ZR Zoological Research

Supplementary Materials

Decoding hereditary spastic paraplegia pathogenicity through transcriptomic profiling

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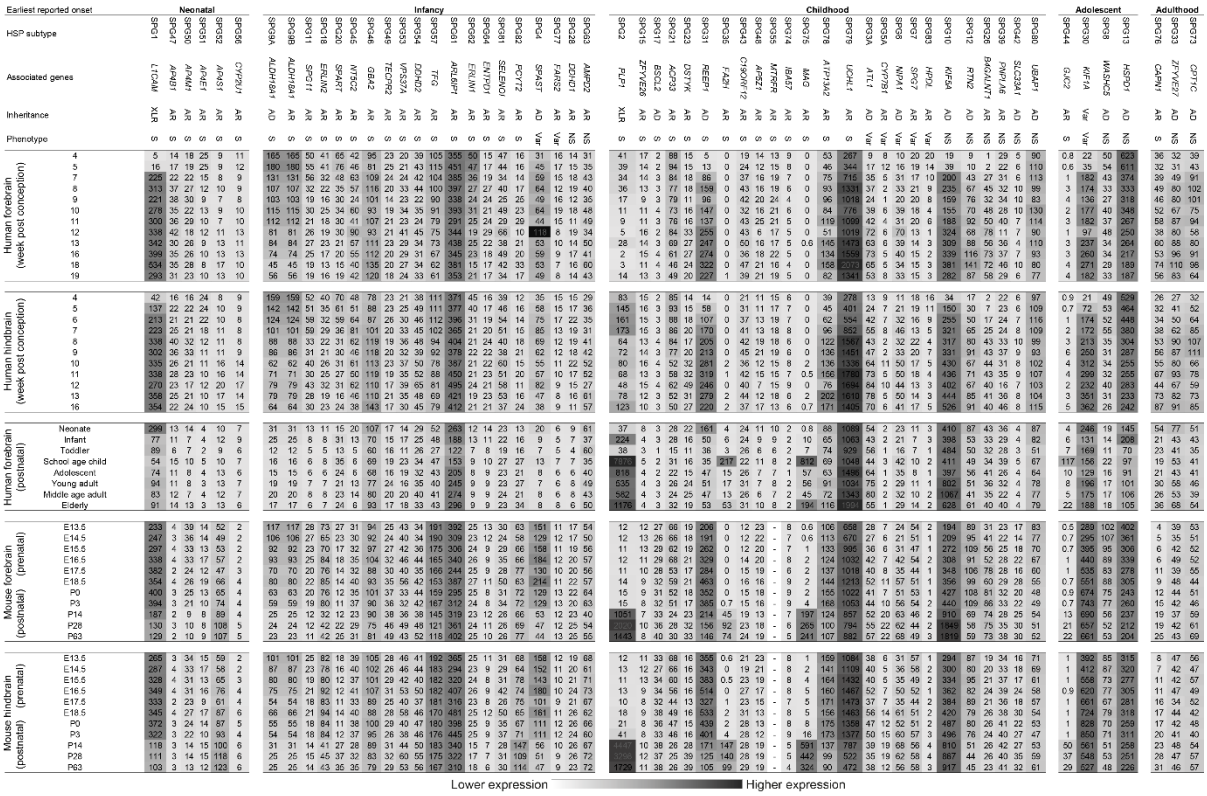
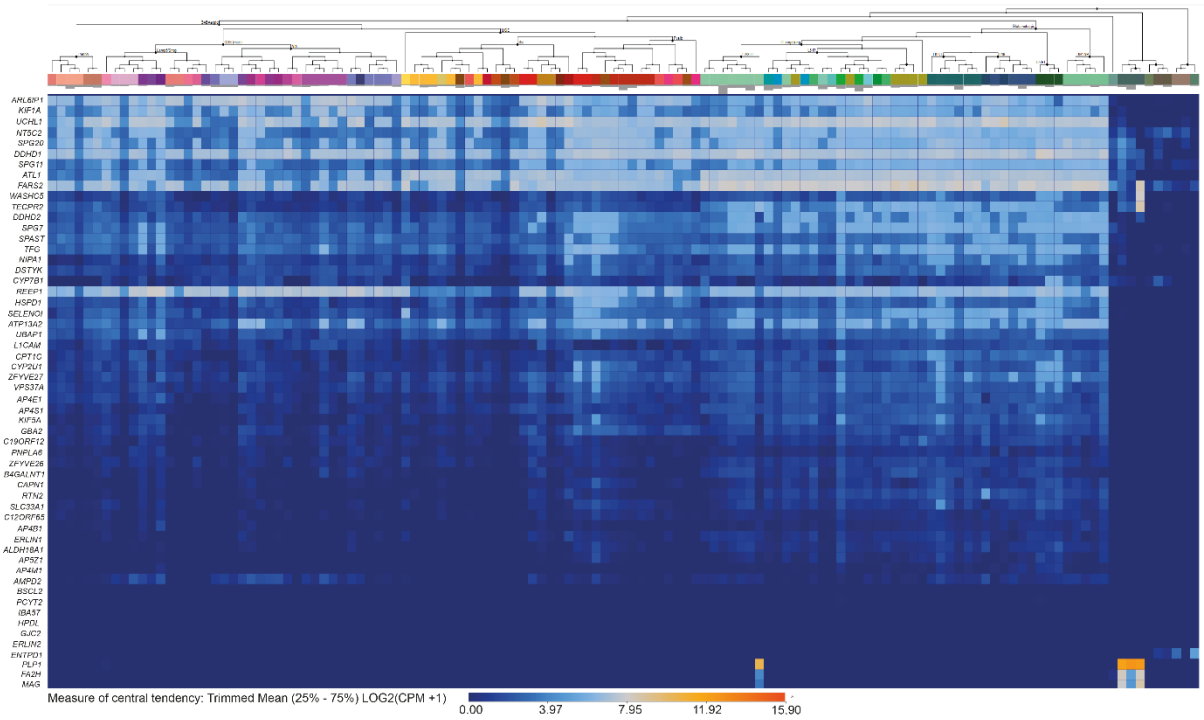
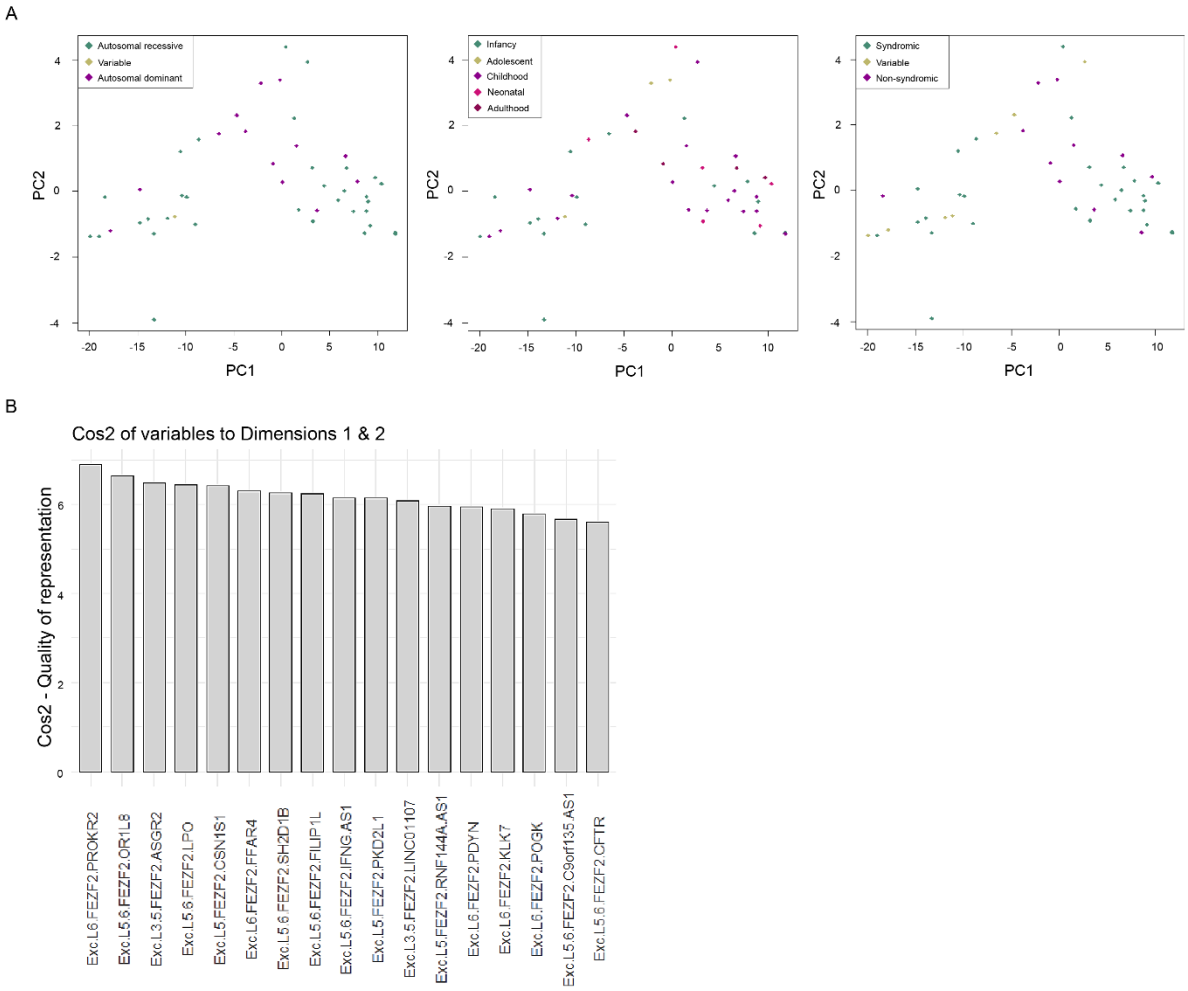


