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Biological Psychiatry 74 (5) 2013 ; 384–391

DOI: 10.1016/j.biopsych.2013.01.031

Autosomal Dominant Frontotemporal Lobar Degeneration Due to the *C9ORF72* Hexanucleotide Repeat Expansion: Late-Onset Psychotic Clinical Presentation

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Background. A hexanucleotide repeat expansion in the first intron of *C9ORF72* has been shown to be responsible for a high number of familial cases of amyotrophic lateral sclerosis or frontotemporal lobar degeneration (FTLD). Atypical presentations have been described, particularly psychosis.
Methods. We determined the frequency of the hexanucleotide repeat expansions in a population of 651 FTLD patients and compared the clinical characteristics of carriers and noncarriers. In addition, we genotyped 21 patients with corticobasal syndrome, 31 patients with progressive supranuclear palsy, and 222 control subjects.
Results. The pathogenic repeat expansion was detected in 39 (6%) patients with FTLD (17 male and 22 female subjects); however, it was not detected in any corticobasal syndrome and progressive

supranuclear palsy patients or controls. Twenty-four of 39 carriers had positive family history for dementia and/or amyotrophic lateral sclerosis (61.5%), whereas only 145 of 612 noncarriers had positive family history (23.7%; p .000001). Clinical phenotypes of carriers included 29 patients with the behavioral variant frontotemporal dementia (bvFTD; 5.2% of all bvFTD cases), 8 with bvFTD/motor neuron disease (32% bvFTD/motor neuron disease cases), 2 with semantic dementia (5.9% of patients with semantic dementia), and none with progressive nonfluent aphasia. The presentation with late-onset psychosis (median age ¼ 63 years) was more frequent in carriers than noncarriers (10/33 vs. 3/37, p ¼ .029), as well as the presence of cognitive impairment at onset (15/33 vs. 5/37; p ¼ .0039).
Conclusions. The repeat expansion in *C9ORF72* is a common cause of FTLD and often presents with late-onset psychosis or memory impairment.

Key Words: *C9ORF72*, clinical presentation, dementia, frontotemporal lobar degeneration, hexanecleotide repeat expansion, late onset psychosis, phenotype.

A hexanucleotide repeat expansion in the first intron of *C9ORF72* was shown to be responsible for a high number of autosomal dominant inherited amyotrophic lateral sclerosis (ALS) or frontotemporal lobar degeneration (FTLD), with or without concomitant motor neuron disease (MND) 1 and 2. The brain pathology in mutation carriers is associated with TDP-43 inclusions, p62 inclusions, and nuclear RNA foci.

This mutation causes the loss of one alternatively spliced transcript, whose function is still unknown. Wild-type alleles contain no more than 30 repeats, whereas mutated alleles have hundreds to thousands of repeats (1). Multiple studies demonstrated that the *C9ORF72* mutation represents a major cause of both familial FTLD (12%) and ALS (22.5%) (1), with a higher prevalence in the northern European population, reaching a prevalence of 46% of all familial ALS, 21.1% of sporadic ALS, and 29.3% of FTLD in the Finnish population (2). A third study, performed on a Flanders-Belgian cohort of FTLD, ALS, and FTLD-ALS subjects, confirmed the importance of *C9ORF72* mutation in FTLD-ALS cases (30% FTLD-ALS) and showed that, in FTLD cases, *C9ORF72* mutations occur at a frequency comparable with that of mutations in GRN (6% vs. 7%) (3). Furthermore, data obtained in additional cohorts of patients have been recently published 4, 5, 6, 7, 8, 9, 10 and 11, including two studies in an Italian population of sporadic ALS patients 12, 13 and 14. From a clinical perspective, the large series reported in these studies shows that the predominant phenotypes are consistent with the behavioral variant frontotemporal dementia (bvFTD) and ALS, with different phenotypic presentation, even in the same family (i.e., bvFTD, ALS, or a combination of both). Nevertheless, it was suggested that psychosis and obsessive-compulsive disorder were common symptoms at disease onset in patients with FTLD carrying the repeat expansion5, 15 and 16. Moreover, a case showing mystic delusion with visual and auditory hallucinations in the absence of neurological symptoms and brain atrophy was recently described (17). In addition, presentation with memory impairment occurs quite often (50% to 65%, according to Mahoney et al. [8]), possibly leading to a clinical diagnosis of Alzheimer's disease (AD) 17 and 18.

Herein, we provide a detailed genotype-phenotype description of a large series of FTLD cases carrying the expansion, including both patients with behavioral symptoms, as well as subjects with uncommon presentations, i.e., late-onset psychiatric symptoms or memory deficits.

