Investigation of C9orf72 in Four Neurodegenerative Disorders

Contributors

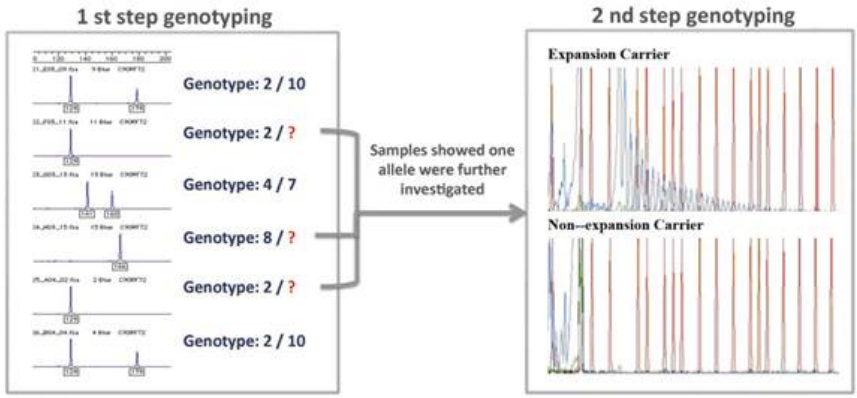
Zhengrui Xi, PhD1, Lorne Zinman, MD2, Yakov Grinberg, PhD1, Danielle Moreno, BSc1, Christine Sato, MSc1, Juan M. Bilbao, MD2, Mahdi Ghani, MD1, Isabel Hernández, MD3, Agustín Ruiz, MD PhD3, Mercè Boada, MD PhD3,4, Francisco J. Morón, PhD5, Anthony E. Lang, MD6,7, Connie Marras, MD PhD 6,7, Amalia Bruni, MD8, Rosanna Colao, MD8, Raffaele G Maletta, MD8, Gianfranco Puccio, MD8, Innocenzo Rainero, MD PhD9, Lorenzo Pinessi, MD9, Daniela Galimberti, PhD10, Karen E Morrison, PhD11, Catriona Moorby, BSc11, Joanne D Stockton, BSc11, Mario Masellis, MD2,7,12, Sandra E Black, MD2,7,12, Lili-Naz Hazrati, MD1, Yan Liang, PhD1, Jan van Haersma de With1, Luis Fornazzari, MD13, Roque Villagra, MD14, Ricardo Rojas-Garcia MD, PhD15, Jordi Clarimón, PhD15, Richard Mayeux, MD16, Janice Robertson, PhD1, Peter St George-Hyslop, MD FRCP(C)1,7,17+, and Ekaterina Rogaeva, PhD1,7+

Online-only material

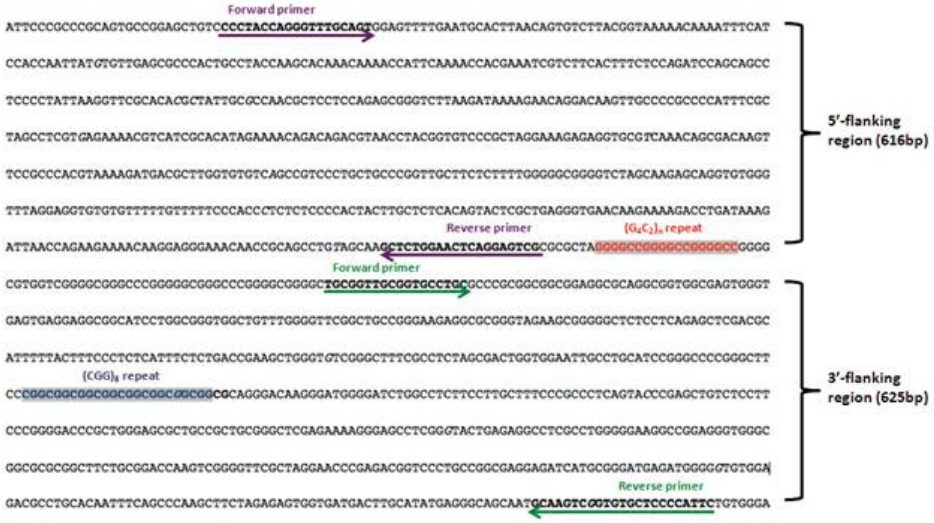
- **eFigure 1.** PCR products of repeat-primed PCR reactions separated on an ABI3100 DNA Analyzer and visualized by GeneScan software.
- **eFigure 2**. Pedigrees of patients carrying the G4C2 expansion or intermediate sized alleles (21-23 repeats).
- **eTable 1**. Analysis of MAPT H1/H2 haplotypes and APOE genotypes in ALS and FTLD C9orf72 expansion carriers.
- **eTable 2.** Clinical characteristics of carriers of the expansion allele (>30 repeats) and intermediate allele (20-29 repeats) in the C9orf72 gene among patients with parkinsonism.
- **eTable3.** Distribution of the C9orf72 alleles with <30repeats in controls and the four neurodegenerative diseases.
- **eTable 4.** Association tests of the C9orf72 alleles with <30 repeats in four neurodegenerative diseases by CLUMP software.
- Case-reports on c9orf72 expansion carriers

eFigure 1. Genotyping assays. A. The workflow for the 2-step genotyping is shown. PCR products from the 1st step (left panel) and products of repeat-primed PCR reaction from the 2nd step (right panel) were separated on an ABI 3100 DNA analyzer and visualized by Genotyper software or by GeneScan software. One expansion carrier (right panel top) and one non-expansion carrier (right panel bottom) are shown.B. The flanking sequence of the G4C2-repeat is shown. Two sets of primers were used to amplify the 5' flanking region (purple font) and 3' flanking region (green font) of the G4C2-repeat. The G4C2-repeat is shown in red font and a downstream short tandem repeat (CGG)8 is shown in blue font.