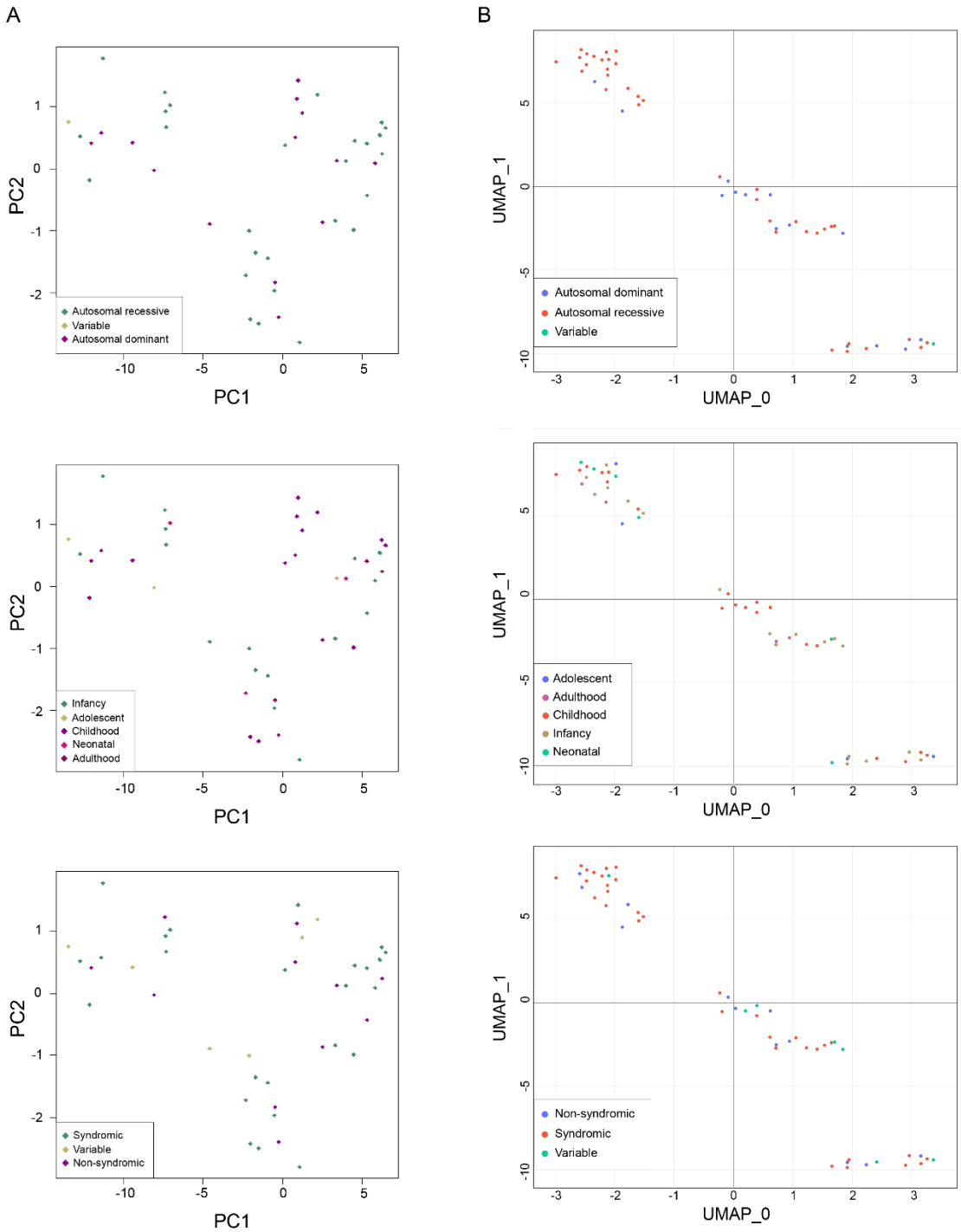
Supplementary Figure S1. Heatmap showing forebrain/hindbrain tissue mRNA expression profiles (TPM) of HSP associated genes in normal human and mouse tissues at each developmental stage.