Methods and Materials

Patients and Clinical Workup

The dataset consisted of 651 patients (311 male and 340 female patients, mean age at disease onset ± standard deviation: 66.2 ± 8.6 years, range: 32–85) that we admitted to the Alzheimer Center of the University of Milan, Policlinico and Sacco Hospitals, Ospedale S. Raffaele and Multimedica (Milan), Neurogenetic Regional Centre (Lamezia Terme, Catanzaro), Universities of Florence, Turin, Rome, and Padua. The clinical workup included detailed past medical history, general and neurological examination, routine blood tests, formal neurocognitive assessment (17), brain computed tomography (CT) scan or magnetic resonance imaging (MRI), and, if possible, [^{18}F]-fludeoxyglucose positron emission tomography and cerebrospinal fluid (CSF) biomarkers amyloid beta(Aβ), total tau (tau), and tau phosphorylated at position 181 (pTau) determination. The presence of significant vascular brain damage was excluded (Hachinski Ischemic Score < 4). When psychiatric disorders at onset were evident or suspected, patients were referred to the Psychiatric Unit of the Fondazione Cà Granda, Istituto Di Ricovero e Cura a Carattere Scientifico Ospedale Maggiore Policlinico (Milan) for clinical interview and characterization by the administration of semistructured interviews based on DSM-IV criteria (Structured Clinical Interview for DSM-IV Axis I Disorders and Structured Clinical Interview for DSM-IV Axis II Disorders) 19 and 20 (evaluation performed by BD and ACA).

Frontotemporal lobar degeneration was diagnosed according to current consensus criteria 21 and 22, identifying three clinical syndromes: bvFTD (n = 553), progressive nonfluent aphasia (PNFA, n = 64), and semantic dementia (SD, n = 34). Twenty-five patients with bvFTD and one with PNFA had concurrent MND. In addition, 21 patients with corticobasal syndrome (CBS; 7 male and 14 female patients; mean age at disease onset ± standard deviation: 64.3 ± 7.4 years, range: 47–77) and 31 patients with progressive supranuclear palsy (PSP; 16 male and 15 female patients; mean age at disease onset ± standard deviation: 61.2 ± 7.9 years, range: 50–84), diagnosed with current criteria (23), were included.

Control subjects consisted of 222 healthy age- and gender-matched subjects (92 male and 130 female subjects; mean age ± standard deviation: 67.8 ± 9.3 years, range: 51–89). These individuals did not have neurological or psychiatric disorders. Both patients and control subjects were of mainland Italian ancestry. Written informed consent was provided by patients or their caregivers.

C9ORF72 Genotyping

High molecular weight DNA was isolated from whole blood using a Flexigene Kit (Qiagen, Hildren, Gemany). *C9ORF72* genotyping was carried out by repeat-primed polymerase chain reaction and sequencing (1). This method allows detection of 30 to 50 repeats; according to current literature (24), a characteristic stutter amplification pattern (> 30 repeats) on the electropherogram is considered evidence of a pathogenic repeat expansion.

Statistical Analysis

Sigma Stat 3.1 software (Jandel Corp., San Rafael, California) was used for statistical analysis. Continuous variables (i.e., age at symptom onset) were compared with *t* test, whereas discrete variables (i.e., gender, phenotypic presentation) were compared with the chi-square.

Results

We tested 651 patients with FTLD, 21 patients with CBS, 31 patients with PSP, and 222 control subjects. A clinically documented family history for dementia was reported for 169 patients (147 with bvFTD, 9 with bvFTD/MND, 8 with PNFA, and 4 with SD).

The pathogenic repeat expansion was detected in 39 (6%) FTLD patients (17 male and 22 female patients); however, it was not detected in any CBS and PSP patients or control subjects. *C9ORF72* repeat expansion carriers were not significantly different in mean age at onset (63.9 ± 8.1 years, range: 48–77 vs. 66.3 ± 8.6, range 32–85, $p > .05$) or gender distribution ($p > .05$) compared with noncarriers. The frequency of carriers was almost the same in all regions of Italy (North, Center, South). Among carriers, 24 of 39 carriers had a positive family history for dementia and/or ALS (61.5%), whereas only 145 of 612 noncarriers had a positive family history (23.7%; $p < .000001$).

Clinical phenotypes of carriers included: 29 patients with bvFTD (5.2% of all cases diagnosed with bvFTD), 8 with bvFTD/MND (32% of cases with bvFTD/MND), 2 with SD (5.9% of patients with SD), and none with PNFA (Figure 1 and Figure 2 and Figure 1 and Figure 2). MAPT and GRN sequencing was carried out in 128 and 353 FTLD patients, respectively [positive cases reported elsewhere 25, 26, 27, 28, 29, 30 and 31, along with an estimation of the frequency of the Italian population described previously (32)]. None of the MAPT and GRN mutation carriers was positive for the *C9ORF72* hexanucleotide expansion. Symptom details at onset were available for 33 of 39 carriers and 37 of 612 noncarriers, and imaging data were obtained for 29 carriers (Table 1). The presentation with psychosis was more frequent in carriers (10/33) than noncarriers (3/37; 30.3 versus 8.1%, $p = .029$). Psychotic symptoms mainly included hallucinations ($n = 4$) and delusions ($n = 5$), whereas one patient developed aggressiveness followed by hypomanic status. The presence of memory impairment at onset, including both learning and delayed recall, was more frequent in carriers than noncarriers (15/33 vs. 5/37; 45.4% vs. 13.5%, $p = .0039$). Parkinsonism was observed in four carriers: in two cases as the first symptom at onset (patients 10 and 27) and in two cases (patients 21 and 30) after behavioral or psychiatric disturbance appearance; none of the noncarriers showed parkinsonism at onset. Atypical imaging was observed in 12 of 29 cases: in 2 of the cases (6.9%), no brain atrophy was present at MRI, whereas 10 patients (34.5%) showed diffuse atrophy.

