Supplementary Table 1 *Clinical information on cases included in this study*

Group	Sample #	Clinical diagnosis	Pathological diagnosis	Sex	Race	Motor neuron disease			Age of death (years)	PMI (hours)	Braak stage	TDP-43 pathology	TDP-43 type	FHx MND	FHx FTD	FHx Neurodegeneration
						Site of onset	Age of onset (years)	Duration (months)								
Non-neurological disease control (control)	24	Healthy	Normal	F	White/ED	n/a	n/a	n/a	64.9	30	1	0	0	no	no	yes
	86	Healthy	Normal	M	White/ED	n/a	n/a	n/a	76.6	18	2	0	0	no	no	no
	90	Healthy	Normal	F	White/ED	n/a	n/a	n/a	62.1	2	0	0	0	no	no	no
	91	Healthy	Normal	F	White/ED	n/a	n/a	n/a	72.9	18	1	0	0	no	no	no
	93	Healthy	Normal	M	White/ED	n/a	n/a	n/a	80.8	15	1	0	0	no	no	yes
	94	aMCI	Normal	M	White/ED	n/a	n/a	n/a	75.1	17	0	n/a	n/a	n/a	n/a	n/a
	95	Healthy (depression)	Normal	M	White/ED	n/a	n/a	n/a	78.2	13	2	0	0	no	no	yes
	97	Healthy (depression)	Normal	M	Hispanic/Latino	n/a	n/a	n/a	78.3	8	2.5	0	0	no	no	yes
	100[†]	Healthy	Normal	M	White/ED	n/a	n/a	n/a	55	13	0	n/a	n/a	n/a	n/a	n/a
Other disease control	20	AD	PA	M	White/ED	n/a	72	112	81	9	3	0	0	no	no	no
	23	AD	AGD/Fahr	M	White/ED	n/a	72	50	75	10	3	0	0	no	no	no
	25	CBD	Vascular disease	M	White/ED	n/a	63	79	69	8	2	0	0	n/a	n/a	n/a
sALS	11	ALS	ALS/PA	F	White/ED	Bulbar	60.2	15.1	61.4	10	2	1	ALS	no	no	no
	12	ALS	ALS	M	White/ED	Upper limbs	45.2	59.0	50.1	9	1	1	ALS	no	no	no
	13	ALS	ALS	M	White/ED	Upper limbs	49.9	46.8	53.8	6	1	1	ALS	no	no	no
	14	ALS	ALS/SC	M	White/ED	Lower limbs	61.2	64.1	66.6	13	1	1	ALS	no	no	no
	70	ALS	ALS	F	White/ED	Upper limbs	48.8	53.9	53.2	16	0	1	ALS	no	no	no
	71	ALS	ALS	M	White/ED	Upper limbs	45.4	24.6	47.5	5	4	1	ALS	possible	no	no
	72	ALS	ALS/PA	F	White/ED	Bulbar	57.6	39.0	60.9	16	0	1	ALS	possible	possible	no
	73	ALS	ALS/SC	F	White/ED	Upper limbs	64.1	12.6	65.2	7	1	1	ALS	no	no	yes
	74	ALS	ALS	F	White/ED	Upper limbs	66.5	31.9	69.2	3	0.5	1	ALS	no	no	no
	75	ALS	ALS	F	White/ED	Bulbar	67.2	38.1	70.4	12	2	1	ALS	no	no	no
c9ALS	1	Bulbar palsy	ALS/PA	F	White/ED	Bulbar	62.5	21.7	64.3	15	2	1	ALS	no	no	no
	2	ALS	ALS	M	White/ED	Bulbar	56.1	26.8	58.3	6	1.5	1	ALS	no	no	no
	6	ALS	ALS	M	White/ED	Upper limbs	52.3	76.4	58.7	18	1	1	ALS	yes	no	yes
	7	ALS-MCI	ALS	M	White/ED	Bulbar	49.5	49.6	53.6	7	0.5	1	ALS	possible	no	no
	34	ALS	ALS	F	White/ED	Bulbar	47.3	34.0	50.2	8	0.5	1	ALS	no	no	yes
	42*	ALS	ALS	F	White/ED	Upper limbs	48.4	10.8	49.3	5	2	1	ALS	no	no	yes
	57	ALS	ALS	F	White/ED	Lower limbs	49.7	15.3	51.0	18	0.5	1	ALS	no	no	no
	62	ALS	ALS	F	White/ED	Lower limbs	41.3	15.2	42.6	3	2	1	ALS	adopted	adopted	adopted
	63	ALS	ALS	F	White/ED	Lower limbs	45.6	47.2	49.5	6	0.5	1	ALS	yes	no	no
PSP	283	PSP	PSP/PA	F	White/ED	n/a	n/a	n/a	60	18	2	0	0	no	no	no
	285	PSP	PSP/AGD	F	White/ED	n/a	n/a	n/a	57	5	4	0	0	n/a	n/a	n/a
	286	PSP	PSP	M	White/ED	n/a	n/a	n/a	57	4	2	0	0	adopted	adopted	adopted
	287	PSP	PSP	F	White/ED	n/a	n/a	n/a	59	7	1	0	0	no	no	no
	288	PSP	PSP	M	White/ED	n/a	n/a	n/a	64	5	1	0	0	no	no	no
	290	PSP	PSP/AGD	F	White/ED	n/a	n/a	n/a	60	7	1	0	0	no	no	no
	291	PSP	PSP	F	White/ED	n/a	n/a	n/a	59	9	1	0	0	no	no	no
	292	PSP	PSP	M	White/ED	n/a	n/a	n/a	58	6	0	0	0	np	np	np
	293	PSP	PSP	M	White/ED	n/a	n/a	n/a	52	10	0.5	0	0	no	no	no
	294	PSP	PSP	F	White/ED	n/a	n/a	n/a	57	6	1	0	0	yes	no	no
	295	PSP	PSP	F	White/ED	n/a	n/a	n/a	59	5	1	0	0	no	no	Yes
	296	PSP	PSP	F	White/ED	n/a	n/a	n/a	64	4	2	0	0	no	no	no
	298	PSP	PSP	M	White/ED	n/a	n/a	n/a	59	12	2	0	0	no	no	no

ALS: amyotrophic lateral sclerosis; aMCI: amnesic mild cognitive impairment; ED: European-descent; F: female; FCx: frontal cortex; FHx: family history; FTD: frontotemporal dementia; M: male; MCI: mild cognitive impairment; MND: motor neuron disease; PA: pathological aging; PMI: post-mortem interval; PSP: progressive supranuclear palsy; SC: senile change; n/a: not available. *: case #42 was not included in the RNAseq analyses but was included in qRT-PCRs for expression and AS validations. †: frontal cortex tissue from case #100 was used for RNAseq studies but cerebellar tissue from this case was unavailable. Note three “other disease control” cases were included in qRT-PCR validations in the motor cortex tissues only due to the unavailability of motor cortex tissues for non-neurological disease control cases #91 and #93.

Supplementary Table 2 *Notable biological processes involving c9ALS differentially expressed genes*