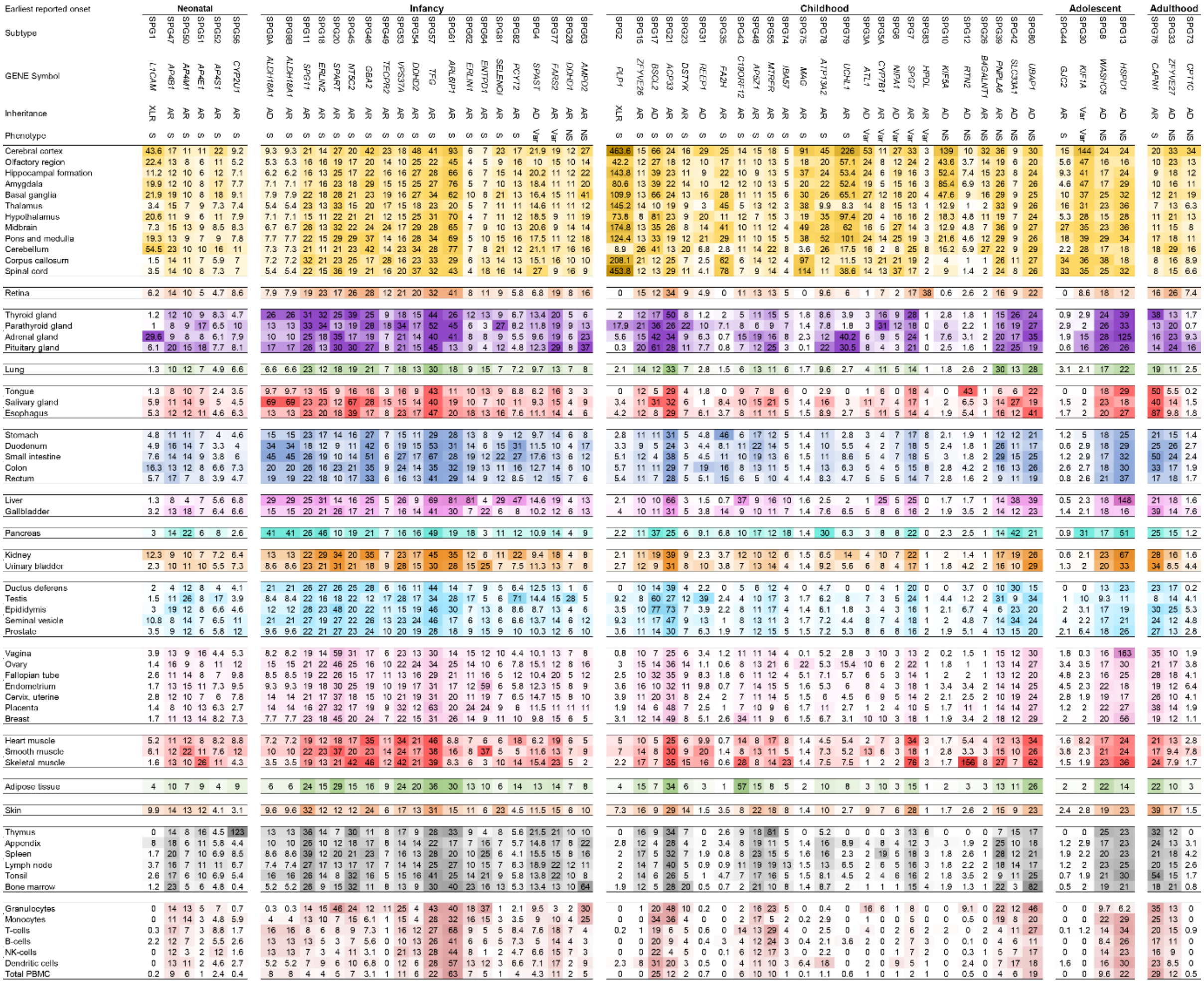
Supplementary Figure S2. Heatmap visualizing expression patterns of HSP-associated genes across transcriptomic cell types in the human primary motor cortex by sc-RNA-seq.



