Supplemental Information

Supplemental Materials and Methods

Methods S1. Description of clinical cases carrying pathogenic *HTT* repeat expansions. Related to Table 2.

Patient #1

The patient developed asymmetric, transiently levodopa-responsive tremor at age 68, followed by the development of progressive postural and oculomotor problems within three years from symptom onset. He fulfilled the MDS clinical criteria for probable PSP. MRI showed atrophy of the mesencephalon (Colibri sign) and reduced dopamine transporter uptake on SPECT. The clinical course was very slowly progressive. Examination twelve years after symptom onset revealed mild dementia, characterized by psychomotor slowing, reduced verbal fluency, attention, and episodic memory, with a mini-mental status examination of 24/30. There was no family history of neurological disease. The patient passed away at age 83. An autopsy was not performed.

Patient #2

The patient developed behavioral changes at the age of 56, and she was diagnosed with behavioral variant FTD. By report, her elderly mother had been diagnosed with Alzheimer's disease.

Patient #3

The patient was a woman who developed language disturbances at the age of 57. She was subsequently diagnosed as having nonfluent primary progressive aphasia FTD subtype. There was no family history of neurological disease.

Patient #4

The patient was a 19-year-old woman who had presented with a two-year history of progressive academic performance decline, dysarthria, bradykinesia, and gait disturbance. Her speech had become progressively slurred and soft, and her handwriting had deteriorated. She did not report any falls, but she did have several episodes of syncope that were initially diagnosed as seizures. Cranial nerve examination revealed supranuclear vertical gaze palsy, masked facies, and dysarthria. She also had bradykinesia with cogwheeling in her upper limbs, and spasticity and hyperreflexia in the lower limbs. Brain MRI showed basal ganglia iron deposition. She was

started on carbidopa/levodopa but did not improve. An initial genetic screen of *HTT* was reported as normal. The patient's father was said to have a similar neurological syndrome consisting of cognitive decline, gait disorder, and dysarthria that started in his late twenties. The genetic screening was repeated at a later stage in her illness to investigate early-onset, familial dementia. This testing correctly identified an expanded *HTT* repeat allele, and her diagnosis was updated to young-onset Huntington's disease (Westphal syndrome).

Patient #5

The patient developed symptoms of ALS at the age of 56 and died eleven years later of respiratory failure after a typical course of motor neuron disease. An MRI of the brain performed approximately ten years prior to death did not show significant cerebral or striatal atrophy.

Patient #6

The patient presented at the age of 44 with personality changes (short temper) and decreased initiative (apathy). His memory was intact, and neuropsychological evaluation was consistent with FTD. His father had speech loss and gait disturbance at the age of 40 and died from his illness at the age of 52.

Patient #7

This right-handed man presented with lower limb weakness at the age of 76. His sibling had been diagnosed with ALS. Neurological examination at the age of 84 revealed an ALS Functional Rating Scale of 17 (maximum score of the ALSFRS-R = 40). He had upper and lower motor neuron signs in the bulbar region, the upper limbs, and the lower limbs. Additionally, he was diagnosed with FTD. He was placed on non-invasive positive pressure ventilation for respiratory failure.

Patient #8

This patient was a man who developed a right foot drop at the age of 62. He was initially diagnosed with primary lateral sclerosis and had a baclofen pump implanted for treating spasticity. His symptoms progressed, and the diagnosis was changed to ALS based on neurophysiological testing. Before death, he was unable to ambulate, used a motorized wheelchair, had limited hand movements, wore a cervical collar to correct head tilt, and used an eye gaze system to communicate. He died at the age of 70 due to respiratory failure.