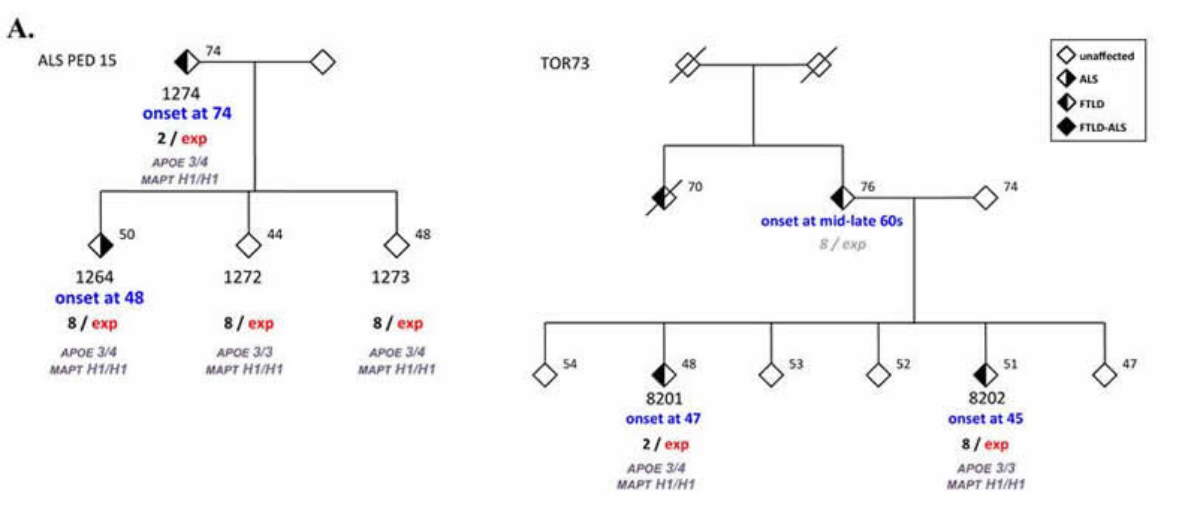
eFigure 1A

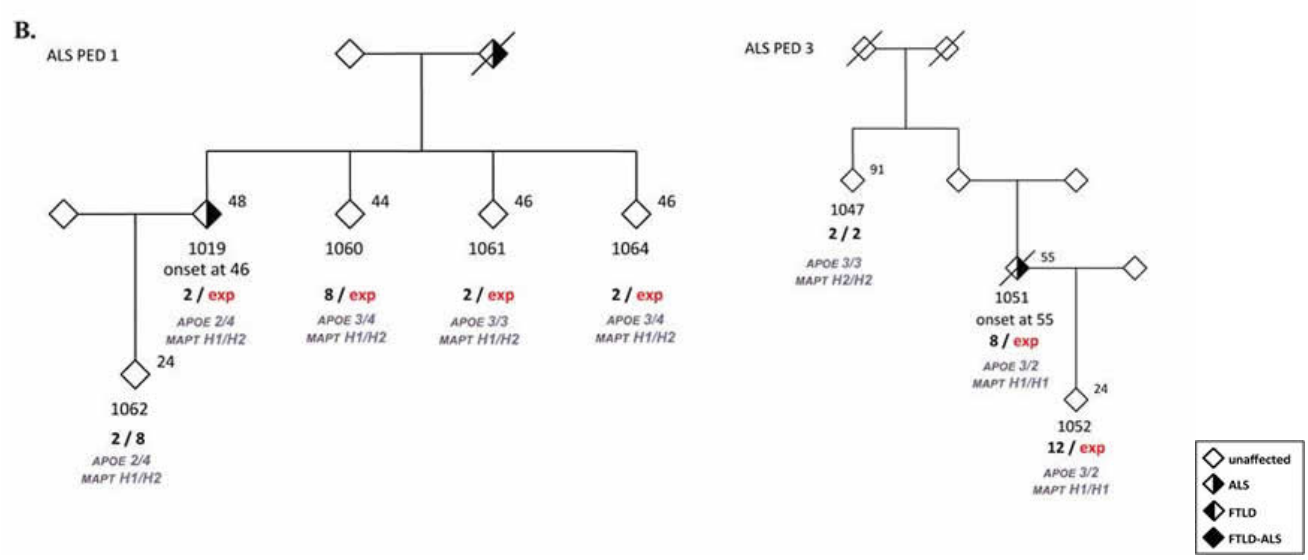


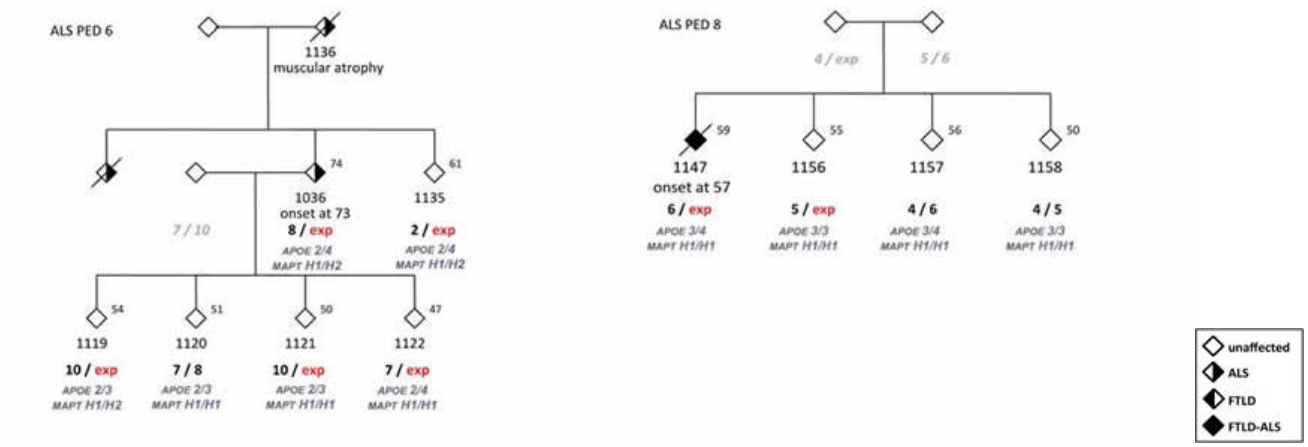
eFigure 1B

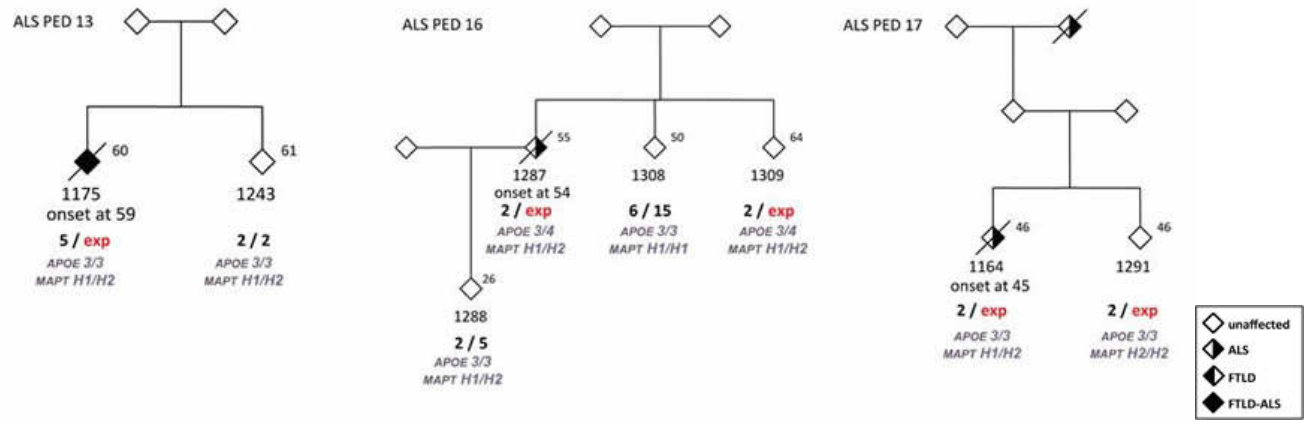


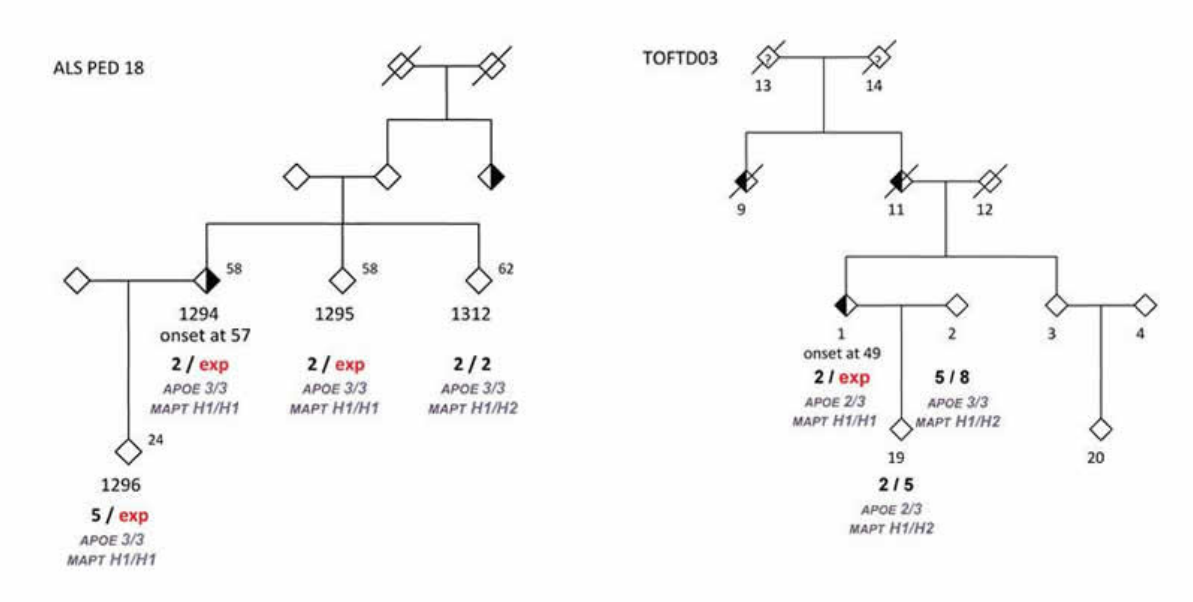
eFigure 2. Pedigrees of patients carrying the G4C2 expansion or intermediate sized alleles (21-23 repeats). An individual's genotype is shown beneath the corresponding diamond. Arabic numbers indicate the number of repeats and "exp" stands for expansion allele. Inferred genotypes are shown in gray Italic font. APOE genotype and MAPT haplotype are also shown below the C9orf72 genotype. Age at examination is shown on the left upper corner.Age of onset is also indicated for patients. The gender of family members is masked to protect privacy. A. Two pedigrees showing genetic anticipation for age of onset in the younger generation. B. FTLD/ALS pedigrees. C.Two Alzheimer's Disease familiesof the probands with 23 and 21 repeats allele (there is no evidence of segregation of these intermediate alleles with the disease).