Supplementary Figure S3. Selection of FEZF2+ pyramidal neuronal populations for further HSP gene expression profile dimensionality reduction analysis.



Supplementary Figure S4. Dimensional reduction analysis of selected mouse isocortical extratelencephalic (ET) neuronal populations.



Supplementary Figure S5. Heatmap showing tissue specific mRNA expression levels of HSP associated genes in normal human tissues.

Supplementary Table S1 List of genes associated with HSP

HSP subtype	HGNC approved gene symbol	Reported association to neurological conditions other than HSP
SPG1	*L1CAM*	Hirschsprung disease, hydrocephalus
SPG2	*PLP1*	Leukodystrophy
SPG3A	*ATL1*	Sensory neuropathy
SPG4	*SPAST*	
SPG5A	*CYP7B1*	
SPG6	*NIPA1*	
SPG7	*SPG7*	
SPG8	*WASHC5*	Ritscher-Schinzel syndrome
SPG9A/9B	*ALDH18A1*	
SPG10	*KIF5A*	Amyotrophic lateral sclerosis, epilepsy
SPG11	*SPG11*	Amyotrophic lateral sclerosis, Charcot-Marie-Tooth disease, homocarnosinosis
SPG12	*RTN2*	
SPG13	*HSPD1*	Leukodystrophy
SPG14	*SPG14*	
SPG15	*ZFYVE26*	
SPG16	*SPG16*	
SPG17	*BSCL2*	Encephalopathy, distal motor neuropathy
SPG18	*ERLIN2*	
SPG19	*SPG19*	
SPG20	*SPART*	
SPG21	*ACP33*	
SPG23	*DSTYK*	
SPG24	*SPG24*	
SPG25	*SPG25*	
SPG26	*B4GALNT1*	
SPG27	*SPG27*	
SPG28	*DDHD1*	
SPG29	*SPG29*	
SPG30	*KIF1A*	Sensory neuropathy, NESCAV syndrome
SPG31	*REEP1*	Distal motor neuropathy
SPG32	*SPG32*	
SPG33	*ZFYVE27*	
SPG34	*SPG34*	
SPG35	*FA2H*	
SPG36	*SPG36*	
SPG37	*SPG37*	
SPG38	*SPG38*	
SPG39	*PNPLA6*	Boucher-Neuhauser syndrome, Laurence-Moon syndrome, Olver-Mcfarlane syndrome.

SPG41	*SPG41*	
SPG42	*SLC33A1*	
SPG43	*C19ORF12*	Brain iron accumulation associated neurodegeneration, mitochondrial membrane protein-associated neurodegeneration
SPG44	*GJC2*	Leukodystrophy
SPG45	*NT5C2*	
SPG46	*GBA2*	Cerebellar ataxia
SPG47	*AP4B1*	
SPG48	*AP5Z1*	
SPG49	*TECPR2*	Sensory and autonomic neuropathy
SPG50	*AP4M1*	
SPG51	*AP4E1*	
SPG52	*AP4S1*	
SPG53	*VPS37A*	
SPG54	*DDHD2*	
SPG55	*MTRFR*	
SPG56	*CYP2U1*	
SPG57	*TFG*	Charcot-Marie-Tooth disease, motor and sensory neuropathy
SPG61	*ARL6IP1*	
SPG62	*ERLIN1*	
SPG63	*AMPD2*	Pontocerebellar hypoplasia
SPG64	*ENTPD1*	
SPG73	*CPT1C*	
SPG74	*IBA57*	Multiple mitochondrial dysfunction syndrome
SPG75	*MAG*	
SPG76	*CAPN1*	
SPG77	*FARS2*	
SPG78	*ATP13A2*	Brain iron accumulation associated neurodegeneration, Kufor-Rakeb syndrome
SPG79	*UCHL1*	
SPG80	*UBAP1*	
SPG81	*SELENOI*	
SPG82	*PCYT2*	
SPG83	*HPDL*	