	Cluster ID (Enrichment score)	GO term ID		Count	*P* value	Total genes in cluster	Genes
CEREBELLUM	Inflammatory response (5.165)	GO:0006954	Inflammatory response	19	2.40E-06	30	*C7, C9, CCL22, CCL26, CCR2, CCR5, CD163, COL3A1, CR1, CRH, CXCL6, DRD5, F13A1, FCGR1C, FCN2, HIST1H2BJ, HMOX1, IL1RL2, LY6G6D, LYVE1, MMRN1, PLA2G2A, S100A12, S100A8, S100A9, SELE, SERPINA1, SERPINA3, SH2D1A, VSIG4*
		GO:0009611	Response to wounding	24	6.03E-06		
		GO:0006952	Defense response	25	2.20E-05		
	Development (4.002)	GO:0001501	Skeletal system development	23	3.35E-09	28	*BMP5, COL3A1, DLX6, GATA4, HAND1, HOXA10, HOXA11, HOXA13, HOXA3, HOXA4, HOXA5, HOXA6, HOXB6, HOXC10, HOXC11, HOXC13, HOXD10, HOXD8, HOXD9, IBSP, MEPE, MGP, OVOL2, PDX1, PITX1, SHOX2, SIX1, STC1*
		GO:0009952	Anterior/posterior pattern formation	14	2.13E-07		
		GO:0048598	Embryonic morphogenesis	18	4.67E-06		
		GO:0009954	Proximal/distal pattern formation	6	2.10E-05		
		GO:0035107	Appendage morphogenesis	9	1.32E-04		
		GO:0035108	Limb morphogenesis	9	1.32E-04		
		GO:0060173	Limb development	9	1.74E-04		
		GO:0048736	Appendage development	9	1.74E-04		
		GO:0035113	Embryonic appendage morphogenesis	8	3.58E-04		
		GO:0030326	Embryonic limb morphogenesis	8	3.58E-04		
		GO:0001708	Cell fate specification	5	7.47E-03		
		GO:0035136	Forelimb morphogenesis	3	4.37E-02		
	Morphogenesis (3.830)	GO:0001501	Skeletal system development	23	3.35E-09	34	*BMP5, COL3A1, CSDAP1, DLX6, FOXJ1, GATA4, GATA6, HAND1, HOXA10, HOXA11, HOXA13, HOXA3, HOXA4, HOXA5, HOXA6, HOXB6, HOXC10, HOXC11, HOXC13, HOXD10, HOXD8, HOXD9, IBSP, LEFTY2, MEPE, MGP, NLRP5, OVOL2, PDX1, PITX1, PITX2, SHOX2, SIX1, STC1*
		GO:0007389	Pattern specification process	20	2.55E-08		
		GO:0009952	Anterior/posterior pattern formation	14	2.13E-07		
		GO:0003002	Regionalization	15	1.91E-06		
		GO:0048598	Embryonic morphogenesis	18	4.67E-06		
		GO:0048705	Skeletal system morphogenesis	11	7.91E-06		
		GO:0048704	Embryonic skeletal system morphogenesi	8	2.38E-05		
		GO:0048562	Embryonic organ morphogenesis	11	3.57E-05		
		GO:0048568	Embryonic organ development	12	6.55E-05		
		GO:0048706	Embryonic skeletal system development	8	1.67E-04		
		GO:0035113	Embryonic appendage morphogenesis	8	3.58E-04		
		GO:0030326	Embryonic limb morphogenesis	8	3.58E-04		
		GO:0043009	Chordate embryonic development	14	1.70E-03		
		GO:0009792	Embryonic development ending in birth or	14	1.84E-03		
		GO:0030878	Thyroid gland development	3	1.38E-02		
	Response to protein (2.920)	GO:0006986	Response to unfolded protein	8	9.99E-05	22	*AURKAPS1, CALCR, COL3A1, DNAJA1, DNAJB1, DRD5, FABP4, HMOX1, HSPA1A, HSPA1B, HSPA6, HSPA7, HSPB1, HSPH1, IGFBP2, LY6G6D, MAPK15, MGP, SELE, SERPINA1, SERPINH1, SRD5A2*
		GO:0051789	Response to protein stimulus	8	1.24E-03		
		GO:0010033	Response to organic substance	20	1.41E-02		
FRONTAL CORTEX	Inflammatory response (3.487)	GO:0006954	Inflammatory response	12	6.66E-05	16	*APOA2, CARD18, CCL17, CCL26, CD44, CRP, F2, GP9, HRH4, IFNA2, IFNA6, MMRN1, PLA2G2A, S100A12, SELP, SERPINA3*
		GO:0009611	Response to wounding	14	3.62E-04		
		GO:0006952	Defense response	14	1.44E-03		
	Response to protein (1.897)	GO:0006986	Response to unfolded protein	7	2.65E-03	7	*DNAJB1, HSPA1A, HSPA1B, HSPA6, HSPA7, HSPB1, SERPINH1*
		GO:0051789	Response to protein stimulus	7	1.13E-02		
	Cell death (0.876)	GO:0042981	Regulation of apoptosis	14	3.01E-02	14	*AGTR2, BAG3, CARD18, CASP14, CD44, CD70, F2, HSPA1A, HSPA1B, HSPB1, IFNA2, TBX5, TEX11, SFN*
		GO:0043067	Regulation of programmed cell death	14	3.21E-02		
		GO:0010941	Regulation of cell death	14	3.29E-02		

Supplementary Table 3 *Notable biological processes involving sALS differentially expressed genes*

	Cluster ID (Enrichment score)	GO term ID		Count	*P* value	Total genes in cluster	Genes
CEREBELLUM	Inflammatory response (2.862)	GO:0006952	Defense response	13	3.62E-05	14	*CARD18, CCR5, CR1, CXCL11, FCGR1C, FCN2, IL1RL2, IL9, LPA, LTF, LY6G6D, PLA2G2A, PLA2G2D, TRAT1*
		GO:0006954	Inflammatory response	7	4.97E-03		
		GO:0009611	Response to wounding	8	1.44E-02		
	Morphogenesis (1.234)	GO:0048562	Embryonic organ morphogenesis	5	4.02E-03	5	*FOXE1, FOXG1, HOXA4, PTPRQ, WNT1*
		GO:0048568	Embryonic organ development	5	9.86E-03		
		GO:0042472	Inner ear morphogenesis	3	3.05E-02		
		GO:0042471	Ear morphogenesis	3	4.12E-02		
	Ion homeostasis (1.168)	GO:0050801	Ion homeostasis	7	1.45E-02	7	*ADIPOQ, CCR5, CHRNA1, LTF, MT1H, NPPB, SCARA5*
		GO:0006873	Cellular ion homeostasis	6	3.56E-02		
		GO:0055082	Cellular chemical homeostasis	6	3.77E-02		
		GO:0048878	Chemical homeostasis	7	3.83E-02		
FRONTAL CORTEX	Hematopoiesis and immune system development (1.924)	GO:0020027	Hemoglobin metabolic process	3	8.79E-04	5	*AHSP, ALAS2, EPB42, IL4, PAX1*
		GO:0030097	Hemopoiesis	5	2.17E-02		
		GO:0048534	Hemopoietic or lymphoid organ de	5	2.96E-02		
		GO:0002520	Immune system development	5	3.57E-02		
	G-protein signaling (0.997)	GO:0007186	G-protein coupled receptor protein	11	2.76E-02	11	*BRS3, CXCL10, CXCL11, GABRR2, HRH4, OR10H5, OR13C5, OR2M4, OR52N2, RXFP2, TAAR3*
	Defense response (0.870)	GO:0006952	Defense response	8	2.02E-02	8	*CXCL10, CXCL11, HRH4, IFNA8, IL4, PLA2G2A, PSG7, SLAMF7*
	Ion homeostasis (0.841)	GO:0050801	Ion homeostasis	6	3.68E-02	6	*ALAS2, CHRNG, EPB42, OXT, RHAG, SLC4A1*

Supplementary Table 4 *Notable gene ontology (GO) terms based on analysis of down- or up-regulated genes in c9ALS*

		Downregulated			**Upregulated**		
	GO Category	**GO Term**		***P* Value**	**GO Term**		***P* Value**
Cerebellum	**Biological function**	GO:0007186	G-protein coupled receptor protein signaling pathway	3.04E-02	GO:0007389	Pattern specification process	8.46E-10
		GO:0050890	Cognition	3.52E-02	GO:0001501	Skeletal system development	2.70E-09
		GO:0030808	Regulation of nucleotide biosynthetic process	3.63E-02	GO:0048598	Embryonic morphogenesis	2.70E-07
		GO:0006955	Immune response	3.84E-02	GO:0006986	Response to unfolded protein	2.74E-05
		GO:0006140	Regulation of nucleotide metabolic process	3.99E-02	GO:0006954	Inflammatory response	5.41E-05
	Cellular component				GO:0005576	Extracellular region	1.01E-08
		GO:0016021	Integral to membrane	2.04E-02	GO:0032993	Protein-DNA complex	5.32E-04
		GO:0031224	Intrinsic to membrane	3.14E-02	GO:0000786	Nucleosome	8.72E-04
		GO:0000267	Cell fraction	3.34E-02	GO:0044449	Contractile fiber part	1.09E-02
					GO:0031093	Platelet alpha granule lumen	1.24E-02
	Molecular function	N/A		N/A	GO:0043565	Sequence-specific DNA binding	1.47E-08
					GO:0003700	Transcription factor activity	1.73E-05
					GO:0003702	RNA polymerase II transcription factor activity	1.37E-02
					GO:0030414	Peptidase inhibitor activity	1.42E-02
					GO:0019865	Immunoglobulin binding	1.55E-02
Frontal cortex	**Biological function**				GO:0006954	Inflammatory response	3.98E-06
		GO:0015669	Gas transport	3.78E-08	GO:0009611	Response to wounding	1.65E-05
		GO:0015671	Oxygen transport	2.00E-06	GO:0006952	Defense response	7.73E-05
		GO:0020027	Hemoglobin metabolic process	1.98E-02	GO:0006986	Response to unfolded protein	8.95E-04
					GO:0007586	Digestion	2.25E-03
	Cellular component				GO:0005615	Extracellular space	1.35E-07
		GO:0005833	Hemoglobin complex	4.68E-09	GO:0030485	Smooth muscle contractile fiber	2.45E-02
		GO:0044445	Cytosolic part	1.70E-04	GO:0030141	Secretory granule	2.52E-02
		GO:0005829	Cytosol	3.27E-02	GO:0043292	Contractile fiber	3.89E-02
					GO:0031091	Platelet alpha granule	4.69E-02
	Molecular function	GO:0005344	Oxygen transporter activity	2.01E-06	GO:0004857	Enzyme inhibitor activity	2.51E-03
		GO:0019825	Oxygen binding	8.34E-05	GO:0005179	Hormone activity	6.43E-03
		GO:0020037	Heme binding	1.76E-03	GO:0005125	Cytokine activity	1.09E-02
		GO:0030492	Hemoglobin binding	6.00E-03	GO:0030414	Peptidase inhibitor activity	2.09E-02
		GO:0030506	Ankyrin binding	1.39E-02	GO:0005518	Collagen binding	2.52E-02

Supplementary Table 5 *Notable gene ontology (GO) terms based on analysis of down- or up-regulated genes in sALS*