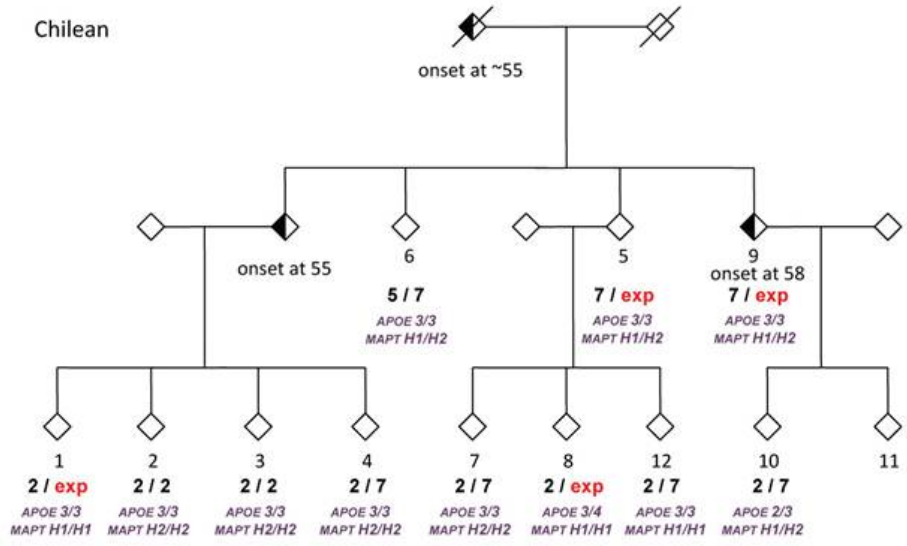



B.
ALS PED 1
48
44
46
46
1019
onset at 46
2 / exp
APOE 2/4
MAPT H1/H2
1060
8 / exp
APOE 3/4
MAPT H1/H2
1061
2 / exp
APOE 3/3
MAPT H1/H2
1064
2 / exp
APOE 3/4
MAPT H1/H2
24
1062
2 / 8
APOE 2/4
MAPT H1/H2
ALS PED 3
91
1047
2 / 2
APOE 3/3
MAPT H2/H2
55
1051
onset at 55
8 / exp
APOE 3/2
MAPT H1/H1
24
1052
12 / exp
APOE 3/2
MAPT H1/H1
unaffected
ALS
FTLD
FTLD-ALS

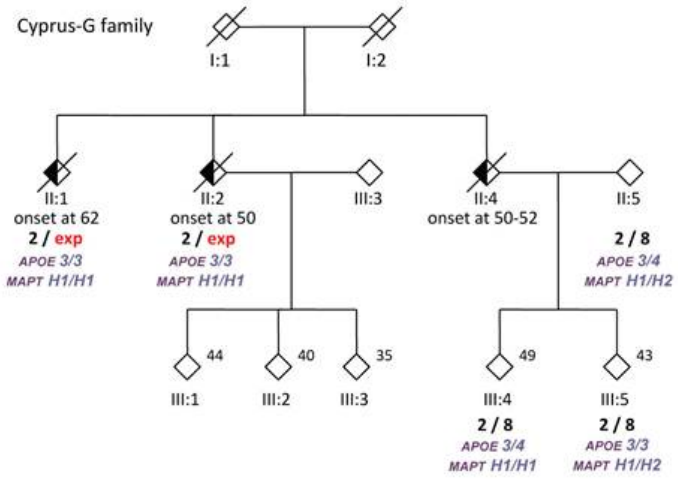

ALS PED 6
1136
muscular atrophy
74
61
1036
onset at 73
8 / exp
APOE 2/4
MAPT H1/H2
1135
2 / exp
APOE 2/4
MAPT H1/H2
7 / 10
54
51
50
47
1119
10 / exp
APOE 2/3
MAPT H1/H2
1120
7 / 8
APOE 2/3
MAPT H1/H1
1121
10 / exp
APOE 2/3
MAPT H1/H1
1122
7 / exp
APOE 2/4
MAPT H1/H1
ALS PED 8
4 / exp
5 / 6
59
55
56
50
1147
onset at 57
6 / exp
APOE 3/4
MAPT H1/H1
1156
5 / exp
APOE 3/3
MAPT H1/H1
1157
4 / 6
APOE 3/4
MAPT H1/H1
1158
4 / 5
APOE 3/3
MAPT H1/H1
unaffected
ALS
FTLD
FTLD-ALS

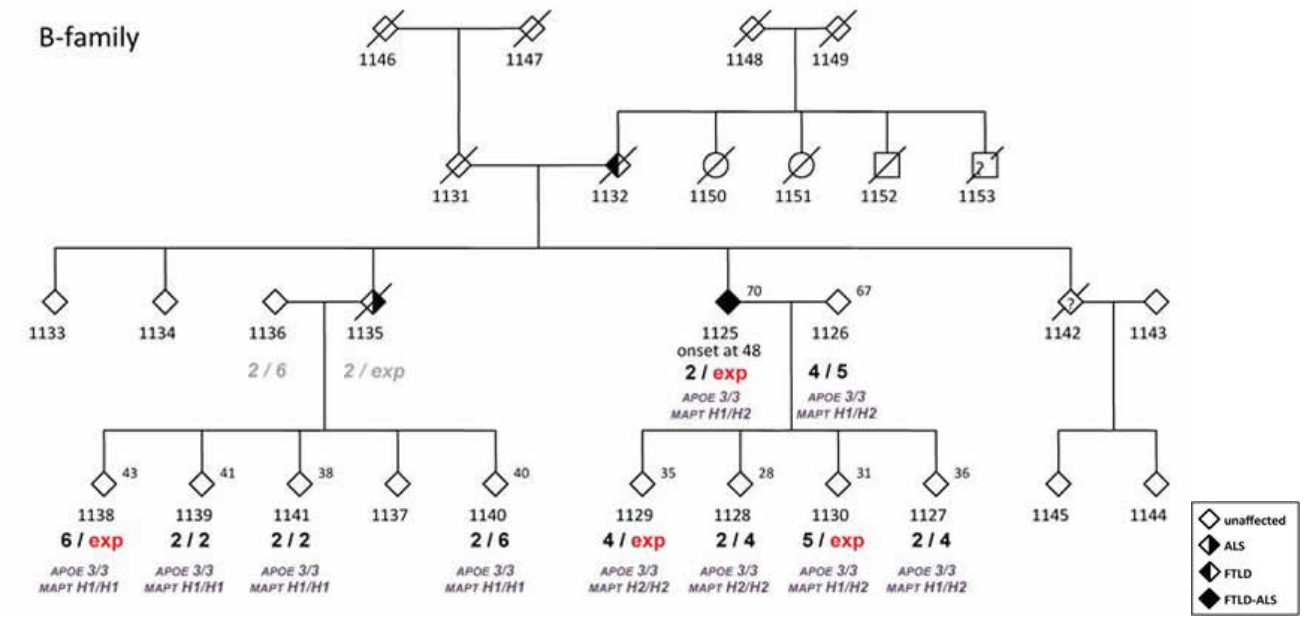

ALS PED 13
60
61
1175
onset at 59
5 / exp
APOE 3/3
MAPT H1/H2
1243
2 / 2
APOE 3/3
MAPT H1/H2
ALS PED 16
55
50
64
1287
onset at 54
2 / exp
APOE 3/4
MAPT H1/H2
1308
6 / 15
APOE 3/3
MAPT H1/H1
1309
2 / exp
APOE 3/4
MAPT H1/H2
26
1288
2 / 5
APOE 3/3
MAPT H1/H2
ALS PED 17
46
46
1164
onset at 45
2 / exp
APOE 3/3
MAPT H1/H2
1291
2 / exp
APOE 3/3
MAPT H2/H2
unaffected
ALS
FTLD
FTLD-ALS