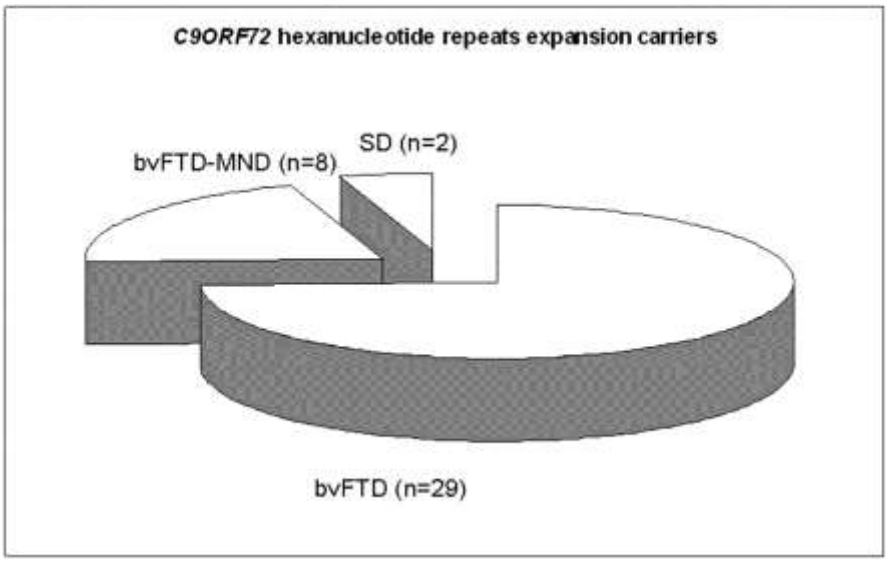

Figure 1. Clinical diagnoses of *C9ORF72* hexanucleotide repeat expansion carriers. bvFTD, behavioral variant frontotemporal dementia; MND, motor neuron disease; SD, semantic dementia.

