S.; Pearl, J.R.; Cantle, J.P.; Bragg, R.M.; Skene, P.J.; Coffey, S.R.; E Bergey, D.; Wheeler, V.C.; E MacDonald, M.; Baliga, N.S.; et al. Transcriptional regulatory networks underlying gene expression changes in Huntington's disease. *Mol. Syst. Biol.* **2018**, *14*, e7435, https://doi.org/10.15252/msb.20167435.
115. Kikkawa, T.; Casingal, C.; Chun, S.H.; Shinohara, H.; Hiraoka, K.; Osumi, N. The role of Pax6 in brain development and its impact on pathogenesis of autism spectrum disorder. *Brain Res.* **2018**, *1705*, 95–103, https://doi.org/10.1016/j.brainres.2018.02.041.
116. Mishra, S.; Maurya, S.; Srivastava, K.; Shukla, S.; Mishra, R. Pax6 influences expression patterns of genes involved in neurodegeneration. *Ann. Neurosci.* **2015**, *22*, 226–231, https://doi.org/10.5214/ans.0972.7531.220407.
117. Chandrasekaran, S.; Bonchev, D. Network analysis of human post-mortem microarrays reveals novel genes, microRNAs, and mechanistic scenarios of potential importance in fighting huntington's disease. *Comput. Struct. Biotechnol. J.* **2016**, *14*, 117–130, https://doi.org/10.1016/j.csbj.2016.02.001.
118. Breen, M.S.; Ozcan, S.; Ramsey, J.M.; Wang, Z.; Ma'Ayan, A.; Rustogi, N.; Gottschalk, M.G.; Webster, M.J.; Weickert, C.S.; Buxbaum, J.D.; et al. Temporal proteomic profiling of postnatal human cortical development. *Transl. Psychiatry* **2018**, *8*, 267, https://doi.org/10.1038/s41398-018-0306-4.
119. Laumonnier, F.; Cuthbert, P.C.; Grant, S.G. The Role of Neuronal Complexes in Human X-Linked Brain Diseases. *Am. J. Hum. Genet.* **2007**, *80*, 205–220, https://doi.org/10.1086/511441.
120. Hui, L.; Slonim, D.; Wick, H.C.; Johnson, K.L.; Koide, K.; Bianchi, D.W. Novel neurodevelopmental information revealed in amniotic fluid supernatant transcripts from fetuses with trisomies 18 and 21. *Qual. Life Res.* **2012**, *131*, 1751–1759, https://doi.org/10.1007/s00439-012-1195-x.
121. Marsh, A.G.; Cottrell, M.T.; Goldman, M.F. Epigenetic DNA Methylation Profiling with MSRE: A Quantitative NGS Approach Using a Parkinson's Disease Test Case. *Front. Genet.* **2016**, *7*, 191, https://doi.org/10.3389/fgene.2016.00191.
122. Kumar, A.; Zhang, J.; Tallaksen-Greene, S.; Crowley, M.R.; Crossman, D.; Morton, A.J.; Van Groen, T.; Kadish, I.; Albin, R.L.; Lesort, M.; et al. Allelic series of Huntington's disease knock-in mice reveals expression discorrelates. *Hum. Mol. Genet.* **2016**, *25*, 1619–1636, https://doi.org/10.1093/hmg/ddw040.
123. Corrêa, T.; Venâncio, A.C.; Galera, M.F.; Riegel, M. Candidate Genes Associated with Delayed Neuropsychomotor Development and Seizures in a Patient with Ring Chromosome 20.. *Case Rep. Genet.* **2020**, *2020*, 5957415–6, https://doi.org/10.1155/2020/5957415.
124. Qureshi, I.A.; Gokhan, S.; Mehler, M.F. REST and CoREST are transcriptional and epigenetic regulators of seminal neural fate decisions. *Cell Cycle* **2010**, *9*, 4477–4486, https://doi.org/10.4161/cc.9.22.13973.
125. Lee, M.T.M.; Chen, C.H.; Lee, C.S.; Chong, M.Y.; Ouyang, W.C.; Chiu, N.Y.; Chuo, L.J.; Tan, H.K.L.; Lane, H.Y.; Chang, T.J.; et al. Genome-wide association study of bipolar I disorder in the Han Chinese population. *Mol. Psychiatry* **2010**, *16*, 548–556, https://doi.org/10.1038/mp.2010.43.