Supplementary Table S2 List of HSP genes identified from rhesus monkey brain and average cortical expression by age

			Averaged expression by age		
	HSP subtype	Symbol	5.75 (n = 4)	16.5 (n = 2)	24 (n = 1)
Adult.	SPG73	*CPT1C*	4.989073445	4.989419	4.985567
Adult.	SPG33	*ZFYVE27*	7.109103806	7.10401	7.140942
Adult.	SPG76	*CAPN1*	7.216363539	7.278123	7.120605
Adol.	SPG13	*HSPD1*	6.069200117	6.074412	6.079972
Adol.	SPG30	*KIF1A*	9.063097963	9.017894	9.059115
Childhood	SPG80	*UBAP1*	6.248539296	6.195004	6.346933
Childhood	SPG39	*PNPLA6*	6.454761789	6.466153	6.419514
Childhood	SPG26	*B4GALNT1*	4.921820554	4.866581	4.981878
Childhood	SPG12	*RTN2*	4.661147914	4.646705	4.640942
Childhood	SPG83	*HPDL*	1.549666546	1.577375	1.419267
Childhood	SPG7	*SPG7*	6.834505635	6.916359	6.666004
Childhood	SPG6	*NIPA1*	6.724166776	6.715201	6.735772
Childhood	SPG5A	*CYP7B1*	3.715281748	3.705905	3.686841
Childhood	SPG3A	*ATL1*	6.896267671	6.885668	6.883168
Childhood	SPG79	*UCHL1*	8.635203608	8.605775	8.665398
Childhood	SPG78	*ATP13A2*	8.663981318	8.661025	8.661176
Childhood	SPG75	*MAG*	3.491268114	3.454769	3.621977
Childhood	SPG48	*AP5Z1*	6.257186207	6.266809	6.270654
Childhood	SPG35	*FA2H*	4.683975436	4.741617	4.629831
Childhood	SPG31	*REEP1*	3.14573012	3.130801	3.119082
Childhood	SPG23	*DSTYK*	6.384339033	6.394815	6.359493
Childhood	SPG17	*BSCL2*	10.22652729	10.24413	10.17115
Childhood	SPG15	*ZFYVE26*	4.381906137	4.3494	4.441523
Childhood	SPG2	*PLP1*	10.58574904	10.6132	10.5326
Infancy	SPG63	*AMPD2*	7.407009048	7.39125	7.408616
Infancy	SPG28	*DDHD1*	6.431497958	6.392015	6.476244
Infancy	SPG77	*FARS2*	5.011415642	5.055989	4.9402
Infancy	SPG4	*SPAST*	5.133809311	5.163894	5.08781
Infancy	SPG82	*PCYT2*	6.165597562	6.237175	6.024905
Infancy	SPG62	*ERLIN1*	4.591077338	4.596927	4.58045
Infancy	SPG61	*ARL6IP1*	8.625928848	8.32416	9.236635
Infancy	SPG57	*TFG*	5.695343884	5.701096	5.699016
Infancy	SPG54	*DDHD2*	7.338454584	7.292372	7.429301
Infancy	SPG49	*TECPR2*	4.128680725	4.188984	4.088458
Infancy	SPG46	*GBA2*	6.41666929	6.380121	6.473795
Infancy	SPG45	*NT5C2*	6.44659989	6.456299	6.449627

	SPG18	*ERLIN2*	6.131058204	6.085902	6.205445
	SPG11	*SPG11*	6.329148662	6.330945	6.306984
	SPG9A/9B	*ALDH18A1*	5.918271401	5.882059	5.976919
Neonatal	SPG52	*AP4S1*	3.56377823	3.643461	3.454884
	SPG51	*AP4E1*	3.439138519	3.411397	3.521496
	SPG50	*AP4M1*	3.344894579	3.4122	3.248671
	SPG47	*AP4B1*	3.832684867	3.811203	3.900783
	SPG1	*L1CAM*	7.604234024	7.557543	7.64518

