Supplementary Table 1. Dataset quality control

Quality control criteria applied	Total	Cases	Controls
Total samples in initial dataset	15,722	5,073	10,649
Samples successfully incorporated into VCF	15,428	4,851	10,577
Initial sample QC: (1) Removed call rate <90 (2) Removed dp Mean <10 (3) Removed gq Mean <65	14,143	4,569	10,575
Sex imputation: (1) Removed samples with ambiguous sex	15,128	4,558	10,570
Principal component analysis: (1) Case vs controls (2) Case, controls, and 1000 Genomes (3) Isolated overlapping case and control samples	12,317	4,429	7,888
Identity by descent: (1) Removed related or duplicated samples, IBD > 0.2	11,703	3,864	7,839

Supplementary Table 2. Proposed ALS genes and their signals under the protein-truncating variant model

Gene	Qualifying variants in cases (3,864)	Qualifying variants in controls (7,839)	Qualifying variants in total controls (28,910)	OR N_{cases}: 3,864 $N_{controls}$: 7,839	P-value N_{cases}: 3,864 $N_{controls}$: 7,839	OR N_{cases}: 3,864 $N_{controls}$: 28,910	P-value N_{cases}: 3,864 $N_{controls}$: 28,910
ALS2	2	5	17	0.81	1.00	0.88	1.00
ANG	NA	NA	NA	NA	NA	NA	NA
ARHGEF28	5	4	16	2.54	0.17	2.34	0.09
ARPP21	0	1	10	0.68	1.00	0.36	0.62
ATXN2	0	1	45	0.68	1.00	0.08	8.38×10-3#
C21orf2	1	2	9	1.01	0.02	0.84	1.00
C9orf72	1	2	13	1.01	0.02	0.58	1.00
CENPV	NA	NA	NA	NA	NA	NA	NA
CHMP2B	4	1	31	8.12	0.04	0.97	1.00
DAO	0	2	27	0.41	1.00	0.14	0.07
DCTN1	1	1	9	2.03	0.55	0.83	1.00
FIG4	9	13	51	1.41	0.50	1.32	0.42
FUS	6	0	0	26.41	1.29×10-3	97.40	2.68×10-6#
GRN	1	1	8	2.03	0.55	0.94	1.00
HNRNPA1	0	1	18	0.68	1.00	0.20	0.26
HNRNPA2B1	NA	NA	NA	NA	NA	NA	NA
KIF5A	3	0	2	14.21	0.04	11.23	0.01#
MAPT	0	2	46	0.41	1.00	0.08	5.067×10-3#

MATR3	NA	NA	NA	NA	NA	NA	NA
MOBP	NA	NA	NA	NA	NA	NA	NA
NEFH	0	1	8	0.68	1.00	0.44	0.61
NEK1	25	4	29	12.80	4.59×10-9*	6.48	3.03×10-10#
OPTN	13	4	38	6.60	3.04×10-4	2.56	6.90×10-3
PFN1	NA	NA	NA	NA	NA	NA	NA
PNPLA6	3	8	44	0.76	1.00	0.51	0.36
PRPH	1	2	20	1.01	1.00	0.37	0.50
SCFD1	0	1	12	0.68	1.00	0.30	0.38
SETX	1	4	28	0.51	1.00	0.27	0.25
SIGMAR1	1	0	3	6.09	0.33	2.49	0.39
SOD1	1	1	2	2.03	0.55	3.74	0.31
SQSTM1	0	3	9	0.11	0.56	0.39	0.61
TAF15	NA	NA	NA	NA	NA	NA	NA
TARDBP	NA	NA	NA	NA	NA	NA	NA
TBK1	5	0	3	22.34	3.92×10-3	12.48	9.35×10-4#
UBQLN2	NA	NA	NA	NA	NA	NA	NA
UNC13A	NA	NA	NA	NA	NA	NA	NA
VAPB	NA	NA	NA	NA	NA	NA	NA
VCP	NA	NA	NA	NA	NA	NA	NA

*Passed exome-wide significance (P-value <2.5×10-6) in first analysis (3,864 cases and 7,839 controls.
#OR direction is maintained in secondary analysis (3,864 cases and 28,910 controls) and P-value is lower.
NA values in cells implies there were no qualifying variants in this gene under this model. The results displayed are from a burden analysis using Fisher's exact test as well as SKAT, with previously defined covariates (sample sex,

PC1-PC10, and total exome count). Exome-wide correction for multiple testing was set at (P<2.5×10-6), which was the 5% type-I error rate multiplied by the number of genes tested.