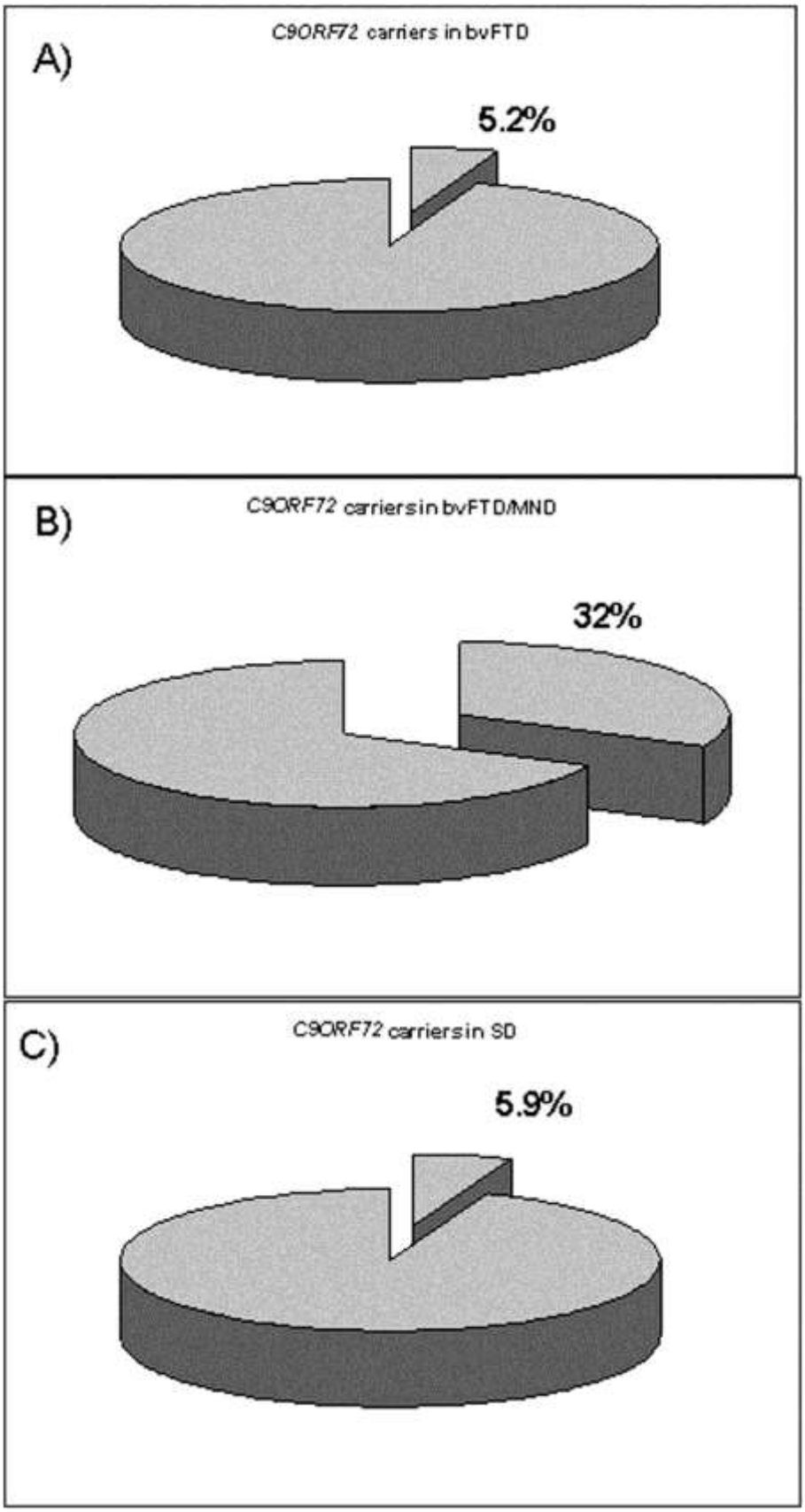

Figure 2. Percentage of mutation carriers as compared with noncarriers in patients with a clinical diagnosis of (A) behavioral variant frontotemporal dementia (bvFTD), (B) bvFTD/motor neuron disease (MND), and (C) semantic dementia (SD).

Table 1. Characteristics of *C9ORF72* Repeat Expansion Carriers.

Patient	Age at Onset	Gender	Clinical Diagnosis	Family History for Dementia	Symptoms at Onset				Brain Atrophy		
					Behavior	Language	Memory	Psychiatric[a]	Absent	Diffuse	Focal Anterior
#1	57	F	bvFTD	+	x			x		x	
#2	75	F	bvFTD	–	x						
#3	52	M	bvFTD	+			x				x
#4	70	F	bvFTD	–	x			x			x
#5	74	F	bvFTD	–	x						
#6	57	M	bvFTD/MND	+	x	x	x			x	
#7	68	F	SD	–	x	x					x
#8	72	F	bvFTD	+		x	x				x
#9	59	M	bvFTD	–	x		x				x
#10	49	M	bvFTD	+	x						x
#11	73	F	bvFTD/MND	+	x					x	
#12	77	F	bvFTD	–	x		x			x	
#13	58	M	bvFTD	+	x						x
#14	66	F	bvFTD	+	x					x	
#15	60	F	bvFTD	+				x			
#16	62	M	SD	–		x					x
#17	71	F	bvFTD	+			x		x		
#18	65	M	bvFTD	+	x			x		x	
#19	66	M	bvFTD/MND	–	x			x			x
#20	60	F	bvFTD	–	x		x		x		
#21	48	M	bvFTD/MND	+			x	x			x
#22	49	F	bvFTD	–							
#23	65	F	bvFTD	–							
#24		M	bvFTD	–							
#25	50	F	bvFTD	+							
#26	55	F	bvFTD	+							x
#27	70	M	bvFTD	+	x		x	x			x
#28	74	F	bvFTD	+	x						
#29	60	F	bvFTD	+				x		x	
#30	71	M	bvFTD	+			x				x
#31	52	M	bvFTD/MND	+	x		x			x	
#32	71	F	bvFTD	+							
#33	65	F	bvFTD/MND	+	x	x	x				
#34	71	M	bvFTD/MND	–			x				x
#35	64	M	bvFTD	+	x			x		x	
#36	76	F	bvFTD	–			x				x
#37	66	M	bvFTD	+	x		x				x
#38	57	F	bvFTD	+	x					x	
#39	62	F	bvFTD/MND	–	x			x			x

bvFTD, behavioral variant frontotemporal dementia; F, female; M, male; MND, motor neuron disease; SD, semantic dementia.

[a]Hallucinations (n = 4), delusions (n = 5), hypomanic status (n = 1).

Regarding carriers with FTD/MND, symptoms of MND appeared, on average, 3 years after the bvFTD diagnosis, although the range was extremely wide (.5–9 years). Cerebrospinal fluid Aβ, tau, and pTau levels, evaluated in patients 3, 4, 5, 6, 9, and 21, were within reference values 33 and 34. Autopsy was available for case 39 only. Macroscopically, the brain showed gross frontal atrophy. Histopathology showed TDP-43 immunoreactive cytoplasmic inclusions in anterior horn motor neurons and dentate neurons of the hippocampus, as well as p62-positive intranuclear inclusions in cerebellarneurons of the granular layer (Figure 3).