		Downregulated		**Upregulated**	
	GO Category	**GO Term**	**P Value**	**GO Term**	**P Value**
Cerebellum	**Biological function**	GO:0048568 Embryonic organ development	5.24E-03	GO:0006952 Defense response	3.10E-05
		GO:0051252 Regulation of RNA metabolic process	8.62E-03	GO:0006955 Immune response	2.35E-03
		GO:0043583 Ear development	1.64E-02	GO:0006954 Inflammatory response	1.16E-02
		GO:0006355 Regulation of transcription, DNA-dependent	2.37E-02	GO:0007210 Serotonin receptor signaling pathway	1.36E-02
		GO:0048598 Embryonic morphogenesis	2.49E-02	GO:0009611 Response to wounding	1.40E-02
	Cellular component	GO:0044421 Extracellular region part	4.76E-03	GO:0005576 Extracellular region	4.76E-02
		GO:0005615 Extracellular space	1.77E-02		
		GO:0005576 Extracellular region	2.94E-02		
	Molecular function	GO:0046870 Cadmium ion binding	2.44E-02	GO:0004620 Phospholipase activity	2.82E-02
		GO:0005179 Hormone activity	2.89E-02	GO:0016298 Lipase activity	3.96E-02
		GO:0003700 Transcription factor activity	2.97E-02	GO:0004993 Serotonin receptor activity	4.03E-02
Frontal cortex	**Biological function**	GO:0015669 Gas transport	1.05E-05		
		GO:0020027 Hemoglobin metabolic process	2.57E-04	GO:0007600 Sensory perception	2.04E-02
		GO:0015671 Oxygen transport	4.43E-04	GO:0007186 G-protein coupled receptor protein sig	2.10E-02
		GO:0030097 Hemopoiesis	2.48E-03	GO:0050890 Cognition	3.18E-02
		GO:0050801 Ion homeostasis	2.91E-03		
	Cellular component	GO:0005833 Hemoglobin complex	1.62E-06	N/A	N/A
		GO:0044445 Cytosolic part	3.51E-03		
		GO:0005615 Extracellular space	1.12E-02		
		GO:0005576 Extracellular region	4.10E-02		
		GO:0044421 Extracellular region part	4.15E-02		
	Molecular function	GO:0005344 Oxygen transporter activity	4.23E-04	N/A	N/A
		GO:0019825 Oxygen binding	4.69E-03		
		GO:0030506 Ankyrin binding	1.66E-02		
		GO:0020037 Heme binding	3.36E-02		
		GO:0046906 Tetrapyrrole binding	3.78E-02		

Supplementary Table 6 *Weighted gene co-expression correlation network analyses (WGCNA) reveal significantly altered gene modules in cerebellum and frontal cortex of sALS*

Cerebellum

Module name	***P* value**	**Gene count**	**Notable GO terms**	**Enrichment *P* value**
MEtan	0.0161	80	Ca^{2+} ion transport, synaptic transmission	2.30E-05
MElightgreen	0.0191	59	Pyrimidine biosynthesis	2.90E-02
MEred	0.0279	162	Nerve impulse, synaptic transmission, cytoskeleton	6.70E-06

Frontal cortex

Module name	***P* value**	**Gene count**	**Notable GO terms**	**Enrichment *P* value**
MEpurple	0.0010	65	Oxidative phosphorylation	1.60E-04
MEskyblue	0.0025	34	Transcription	1.70E-03
MEbrown	0.0026	118	Electron transport chain	1.10E-07
MEsteelblue	0.0051	31	RNA elongation	3.30E-05
MElightyellow	0.0170	41	Translation elongation/Ribosomes	6.00E-56
MEdarkorange	0.0268	35	Protein localization	1.40E-02
MEdarkgrey	0.0273	37	Cell motion	1.10E-03
MElightcyan	0.0373	50	Oxidative phosphorylation	2.30E-12
MEdarkolivegreen	0.0389	27	Protein localization	5.00E-04
MEsaddlebrown	0.0405	33	Response to protein stimulus	1.50E-02
MEyellow	0.0414	87	Intracellular transport	3.10E-04
MEpink	0.0419	73	Cellular macromolecule catabolic process	3.90E-03

WGCNA co-expression analyses were performed with data from sALS cerebellum and frontal cortex (*versus* controls, $P < 0.05$). All significant modules are shown. The most notable gene ontology (GO) terms and their enrichment *P* value are included for each module.

Supplementary Table 7 *Top biological processes from gene ontology analyses of AS genes in c9ALS*