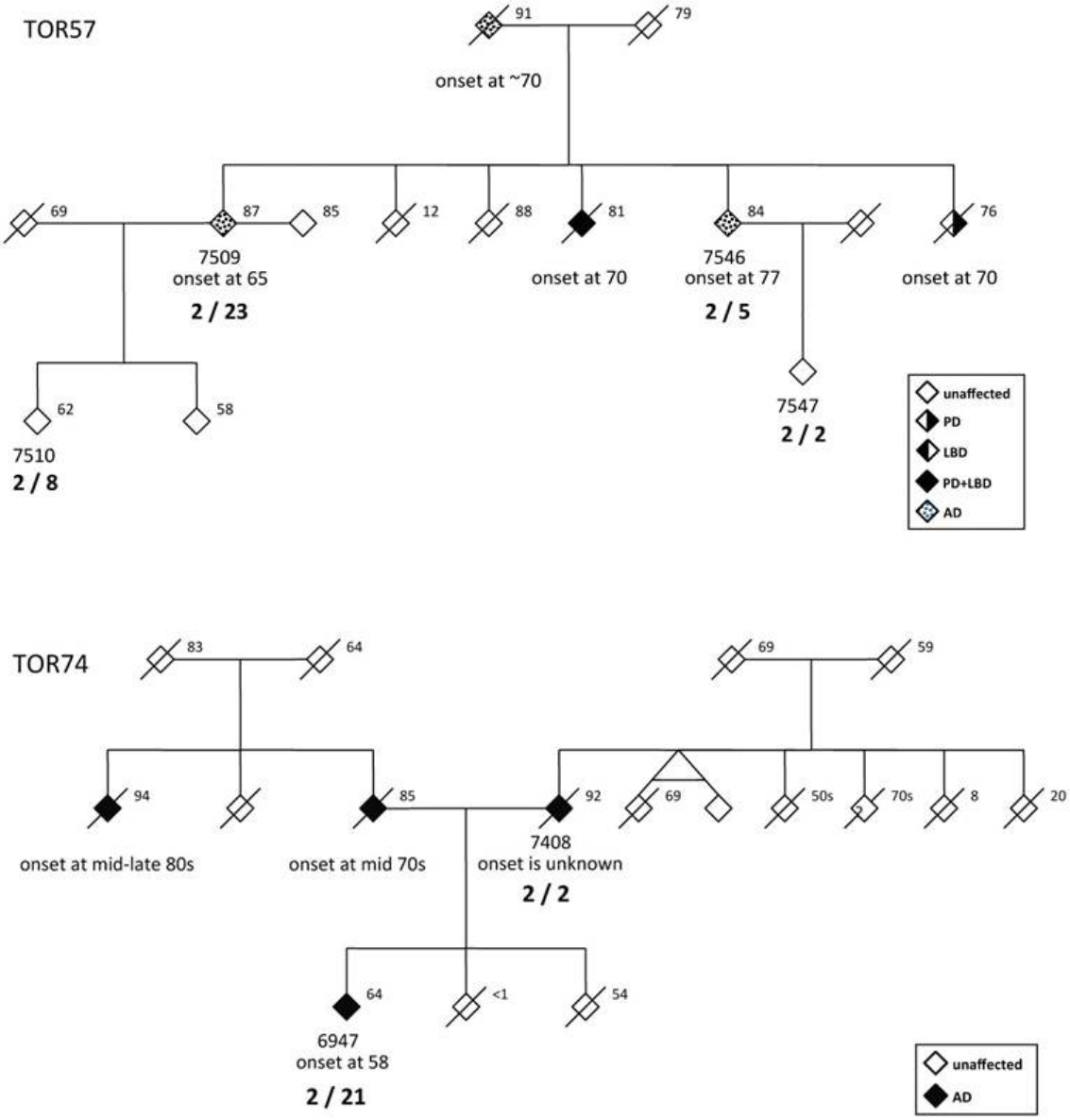

ALS PED 18
58
58
62
1294
onset at 57
2 / exp
APOE 3/3
MAPT H1/H1
1295
2 / exp
APOE 3/3
MAPT H1/H1
1312
2 / 2
APOE 3/3
MAPT H1/H2
24
1296
5 / exp
APOE 3/3
MAPT H1/H1
TOFTD03
13
14
9
11
12
1
onset at 49
2 / exp
APOE 2/3
MAPT H1/H1
2
5 / 8
APOE 3/3
MAPT H1/H2
3
4
19
2 / 5
APOE 2/3
MAPT H1/H2
20


Chilean
onset at ~55
onset at 55
6
5 / 7
APOE 3/3
MAPT H1/H2
5
7 / exp
APOE 3/3
MAPT H1/H2
9
onset at 58
7 / exp
APOE 3/3
MAPT H1/H2
1
2 / exp
APOE 3/3
MAPT H1/H1
2
2 / 2
APOE 3/3
MAPT H2/H2
3
2 / 2
APOE 3/3
MAPT H2/H2
4
2 / 7
APOE 3/3
MAPT H2/H2
7
2 / 7
APOE 3/3
MAPT H2/H2
8
2 / exp
APOE 3/4
MAPT H1/H1
12
2 / 7
APOE 3/3
MAPT H1/H1
10
2 / 7
APOE 2/3
MAPT H1/H2
11


unaffected
ALS
FTLD
FTLD-ALS


Cyprus-G family
I:1
I:2
II:1
onset at 62
2 / exp
APOE 3/3
MAPT H1/H1
II:2
onset at 50
2 / exp
APOE 3/3
MAPT H1/H1
III:3
II:4
onset at 50-52
II:5
2 / 8
APOE 3/4
MAPT H1/H2
44
40
35
49
43
III:1
III:2
III:3
III:4
2 / 8
APOE 3/4
MAPT H1/H1
III:5
2 / 8
APOE 3/3
MAPT H1/H2