126. Benes, F.M. Amygdalocortical Circuitry in Schizophrenia: From Circuits to Molecules. *Neuropsychopharmacology* **2009**, *35*, 239–257, https://doi.org/10.1038/npp.2009.116.
127. Sibille, E.; Wang, Y.; Joeyen-Waldorf, J.; Gaiteri, C.; Surget, A.; Oh, S.; Belzung, C.; Tseng, G.C.; Lewis, D. A Molecular Signature of Depression in the Amygdala. *Am. J. Psychiatry* **2009**, *166*, 1011–1024, https://doi.org/10.1176/appi.ajp.2009.08121760.
128. Takehashi, M.; Alioto, T.; Stedeford, T.; Persad, A.S.; Banasik, M.; Masliah, E.; Tanaka, S.; Ueda, K. Septin 3 Gene Polymorphism in Alzheimer's Disease. *Gene Expr.* **2003**, *11*, 263–270, https://doi.org/10.3727/000000003783992243.
129. Teuling, E.; Bourgonje, A.; Veenje, S.; Thijssen, K.; De Boer, J.; Van Der Velde, J.; Swertz, M.; Nollen, E. Modifiers of mutant huntingtin aggregationfunctional conservation of C. elegans-modifiers of polyglutamine aggregation. *PLoS Curr.* **2011**, *3*, RRN1255, https://doi.org/10.1371/currents.rrn1255.
130. Carvill, G.L.; Helbig, K.L.; Myers, C.T.; Scala, M.; Huether, R.; Lewis, S.; Kruer, T.N.; Guida, B.S.; Bakhtiari, S.; Sebe, J.; et al. Damaging de novo missense variants inEEF1A2lead to a developmental and degenerative epileptic-dyskinetic encephalopathy. *Hum. Mutat.* **2020**, *41*, 1263–1279, https://doi.org/10.1002/humu.24015.
131. Lance, E.; Kronenbuerger, M.; Cohen, J.S.; Furmanski, O.; Singer, H.S.; Fatemi, A. Successful treatment of choreo-athetotic movements in a patient with an EEF1A2 gene variant. *SAGE Open Med Case Rep.* **2018**, *6*, https://doi.org/10.1177/2050313x18807622.
132. Lin, M.; Pedrosa, E.; Hrabovsky, A.; Chen, J.; Puliafito, B.R.; Gilbert, S.R.; Zheng, D.; Lachman, H.M. Integrative transcriptome network analysis of iPSC-derived neurons from schizophrenia and schizoaffective disorder patients with 22q11.2 deletion. *BMC Syst. Biol.* **2016**, *10*, 1–20, https://doi.org/10.1186/s12918-016-0366-0.
133. Dong, X.; Cong, S. Identification of differentially expressed genes and regulatory relationships in Huntington's disease by bioinformatics analysis. *Mol. Med. Rep.* **2018**, *17*, 4317–4326, https://doi.org/10.3892/mmr.2018.8410.
134. Manap, A.S.A.; Madhavan, P.; Vijayabalan, S.; Chia, A.; Fukui, K. Explicating anti-amyloidogenic role of curcumin and piperine via amyloid beta (Aβ) explicit pathway: Recovery and reversal paradigm effects. *PeerJ* **2020**, *8*, e10003, https://doi.org/10.7717/peerj.10003.

135. Pehlivan, S.; Fedakar, R.; Eren, B.; Akyol, S.; Eren, F.; Inanir, N.T.; Gurses, M.S.; Ural, M.N.; Tagil, S.M.; Demircan, K. ADAMTS4, 5, 9, and 15 Expressions in the Autopsied Brain of Patients with Alzheimer's Disease: A Preliminary Immunohistochemistry Study. **2016**, *26*, 7–14, https://doi.org/10.5455/bcp.20150706034008.