	Cluster ID (Enrichment score)	GO term ID		Count	*P* value	Total genes in cluster	Genes
CEREBELLUM	Proteolysis (4.786)	GO:0044265	Cellular macromolecule catabolic process	154	2.01E-08	208	*AUH, BAX, BRCA1, BRCC3, BUB3, C12ORF51, C2, C9ORF3, CAPN10, CAPN3, CAPN7, CASP12, CBLB, CCNB1IP1, CCNH, CD46, CDC23, CDK7, CFLAR, CHFR, CLN3, CLN6, CLU, CRBN, CTSB, CUL2, CUL4A, DCAF15, DDB2, DDI2, DET1, DFFB, DLD, DNASE1, DNASE1L1, DPP7, DPP8, DPP9, DZIP3, E4F1, EDEM3, EIF3E, EML2, ERCC1, ERCC2, ERLEC1, ERLIN1, ERLIN2, F3, FANCL, FBXL20, FBXL3, FBXL6, FBXO25, FBXO27, FBXO28, FBXO33, FBXO7, FBXW11, FBXW5, FBXW7, FKBP1A, FOLH1, G2E3, GTF2H3, GUSB, HDAC6, HECTD2, HECTD3, HECW1, HERC3, KDM2B, KLHL20, LDLR, LGMN, LRP8, LRSAM1, MAD2L1, MAGOH, MAN2B1, MARCH6, MARCH7, MARCH8, METAP1, MGEA5, MLH1, MUTYH, MYCBP2, MYSM1, NAALAD2, NGLY1, NPEPL1, OGG1, OS9, P2RX7, PABPC4, PAN2, PAN3, PARN, PCNP, PCSK4, PIGK, PMPCA, PPP2R5C, PREPL, PRSS22, PRSS27, PSMB10, PSMC1, PSMD13, PSMD5, QPCTL, RAB40B, RABGEF1, RBCK1, RCE1, RELA, RFWD2, RNASET2, RNF111, RNF123, RNF138, RNF144B, RNF167, RNF19B, RNF7, RNF8, RNH1, RNPS1, RPS6KA5, SCPEP1, SENP2, SENP5, SENP6, SENP7, SERPING1, SMG7, SMUG1, SOCS7, SPOP, TBL1X, TCEB1, TDG, THOP1, TRIM33, TRIM5, TRIP12, UBA2, UBA3, UBA5, UBE2B, UBE2D4, UBE2H, UBE2J2, UBE2Q2, UBE2W, UBE3A, UBE3C, UBE4B, UBL7, UFM1, UPF1, UPF3A, UPF3B, USP12, USP14, USP15, USP24, USP25, USP28, USP3, USP30, USP33, USP37, USP4, USP42, USP47, USP5, USP53, USP54, USP8, WDR48, WDR7, WSB1, XIAP, XPA, XPNPEP1, XRCC6BP1, XRN2, YME1L1, ZCCHC11*
		GO:0009057	Macromolecule catabolic process	161	7.57E-08		
		GO:0051603	Proteolysis involved in cellular protein catabolic process	122	6.98E-06		
		GO:0044257	Cellular protein catabolic process	122	8.91E-06		
		GO:0030163	Protein catabolic process	125	9.58E-06		
		GO:0019941	Modification-dependent protein catabolic process	116	1.59E-05		
		GO:0043632	Modification-dependent macromolecule catabolic process	116	1.59E-05		
		GO:0006508	Proteolysis	170	1.71E-02		
		GO:0006511	Ubiquitin-dependent protein catabolic process	46	2.14E-02		
	Response to stress and DNA damage (4.536)	GO:0033554	Cellular response to stress	117	4.93E-06	148	*ALKBH1, ALKBH3, ANKRD17, APEX1, APTX, ASNS, ATG16L1, ATG5, ATG9A, ATRIP, ATRX, ATXN3, BAX, BCL3, BRCA1, BRCC3, C11ORF30, C9ORF80, CASP12, CCDC111, CCDC88A, CCNH, CDK7, CEP63, CHD1L, CHTF8, CLN3, COL4A3BP, CUL4A, DCLRE1C, DDB2, DDIT3, DFFB, DNASE1, DNASE1L1, DNMT1, E4F1, EIF2AK4, ERCC1, ERCC2, ERCC8, FANCL, FOXP1, GAB1, GIN1, GINS3, GTF2H3, HDAC6, HEMK1, HIF1A, HINFP, HMGB2, HUS1, IFI16, IGHMBP2, ING4, KAT5, KIN, LIG1, MAP2K4, MAP2K7, MAP3K12, MAP3K4, MAP3K6, MAP3K9, MAPK10, MAPK12, MAPK9, MBIP, MCM3, MCM3AP, MINK1, MLH1, MLH3, MLL5, MMS19, MRE11A, MRPS35, MUS81, MUTYH, MYO6, NAP1L1, NCOA6, NEIL1, NEK11, NFIB, NOL8, NUP98, OBFC2B, OGG1, OS9, PCBP4, PGAP2, PICK1, PIWIL4, PML, PMS1, PMS2, POLA2, POLB, POLK, POLL, POLM, PPFIBP1, PPIA, PRKDC, PRMT7, PTPRK, PXN, PYCR1, RAD1, RAD51C, RAD52, RB1CC1, RBBP8, RBM14, RBM38, RBPJ, RFC1, RFC2, RIF1, RIPK1, RNF8, RPAIN, SH2D3C, SIRT7, SMUG1, STAC, STRADB, TAOK3, TDG, TDP1, TERF1, TERF2, TNIK, TOP3A, TOP3B, TPM1, UBE2B, UPF1, VAPB, XIAP, XPA, XRCC1, XRCC3, XRCC6BP1, XRN2, ZMAT3*
		GO:0006974	Response to DNA damage stimulus	82	1.58E-05		
		GO:0006281	DNA repair	65	3.75E-05		
		GO:0006259	DNA metabolic process	99	2.47E-04		
	Protein transport (4.303)	GO:0045184	Establishment of protein localization	158	1.25E-07	210	*AAAS, ACTN4, AFTPH, AGAP1, AGAP3, AGFG1, AKAP10, ANK3, AP1G2, AP1S2, AP2B1, AP2M1, AP3B2, AP3S1, AP4M1, AP4S1, APBA2, ARFGAP1, ARFIP1, ARHGAP33, ATG16L1, ATG4A, ATG4D, ATG7, ATG9A, ATP7B, BAK1, BAX, BBS4, BCL3, BID, BLZF1, CADPS, CADPS2, CAMK1, CBLB, CHCHD4, CHMP7, CLINT1, CLTA, CLTB, CLTCL1, COG3, COG6, COPA, COPE, COPZ2, CPT1B, CSPG5, DDX19A, DDX19B, DMD, DSCR3, DST, DVL1, EIF4ENIF1, ERC1, ERGIC2, EXOC3, EXOC6, EXOC6B, EXOC7, FAM125B, FGFR1OP, FLNA, G3BP2, GGA1, GGA3, GIPC1, GNPTG, GOLT1B, GRIN2C, GRPEL2, GTF2A1L, HDAC6, HINFP, HOOK2, HPS4, KATNA1, KIF1B, KLC1, LMAN2L, LMF1, LRSAM1, MAMDC4, MCM3AP, MGEA5, MIA3, MITD1, MLH3, MLX, MON2, MTX1, MUTED, MVP, MYH10, MYH14, MYO6, NAPG, NDE1, NECAP1, NECAP2, NPEPL1, NUP153, NUP188, NUP54, NUP62, NUP88, NUP98, NUPL1, NUPL2, NXF1, OPA1, OS9, PAX6, PEX1, PEX10, PEX19, PEX3, PEX7, PICK1, PLDN, PML, POLA2, POM121, PTPRK, PUM1, RAB11FIP3, RAB1A, RAB34, RAB35, RAB3IP, RAB40B, RAB4A, RABGEF1, RAE1, RHOT1, RHOT2, RIMS2, RPAIN, RPH3AL, RPS15, RRBP1, RUFY1, SAR1A, SAR1B, SCFD1, SEC16A, SEC23A, SEC23IP, SEC31A, SEC31B, SELENBP1, SENP2, SFT2D1, SH3GLB1, SLC11A1, SLC25A10, SMG7, SNAPIN, SNX11, SNX14, SNX16, SNX25, SNX4, SNX5, SPAST, SRP9, SSR1, STAM, STAM2, STON1, STRADA, STRADB, STX18, STX1A, STX3, STXBP1, STXBP4, SYNRG, SYTL2, TERF2, THOC1, THOC2, TIMM44, TNPO3, TOMM40L, TPM1, TRAK2, TRAPPC2, TRAPPC2L, TRPC4AP, UNC50, UPF1, VPS13D, VPS26A, VPS29, VPS33B, VPS37A, VPS4B, VPS53, VTA1, VTI1A, VTI1B, XPO1, XPO4, YWHAH, ZDHHC17, ZMAT3, ZNF384*
		GO:0015031	Protein transport	155	3.26E-07		
		GO:0008104	Protein localization	174	4.71E-07		
		GO:0046907	Intracellular transport	127	5.33E-05		
		GO:0034613	Cellular protein localization	83	2.96E-04		
		GO:0070727	Cellular macromolecule localization	83	3.76E-04		
		GO:0006886	Intracellular protein transport	74	1.17E-03		
	Phosphorylation (4.123)	GO:0006468	Protein amino acid phosphorylation	131	1.83E-05	177	*AATK, ABI1, ABI2, ABL2, ACP1, ACVR1, ACVR1B, ADAM10, AKT2, ATP6V1E1, AURKA, AURKC, BRSK2, CAMK1, CAMK1G, CAMK2B, CAMK2D, CAMK2G, CAMKK1, CAMKK2, CASK, CDK10, CDK11B, CDK16, CDK20, CDK7, CDK8, CIT, CLK4, COL4A3BP, CSNK1A1, CSNK1G3, DAPK1, DDR1, DGUOK, DLD, DUSP11, DYRK4, EEF2K, EFNA1, EIF2AK4, EPM2A, ERC1, FES, FGR, FLT3, FRS2, FUK, FYN, GAB1, GAK, GMFB, GPD2, GRK4, GRK6, HUS1, IKBKB, ILK, ILKAP, INPP1, IP6K2, IRAK1, KALRN, KSR1, LIPE, LRRK2, MADD, MAP2, MAP2K2, MAP2K3, MAP2K4, MAP2K7, MAP3K12, MAP3K4, MAP3K6, MAP3K7, MAP3K9, MAP4K4, MAPK10, MAPK11, MAPK12, MAPK7, MAPK9, MARK1, MARK2, MARK3, MARK4, MAST1, MASTL, MINK1, MKNK1, MKNK2, MON2, MST4, MTM1, MTMR1, MTMR11, MTMR14, MTMR2, MTMR3, NDUFB10, NDUFS2, NEK11, NEK6, NEK9, NPR2, NRBP2, NTRK2, NTRK3, P2RX7, PAK6, PAN3, PDK1, PDP1, PHKG1, PHKG2, PI4KB, PICK1, PIK3CB, PIP5K1A, PIP5K1B, PML, PPA2, PPAP2A, PPM1A, PPP5C, PPP6C, PRKACB, PRKDC, PTK2, PTP4A3, PTPN12, PTPN13, PTPN23, PTPN4, PTPRD, PTPRE, PTPRF, PTPRK, PTPRM, PTPRN2, PTPRO, PXK, RIPK1, RPS6KA5, RPS6KB1, RPS6KB2, RPS6KL1, SBF1, SBF2, SCYL2, SMAD2, SNRK, SSH3, STK38L, STK40, STRADA, STRADB, SYNJ1, TAOK3, TAZ, TBCK, TEK, TEX14, TGFBR1, TNIK, TNK2, TRIO, TRPM7, TWF1, UGP2, ULK2, ULK3, UQCRH, VRK3, WNK1, WNK3*
		GO:0006793	Phosphorus metabolic process	177	5.93E-05		
		GO:0006796	Phosphate metabolic process	177	5.93E-05		
		GO:0016310	Phosphorylation	144	5.00E-04		
	RNA transport (4.109)	GO:0015931	Nucleobase, nucleoside, nucleotide and nucleic acid transport	33	3.91E-05	33	*AGFG1, ATXN2, CKAP5, DDX19A, DDX19B, ENY2, G3BP2, HNRNPA1L2, MAGOH, MVP, NUP153, NUP188, NUP54, NUP62, NUP88, NUP98, NUPL1, NUPL2, NXF1, POM121, RAE1, SENP2, SLC23A2, SLC25A19, SLC29A1, SLC29A2, SMG7, THOC1, THOC2, UPF1, UPF3A, UPF3B, XPO1*
		GO:0051028	mRNA transport	27	7.56E-05		
		GO:0051236	Establishment of RNA localization	29	8.05E-05		
		GO:0050657	Nucleic acid transport	29	8.05E-05		
		GO:0050658	RNA transport	29	8.05E-05		
		GO:0006403	RNA localization	29	1.44E-04		
	Protein modification (3.780)	GO:0070647	Protein modification by small protein conjugation or removal	44	8.68E-06	44	*ATXN7, BRCA1, BRCC3, CHFR, CTR9, DDB2, DZIP3, ENY2, ERCC8, FBXL3, FBXO25, FBXW11, FBXW7, G2E3, HDAC6, KAT2A, LMO7, LRSAM1, MYSM1, NOSIP, OS9, PCNP, PPIL2, RNF144B, RNF167, RNF7, RNF8, SENP2, SENP7, SOCS7, TRIM23, TRIM33, TRIP12, TRRAP, UBA3, UBE2B, UBE2H, UBE3A, UBE3C, UBE4B, USP12, USP33, WDR48, WDSUB1*
		GO:0000209	Protein polyubiquitination	12	3.52E-04		
		GO:0032446	Protein modification by small protein conjugation	34	4.02E-04		
		GO:0016567	Protein ubiquitination	31	6.21E-04		
	Endocytosis (3.561)	GO:0016192	Vesicle-mediated transport	124	2.72E-07	139	*ABCA7, AGAP3, AMPH, ANK1, AP1G2, AP1S2, AP2B1, AP2M1, AP3B2, AP3S1, AP4M1, AP4S1, ARFGAP1, ARRB2, ASGR1, ATG7, BAK1, BAX, BID, BLZF1, CACNA1A, CACNA1C, CADPS, CADPS2, CAP1, CCDC88A, CHMP7, CLINT1, CLN3, CLTA, CLTB, CLTCL1, CNIH, COG3, COPA, COPE, COPZ2, CPNE1, CPNE6, CRCP, DAB2, DENND1A, DNM1, DNM1L, DOC2A, DYSF, ELMO2, ELMO3, EPN2, EPS15L1, ERC1, ERGIC2, EXOC3, EXOC6, EXOC6B, EXOC7, FLNA, GGA1, GGA3, GNPAT, GOLGA4, GOLT1B, GRK4, GSN, GTF2A1L, HOOK2, ITSN1, ITSN2, KALRN, LAT, LDLR, LDLRAP1, LMAN2L, LRP12, LRP8, LRSAM1, MIA3, MON2, MUTED, MYH10, MYO6, NAPG, NECAP1, NECAP2, NPEPL1, NRAS, NRCAM, OPA1, P2RX7, PCSK4, PI4KB, PICALM, PICK1, PLDN, PLSCR1, PLSCR4, PUM1, RAB1A, RAB34, RAB35, RAB3IP, RABEPK, RABGEF1, RPH3AL, RTN3, RUFY1, SAR1A, SAR1B, SCARB1, SCFD1, SEC16A, SEC23A, SEC31A, SEC31B, SH3GLB1, SLC11A1, SNAP91, SNAPIN, SNX4, SPAST, STON1, STX18, STX1A, STX3, STXBP1, SYNJ1, SYNRG, SYTL2, TAZ, TRAPPC2, TRAPPC2L, TRAPPC6A, UNC13D, VAV3, VPS26A, VPS33B, VPS4B, VTI1A, VTI1B*
		GO:0016044	Membrane organization	77	4.87E-04		
		GO:0006897	Endocytosis	45	6.57E-03		
		GO:0010324	Membrane invagination	45	6.57E-03		