Supplemental Figures

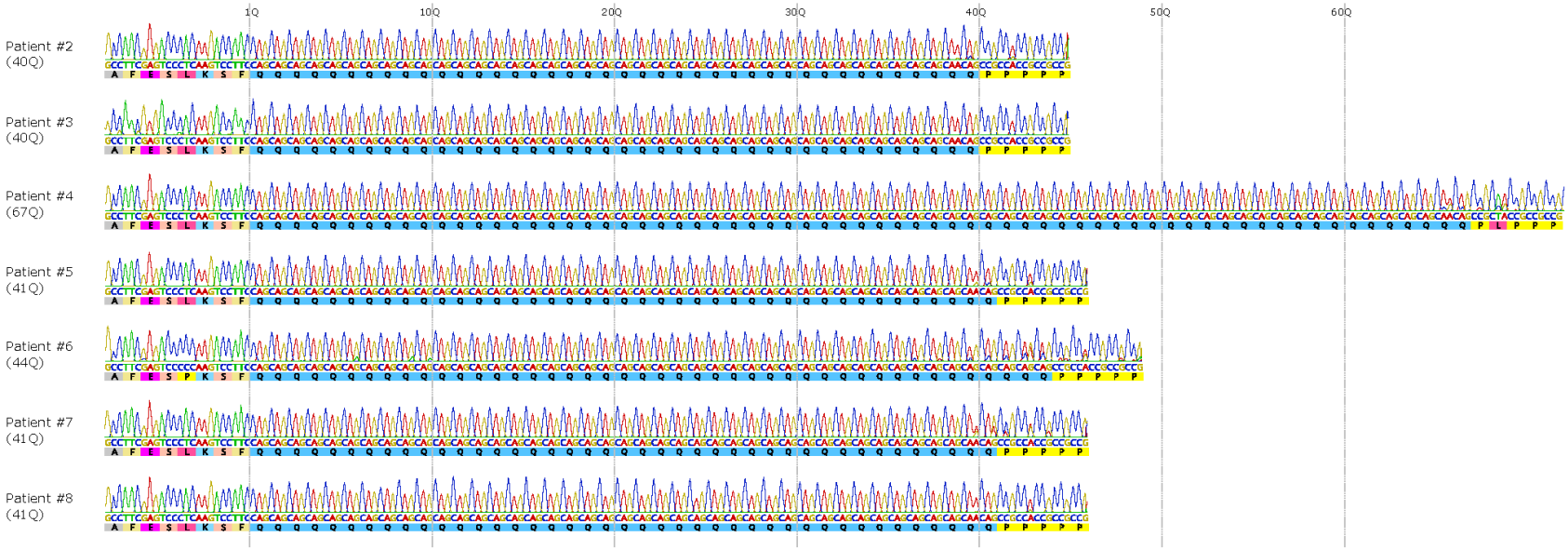

Figure S1. Sanger sequencing chromatograms of the *HTT* CAG repeat expansion. Related to Figure 1.

HTT CAG repeat length was assessed by cloning followed by Sanger sequencing for seven of the eight FTD/ALS patients carrying full-penetrance pathogenic repeat expansions (≥ 40 CAG repeats). DNA was not available for the eighth patient (Patient #1).