136. Hong, C.C.; Tang, A.T.; Detter, M.R.; Choi, J.P.; Wang, R.; Yang, X.; Guerrero, A.A.; Wittig, C.F.; Hobson, N.; Girard, R.; et al. Cerebral cavernous malformations are driven by ADAMTS5 proteolysis of versican. *J. Exp. Med.* **2020**, *217*, https://doi.org/10.1084/jem.20200140.
137. Zhou, J.; Zhang, W.; Wei, C.; Zhang, Z.; Yi, D.; Peng, X.; Peng, J.; Yin, R.; Zheng, Z.; Qi, H.; et al. Weighted correlation network bioinformatics uncovers a key molecular biosignature driving the left-sided heart failure. *BMC Med Genom.* **2020**, *13*, 1–13, https://doi.org/10.1186/s12920-020-00750-9.
138. Waters, C.W.; Varuzhanyan, G.; Talmadge, R.J.; Voss, A.A. Huntington disease skeletal muscle is hyperexcitable owing to chloride and potassium channel dysfunction. *Proc. Natl. Acad. Sci.* **2013**, *110*, 9160–9165, https://doi.org/10.1073/pnas.1220068110.
139. Chandrasekaran, S.; Bonchev, D. A NETWORK VIEW ON PARKINSON'S DISEASE. *Comput. Struct. Biotechnol. J.* **2013**, *7*, e201304004, https://doi.org/10.5936/csbj.201304004.
140. Chiang, M.-C.; Chen, H.-M.; Lee, Y.-H.; Chang, H.-H.; Wu, Y.-C.; Soong, B.-W.; Chen, C.-M.; Wu, Y.-R.; Liu, C.-S.; Niu, D.-M.; et al. Dysregulation of C/EBPα by mutant Huntingtin causes the urea cycle deficiency in Huntington's disease. *Hum. Mol. Genet.* **2007**, *16*, 483–498, https://doi.org/10.1093/hmg/ddl481.
141. Jeong, H.; Moye, L.S.; Southey, B.R.; Hernandez, A.G.; Dripps, I.; Romanova, E.V.; Rubakhin, S.S.; Sweedler, J.V.; Pradhan, A.A.; Rodriguez-Zas, S.L. Gene Network Dysregulation in the Trigeminal Ganglia and Nucleus Accumbens of a Model of Chronic Migraine-Associated Hyperalgesia. *Front. Syst. Neurosci.* **2018**, *12*, https://doi.org/10.3389/fnsys.2018.00063.
142. Miller, J.R.C.; Lo, K.K.; Andre, R.; Moss, D.J.H.; Träger, U.; Stone, T.C.; Jones, L.; Holmans, P.; Plagnol, V.; Tabrizi, S.J. RNA-Seq of Huntington's disease patient myeloid cells reveals innate transcriptional dysregulation associated with proinflammatory pathway activation. *Hum. Mol. Genet.* **2016**, *25*, 2893–2904, https://doi.org/10.1093/hmg/ddw142.
143. Li, J.; Khankan, R.R.; Caneda, C.; Godoy, M.I.; Haney, M.S.; Krawczyk, M.C.; Bassik, M.C.; Sloan, S.A.; Zhang, Y. Astrocyte-to-astrocyte contact and a positive feedback loop of growth factor signaling regulate astrocyte maturation.. *Glia* **2019**, *67*, 1571–1597, https://doi.org/10.1002/glia.23630.
144. Agostoni, E.; Michelazzi, S.; Maurutto, M.; Carnemolla, A.; Ciani, Y.; Vatta, P.; Roncaglia, P.; Zucchelli, S.; Leanza, G.; Mantovani, F.; et al. Effects of Pin1 Loss in HdhQ111 Knock-in Mice. *Front. Cell. Neurosci.* **2016**, *10*, 110–110, https://doi.org/10.3389/fncel.2016.00110.
145. Wang, F.; Yang, Y.; Lin, X.; Wang, J.-Q.; Wu, Y.-S.; Xie, W.; Wang, D.; Zhu, S.; Liao, Y.-Q.; Sun, Q.; et al. Genome-wide loss of 5-hmC is a novel epigenetic feature of Huntington's disease. *Hum. Mol. Genet.* **2013**, *22*, 3641–3653, https://doi.org/10.1093/hmg/ddt214.