Supplementary Table 7 (continued) *Top biological processes from gene ontology analyses of AS genes in c9ALS*

	Cluster ID (Enrichment score)	GO term ID		Count	*P* value	Total genes in cluster	Genes
FRONTAL CORTEX	Protein transport (3.164)	GO:0046907	Intracellular transport	51	4.20E-07	79	*AAAS, ACD, APBA2, APBA3, APP, ARFGAP2, ARHGAP33, ATG16L2, ATP5D, ATP5O, BAX, BBS2, BCL2L1, BET1L, BID, CALR, CBY1, CDC37, CHKB, CHMP1A, CHMP2A, CLTC, COPE, CSE1L, CTSA, DDX19B, DSCR3, EIF4ENIF1, FLNA, FTH1, GDI1, GGA1, GIPC1, GNAS, GNPTG, HNRNPA1, KLC1, LIN7B, MAPK8IP3, MLH3, MRPL45, MYL6, NAPA, NDUFA13, NEDD8, NFKBIB, NUP88, NUPL1, OS9, PABPN1, PAX6, PICK1, PRKCB, RAB15, RAB18, RAB26, RAB3IP, RAB40B, RANBP1, RANGRF, RHOT1, RPAIN, RPL23, SCAMP5, SCYL1, SNAP25, SNUPN, SPTBN4, STARD3, STX10, STX8, TIMM8B, TIMM9, TOMM40, TRAPPC4, TRIM3, VAMP2, YWHAE, YWHAH*
		GO:0008104	Protein localization	59	5.57E-06		
		GO:0045184	Establishment of protein localization	49	1.38E-04		
		GO:0015031	Protein transport	48	2.05E-04		
		GO:0034613	Cellular protein localization	29	9.35E-04		
		GO:0070727	Cellular macromolecule localization	29	1.06E-03		
		GO:0006886	Intracellular protein transport	24	8.88E-03		
		GO:0033365	Protein localization in organelle	12	1.64E-02		
		GO:0006605	Protein targeting	15	2.37E-02		
	RNA processing (2.954)	GO:0008380	RNA splicing	24	2.50E-04	39	*APLP1, APP, ARL6IP4, BCAS2, CELF1, CSTF3, DDX17, DDX5, DDX54, EXOSC1, GEMIN7, HNRNPA1, HNRNPH3, NHP2L1, NOLC1, NOP2, PABPN1, PAN2, PCBP2, PIN4, POLR2I, PPP2R1A, QTRT1, RBM3, RBM39, RBM4, RNH1, RPS24, RPS28, SNRNP70, SNRPD1, SNRPD2, SNRPN, SNUPN, SRRM2, TRMT1, U2AF1, U2AF1L4, UPF3B*
		GO:0006396	RNA processing	37	3.59E-04		
		GO:0000375	RNA splicing, via transesterification reactions	15	1.26E-03		
		GO:0000377	RNA splicing, via transesterification reactions with bulged adenosine as nucleophile	15	1.26E-03		
		GO:0000398	Nuclear mRNA splicing, via spliceosome	15	1.26E-03		
		GO:0006397	mRNA processing	23	2.98E-03		
		GO:0016071	mRNA metabolic process	25	3.98E-03		
	Phosphorylation (1.918)	GO:0016310	Phosphorylation	45	3.27E-03	49	*ADRBK1, ADRBK2, AKT2, APP, ATP5D, ATP5G2, ATP5O, AXL, BRSK2, CAMK2G, CDC42BPB, CDK10, CDK17, CDK4, CIT, CLK3, CSK, ERBB3, FGFR2, ILK, MAP2K2, MAPK8IP3, MARK2, MAST1, MATK, MKNK2, MVD, NDUFA3, NDUFB10, NDUFV1, NDUFV3, NEK9, NME2, P2RX7, PHKG2, PICK1, PNCK, PPP1CA, PPP2R1A, PRKCB, PTP4A2, PTPRA, RPS6KL1, SBF1, SCYL1, TRIM28, ULK3, UQCRH, WNK1*
		GO:0006796	Phosphate metabolic process	49	1.61E-02		
		GO:0006793	Phosphorus metabolic process	49	1.61E-02		
		GO:0006468	Protein amino acid phosphorylation	35	2.52E-02		
	Gene silencing (1.762)	GO:0016458	Gene silencing	8	3.78E-03	10	*CELF1, CHMP1A, HDAC10, HDAC5, RBM3, RBM4, SIRT2, SIRT6, SMARCA4, TNRC6C*
		GO:0006476	Protein amino acid deacetylation	5	7.24E-03		
		GO:0006342	Chromatin silencing	4	2.53E-02		
		GO:0045814	Negative regulation of gene expression, epigenetic	4	3.81E-02		
	Chromatin modification (1.385)	GO:0006476	Protein amino acid deacetylation	5	7.24E-03	19	*BANP, BPTF, BRD1, C20ORF20, CREBBP, HDAC10, HDAC5, HSF4, KAT2A, KAT5, KDM2B, PHF21A, RBM4, SIRT2, SIRT6, SMARCA1, SMARCA4, SMARCC2, SMARCE1*
		GO:0016568	Chromatin modification	18	2.08E-02		
		GO:0016575	Histone deacetylation	4	2.16E-02		
		GO:0016569	Covalent chromatin modification	10	3.82E-02		

Supplementary Table 8 *Top biological pathways from gene ontology analyses of AS genes in sALS*