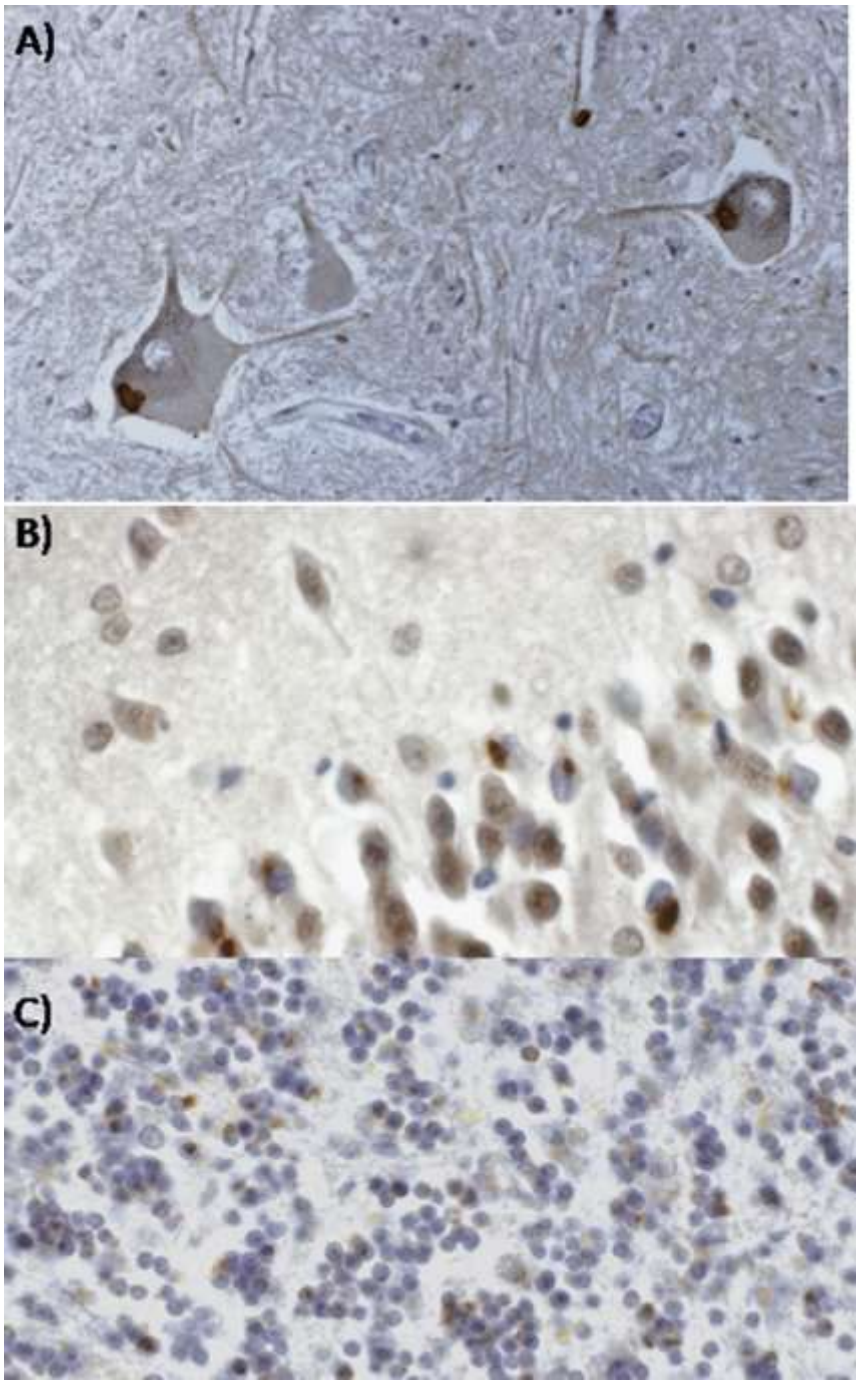

Figure 3. Postmortem neuropathology of case 39. TDP-43 immunoreactive neuronal cytoplasmic inclusions were evident in anterior horn motor neurons (A) and dentate gyrus of hippocampus (B). Frequent small round p62-positive intranuclear inclusions were present in the granular cell layer of cerebellum (C).

Detailed medical histories of patients with atypical presentations are herein reported.

Patient 1

The detailed history of patient 1 has been previously described (17). Briefly, she started developing psychiatric symptoms (behavioral changes: she became suspicious and jealous toward her husband) at 57 years of age. Then, she developed further behavioral disturbances, in particular agitation, aggressiveness, and swearing, and was referred to a psychiatric center. She came to our attention at age 60, when symptoms had an ecological impact. Her father was diagnosed with AD and died at 61

years of age. At the last examination in 2011, she showed marked cognitive decline, particularly in language ability (becoming completely aphasic). Behavioral symptoms were well controlled with Quetiapine.

Patient 3

The detailed history of patient 3 has been previously described (17). Briefly, the patient was diagnosed with "mild cognitive impairment due to depressive syndrome" at 52 years of age and a few months later was diagnosed with AD. He came to our attention 1 year later, and at that time, his wife reported mood deflection, characterized by apathy, social withdrawal, and irritability. In addition, the patient presented speech disturbances and also developed topographical disorientation, apraxia in dressing and in daily activities, perseverative stereotyped behaviors, and episodes in which he was not able to identify his relatives. Positive family history for dementia was present: his mother, aged 74, was diagnosed with AD in her seventies (and is at present alive).

Patient 4

Patient 4 developed psychobehavioral disturbances at the age of 70, including slowing and lacking logical speech and perseverative behaviors. Cerebrospinal fluid biomarkerswere within normal ranges (Aβ = 770 pg/mL; tau = 121 pg/mL, pTau = 20 pg/mL). Bilateral frontal atrophy was observed on MRI, as well as hypometabolism in the same regions on [^{18}F]fludeoxyglucose positron emission tomography imaging. She was diagnosed with bvFTD but did not show up at follow-up visits.

Patient 6

Patient 6 came to our attention at 57 years of age, with a positive family history of motor neuron disorders: mother affected by ALS and died at 55 years of age. About 10 months before, he had started to develop psychomotor slowing, language difficulties (impairment of expression and comprehension), and prominent psychobehavioral disturbances (particularly disinhibition). A few months later, he developed also dysarthria and dysphagia. He showed diffuse fasciculations on both upper and lower limbs. Cerebrospinal fluid tau levels were normal (75 pg/mL) and electromyography findings were compatible with MND. He was diagnosed with behavioral bvFTD/MND.