Supplementary Table 3. Proposed ALS genes and their signals under the damaging missense model

Gene	Qualifying variants in cases (3,864)	Qualifying variants in controls (7,839)	Qualifying variants in total controls (28,910)	OR N_{cases}: 3,864 $N_{controls}$: 7,839	P-value N_{cases}: 3,864 $N_{controls}$: 7,839	OR N_{cases}: 3,864 $N_{controls}$: 28,910	P-value N_{cases}: 3,864 $N_{controls}$: 28,910
ALS2	7	17	73	0.84	0.83	0.72	0.49
ANG	0	2	8	0.41	1.00	0.44	0.61
ARHGEF28	12	14	128	1.74	0.21	0.70	0.29
ARPP21	3	5	55	1.22	0.72	0.41	0.15
ATXN2	NA	NA	NA	NA	NA	NA	NA
C21orf2	1	3	33	0.68	1.00	0.23	0.18
C9orf72	1	5	25	0.41	0.67	0.30	0.36
CENPV	1	2	13	1.01	1.00	0.58	1.00
CHMP2B	3	1	9	6.09	0.11	2.49	0.16
DAO	3	20	114	0.30	0.05	0.20	7.52×10-4#
DCTN1	9	15	70	1.22	0.67	0.96	1.00
FIG4	7	11	51	1.29	0.62	1.03	0.84
FUS	0	2	7	0.41	1.00	0.50	1.00
GRN	11	13	59	1.72	0.20	1.40	0.35
HNRNPA1	NA	NA	NA	NA	NA	NA	NA
HNRNPA2B1	0	1	2	0.68	1.00	1.50	1.00

KIF5A	3	8	31	0.76	1.00	0.72	0.79
MAPT	7	8	49	1.78	0.28	1.07	0.84
MATR3	6	2	7	6.09	0.02	6.42	2.19×10-3#
MOBP	NA	NA	NA	NA	NA	NA	NA
NEFH	NA	NA	NA	NA	NA	NA	NA
NEK1	10	22	93	0.92	1.00	0.80	0.65
OPTN	12	5	34	4.88	2.79×10-3	2.65	8.99×10-3
PFN1	0	1	65	0.68	1.00	0.06	6.70×10-4#
PNPLA6	7	11	67	1.29	0.62	0.78	0.72
PRPH	8	13	69	1.25	0.65	0.87	0.86
SCFD1	3	8	35	0.76	1.00	0.64	0.62
SETX	32	48	265	1.36	0.19	0.90	0.65
SIGMAR1	1	2	18	1.01	1.00	0.42	0.72
SOD1	21	0	2	87.70	7.55×10-11*	78.98	6.04×10-18#
SQSTM1	5	11	38	0.92	1.00	0.98	1.00
TAF15	NA	NA	NA	NA	NA	NA	NA
TARDBP	NA	NA	NA	NA	NA	NA	NA
TBK1	6	5	24	2.44	0.20	1.87	0.16
UBQLN2	0	3	15	0.29	0.56	0.24	0.24
UNC13A	7	6	49	2.37	0.14	1.07	0.84
VAPB	2	1	4	4.06	0.26	3.74	0.15

VCP	6	0	18	26.41	1.29×10-3	2.50	0.06

*Passed exome-wide significance (P-value <2.5×10-6) in first analysis (3,864 cases and 7,839 controls.
#OR direction is maintained in secondary analysis (3,864 cases and 28,910 controls) and P-value is lower.
NA values in cells implies there were no qualifying variants in this gene under this model. The results displayed are from a burden analysis using Fisher's exact test as well as SKAT, with previously defined covariates (sample sex, PC1-PC10, and total exome count). Exome-wide correction for multiple testing was set at (P<2.5×10-6), which was the 5% type-I error rate multiplied by the number of genes tested.