	Cluster ID (Enrichment score)	GO term ID	GO term	Count	*P* value	Total genes in cluster	Genes
CEREBELLUM	Cytoskeleton (2.871)	GO:0007010	Cytoskeleton organization	32	1.70E-04	32	*ABI2, ABL2, ABLIM3, ARHGEF11, BBS4, CAPN10, CAPN3, CDC42, CDC42BPA, CLASP1, CNTROB, DST, ELN, EPB41, FERMT2, FLNA, FMNL2, HDAC3, KLHL1, LIMCH1, MAP2, MARK1, MICAL1, MYH10, PCM1, PCNT, PLD2, PRC1, SMC3, SORBS1, TRPM7, TUBGCP4*
		GO:0030036	Actin cytoskeleton organization	18	2.73E-03		
		GO:0030029	Actin filament-based process	18	5.25E-03		
	RNA processing (2.515)	GO:0006396	RNA processing	39	5.22E-05	41	*BCAS2, CDK5RAP1, CELF1, CPSF1, CPSF6, CSTF3, DDX54, DHX35, ELAC2, EXOSC3, HNRNPH1, HNRPLL, INTS4, INTS6, LUC7L3, MBNL1, NOL3, PABPC4, POP5, PPIL3, PRMT5, PTBP1, PTBP2, QTRT1, RBM3, RBM5, RBMX, RNMT, RNPS1, RPS15, SF1, SNRPN, SRPK2, SRRM1, TARBP1, THOC2, TRA2B, TSR1, U2AF1L4, WIBG, ZRANB2*
		GO:0006397	mRNA processing	26	1.82E-04		
		GO:0008380	RNA splicing	24	1.85E-04		
		GO:0016071	mRNA metabolic process	27	6.67E-04		
		GO:0000398	Nuclear mRNA splicing, via spliceosome	14	2.98E-03		
		GO:0000375	RNA splicing, via transesterification reactions	14	2.98E-03		
		GO:0000377	RNA splicing, via transesterification reactions with bulged adenosine as nucleophile	14	2.98E-03		
		GO:0022618	Ribonucleoprotein complex assembly	8	1.06E-02		
		GO:0000245	Spliceosome assembly	5	2.51E-02		
	Phosphorylation (1.791)	GO:0006468	Protein amino acid phosphorylation	38	4.16E-03	47	*ABI1, ABI2, ABL2, AURKC, BRSK2, CAMK2A, CDC42BPA, CHUK, CLK4, COL4A3BP, CTDP1, DUSP12, EFNA1, EPHB6, ERC1, FES, GRM4, ILKAP, INPP1, MAP2, MAP3K14, MAP3K9, MAPK10, MAPK12, MARK1, MATK, MTMR2, NDUFV3, OBSCN, PAK6, PRKACB, PTPN4, RPS6KC1, SHC1, SLC20A1, SRPK2, STAT5A, STK25, STK39, TGFA, TLK2, TNK2, TRPM7, ULK3, UQCRH, VRK3, WNK1*
		GO:0016310	Phosphorylation	40	2.47E-02		
		GO:0006793	Phosphorus metabolic process	47	2.59E-02		
		GO:0006796	Phosphate metabolic process	47	2.59E-02		
	Cell projection (1.333)	GO:0030031	Cell projection assembly	10	2.54E-03	15	*ABI2, BBS4, CCDC88A, CDC42, IFT172, IFT88, ITGB4, KLHL1, MAP2, MCF2, MYH10, PCM1, PCNT, SH2B1, TTC8*
		GO:0060271	Cilium morphogenesis	6	5.60E-03		
		GO:0042384	Cilium assembly	5	1.60E-02		
	Dendrite (0.277)	GO:0016358	Dendrite development	5	3.37E-02		
	Ion transport (0.962)	GO:0030001	Metal ion transport	25	3.96E-02	38	*ABCC8, AMACR, ANO1, ATP2B3, BEST1, BSPRY, CACNA1B, CACNB4, CAMK2A, CPT1B, CUTC, FXYD6, GABRA2, GRIA2, GRIA4, GRIK4, HEPH, ITPR1, KCNC4, KCNH1, KCNMA1, KCTD17, KCTD3, SCN8A, SCNN1D, SLC20A1, SLC38A6, SLC39A13, SLC3A2, SLC4A3, SLC4A5, SLC5A2, SLC5A6, SLC8A1, TMEM38B, TOMM40L, TRPM7, WNK1*
		GO:0006811	Ion transport	37	4.88E-02		
	Macromolecular complex (0.910)	GO:0065003	Macromolecular complex assembly	34	2.97E-02	35	*ABI2, APC, ATG16L1, BCS1L, CELF1, EPRS, ERCC2, FLNA, H3F3A, HLA-DMA, IDE, IRF7, JUP, MBNL1, MTMR2, NAP1L1, NUP98, PEX14, PILRB, PRMT5, RBM5, RPS15, SF1, SLC7A6, SRPK2, TAPBP, THRAP3, TNFRSF1A, TRAF2, TRIM5, TSR1, TUBB6, TUBGCP4, UQCRH, ZFYVE9*
		GO:0043933	Macromolecular complex subunit organization	35	4.34E-02		
	Regulation of microtubule polymerization (0.860)	GO:0031114	Regulation of microtubule depolymerization	4	1.73E-02	8	*APC, ARHGEF11, BBS4, BRSK2, CDC42, CLASP1, CLASP2, DST*
		GO:0007026	Negative regulation of microtubule depolymerization	4	1.73E-02		
		GO:0031111	Negative regulation of microtubule polymerization or depolymerization	4	2.05E-02		
		GO:0031110	Regulation of microtubule polymerization or depolymerization	5	2.26E-02		
		GO:0032886	Regulation of microtubule-based process	6	2.85E-02		
		GO:0007163	Establishment or maintenance of cell polarity	6	2.85E-02		
	Organelle localization (0.837)	GO:0051656	Establishment of organelle localization	7	3.44E-02	7	*ARFGAP1, BBS4, CDC42, GBF1, KIF1B, MYH10, RPS15*
FRONTAL CORTEX	Phosphorylation (1.656)	GO:0016310	Phosphorylation	19	7.80E-03	19	*ABI1, AKT1, APP, ATP5B, ATP5G2, CAMK2G, EIF2AK4, FGFR2, MAPK3, MATK, MINK1, PAK1, PRKCB, SPAG9, STK33, ULK2, ULK3, UQCRH, WNK1*
		GO:0006468	Protein amino acid phosphorylation	16	1.48E-02		
		GO:0006793	Phosphorus metabolic process	19	4.54E-02		
		GO:0006796	Phosphate metabolic process	19	4.54E-02		
	Synapsis (1.334)	GO:0050808	Synapse organization	4	3.72E-02	6	*ANK3, APBB1, APLP2, APP, CADM1, GLRA2*
		GO:0043062	Extracellular structure organization	6	4.73E-02		
	Cell size (1.316)	GO:0008361	Regulation of cell size	9	3.54E-03	9	*AKT1, APBB1, APP, CAPRIN2, CGRRF1, FGFR2, FHL1, NDRG4, NDUFA13*
		GO:0032535	Regulation of cellular component size	9	1.70E-02		
		GO:0045792	Negative regulation of cell size	5	3.17E-02		
		GO:0016049	Cell growth	4	3.72E-02		
	Cell death (1.228)	GO:0008219	Cell death	18	6.01E-03	18	*AKT1, APBB1, APP, BLCAP, CADM1, FAIM2, ITSN1, NCKAP1, NDUFA13, NGFRAP1, PACS2, PAK1, PLP1, PNPLA6, PSME3, RPS3, UBA1, YWHAE*
		GO:0016265	Death	18	6.43E-03		
		GO:0006915	Apoptosis	15	1.41E-02		
		GO:0012501	Programmed cell death	15	1.58E-02		

Supplementary Table 9 *Top biological processes from gene ontology analyses of transcripts with APA usage in c9ALS*