B-family
1146
1147
1148
1149
1131
1132
1150
1151
1152
1153
1133
1134
1136
1135
2 / 6
2 / exp
70
67
1125
onset at 48
2 / exp
APOE 3/3
MAPT H1/H2
1126
4 / 5
APOE 3/3
MAPT H1/H2
1142
1143
43
41
38
40
35
28
31
36
1138
6 / exp
APOE 3/3
MAPT H1/H1
1139
2 / 2
APOE 3/3
MAPT H1/H1
1141
2 / 2
APOE 3/3
MAPT H1/H1
1137
1140
2 / 6
APOE 3/3
MAPT H1/H1
1129
4 / exp
APOE 3/3
MAPT H2/H2
1128
2 / 4
APOE 3/3
MAPT H2/H2
1130
5 / exp
APOE 3/3
MAPT H1/H2
1127
2 / 4
APOE 3/3
MAPT H1/H2
1145
1144
unaffected
ALS
FTLD
FTLD-ALS



eTable 1. Analysis of MAPT H1/H2 haplotypes and APOE genotypes in ALS and FTLD C9orf72 expansion carriers.

		MAPT			
H1/H2 haplotype	**FTLD**	**Freq**	**ALS**	**Freq**	**P valuea**
1 1	18	0.67	19	0.54	0.324
1 2	8	0.30	16	0.46	0.197
2 2	1	0.04	0	-	0.435
Total	27	1.00	35	1.00	0.283
H1, H2 haplotype					
1	44	0.81	54	0.77	0.556
2	10	0.19	16	0.23	0.556
Total	54	1.00	70	1.00	0.556
		APOE			
Genotype	**FTLD**	**Freq**	**ALS**	**Freq**	**P valuea**
2 4	0	-	3	0.09	0.25
3 2	3	0.11	6	0.17	0.719
3 3	18	0.67	16	0.46	0.1
3 4	5	0.19	9	0.26	0.502
4 4	1	0.04	1	0.03	1

total	27	1.00	35	1.00	0.389
Allele					
2	3	0.06	9	0.13	0.173
3	44	0.81	47	0.67	0.073
4	7	0.13	14	0.20	0.3
total	54	1.00	70	1.00	0.13

a. Pearson Chi-square test or Fisher's exact test (when expected value <5) were used to obtain the P value.

eTable 2. Clinical characteristics of carriers of the expansion allele (>30 repeats) and intermediate allele (20-29 repeats) in the C9orf72 gene among patients with parkinsonism.

DNA #	C9ORF72 repeats	Familial history of Neurodegenerative disease	diagnosis	dementia	signs of ALS	dystonia	duration	age at onset
4180	2 / 28	brother with PD & AD	atypical parkinsonism	yes	no	yes	>10 years	65 years
6442	2 / **32**	unknown	atypical parkinsonism	no	no	yes	>38 years	21 years
6855	6 / **39**	brother with PD	PD	no	no	no	>10 years	50 years
8558	2 / 23	no	PD	yes	no	no	9 years	72 years
8625	2 / 24	father with PD	PD	no	no	no	8 years	71 years
8736	2 / 21	no	PD	no	no	no	11 years	77 years

ALS=Amyotrophic lateral sclerosis, FTLD=Frontotemporal Lobar Degeneration, AD=Alzheimer disease and PD=Parkinson disease.

eTable 3. Distribution of the C9orf72 alleles with <30repeats in controls and the four neurodegenerative diseases (only p<0.05 are shown).

Alleles	Controls		FTLD				ALS				AD				PD			
	N	F	N	F	*P*a	OR (95% CI)b	N	F	*P*a	OR (95% CI)b	N	F	*P*a	OR (95% CI)b	N	F	*P*a	OR (95% CI)b
2	640	0.532	516	0.529			359	0.508			442	0.521			302	0.526		
3-4d	27	0.022	22	0.023			28	0.04	**0.03**	1.52 (0.89-2.61)	19	0.022			19	0.033		
5	189	0.157	124	0.127	**0.05**	0.78 (0.61-1.00)	86	0.122	**0.04**	0.75 (0.57-0.98)	120	0.142			69	0.12	**0.04**	0.73 (0.55-0.97)
6	61	0.051	59	0.06			51	0.072			50	0.059			37	0.064		
7	24	0.02	10	0.01			12	0.017			20	0.024			15	0.026		
8	130	0.108	129	0.132			87	0.123			100	0.118			62	0.108		
9	18	0.015	17	0.017			6	0.008			15	0.018			5	0.009		
10	26	0.022	44	0.045	**0.002c**	2.14 (1.31-3.50)	26	0.037	**0.05**	1.73 (1.00-3.01)	31	0.037	**0.04**	1.72 (1.01-2.92)	23	0.04	**0.026**	1.89 (1.07-3.35)
11	31	0.026	17	0.017			8	0.011	**0.03**	0.43 (0.20-0.95)	9	0.011	**0.02**	0.41 (0.19-0.86)	16	0.028		
12	15	0.012	14	0.014			12	0.017			14	0.017			7	0.012		
13-14d	16	0.013	8	0.008			13	0.018			7	0.008			5	0.009		
15-17d	17	0.014	7	0.007			10	0.014			10	0.012			7	0.012		
18-30d	10	0.008	9	0.009			8	0.011			11	0.013			7	0.012		
Totale	1204		976		**0.01**		706		**0.01**		848				574			

1. *2-sided Pearson ?2 test was used. P-value was obtained by comparing corresponding allele to the pool of remaining alleles (df=1), unadjusted.*
2. *Odds Ratio was obtained by comparing associated allele with the pool of the remaining alleles.*
3. *P-value remains to be significant after stringent Bonferroni correction. (p= 0.026).*
4. *Neighboring alleles were grouped when allele number was less than 5.*
5. *P-value for total was calculated by Pearson ?2 test, df=12.*
6. *Abbreviations: F=Allele frequency, P=single allele ?2 p-value, ALS=Amyotrophic lateral sclerosis, FTLD=Frontotemporal Lobar Degeneration, AD=Alzheimer disease and PD=Parkinson disease.*

eTable 4: Association tests of the C9orf72 alleles with <30 repeats in four neurodegenerative diseases by CLUMP software (p<0.05 are shown in bold). Empirical p-values were obtained after 2000 simulations.