Patient 7

Patient 7 started developing cognitive impairment at 68 years of age, predominantly language difficulties and behavioral disturbances. When she came to our attention (at age 72), she presented fluent aphasia, comprehension deficits, and marked behavioral disturbances (stereotyped behaviors, hyperphagia, perseverative activities). She was completely autonomous until her first clinical admission, 4 years after onset. She scored 11 of 30 on Mini Mental State Examination (MMSE), and technetium-99 single-photon emission computed tomography (SPECT) showed frontotemporal bilateral hypoperfusion. She was diagnosed with SD.

Patient 8

Patient 8 came to our attention at 72 years of age. Her daughter reported the appearance, about 3 years earlier, of memory and language impairment, with rapid worsening and functional impairment within 2 years from the onset. Neuropsychological evaluation showed multiple cognitive deficits, with prominent language comprehension impairment; MMSE score was 17 of 30. A technetium-99 SPECT showed right frontolateral and bilateral frontomesial and temporal hypoperfusion consistent with the atrophy seen by conventional MRI. She was thus diagnosed as bvFTD with predominant semantic deficits. During the following years, behavioral disturbances (i.e., fatuity, apathy, and wandering) emerged. She died, 3 years after diagnosis, of ab ingestis pneumonia, suggesting possible motor neuron involvement. Family history was positive: her father was affected by probable dementia

with severe behavioral disturbances, and her sister, 3 years younger, was suffering from ALS and also carried the *C9ORF72* mutation.

Patient 9

At the age of 61 years, patient 9 presented with memory impairment and mild behavioral disturbances (i.e., apathy, social withdrawal, and slight hyperphagia). No familial history of dementia was reported. Two years after onset, neuropsychological assessmentrevealed long-term memory and visuospatial impairment, without any functional impairment. Performances on short-term visuospatial memory, focused and sustained attention, verbal fluency, naming and comprehension tasks were borderline. Cerebrospinal fluid findings were normal. [^{18}F]Fludeoxyglucose positron emission tomography imaging showed left hippocampal and temporopolar hypometabolism, consistent with the atrophy seen on conventional MRI. He was then diagnosed with possible bvFTD.

Patient 11

This patient was referred, at the age of 73 years, to a Neurology Unit for the appearance of fasciculations and swallowing difficulties. According to her relatives, she started showing behavioral disturbances, particularly disinhibition, over several months. She was diagnosed with bvFTD/MND and died at 75.

Patient 18

The patient developed behavioral disturbances (aggressiveness, irritability) at 65 years of age, followed by hypomanic status, and was treated with olanzapine with beneficial effects. His family history was positive for dementia (mother), psychiatric disturbances (aunt), and ALS (two cousins, one of them underwent genetic analysis, which disclosed the presence of the *C9ORF72* hexanucleotide expansion).

Patient 19

Patient 19 came to our attention at 75 years of age; his sister-in-law reported that slight behavioral disturbances had begun almost 9 years before, but such symptoms started to impact his ability to function alone only over the last 3 years, so the patient started living with his son's family. In particular, over the last 2 years, the patient became uninterested in activities he usually did in the past, sexually disinhibited, extroverted, and confabulatory. On examination, he showed sexual delusions, and scored 25 of 30 on MMSE. A CT scan showed a marked frontotemporal atrophy. He was diagnosed with bvFTD. After a few months, he developed dysphagia, and electromyography was compatible with MND. He died approximately 1 year and a half after the initial bvFTD diagnosis.

Patient 20

Patient 20 became apathetic and irritable at 60 years of age. After 2 years, she developed slight memory impairment, attention deficits, and hyperphagia and was referred to our attention. At examination, she scored 25 of 30 on MMSE; the MRI was normal, whereas on technetium-99 SPECT, hypoperfusion of the frontal medial gyruswas present. One year later, at 63, both cognitive and behavioral symptoms worsened (MMSE = 20/30), and a second MRI confirmed the presence of frontal cortical atrophy. She was diagnosed with bvFTD. Six months later, symptoms were severely worsened (MMSE = 15). At the last follow-up visit (4 months later), she was completely aphasic. In addition, hyperphagia was reported by his relatives.

Patient 21

At the age of 48 years, patient 21 developed cognitive and psychiatric disturbances, including obsessive-compulsive symptoms, nighttime wandering, and paranoid delusions. A treatment with

olanzapine was started, rapidly followed by the development of an akinetic-rigid syndrome, which partially reversed with neuroleptic withdrawal. He was also hyperphagic and had poor personal hygiene. At the time of first evaluation, he had deficit in verbal fluency and other executive functions (MMSE = 29/30). Family history was positive for both dementia (mother, died at 75) and ALS (a maternal cousin). Neurological examination showed mild extrapyramidal signs (rigidity, bradykinesia), increased deep reflexes for all four limbs. At 53, he underwent MRI, which showed very mild anterior cingulate atrophy (Figure 4A), whereas positron emission tomography scanshowed bilateral superior and mesial frontal and left temporal hypometabolism. Total tau and pTau CSF biomarkers were within normal ranges (85 and 31 pg/mL, respectively). At 51, he developed gait difficulties, with frequent falls. Physical examination showed spastic paraparesis and diffuse limb and tongue fasciculations, and bvFTD/MND was diagnosed. The patient is now 59, bedridden in akinetic mutism, and MRI showed severe anterior cingulate and mesial frontal atrophy (Figure 4B).