	Cluster ID (Enrichment score)	GO term ID		Count	*P* value	Total genes in cluster	Genes
CEREBELLUM	ncRNA and rRNA processing (1.840)	GO:0034470	ncRNA processing	23	1.41E-03	36	*ADAT3, AIMP1, ATXN2, CDK5RAP1, CDKN2A, EIF2AK4, ERI1, EXOSC7, FARS2, GNL3L, INTS9, KRR1, LSM6, METTL1, NAF1, NIP7, NUFIP1, PHAX, PRMT5, PUS1, RPP14, RPP30, SF3A1, SF3A3, SLU7, TARBP2, TARSL2, TGS1, TRMT2B, TRMU, TRNT1, TSEN34, TYW1B, UTP14A, UTP6, WDR55*
		GO:0008033	tRNA processing	13	1.47E-03		
		GO:0006399	tRNA metabolic process	16	3.72E-03		
		GO:0034660	ncRNA metabolic process	25	4.37E-03		
		GO:0022613	Ribonucleoprotein complex biogenesis	20	9.33E-03		
	Phosphorylation (1.640)	GO:0006468	Protein amino acid phosphorylation	55	9.73E-03	74	*ABI3, AKAP9, ARAF, ATP6V1C1, ATR, AURKC, AXL, BRAF, BRD4, BTK, CAD, CAMK1D, CAV2, CDK13, CDK16, CDK3, CLK2, CLK4, EIF2AK4, EPHB2, EPM2A, ERCC3, FES, FPGT, GADD45G, GHR, GK, GLYCTK, GPD1, HIPK4, INPPL1, IP6K2, LRRK2, LTK, MAP3K4, MAP4K4, MAPK6, MAPK8, MAPKAPK5, MARK3, MASTL, MDFI, MERTK, MON2, MTM1, MTMR1, NDUFA6, NEK6, PASK, PDE6G, PKN3, PLK2, PNCK, PPM1A, PPM1D, PPP1CB, PPP6C, PRKD1, PRPF4B, PTP4A1, PTPN5, PTPRG, SHC1, STAT4, STK17A, STRADB, TESK1, TGFB1, THTPA, TIE1, TNNI3K, TP53RK, WNK4, WNT2*
		GO:0006796	Phosphate metabolic process	73	2.29E-02		
		GO:0006793	Phosphorus metabolic process	73	2.29E-02		
	Regulation of DNA binding (1.392)	GO:0051098	Regulation of binding	17	1.75E-02	17	*ABRA, ATR, BRD4, CDKN2A, CREBZF, DPH3, ID1, MDFI, MTDH, NR0B1, NRG1, PYCARD, RHEBL1, SMARCA4, TGFB1, TLR3, UBE2N*
		GO:0051101	Regulation of DNA binding	14	2.49E-02		
		GO:0051099	Positive regulation of binding	10	3.83E-02		
		GO:0051090	Regulation of transcription factor activity	12	3.86E-02		
	Peroxisome (1.299)	GO:0016558	Protein import into peroxisome matrix	4	1.77E-02	4	*PEX6, PEX13, PEX16, PEX26*
		GO:0006625	Protein targeting to peroxisome	4	4.50E-02		
	Unfolded protein response (1.257)	GO:0006984	ER-nuclear signaling pathway	7	1.50E-02	7	*ATG10, CRIPAK, DERL2, DERL3, EIF2AK4, ERO1L, VAPB*
		GO:0034620	Cellular response to unfolded protein	5	3.16E-02		
		GO:0030968	ER unfolded protein response	5	3.16E-02		
		GO:0034976	Response to ER stress	6	4.64E-02		
	Transcription (1.230)	GO:0045449	Regulation of transcription	174	3.35E-02	182	*ACTR5, AEBP2, AHCTF1, APOBEC3F, ARID2, ASF1A, ATAD2, ATF1, ATXN7, BARHL1, BMP4, BRPF1, BRWD1, CAND1, CAND2, CARHSP1, CBFA2T3, CDCA7L, CDKN2A, CNOT3, CNOT6, COPS2, CRABP2, CREB3L4, CREBZF, CRK, CRX, CTNNB1, ELL2, ELL3, EMX1, ERCC3, ESR2, FHL2, FOXP1, GATAD1, GTF2E2, GTF3C5, HAT1, HDAC10, HDAC3, HIF3A, HOMEZ, ID1, IGSF1, IRAK1BP1, IRX2, IVNS1ABP, KCNH6, KDM5A, KIAA2018, KLF10, LBX1, LIMD1, MAF, MBD1, MBD2, MCM5, MDFI, MED24, MED6, MLF1, MNAT1, MTDH, MURC, MXD3, MYC, MYCBP, MYEF2, MYNN, NAA15, NFATC2IP, NFX1, NFYB, NR0B1, NRG1, NTF3, NUFIP1, PASK, PAX2, PGBD1, PHF19, POLR1B, POU2F1, PPARA, PPM1A, PPP1R13L, PPRC1, PRDM8, PRMT5, PSPC1, PYCARD, RARB, RASD1, RBPJ, RCOR2, RHEBL1, RING1, RQCD1, RRAGC, SAP130, SAP30L, SLC11A1, SMAD6, SMARCA4, SMARCE1, SMURF2, SOHLH1, SORBS3, SPI1, SRA1, STAT4, SUV39H2, TAF11, TAF1A, TARBP2, TCF19, TFAM, TFCP2, TGFB1, TGS1, TIAL1, TLR3, TMF1, TRAK2, TRIM16, TRIP4, UBE2N, WHSC1, WHSC1L1, WNT1, WWP1, ZBTB8A, ZFP14, ZFX, ZIK1, ZIM2, ZNF107, ZNF132, ZNF154, ZNF19, ZNF223, ZNF230, ZNF250, ZNF316, ZNF329, ZNF419, ZNF426, ZNF43, ZNF467, ZNF473, ZNF486, ZNF524, ZNF546, ZNF548, ZNF551, ZNF552, ZNF555, ZNF566, ZNF568, ZNF577, ZNF585A, ZNF593, ZNF611, ZNF619, ZNF623, ZNF626, ZNF655, ZNF669, ZNF670, ZNF682, ZNF692, ZNF76, ZNF775, ZNF790, ZNF814, ZNF818P, ZNF827, ZNF846, ZNF852, ZSCAN1*
		GO:0006350	Transcription	143	3.40E-02		
FRONTAL CORTEX	Transcription (2.640)	GO:0006355	Regulation of transcription, DNA-depend	92	4.95E-04	129	*ANKRD1, ARNTL2, ASXL3, ATF1, ATF3, ATF7, BARX2, BATF, BATF3, BLM, BRCA2, CBFA2T2, CBFA2T3, CBX2, CDC73, CIITA, DLX2, DNMT3A, DNMT3B, DPF3, E2F7, EHF, ELF5, ERCC3, FOXN4, FOXP3, GATA6, GATAD2B, GLRX2, GMCL1, GMCL1L, GMEB1, GSX1, GTF3C3, HAT1, HCFC2, HES4, HIC1, HMGA2, HNF4A, HSF2BP, HSF4, IGSF1, IL16, ING5, IRAK3, IRX3, IRX6, ISL2, KHDRBS1, KRTAP1-1, MED14, MED18, MIER1, MOV10, MTF1, MYBL2, MYT1, NAA16, NEUROG3, NFATC1, NFATC2, NHLH1, NKX2-1, NKX2-8, NPAS2, NTF3, ONECUT1, OSM, PAPOLG, PAX1, PER3, PEX14, PKNOX1, POLR1A, POU2AF1, POU3F4, PRDM16, PROX2, RCOR3, RUNX1, SKI, SLA2, SOX13, SOX3, SOX5, SOX6, SP6, STAT6, TAF1A, TARBP1, TBX5, TCF7L1, TEAD4, TFB2M, TGFBRAP1, UBC, VDR, VGLL1, ZFP92, ZGLP1, ZNF180, ZNF20, ZNF200, ZNF208, ZNF230, ZNF235, ZNF281, ZNF334, ZNF345, ZNF347, ZNF460, ZNF480, ZNF492, ZNF524, ZNF547, ZNF568, ZNF573, ZNF582, ZNF600, ZNF674, ZNF676, ZNF701, ZNF849P, ZNF98, ZNHIT3, ZSCAN18, ZSCAN2, ZZZ3*
		GO:0051252	Regulation of RNA metabolic process	92	1.02E-03		
		GO:0045449	Regulation of transcription	120	4.64E-03		
		GO:0006350	Transcription	97	1.18E-02		
	Positive regulation of transcription (1.614)	GO:0045944	Positive regulation of transcription from RNA polymerase II promoter	26	2.64E-03	50	*ANKRD1, APOA5, AVPR1A, BARX2, BLM, CBX2, CD3E, CIITA, DLX2, DNMT3A, DNMT3B, EHF, ERCC3, FOXP3, GATA6, GSX1, HCFC2, HNF4A, HSF4, ING5, MED14, MED18, MTF1, NAA16, NEUROG3, NFATC2, NKX2-1, NPAS2, NTF3, ONECUT1, OSM, P2RX4, PAX1, PKNOX1, PRDM16, RUNX1, SKI, SLA2, SOX5, SOX6, STAT6, TARBP1, TBX5, TCF7L1, TEAD4, UBC, VDR, ZGLP1, ZNF281, ZNF345*
		GO:0045893	Positive regulation of transcription, DNA-dependent	29	9.98E-03		
		GO:0006357	Regulation of transcription from RNA polymerase II promoter	40	1.13E-02		
		GO:0051254	Positive regulation of RNA metabolic process	29	1.14E-02		
		GO:0010628	Positive regulation of gene expression	33	1.47E-02		
		GO:0045941	Positive regulation of transcription	32	1.67E-02		
		GO:0031328	Positive regulation of cellular biosynthetic process	36	3.09E-02		
		GO:0009891	Positive regulation of biosynthetic process	36	3.62E-02		
	Amino acid biogenesis (1.505)	GO:0042401	Biogenic amine biosynthetic process	7	6.68E-04	14	*AANAT, AGMAT, DNMT3B, ETNK2, GCLM, GGT7, GLRX2, HDC, NAGS, PAH, PLA2G5, SHMT1, TH, TMLHE*
		GO:0042398	Cellular amino acid derivative biosynthetic process	9	7.37E-04		
		GO:0009309	Amine biosynthetic process	9	9.64E-03		
		GO:0006575	Cellular amino acid derivative metabolic process	12	4.26E-02		

Supplementary Table 10 *Top biological processes from gene ontology analyses of transcripts with APA usage in sALS*