Empirical p-value a	FTLD	ALS	AD	PD
T1 b	**0.005**	**0.011**	0.428	0.302
T2 c	**0.013**	**0.026**	0.377	0.230
T3 (Allele) d	**0.014** (10 repeats)	0.302 (11 repeats)	0.139 (11 repeats)	0.234 (10 repeats)
T4 e	0.124	**0.021**	0.775	0.326

1. *Empirical p-values were obtained by counting the number of times the chi-square value of the real data was achieved by the simulated tables.*
2. *T1 is a Pearson chi-squared statistic of the "raw" contingency table.*
3. *T2 is a Pearson chi-squared statistic calculated after grouping alleles with small expected values (<5).*
4. *T3 is the largest of the chi-square statistics of 2?2 tables in which each allele is compared in turn with the rest grouped together (the allele showing the largest chi-square).*
5. *T4 is the largest of the chi-square statistic of all possible 2?2 tables comparing any combination of alleles against the rest.*

CASE-REPORTS ON C9orf72 EXPANSION CARRIERS

T-51. Female age 62 with a 7 year history of mild progressive cognitive symptoms including obsessiveness, poor judgment, distractibility, repetitiveness, forgetfulness, dependency and ruminations. ALS symptoms include a 2 year history of weakness of left leg, then right leg and upper extremities, not meeting El Escorial criteria, but ultimately still diagnosed clinically as likely ALS. Family history reveals father died of ALS without dementia at age 60, and paternal uncle had "Alzheimer's disease". The patient died at age 63, about 8 years after symptom onset. Pathology showed FTD-MND with ubiquinated inclusions in dentate gyrus granule cells as well as neocortex, also ALS changes with loss of Betz cells and anterior horn cells. Also noted were moderate numbers of neurofibrillary tangles in mesial temporal lobe.

T-105. Male age 60 with 5 year history of behavioral and cognitive symptoms including depression, alcohol use, obsession with finances, and loss of interest in foods, sex, and maintenance of personal appearance, then with difficulties with insight, and verbal comprehension. ALS symptoms developed at age 60 with fasciculations, but no weakness, and normal EMG. Family history reveals mother is alive and well at age 91, but maternal uncle was diagnosed with AD and died at age 85, and maternal grandfather died at age 80 with dementia; two siblings are normal, but one sibling might have similar symptoms. The patient died at age 62 after 7 years of symptoms. Pathology revealed FTD-MND with ubiquitinated inclusions in cortex and dentate gyrus, and corticospinal tract degeneration and severe loss of anterior horn cells. Also seen were minimal AD changes and a single Lewy body in the substantianigra.

T-123. Male age 70 with 6 year history of behavioral and cognitive symptoms including disinhibition, euphoria, poor judgment, agitation, frustration, followed by impairments in visuospatial abilities, memory and orientation. ALS symptoms developed at age 70 with dysphagia, hypophonia, fasciculations, atrophy, quadriparesis, and hypereflexia, and EMG confirmation of MND. Family history reveals mental illness in father, paternal uncle, and paternal cousin, and parkinsonism in maternal uncle, but normal sibling. The patient died at age 70 after 6 years of symptoms. Pathology revealed FTD-MND with ubiquitinated inclusions in cortex and dentate gyrus granule cells, no loss of Betz cells, but muscle and nerve changes consistent with motor neuron involvement. Also noted were some neurofibrillary tangles in mesial temporal lobe.

T-332. Male age 58 with 4 year progressive decreased interest in conversations and activities, 2 years speech change with slower, more effortful speech and paraphasic errors, and 6 months memory impairment. Some nasal speech and diagnosis was made of progressive supranuclear palsy. No ALS symptoms. Family history reveals father died at age 75 of ALS without dementia after a 10 year illness; mother and sibling are normal. The patient died at age 62 after 8 year of symptoms. Pathology revealed FTD-MND with ubiquinated inclusions in frontal cortex, dentate gyrus, and striatum, loss of Betz cells, but no loss of hypoglossal neurons.

T-561. Male age 78 with 5 year history of memory decline, problems with remembering rules of bridge, emotional lability, childishness, effusiveness, intrusiveness, boisterousness, verbal perseveration, and problems with gait apraxia. He also developed echolalia, palilalia, grunting, moaning noises, and pseudobulbar tearing. Developed incontinence, more praxis problems, then falls, pneumonia, and parkinsonism. Only ALS symptoms were dysphagia, with no diagnostic impression of ALS during life. Family history reveals no dementia. The patient died at age at age 80 after 7 years of symptoms. Pathology showed FTD with no evident inclusions, but with marked neuronal cell losses and gliosis in superficial layers of frontal lobes. Also noted were a few infarcts, rare NFT in mesial temporal lobe, and no neuritic or diffuse plaques.

T-3835. Male age 63 with 15 year history of depression, but clear symptoms started 8 years prior to evaluation, with suicidality, and progressive memory problems, including failure to recognize family members, forgetting dates, getting lost driving, and then increased appetite for sweets, compulsive workaholism, trash-scavenging, nervousness, and replacing things in wrong position. Only motor symptoms were possibly decreased manual dexterity and mild gait imbalance. Family history reveals mother had depression, incontinence, repetitiveness, and obsession with sweets and died at age 88, a sister age 62 is nursing-home confined due to "strokes", and a brother died at age 51 of cancer. The patient died at 74 after at least 18 years of symptoms.Pathology revealed FTD-MND, with ubiquitinated inclusions in cortical neurons and dentate gyrus granule cells. Also noted were rare mesial temporal neurofibrillary tangles, very rare glial cytoplasmic inclusions, and a number of Lewy bodies in substantianigra and nucleus coeruleus.