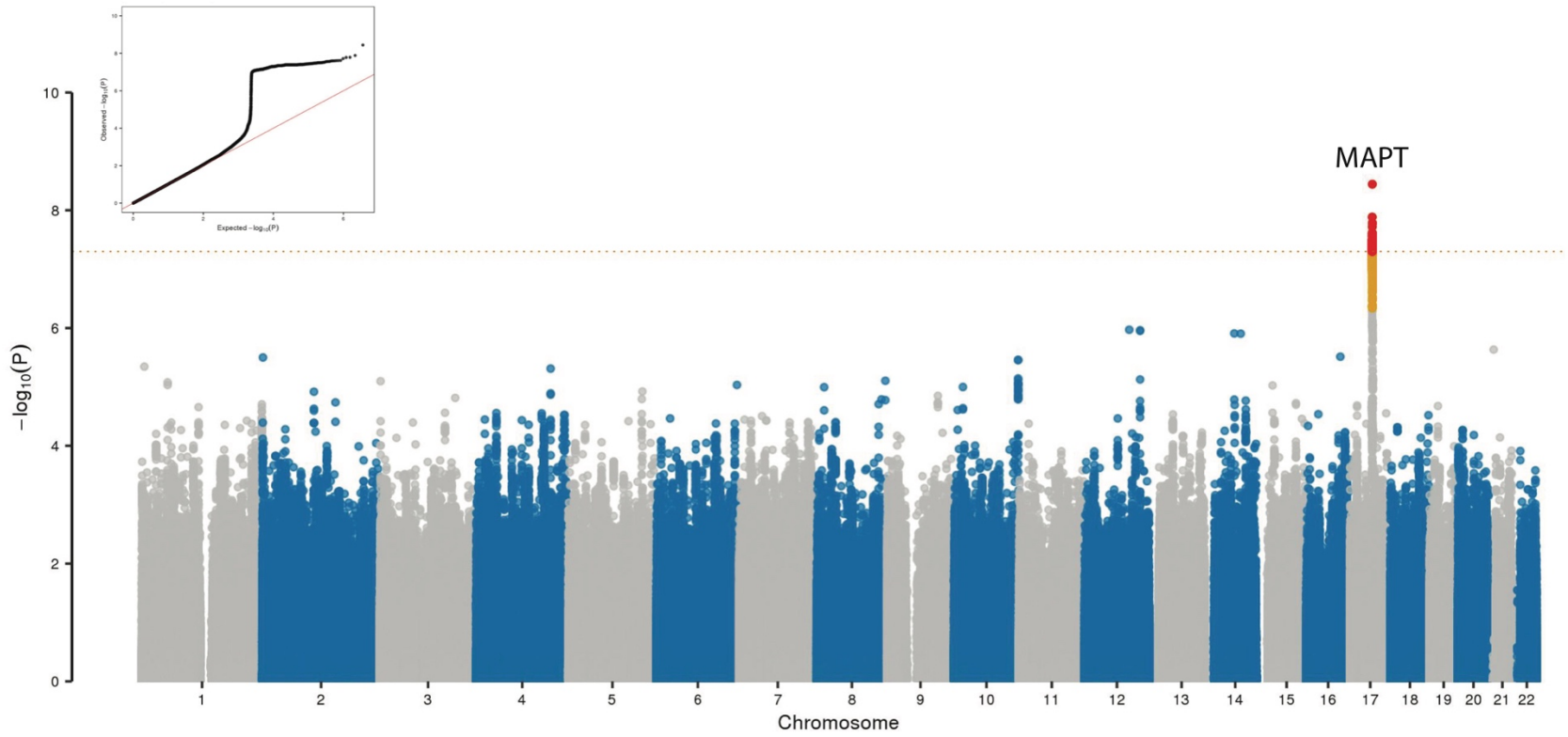

Figure S2. Genome-wide association study of the FTD/ALS discovery cohort. Related to Figure 1.

Manhattan plot depicting GWAS results (MAF >5%) based on 2,451 cases and 4,029 controls that passed filtering metrics for the FTD/ALS patient cohort. Chromosomal positions (build hg38) are depicted on the x-axis, and association *p*-values are indicated on the y-axis using a -$\log_{10}$ scale. Genome-wide significant signals are shown by red dots, and orange dots indicate suggestive variants. The name The horizontal dashed line indicates the Bonferroni threshold for genome-wide significance. The gene with the closest proximity to the top variant at the significant locus on chromosome 17 is shown. The insert figure shows the quartile-quartile plot ($\lambda = 1.016$, $\lambda_{1000} = 1.005$).