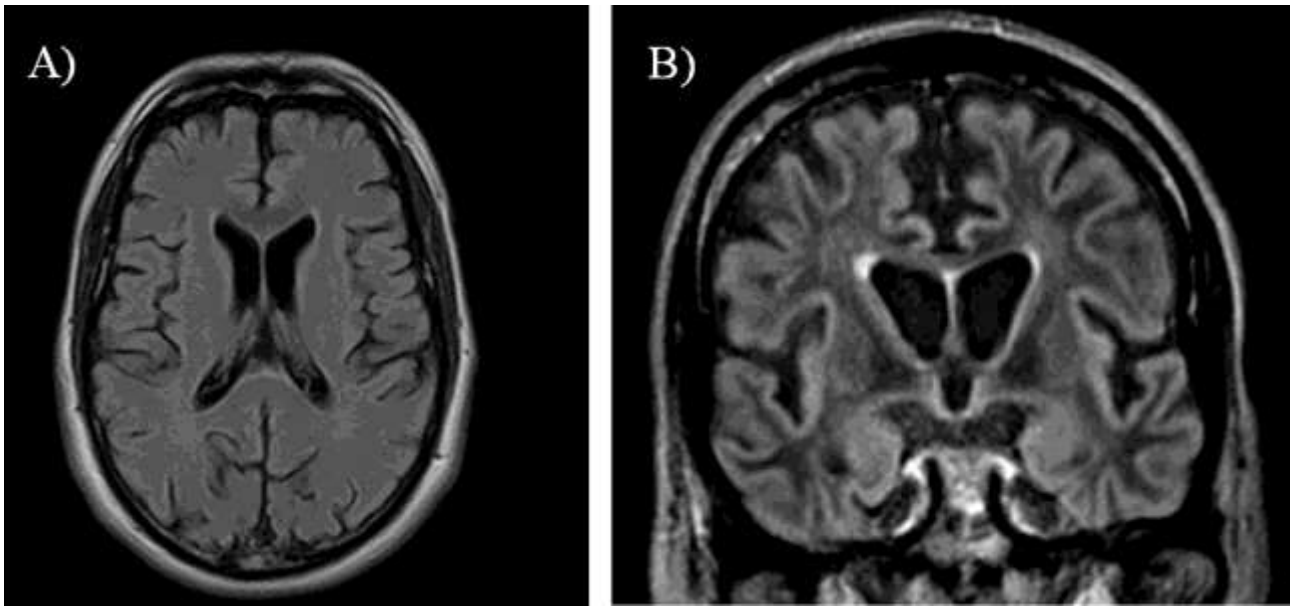

Figure 4. Brain magnetic resonance imaging T1-w axial (A) and fluid attenuated inversion recovery coronal (B) images of patient 21. Image in (A) was obtained at the age of 53 (after 5 years from disease onset) and showed very mild anterior cingulate atrophy. Image in (B), at 59 years old, showed widespread cortical atrophy prevalent in the cingulate cortex.

Patient 27

Patient 27 was referred to the Neurology Unit for postural tremor. After 2 years, he developed behavioral disturbances, visual hallucinations, and memory impairment. He was lost at follow-up.

Patient 30

Patient 30 developed slight cognitive impairment at 71 years of age. At that time, he scored 29 of 30 on MMSE. His family history was positive: his mother, grandmother, and an aunt (with a presenile

onset) were demented. In addition, he had a brother with unspecified psychiatric disturbances and a sister with mood disorders and dementia. After 2 years, memory impairment worsened, and behavioral disturbances appeared, although the patient was still autonomous in activities of daily living. After 2 additional years, the patient became aphasic and extrapyramidal signs were observed; at that time, activities of daily living score was 0.

Patient 35

Patient 35 developed behavioral disturbances (elated mood and disinhibition) at age 64; later on, he became apathetic and had visual hallucinations (he saw a boy coming out of a grave). He had a positive family history: his mother and brother were demented, and a sister showed slight memory impairment. He scored 17 on MMSE, and at MRI, cortical-subcortical atrophy was observed. One year later, he developed urinary incontinence, camptocormia, and eventually progressive akinetic mutism. He scored 10 on MMSE. After an additional year, movement disturbances worsened, and the patient was not able to attend any more follow-up visits. He died 7 years after the initial diagnosis of bvFTD.

Patient 36

Patient 36 came to our attention at 76 years of age for memory deficits. She scored 24 on MMSE. A CT scan showed a marked bilateral frontal atrophy, and the technetium-99 SPECT showed hypoperfusion in the same regions. In the latter 2 years, despite an episode of temporal disorientation, her MMSE remained stable, and she started developing behavioral disturbances: elated mood, lack of insight, obsessive ideation, and poor personal hygiene. She was diagnosed with bvFTD but did not attend follow-up visits.