Supplementary Table 4. Summary of HSP genes and associated neurological diseases.

Gene	Disease	ClinVar entries	
		Pathogenic	Likely pathogenic
DNAJB2	Charcot-Marie-Tooth disease, spinal muscular atrophy, distal,	7	2
DNAJB5	Peripheral neuropathy, skeletal myopathy, peripheral neuropathy	0	1
DNAJB6	Limb-girdle muscular dystrophy, type 1E; frontotemporal dementia	9	2
DNAJB13	Ciliary dyskinesia, primary, 34	2	0
DNAJC3	Combined cerebellar and peripheral ataxia with hearing loss and diabetes mellitus	0	1
DNAJC5	Neuronal ceroid lipofuscinosis	2	0
DNAJC6	Early onset Parkinson disease	5	0
DNAJC7	Amyotrophic lateral sclerosis	0	0
DNAJC11	Spasticity, motor neuron pathology	0	0
DNAJC12	Hyperphenylalaninemia, mild, non-bh4-deficient	2	0
DNAJC13	Parkinson disease	0	0
DNAJC19	3-methylglutaconic aciduria type V	2	1
DNAJC29	Spastic ataxia of Charlevoix Saguenay	0	0
HSPB1	Charcot-Marie-Tooth disease, distal hereditary motor neuronopathy	12	13
HSPB8	Charcot-Marie-Tooth disease, distal hereditary motor neuronopathy	4	2
HSPD1	Spastic paraplegia	2	2
CCT5	Neuropathy, hereditary sensory, with spastic paraplegia	0	1

Some genes are associated with a disease but no pathogenic or likely pathogenic variants were reported in ClinVar.

Supplementary Table 5. Neurodegenerative disease genes

ABCA7	*BST1*	*CSF1R*	*ECHDC3*	*GCH1*	*ITM2B*	*NR4A2*	*PLD3*	*SCARB2*	*SPPL2A*	*TYROBP*
ACMSD	*C9orf72*	*DAO*	*EIF4G1*	*GIGYF2*	*LRRK2*	*NUCKS1*	*PM20D1*	*SCIMP*	*SQSTM1*	*UBA1*
ALS2	*CASS4*	*DCTN1*	*EPHA1*	*GPNMB*	*MAPT*	*OPTN*	*PNPLA6*	*SETX*	*STK39*	*UBQLN2*
ANG	*CCDC62*	*DDRGK1*	*FAM47E*	*GRN*	*MC1R*	*PANK2*	*PRNP*	*SIGMAR1*	*STX1B*	*UCHL1*
APOE	*CD2AP*	*DGKQ*	*FBXO7*	*HBEGF*	*MCCC1*	*PARK2*	*PRPH*	*SIPA1L2*	*TAF15*	*UNC13A*
APP	*CD33*	*DLG2*	*FERMT2*	*HLA-DRB5*	*MEF2C*	*PARK7*	*PSEN1*	*SLC24A4*	*TARDBP*	*VAPB*
AR	*CELF1*	*DNAJC13*	*FGF20*	*HNRNPA1*	*MS4A4E*	*PARL*	*PSEN2*	*SMN1*	*TBK1*	*VCP*

ARPP21	*CENPV*	*DNAJC6*	*FIG4*	*HNRNPA2B1*	*MS4A6A*	*PFN1*	*PTGER2*	*SMN2*	*TMEM163*	*VPS13C*
ATP13A2	*CHMP2B*	*DNMT1*	*FUS*	*HTRA2*	*NEFH*	*PICALM*	*PTK2B*	*SNCA*	*TMEM175*	*VPS35*
ATXN2	*CLU*	*DSG2*	*GAK*	*INPP5D*	*NEK1*	*PINK1*	*RAB7L1*	*SOD1*	*TMEM229B*	*ZCWPW1*
BIN1	*CR1*	*DYNC1H1*	*GBA*	*INPP5F*	*NME8*	*PLA2G6*	*RIT2*	*SORL1*	*TREM2*	