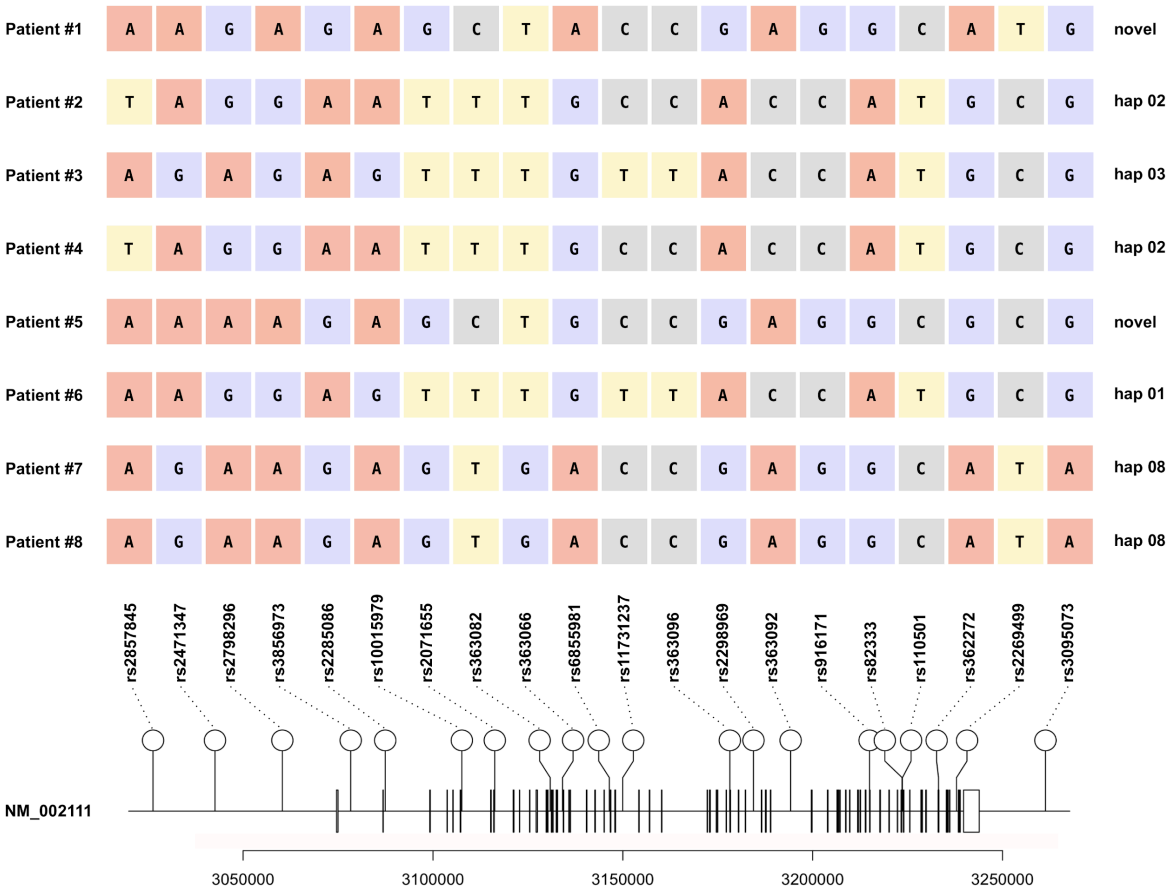

Figure S3. The occurrence of known haplotypes across the *HTT* locus. Related to Figure 1.

Haplotypes across the *HTT* locus are shown for the eight FTD/ALS patients carrying full penetrance repeat expansions. Numbered haplotypes correspond to known haplotypes associated with Huntington's disease, as defined by Chao and colleagues (Chao et al., 2017). Haplotypes not previously associated with Huntington's disease are marked as "novel." Individual SNPs used to define the haplotypes are shown below, along with their locations along the *HTT* gene (NM_002111).