Supplementary Table S3 List of HSP genes potentially correlated with clinical presentations of Alzheimer's disease (with reference to www.alzdata.org database)

Gene	eQTL	GWAS	PPI	Earl. DEG	Pathology cor. (ab)	Pathology cor. (tau)	CFG
CYP7B1	-	0	-	Yes	0.37,*	0.601,*	2
KIF5A	0	0	-	-	-0.359,*	-0.82,***	1
RTN2	0	2	-	No	-0.544,***	-0.658,***	2
HSPD1	0	0	APP, APOE	Yes	-0.575,***	Ns	3
REEP1	0	0	-	Yes	-0.621,***	-0.858,***	2
ZFYVE27	0	0	-	No	Ns	-0.608,*	1
GBA2	-	0	-	-	Ns	-0.718,**	1
AP4M1	2	2	-	-	-0.473,**	Ns	3
AP4S1	-	0	-	-	-0.432,**	Ns	1
TFG	0	0	-	-	Ns	-0.622,*	1
AMPD2	1	0	-	-	Ns	-0.649,**	2
MAG	1	0	APP, PSEN2	Yes	0.433,**	Ns	4
CAPN1	2	0	PSEN2	Yes	0.327,*	Ns	4
FARS2	0	0	-	Yes	Ns	0.745,**	2
UCHL1	1	0	-	Yes	-0.338,*	Ns	3
UBAP1	-	0	-	Yes	-0.401,**	Ns	2
PCYT2	1	-	-	Yes	Ns	-0.743,**	3

Supplementary Table S4 Cross-species mean HSP gene expression in human post-mortem, marmoset, and mouse layer 5 extratelencephalic (ET) specimens

Name	Subtype	Earliest reported onset	Motor involvement in mouse	Inheritance	Phenotype	L5 ET mean expr._(human)	L5 ET equivalent mean expr._(marmoset)	L5 ET equivalent population mean expr._(mouse)
L1CAM	SPG1	Neonatal	N.A.	XLR	Syndromic	2.50320506	2.06970191	2.4786849
AP4B1	SPG47	Neonatal	N.A.	AR	Syndromic	1.83428025	1.67597699	0.001410398
AP4M1	SPG50	Neonatal	N.A.	AR	Syndromic	2.30576205	0.488226444	1.67390072
AP4E1	SPG51	Neonatal	N.A.	AR	Syndromic	3.02564096	2.51064634	2.1164546
AP4S1	SPG52	Neonatal	N.A.	AR	Syndromic	2.42715621	1.92109215	3.44838905
CYP2U1	SPG56	Neonatal	N.A.	AR	Syndromic	4.65701485	1.09143281	2.34691644
ALDH18A1	SPG9A/9B	Infancy	N.A.	Var	Syndromic	2.36003065	1.57934618	1.28657353
SPG11	SPG11	Infancy	Yes	AR	Syndromic	4.72942162	4.36034584	1.89516735
ERLIN2	SPG18	Infancy	N.A.	AR	Syndromic	0.739109874	0.351452917	1.36586702
SPG20	SPG20	Infancy	Yes	AR	Syndromic	5.75433397	2.33385515	1.23311675
NT5C2	SPG45	Infancy	No	AR	Syndromic	5.07899904	4.49530315	4.16266584
GBA2	SPG46	Infancy	No	AR	Syndromic	2.74373531	0.962049127	2.8253665
TECPR2	SPG49	Infancy	N.A.	AR	Syndromic	4.1878643	6.16226196	4.9389863
VPS37A	SPG53	Infancy	N.A.	AR	Syndromic	3.30233836	3.68374252	3.65616012
DDHD2	SPG54	Infancy	Yes	AR	Syndromic	4.07473755	3.37199402	5.29261637
TFG	SPG57	Infancy	N.A.	AR	Syndromic	4.55394077	3.77310872	3.26379275
ERLIN1	SPG62	Infancy	N.A.	AR	Syndromic	1.98350084	1.74787068	2.58782506
ENTP	SPG6	Infanc	No	AR	Syndromi	0.756665	2.34869742	0.4370367