146. Salvalaio, M.; D'Avanzo, F.; Rigon, L.; Zanetti, A.; D'Angelo, M.; Valle, G.; Scarpa, M.; Tomanin, R. Brain RNA-Seq Profiling of the Mucopolysaccharidosis Type II Mouse Model. *Int. J. Mol. Sci.* **2017**, *18*, 1072, https://doi.org/10.3390/ijms18051072.
147. Yamanaka, T.; Wong, H.K.; Tosaki, A.; Bauer, P.O.; Wada, K.; Kurosawa, M.; Shimogori, T.; Hattori, N.; Nukina, N. Large-Scale RNA Interference Screening in Mammalian Cells Identifies Novel Regulators of Mutant Huntingtin Aggregation. *PLoS ONE* **2014**, *9*, e93891, https://doi.org/10.1371/journal.pone.0093891.
148. Strand, A.D.; Aragaki, A.K.; Shaw, D.; Bird, T.; Holton, J.; Turner, C.; Tapscott, S.J.; Tabrizi, S.J.; Schapira, A.H.; Kooperberg, C.; et al. Gene expression in Huntington's disease skeletal muscle: A potential biomarker. *Hum. Mol. Genet.* **2005**, *14*, 1863–1876, https://doi.org/10.1093/hmg/ddi192.
149. Li, M.D.; Burns, T.C.; A Morgan, A.; Khatri, P. Integrated multi-cohort transcriptional meta-analysis of neurodegenerative diseases. *Acta Neuropathol. Commun.* **2014**, *2*, 1–23, https://doi.org/10.1186/s40478-014-0093-y.
150. Moradifard, S.; Hoseinbeyki, M.; Ganji, S.M.; Minuchehr, Z. Analysis of microRNA and Gene Expression Profiles in Alzheimer's Disease: A Meta-Analysis Approach. *Sci. Rep.* **2018**, *8*, 1–17, https://doi.org/10.1038/s41598-018-20959-0.
151. The HD iPSC Consortium Induced Pluripotent Stem Cells from Patients with Huntington's Disease Show CAG-Repeat-Expansion-Associated Phenotypes. *Cell Stem Cell* **2012**, *11*, 264–278, https://doi.org/10.1016/j.stem.2012.04.027.
152. Loera-Valencia, R.; Piras, A.; Ismail, M.A.M.; Manchanda, S.; Eyjolfsdottir, H.; Saido, T.C.; Johansson, J.; Eriksdotter, M.; Winblad, B.; Nilsson, P. Targeting Alzheimer's disease with gene and cell therapies. *J. Intern. Med.* **2018**, *284*, 2–36, https://doi.org/10.1111/joim.12759.
153. Tao, B.; Ling, Y.; Zhang, Y.; Li, S.; Zhou, P.; Wang, X.; Li, B.; Jun, Z.; Zhang, W.; Xu, C.; et al. CA 10 and CA 11 negatively regulate neuronal activity-dependent growth of gliomas. *Mol. Oncol.* **2019**, *13*, 1018–1032, https://doi.org/10.1002/1878-0261.12445.
154. Krüger, R.; Schöls, L.; Müller, T.; Kuhn, W.; Woitalla, D.; Przuntek, H.; Epplen, J.T.; Riess, O. Evaluation of the γ-synuclein gene in German Parkinson's disease patients. *Neurosci. Lett.* **2001**, *310*, 191–193, https://doi.org/10.1016/s0304-3940(01)02127-9.
155. Mahinrad, S.; Bulk, M.; van der Velpen, I.; Mahfouz, A.; van Roon-Mom, W.; Fedarko, N.; Yasar, S.; Sabayan, B.; van Heemst, D.; van der Weerd, L. Natriuretic Peptides in Post-mortem Brain Tissue and Cerebrospinal Fluid of Non-demented Humans and Alzheimer's Disease Patients. *Front. Neurosci.* **2018**, *12*, 864, https://doi.org/10.3389/fnins.2018.00864.