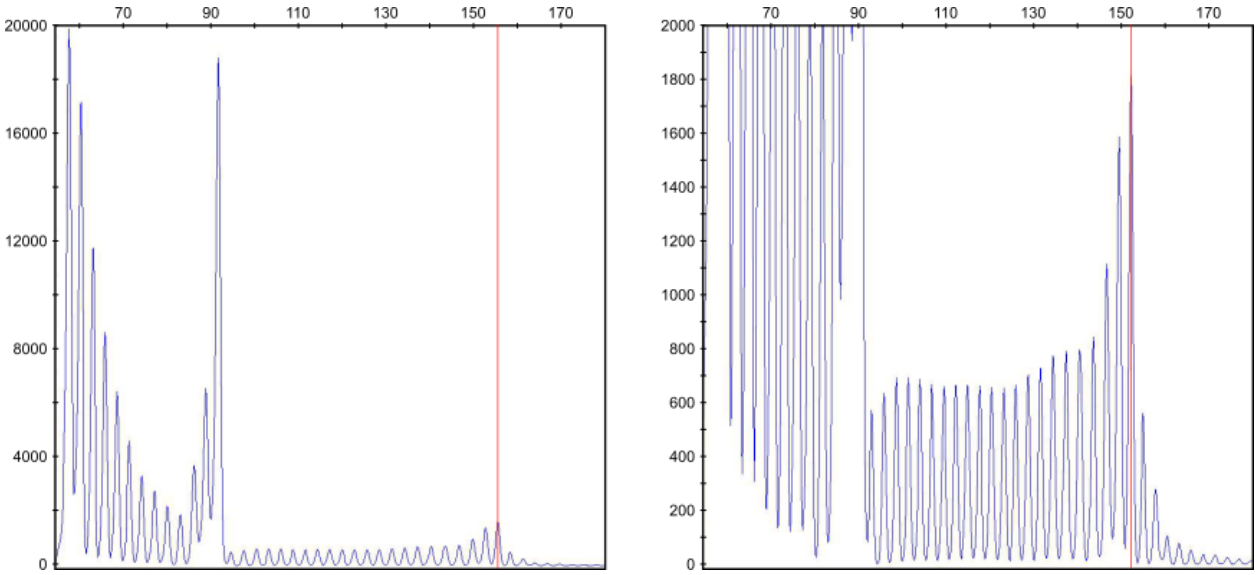

Figure S4. A representative chromatogram from the repeat-primed PCR assay used to quantify somatic mosaicism of the *HTT* CAG repeat expansion. Related to Figure 2.

The left panel shows the maximum view chromatogram, and the right panel shows a magnified view of the expanded allele. The red line indicates the modal peak, and expansion peaks can be visualized to the right of this peak.

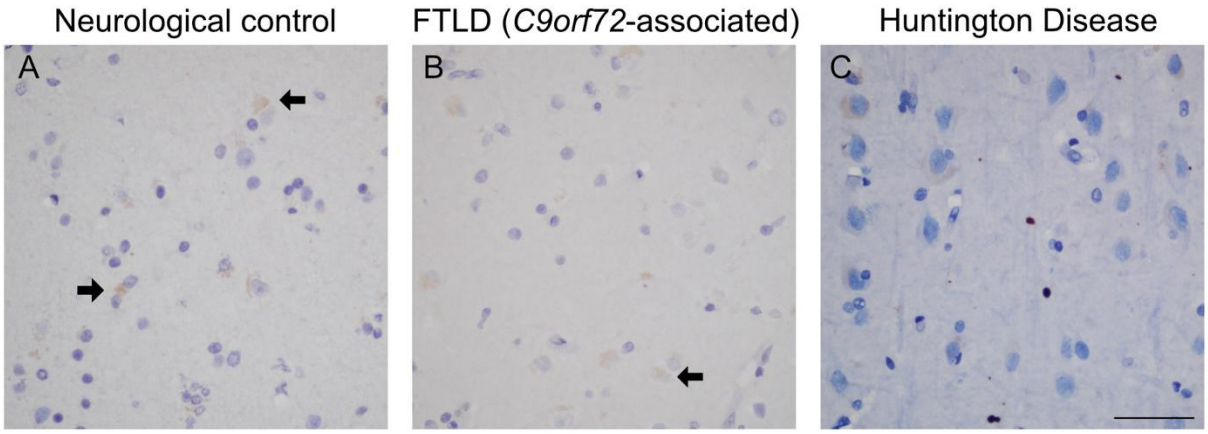

Figure S5. Photomicrographs of layer V of the prefrontal cortex (BA9) immunostained against huntingtin. Related to Figure 3.