D1	4	y			c	23		83
EPT1	SPG81	Infancy	N.A.	AR	Syndromic	4.66513681	2.02786827	0
PCYT2	SPG82	Infancy	N.A.	AR	Syndromic	1.28084934	1.98453152	4.66296339
SPAST	SPG4	Infancy	No	AD	Variable	3.89047933	4.24987459	4.32848454
FARS2	SPG77	Infancy	N.A.	AR	Variable	7.34273005	6.18280315	5.29301691
DDHD1	SPG28	Infancy	No	AR	Non-syndromic	7.72931242	6.4148922	4.04439974
AMPD2	SPG63	Infancy	No	AR	Non-syndromic	1.75131118	1.70578659	0.799930871
PLP1	SPG2	Childhood	N.A.	XLR	Syndromic	1.18149042	0.852893293	0.847324371
ZFYVE26	SPG15	Childhood	Yes	AR	Syndromic	2.58151221	0.804045618	1.84758019
SPG21	SPG21	Childhood	Yes	AR	Syndromic	2.02964735	1.27586424	1.02864349
DSTYK	SPG23	Childhood	N.A.	AR	Syndromic	2.77218103	2.10377002	2.5570519
REEP1	SPG31	Childhood	No	AD	Syndromic	6.29898739	5.13639784	7.66371679
FA2H	SPG35	Childhood	No	AR	Syndromic	0.187937066	0.244301096	0.097352043
C19ORF12	SPG43	Childhood	Yes	AR	Syndromic	2.51318479	1.31199896	1.42657638
AP5Z1	SPG48	Childhood	N.A.	AR	Syndromic	2.26030731	1.83817637	1.43680167
C12ORF65	SPG55	Childhood	N.A.	AR	Syndromic	2.11145115	2.67184377	1.43277788
IBA57	SPG74	Childhood	N.A.	AR	Syndromic	0.927921057	0.311998993	0.255454928
MAG	SPG75	Childhood	Yes	AR	Syndromic	0.112143062	0.027179359	0.23252213
ATP13A2	SPG78	Childhood	Yes	AR	Syndromic	4.25276804	4.17109203	2.6567893
UCHL1	SPG79	Childhood	Yes	AR	Syndromic	6.83027411	2.99317384	6.70027637
ATL1	SPG3A	Childhood	No	AD	Variable	6.82794285	6.20265532	5.95867682
CYP7B	SPG5	Childh	No	AR	Variable	4.700247	3.40055108	4.0203332

1	A	ood				76		9
NIPA1	SPG6	Childhood	Yes	AD	Variable	3.79010057	2.93336678	4.54365301
SPG7	SPG7	Childhood	Yes	AR	Variable	4.84560728	2.77523804	0
HPDL	SPG83	Childhood	N.A.	AR	Variable	0.013039044	0.013527054	0.065929204
KIF5A	SPG10	Childhood	N.A.	AD	Non-syndromic	3.74235129	4.23039818	6.69980621
RTN2	SPG12	Childhood	No	AD	Non-syndromic	2.6870265	2.89065623	1.49653625
B4GALNT1	SPG26	Childhood	Yes	AR	Non-syndromic	2.16910696	1.19532812	2.04796052
PNPLA6	SPG39	Childhood	N.A.	AR	Non-syndromic	1.86789775	2.37625241	1.81022537
SLC33A1	SPG42	Childhood	Yes	AD	Non-syndromic	2.97526956	1.64698148	2.5734098
UBAP1	SPG80	Childhood	N.A.	AD	Non-syndromic	3.4125874	3.64147043	2.79652238
GJC2	SPG44	Adolescent	Yes	AR	Syndromic	0.216601104	0.013401804	0.060342919
KIF1A	SPG30	Adolescent	No	Variable	Variable	3.75517201	3.90769029	5.89908028
KIAA0196	SPG8	Adolescent	No	AD	Non-syndromic	3.93094397	2.60671353	0
HSPD1	SPG13	Adolescent	N.A.	AD	Non-syndromic	4.02188969	1.36009514	3.55869055
CAPN1	SPG76	Adulthood	Yes	AR	Syndromic	2.95327067	2.37957168	1.49715149
ZFYVE27	SPG33	Adulthood	N.A.	AD	Non-syndromic	3.95735002	4.13739967	2.861449
CPT1C	SPG73	Adulthood	Yes	AD	Non-syndromic	3.3851254	3.05786562	3.45760512