156. Scholl-Bürgi, S.; Sigl, S.B.; Häberle, J.; Haberlandt, E.; Rostásy, K.; Ertl, C.; Eichinger-Öttl, U.; Heinz-Erian, P.; Karall, D. Amino acids in CSF and plasma in hyperammonaemic coma due to arginase1 deficiency. *J. Inherit. Metab. Dis.* **2008**, *31*, 323–328, https://doi.org/10.1007/s10545-008-0903-0.
157. Fridén, M.; Winiwarter, S.; Jerndal, G.; Bengtsson, O.; Wan, H.; Bredberg, U.; Hammarlund-Udenaes, M.; Antonsson, M. Structure−Brain Exposure Relationships in Rat and Human Using a Novel Data Set of Unbound Drug Concentrations in Brain Interstitial and Cerebrospinal Fluids. *J. Med. Chem.* **2009**, *52*, 6233–6243, https://doi.org/10.1021/jm901036q.

158. Pellegrini, L.; Bonfio, C.; Chadwick, J.; Begum, F.; Skehel, M.; Lancaster, M.A. Human CNS barrier-forming organoids with cerebrospinal fluid production. *Science* **2020**, *369*, https://doi.org/10.1126/science.aaz5626.
159. Elmenhorst, D.; Meyer, P.T.; Matusch, A.; Winz, O.H.; Bauer, A. Caffeine Occupancy of Human Cerebral A_1 Adenosine Receptors: In Vivo Quantification with ^{18}F-CPFPX and PET. *J. Nucl. Med.* **2012**, *53*, 1723–1729, https://doi.org/10.2967/jnumed.112.105114.
160. Johannessen, S.; Gerna, M.; Bakke, J.; Strandjord, R.; Morselli, P. CSF CONCENTRATIONS AND SERUM PROTEIN BINDING OF CARBAMAZEPINE AND CARBAMAZEPINE-10, 11-EPOXIDE IN EPILEPTIC PATIENTS. *Br. J. Clin. Pharmacol.* **1976**, *3*, 575–582, https://doi.org/10.1111/j.1365-2125.1976.tb04878.x.
161. Paulzen, M.; Lammertz, S.E.; Gründer, G.; Veselinovic, T.; Hiemke, C.; Tauber, S.C. Measuring citalopram in blood and central nervous system. *Int. Clin. Psychopharmacol.* **2016**, *31*, 119–126, https://doi.org/10.1097/yic.0000000000000114.
162. Allonen, H.; Andersson, K.-E.; Iisalo, E.; Kanto, J.; Strömblad, L.; Wettrell, G. Passage of Digoxin into Cerebrospinal Fluid in Man. *Acta Pharmacol. et Toxicol.* **2009**, *41*, 193–202, https://doi.org/10.1111/j.1600-0773.1977.tb02139.x.
163. Pardridge, W.M. CSF, blood-brain barrier, and brain drug delivery. *Expert Opin. Drug Deliv.* **2016**, *13*, 963–975, https://doi.org/10.1517/17425247.2016.1171315.
164. González-Sánchez, M.; Jiménez, J.; Narváez, A.; Antequera, D.; Llamas-Velasco, S.; Martín, A.H.-S.; Arjona, J.A.M.; De Munain, A.L.; Bisa, A.L.; Marco, M.-P.; et al. Kynurenic Acid Levels are Increased in the CSF of Alzheimer's Disease Patients. *Biomolecules* **2020**, *10*, 571, doi:10.3390/biom10040571.
165. Vassal, G.; Valteau, D.; Bonnay, M.; Patte, C.; Aubier, F.; Lemerle, J. Cerebrospinal Fluid and Plasma Methotrexate Levels Following High-Dose Regimen Given as a 3-Hour Intravenous Infusion in Children with Nonhodgkin's Lymphoma. *Pediatr. Hematol. Oncol.* **1990**, *7*, 71–77, https://doi.org/10.3109/08880019009034320.
166. Ogutu, B.R.; Newton, C.; Muchohi, S.N.; Otieno, G.O.; Edwards, G.; Watkins, W.M.; Kokwaro, G.O. Pharmacokinetics and clinical effects of phenytoin and fosphenytoin in children with severe malaria and status epilepticus. *Br. J. Clin. Pharmacol.* **2003**, *56*, 112–119, https://doi.org/10.1046/j.1365-2125.2003.01829.x.