(A-B) A 91-year-old woman without antemortem neurological impairment and a 71-year-old man with *C9orf72* FTD. Weak, diffuse, cytoplasmic staining of huntingtin was seen within the neurons (indicated by arrows) in these two brains, and no huntingtin aggregates were found. **(C)** A 75-year-old woman with Huntington's disease (CAG: 42/15) demonstrating extra-nuclear Huntingtin aggregates and faint cytoplasmic staining in a subset of neurons. Scale bar: 50 μm

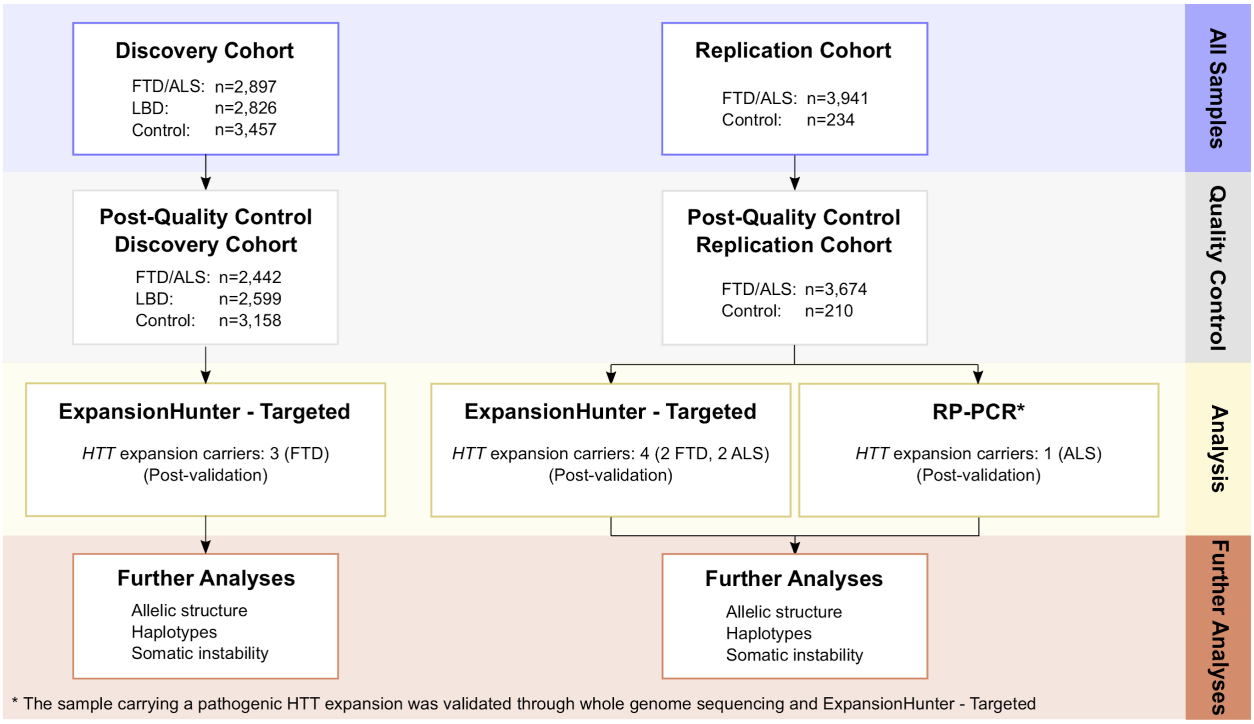

Figure S6. Flow chart outlining the study. Related to Figure 1.

Supplementary Tables

Table S1. Results of ExpansionHunter – Targeted applied to whole-genome sequence data for ten disease-causing repeat expansions. Related to STAR Methods.