	Cluster ID (Enrichment score)	**GO term ID**		**Count**	***P* value**	**Total genes in cluster**	**Genes**
CEREBELLUM	Response to oxidative stress (1.368)	GO:0010035	Response to inorganic substance	13	3.01E-02	17	*ADA, CCL5, CYP11A1, EPX, GLRX2, KCNMA1, MAPK8, NEIL1, PARK7, PEF1, PYCR1, RYR2, S100A16, SLC25A12, STK25, TPM1, UCP3*
		GO:0000302	Response to reactive oxygen species	7	3.12E-02		
		GO:0006979	Response to oxidative stress	11	3.57E-02		
	Peroxisome (1.235)	GO:0007031	Peroxisome organization	4	3.48E-02	4	*PEX14, PEX16, PEX19, SCP2*
	Response to substance (1.063)	GO:0010035	Response to inorganic substance	13	3.01E-02	13	*ADA, CYP11A1, EPX, GLRX2, KCNMA1, MAPK8, PARK7, PEF1, RYR2, S100A16, SLC25A12, TPM1, UCP3*
	Lipid biosynthesis (0.985)	GO:0045017	Glycerolipid biosynthetic process	9	3.72E-03	10	*AGPAT3, ALG9, DGAT2, FABP3, PCK1, PEMT, PI4KB, PIGN, PIGS, PLAUR*
		GO:0046474	Glycerophospholipid biosynthetic process	7	2.04E-02		
		GO:0046489	Phosphoinositide biosynthetic process	5	3.68E-02		
		GO:0008654	Phospholipid biosynthetic process	8	4.29E-02		
FRONTAL CORTEX	Transcription (1.594)	GO:0006350	Transcription	126	1.06E-02	154	*AFAP1L2, AHCTF1, APBB1, AR, ARID4A, ARX, ASXL3, ATF1, ATF3, BARX2, BATF, BAZ1A, BHLHA9, BMP4, BRCA2, BTG2, CALCOCO1, CASK, CBFA2T3, CBFB, CBX4, CDC73, CEBPB, CHD5, CIR1, CRK, DNMT3A, DNMT3B, EDA2R, ELF5, ERCC3, ESR2, ESRRB, FOXN4, FOXP3, GABPB1, GATA3, GMCL1, GMEB1, GPBP1L1, GSX1, GTF2H1, HELLS, HES4, HIPK3, HMGN5, HNF1A, HNRNPF, HOXB6, HTATIP2, IFI16, IGSF1, IKZF5, ING5, IRAK3, IRX3, KDM3A, KHDRBS1, KLF5, LIF, MAP2K3, MAX, MCM8, MEAF6, MED6, MMS19, MYCBP2, NEDD4, NEO1, NFATC2, NKX2-1, OLIG2, ONECUT1, OSM, PAPOLG, PATZ1, PAWR, PAX3, PDE8A, PDLIM1, POLR1A, POLR1B, POU3F4, PRDM16, RBL2, RNF6, RUNX1, RXRG, SCML1, SCML2, SMARCD1, SNIP1, SOHLH2, SP100, SP6, STAT4, TAF1A, TBX5, TCEB3, TCF7L1, TFAP2C, TFB2M, TGFBRAP1, THAP7, TLE3, TRIM33, TROVE2, TSPYL2, VAX1, VGLL1, WT1, XBP1, YY1, ZBTB1, ZBTB17, ZBTB40, ZFP92, ZGLP1, ZNF124, ZNF175, ZNF195, ZNF208, ZNF235, ZNF254, ZNF26, ZNF286A, ZNF329, ZNF347, ZNF358, ZNF396, ZNF43, ZNF431, ZNF460, ZNF486, ZNF514, ZNF519, ZNF527, ZNF547, ZNF568, ZNF573, ZNF600, ZNF611, ZNF665, ZNF670, ZNF674, ZNF676, ZNF687, ZNF69, ZNF708, ZNF8, ZNF837, ZNHIT3, ZSCAN5B, ZZZ3*
		GO:0006355	Regulation of transcription, DNA-dependent	105	2.85E-02		
		GO:0051252	Regulation of RNA metabolic process	106	3.69E-02		
		GO:0045449	Regulation of transcription	147	3.80E-02		
	Neuron differentiation (1.594)	GO:0030182	Neuron differentiation	35	5.56E-03	48	*AFG3L2, APBB1, ARX, B3GNT2, BCL2, BMP4, BTG2, CCL4, CD24, CDC42BPB, CDH1, CEBPB, CXCR4, DOCK7, DSCAM, DSCAML1, EFNA1, ESRRB, FOXN4, GSX1, KLF5, LIF, LIMS1, LPAR3, MCOLN3, MTOR, MYCBP2, NEDD4, NFASC, NKX2-1, NRP2, NTRK3, OLIG2, ONECUT1, PARD6B, PAX3, POU3F4, RET, ROCK1P1, SCARF1, SHROOM4, SLITRK4, SNAP25, STRN, TTC8, UPK3A, VANGL2, VAX1*
		GO:0030030	Cell projection organization	29	1.44E-02		
		GO:0031175	Neuron projection development	22	1.48E-02		
		GO:0048858	Cell projection morphogenesis	20	3.29E-02		
		GO:0000902	Cell morphogenesis	26	4.55E-02		
		GO:0032990	Cell part morphogenesis	20	4.78E-02		
	Germ cell development (1.225)	GO:0007281	Germ cell development	12	1.05E-02	13	*AXIN1, BCL2, BMP4, BRCA2, CXCR4, MOV10L1, MTOR, PDE3A, SOHLH2, TDRD1, TSSK6, WT1, ZGLP1*
		GO:0048599	Oocyte development	5	1.77E-02		
		GO:0009994	Oocyte differentiation	5	2.08E-02		
		GO:0048477	Oogenesis	6	3.69E-02		
	Reproductive process (1.192)	GO:0007281	Germ cell development	12	1.05E-02	24	*ACR, AR, AXIN1, BCL2, BMP4, BMPR1A, BRCA2, CXCR4, FGF9, HNF1A, IDH1, INSL3, LIF, MOV10L1, MTOR, NKX2-1, PDE3A, PIWIL4, PTGDR, SYCP2, TDRD1, TSSK6, WT1, ZGLP1*
		GO:0003006	Reproductive developmental process	22	1.88E-02		
		GO:0048610	Reproductive cellular process	15	2.84E-02		
	Chromatin regulation (1.078)	GO:0006346	Methylation-dependent chromatin silencing	3	2.18E-02	5	*DNMT3A, DNMT3B, HELLS, PIWIL4, TDRD1*
		GO:0006305	DNA alkylation	5	2.79E-02		
		GO:0006306	DNA methylation	5	2.79E-02		

Supplementary Table 11 *Human gene information, chromosomal location and primers used for qRT-PCR*

	Gene	RefSeq	Forward primer	Reverse primer
Expression	*ALAS2*	NM_000032.4; NM_001037968.3; NM_001037967.3	AGGGGCCTTCCTGTCATC	CAGAGCTTGCTGTTGAGTGC
	CHI3L1	NM_001276.2	CCCAACCTGAAGACTCTCTTGT	GGTGTTGGAGGCTATCTTGG
	DNAJB1	NM_006145.2; NM_001300914.1	GGCCTACGACGTGCTCAG	GTGTAGCTGAAAGAGGTACCATTG
	FOXJ1	NM_001454.3	GGGGTGGGAGCAACTTCT	CCTCCTCCGAATAAGTATGTGGT
	HMOX1	NM_002133.2	GGCAGAGGGTGATAGAAGAGG	AGCTCCTGCAACTCCTCAAA
	HSPB1	NM_001540.3	TCCCTGGATGTCAACCACTT	GATGTAGCCATGCTCGTCCT
	HSPA1A	NM_005345.5	CGGCAAGGTGGAGATCAT	GGTGTTCTGCGGGTTCAG
	HSPA1B	NM_005346.4	AAGGGTGTTTCGTTCCCTTT	TAGTGTTTTCGCCAAGCAAA
	HSPH1	NM_006644.3; NM_001286503.1; NM_001286504.1; NM_001286505.1	AGCTGTGTGGACCATATGAAAA	TTGTCAACATATGCTTGTTTAGCTT
	RAB39A	NM_017516.1	CGGCGTGGACTTCTTCTC	TGCGGTAATAAGATCGGGTTAT
	SERPINA3	NM_001085.4	ACTCCAGACAGACGGCTTTG	ATTCTCTCCATTCTCAACTCTGC
	SERPINH1	NM_001207014.1; NM_001235.3	GGTGGAGGTGACCCATGA	CTTGTCAATGGCCTCAGTCA
	SPR	NM_003124.4	GCTCGTGATATGCTGTTCCA	GCATGTCTGTGTCCAGAGGA
	SQRDL	NM_021199.3; NM_001271213.1	TACGTCAAAGACCGCTGCT	ACAGAAATTGTCCTATCAAGTATTCCT
	TTR	NM_000371.3	GCCGTGCATGTGTTCAGA	GCTCTCCAGACTCACTGGTTTT
	Gene	Chromosomal location (GRCh37/hg19)	Forward primer	Reverse primer
Cassette exon	*ACTN1*	chr14:69,345,175-69,345,240	ATGGGTTACAACATGGGAGAAGC	AAGTCAATGAAGGCCTGGAATGTC
	ANKRD12	chr18:9,204,474-9,204,542	TTACTATTAGCCCATCAAGAAATGAAG	TATGTCCTGGATCTGAATCTGTGTC
	ATXN2	chr12:111,902,466-111,902,519	ATGATGCACCCAGCGTCAGC	CCTTGTTGTATGGTAATTTGGGACATG
	DGCR6L	chr22:20,303,642-20,303,742	CGCCTACAGAACGAGCACCGAGTG	GTGTTCCACGGCCTCTAGTTCTCG
	HIF1A	chr14:62,212,409-62,212,535	ATTGGAACATTATTACAGCAGCCAGAC	AGTCTACATGCTAAATCAGAGGGTATTA
	MAPT	chr17:44,087,676-44,087,768	AGGCGGGAAGGTGCAAATAG	TCCTGGTTTATGATGGATGTT
	MARK2	chr11:63,675,732-63,675,776	AGACCGAGTGGAGACGCTCAGACC	CTTGGCCTCCCGAAATTCTTCCTT
	MRPS31	chr13:41,328,155-41,328,228	GCCAGGAGAAGACGGATGAT	GTCTGTTTCAGGTGCTTCTTTAGTAACT
	PARP6	chr15:72,543,186-72,543,295	CCTGCCAAGGAGGCTCGGTTCC	GGGACCCATGGAAGGCAAAGGTG
	PAX6	chr11:31,823,419-31,823,460	GAGCCAGCATGCAGAACAGTCACA	ACTTTTGCATCTGCATGGGTCTGC
	RBM39	chr20:34,317,384-34,317,449	GGCCGCTACAGAAGTCCTTACTCC	ACCCAATCTTTCCTCGGATGG
	U2AF1	chr21:44,520,563-44,520,630	TGACGGTTTGCGCTGTGCC	CCTCACGGCGAAACTTGAC
	ULK3	chr15:75,130,493-75,130,533	GCGGGAGCTGCTTCACACTGAGGT	AAGTATTCAGCTCGGGCCATGAGGTTCT
	ZMYND8	chr20:45,841,287-45,841,370	TACCCCGCCCAGAAGTACCATTCC	TCTTTCGGGAGGAGGCTCTTCGTG
	Gene	RefSeq	Forward primer	Reverse primer
Endogenous control	*RPLPO*	NM_001002.3; NM_053275.3	TCTACAACCCTGAAGTGCTTGAT	CAATCTGCAGACAGACACTGG