T-4440. Female age 68 with 2 year history of memory and behavior problems, inappropriate laughter, somatic complaints (palpitations, cough, voice change, knee pain, bloody stool), uncharacteristic alcohol use, delusions regarding spy agencies, intrusive behavior to passersby, obsessions to specific foods. Progressive decline in speech and behavioral disinhibition was noted. She had a stroke with good recovery, but continued to have progressive loss of activities of daily living, developed increasing echolalia, palilalia, and then muteness, incontinence, bruxism, and parkinsonism. She also developed dysphagia for solids, some thenar atrophy, but no diagnostic impression of ALS during life. Family history shows mother and maternal aunt had alcoholism. The patient died at age 74 after 8 years of symptoms. Pathology showed FTD-MND with TDP-43 positive inclusions in scattered cortical neurons, neuronal loss in hypoglossal nucleus. Also noted were several infarcts, atherosclerosis, amyloid angiopathy, scattered diffuse and neuritic plaques in neocortex, and neurofibrillary tangles mostly in mesial temporal lobe.

SPJMELA6. A 39-year-old man with no family history of ALS presented with progressive muscle weakness. He first noticed distal weakness in the right lower limb.When first seen, six months later, neurological examination revealed diffuse signs of upper motor neuron involvement (overactive deep tendon reflexes of upper and lower extremities with Babinski sign) and paresis of the hip flexors, ankle dorsiflexors and intrinsic muscles of the right hand. Weak muscles were also atrophic and fasciculations of the proximal and distal muscles were present in the four limbs. Subsequently, motor deficits progressed to the four limbs. Difficulties swallowing and dysarthria appeared 25 months after clinical onset.
His cognitive function was normal and no symptoms suggestive of fronto-temporal dysfunction were present during the course of the disease. Electrophysiological studies confirmed the clinical findings by showing acute partial denervation with fibrillations. Motor conduction studies showed low amplitude compound muscle action potentials (CMAPs) and no conduction block was detected. Sensory conduction studies were normal. 36 months after the

clinical onset, he died as a consequence of respiratory failure due to aspiration pneumonia.

BHELA10. A 54-year-old woman, with no family history of ALS, presented with difficulty walking due to an inability to control her right foot. Eight months later, neurological examination showed a prominent bilateral and symmetrical pyramidal syndrome (overactive deep tendon reflexes of upper and lower extremities with Babinski and Hoffmann sign, spastic paraparesis and increased muscle tone); neither muscle atrophy nor fasciculations were present. Coordination and cognitive functions were normal. Electrophysiological studies showed normal sensory and motor conduction studies. No acute denervation was seen in any of the muscles tested one year after onset. Subsequently, progressive muscular weakness and atrophy appeared. Dysarthria and dysphagia also appeared and progressed rapidly. She needed a tube for feeding 3 years after onset of the disease and language was unintelligible. Two years from clinical onset, electrophysiologic studies disclosed ongoing denervation muscle potentials in all muscles tested, corresponding to cervical and lumbar segments. She refused non-invasive ventilation indicated because of the appearance of orthopnea. She died 46 months after as a result of respiratory failure.

M0010497. A 71 year old man with a 5 year history of memory problems manifested as losing objects and getting lost in the neighborhood. About 4 years prior, the patient's wife assumed responsibility of his business affairs.Currently, the patient continues to suffer with memory problemswith some spatial/time disorientation. The patient is completely dependent on his wife and is homebound, is not aggressive and does not suffer from delusions or hallucinations. However, the patient shows impulsive behavior with a tendency to compulsively buy food and shows a lack of initiative. Neuropsychological assessment concluded thatthe patient was disoriented to reality and he showed an impairment of attention, language, visual gnosis, praxis and prefrontal functions.

M0024815. A 50 year old man with a strong history of dementia (father with bvFTD, grandfather and two paternal uncles with dementia) began to develop irritability and difficulty with executive function. Shortly after diagnosis, he stopped working.There were no problems with language. He is still able to carry out basic day to day functions without supervision. The neuropsychological assessment showed a significant slowing of cognitive processing and a severe impairment of verbal learning, verbal working memory, complex visual gnosis, visuoconstructive praxis, visuospatial abilities, inhibition of automatic responses and action verbal fluency. There was a mild impairment of attention, verbal free recall and recognition memory, writing, complex verbal comprehension, phonemic verbal fluency and abstract reasoning. In contrast, he showed a relative preservation of spontaneous speech, confrontational object naming, repetition of sentences, reading, simple visual gnosis, imitational and ideomotor praxis, and category verbal fluency.

M0010098. A 66 year old man with family history of dementia (brother and father) began to suffer from memory problems and disorientation at age 60. The family notes that at that time he was unable to carry out normal activities of daily living. At present, the patient presents with temporal and spatial disorientation, language difficulties, apathy, sleep disorder, bulimia, and a sexual disorder.The neuropsychological assessment showed significant slowing of cognitive processing and a severe impairment of attention, verbal learning, verbal working memory, spontaneous speech (tendency to mutism, stereotyped behaviour), writing, reading, complex verbal comprehension, confrontation object naming, visual gnosis, imitation, inhibition of automatic responses, phonemic and category verbal fluency, and abstract reasoning. There was also a mild impairment of verbal free recall and recognition memory.

M0018127. A 61 year old woman with a family history of dementia (sister and father) showed behavioral changes and memory loss at age 60. She sings excessively and speaks with the characters on the television. She is obsessed with money and is impulsive. She frequently calls in to TV contests and makes inappropriate comments. However, she is still able to function independently most of the time. The neuropsychological assessment showed impairment of visual gnosis and visuoconstructive praxis; and a mild impairment of attention, verbal working memory, inhibition of automatic responses and abstract reasoning.

UD0053. Male age 69 with 5 year history of memory problems, repeating himself, forgetting directions, then balance problems. Some changes in habits, with obsessiveness, decreased engagement, apathy, depression, and weight loss. ALS symptoms include fasciculations diagnosed as ALS, but not definitive. Family history originally negative, but now sibling diagnosed with dementia. Patient is currently alive after 10 years of symptoms.