Gene	Chr	Inheritance*	Lower Bound	Control Pathogenic / Total	Control Pathogenic Freq	FTD Pathogenic / Total	FTD Pathogenic Freq	ALS Pathogenic / Total	ALS Pathogenic Freq	LBD Pathogenic / Total	LBD Pathogenic Freq
AR	X	XL	37	10/3157	0.003168	3/1377	0.002179	3/1065	0.002817	6/2599	0.002309
AR Female	X	XL	37	2/1665	0.001201	1/634	0.001577	1/490	0.002041	2/903	0.002215
AR Male	X	XL	37	8/1454	0.005502	2/743	0.002692	2/575	0.003478	4/1603	0.002495
ATN1	12	AD	48	0/3158	0	0/1377	0	0/1065	0	0/2598	0
ATXN1	6	AD	39	14/3158	0.004433	6/1377	0.004357	4/1065	0.003756	16/2599	0.006156
ATXN3	14	AD	52	0/3158	0	0/1377	0	0/1065	0	0/2599	0
C9orf72	9	AD	30	5/3158	0.001583	59/1377	0.042847	108/1065	0.101408	6/2599	0.002309
DMPK	19	AD	50	4/3158	0.001267	2/1377	0.001452	1/1065	0.000939	2/2599	0.00077
FMR1	X	XL	200	0/3158	0	0/1377	0	0/1065	0	0/2599	0
FMR1 Female	X	XL	200	0/1665	0	0/634	0	0/490	0	0/903	0
FMR1 Male	X	XL	200	0/1455	0	0/743	0	0/575	0	0/1603	0
FXN (hom)	9	AR	66	0/3158	0	0/1377	0	0/1065	0	0/2599	0
HTT (CAG)	**4**	**AD**	**40**	**0/3158**	**0**	**3/1377**	**0.002179**	**0/1065**	**0**	**0/2599**	**0**
PHOX2B	4	AD	25	776/3158	0.245725	296/1377	0.21496	251/1065	0.235681	542/2599	0.208542

* Modes of inheritance: x-linked (XL), autosomal dominant (AD), autosomal recessive (AR); homozygous (hom) refers to biallelic expansion in genes with autosomal recessive. All ten disease-causing repeat expansions have been previously experimentally validated (Dolzhenko et al.; 2017, Dolzhenko et al., 2019).

Table S2. Demographic and clinical features of samples included in the analysis. Related to Table 1.

	FTD (n = 1,476)	ALS (n = 1,065)	LBD (n = 2,599)	Control (n = 3,158)
Female (%)	678 (46.0%)	490 (46.0%)	1,649 (63.4%)	1,483 (47.0%)
Age (IQR)	65.2 (58.0–71.0)	65.6 (59.0–73.0)	74.7 (68.0–82.0)	77.0 (69.0–86.0)
Site of onset				
Cognitive (%)	1,476 (100%)	2 (0.2%)	2,599 (100.0%)	-
Bulbar (%)	-	322 (30.2%)	-	-
Spinal (%)	-	603 (56.6%)	-	-
Family history (%)	67 (4.5%)	111 (10.4%)	240 (9.2%)	-
C9orf72 carrier	50 (3.4%)	104 (9.8%)	-	-

FTD, frontotemporal dementia; ALS, amyotrophic lateral sclerosis; LBD, Lewy body dementia; IQR, interquartile range; *C9orf72* carrier status is based on repeat-primed PCR and ExpansionHunter – Targeted; Site of onset is missing for 138 ALS cases. *C9orf72* status is missing for 6 ALS and 22 FTD cases. The contributing study sites and consortia for these samples were: Pitie-Salpetriere Hospital (Paris), University of Thessalia (Volos), Dublin Brain Bank (Dublin), University of Torino (Torino), University Hospital of Cagliari (Cagliari), University of Bari (Bari), University of Luxembourg (Luxembourg City), Hospital de Sant Pau (Barcelona), University Hospital Mutua de Terrassa (Barcelona), Biobanc-Hospital Clinic - IDIBAPS (Barcelona), Hospital Universitario "Marques de Valdecilla" (Santander), King's College London (London), University College London (London), Imperial College London (London), University of Bristol Brain Bank (Bristol), Newcastle University (Newcastle upon Tyne), The University of Manchester (Manchester), McGill University (Montreal), University of Toronto (Toronto), Virginia Commonwealth University (Richmond, VA), Banner Sun Health Research Institute (Phoenix, AZ), Rush Alzheimer's Disease Center (Chicago, IL), Northwestern University (Evanston, IL), Parkinson's Disease Biomarker Program, Fox Investigation for New Discovery of Biomarkers Program, Indiana University School of Medicine (Indianapolis, IN), National Institutes of Health (Bethesda, MD), New York University Langone Medical Center (New York, NY), Icahn School of Medicine at Mount Sinai (New York, NY), National Cell Repository for Alzheimer's Disease (Indianapolis, IN), University of California San Diego (San Diego, CA), University of California (Irvine, CA), North American Brain Expression Consortium, NINDS Biorepository at Coriell Institute (Camden, NJ), University of Maryland Brain Bank (Baltimore, MD), University of Kansas Medical Center (Kansas City, KS), University of Michigan Brain Bank (Ann Arbor, MI), Mayo Clinic (Jacksonville, FL), Mayo Clinic (Rochester, MN), Brigham & Women's Hospital (Boston, MA), Scripps Translational Science Institute (La Jolla, CA), Johns Hopkins University (Baltimore, MD), Oregon Health & Science University Brain Bank (Portland, OR), and Baltimore Longitudinal Study on Aging (Baltimore, MD).

Table S3. Primer sequences and conditions used for the repeat-primed PCR and for cloning and Sanger sequencing. Related to STAR Methods.

Primers	Sequence
Forward_RPPCR	6FAM-ATGAAGGCCTTCGAGTCCCTCAAGTC
Reverse_RPPCR	ATGAAGGCCTTCGAGTCCCTCAAGTC
HD1F	CCGCTCAGGTTCTGCTTTTA
HD1FR	GGCTGAGGCAGCAGCGGCTG

Thermocycling conditions for the repeat-primed PCR (RPPCR) were as per Jama et al., 2013. HD1F and HD1FR refer to the forward and reverse primers respectively used for PCR amplification prior to cloning. Thermocycling conditions for the Sanger sequencing were as follows: 95°C for 5 minutes, then (94°C for 20 seconds, 70°C for 30 seconds, 72°C for 30 seconds) x 2 cycles, (94°C for 20 seconds, 68°C for 30 seconds, 72°C for 30 seconds) x 3 cycles, (94°C for 20 seconds, 66°C for 30 seconds, 72°C for 30 seconds) x 4 cycles, (94°C for 20 seconds, 64°C for 30 seconds, 72°C for 30 seconds) x 5 cycles, (94°C for 20 seconds, 62°C for 30 seconds, 72°C for 30 seconds) x 6 cycles, (94°C for 20 seconds, 60°C for 30 seconds, 72°C for 30 seconds) x 8 cycles, (94°C for 20 seconds, 58°C for 30 seconds, 72°C for 30 seconds) x 12 cycles, followed by a final extension stage of 72°C for 10 minutes.

Table S4. Conditions used for immunohistochemistry staining of brain and spinal cord tissue. Related to STAR Methods.

Antibody	Company	Catalogue number	Dilution	Primary antibody incubation time (minutes)	Protocol and dilution	Platform
Huntingtin/ p62 double stain	Millipore/ Abcam	MAB5492/ ab207305	1:2000	32/24	64 min (CC1)	Roche Ventana Instrument
Huntingtin single stain	Millipore	MAB5492	1:2000	32	64 min (CC1)	Roche Ventana Instrument
Rabbit Anti-Ubiquitin	Dako	Z0458	1:2000	21 hrs	--	Manual
Anti-polyglutamine-Expansion Diseases Marker Antibody, clone 5TF1-1C2	Millipore Sigma	MAB1574	1:500	21 hrs	--	Manual
Anti-phospho TDP-43 (pS409/410)	Cosmo Bio Co., Ltd	CAC-TIP-PTD-M01	1:2000	21 hrs	pretreat 10min boil citrate buffer, pH 6.0	Manual
Anti-TDP-43	Proteintech	10782-2-AP	1:2000	32	64 min (CC1)	Leica Bond Platform

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