Patient 37

Patient 37 presented at 66 years of age with memory deficits and behavioral disturbances. In particular, he had difficulties with daily living activities and started having strange and perseverative behaviors, like frightening children, buying bread continuously, inability to stand still, and developed a lack of insight. He had a positive family history: an aunt and an uncle with dementia, and a sister with mild memory impairment. After 2 years, symptoms worsened: he was agitated and irritable. Magnetic resonance imaging showed cortical-subcortical cerebral atrophy, mainly in the frontotemporal-parietal areas, MMSE score was 24, and he was diagnosed with bvFTD. After 2 additional years, he developed urinary incontinence and was not able to recognize his wife.

Patient 38

Patient 38 started having difficulties in activities of daily living at 57 years of age. She had a positive family history for dementia (mother and aunt affected) and was initially treated for depression but later diagnosed with AD. When she came to our attention, she was almost mute, hyperphagic, and aggressive. She scored 13 on MMSE; at CT scan and MRI, a cortical-subcortical mild atrophy was evident. She was diagnosed with bvFTD. Two years later, she developed stomach cancer and died 5 years after diagnosis of bvFTD. At that time, she was unable to recognize her relatives, as well as feed herself.

Patient 39

Patient 39 developed delusions at 58 years of age. He was referred to a Psychiatric Center and was treated with neuroleptics. At 65, he developed motor disturbances compatible with MND. He died a few months later at the age of 66. At autopsy, macroscopic examination showed a marked brain atrophy, particularly in the prefrontaland temporal regions. Histopathology included positivity for TDP-43 and p62 (Figure 3).

Discussion

In this confirmatory study, we show that the *C9ORF72* hexanucleotide repeat expansion is a common cause of FTLD in the Italian population, with a frequency (6%) similar to GRN and MAPT mutations (35). In our clinical cohort, this mutation was more frequent in cases with a diagnosis of bvFTD/MND (32%), whereas it was associated with a bvFTD phenotype in 5.2% of all patients that received such a diagnosis. It is not known with certainty whether the presence of the mutation is prognostic for the development of MND in patients with bvFTD. In addition, we could not evaluate the survival curve in mutation carriers versus noncarriers, as the majority of patients are still alive or lost to follow-up. To clarify these points, a longitudinal follow-up of patients is ongoing. Notably, for the first time, we identified two carriers with a diagnosis of SD, while none of the patients with PNFA was a carrier of the *C9ORF72* repeat expansion. In this regard, Boeve et al. (10) and Sha et al. (36) did not find any language presentation in their cohorts of *C9ORF72* carriers, whereas a carrier of the expansion presenting with PNFA was described by Gijselincket et al. (3). As expected, none of the patients with CBS and PSP, supposed tauopathies, were carriers of the mutation, as well as 222 control subjects (total of 548 chromosomes), although, given the small size of the population studied, no definitive results can be drawn.

Regarding symptoms at onset, atypical presentations were common, including psychosis and cognitive impairment. In accordance with previous findings 5 and 24, our data support the hypothesis that psychotic phenomena are likely associated with the *C9ORF72* repeat expansion. Whereas our patients presenting with psychosis developed behavioral disturbances typical of bvFTD concurrently or over time, other cases with pure psychotic symptoms (in the absence of neurological signs and with no atrophy at imaging) have recently been described 13 and 17. In particular, one of these patients showed mystical delusions at onset, and after 9 years, he still presented with psychotic symptoms (mystical-megalomaniac delusions, poorly responsive by antipsychotics) as unique manifestation of the disease (17). Such observations underline the importance of the *C9ORF72* screening in suspicion of an FTLD pathology in patients presenting with late-onset psychosis. However, in this study, psychopathological symptoms might have been underestimated, since this assessment has been carried out only in part of the study population; a future study including psychiatric evaluation would be needed to confirm our data.

Memory deficits represent another atypical feature of *C9ORF72* carriers (15 of 33) and were in some cases the first symptom to be developed, resulting in a clinical diagnosis of amnestic mild cognitive impairment or AD. In this regard, Murray et al. (18) reported that three *C9ORF72* expansion-positive patients, in their neuropathologic series, were clinically diagnosed with AD in life. Moreover, another study of a large cohort of patients carrying different mutations (8) showed that memory impairment was a prominent feature of *C9ORF72* carriers (50% to 65% of cases). Presentation with memory impairment is a characteristic of carriers of GRN and MAPT mutations, as well 35, 36, 37 and 38. In addition, it was recently shown that FTLD in elderly patients does exist as a separate entity from presenile-onset FTLD, being clinically characterized by frequent memory loss (39). Nevertheless, it should be considered that episodic memory deficits could be overestimated in these patients due to language deficits.

Few patients (n = 4) also presented with extrapyramidal symptoms and ataxia, although in two cases, only at disease onset. Atypical movement presentations in *C9ORF72* carriers have previously been reported, including apraxia, involuntary hand movement, bradykinesia, spasticity in all limbs, and atypical parkinsonian syndrome (40).

Mean age at disease onset was similar between carriers and noncarriers, in accordance with previous reports (35). Nevertheless, in contrast with Sha et al. (36), who did not find *C9ORF72* carriers showing symptoms later than 65 years of age, in our cohort, 17 of 39 carriers developed first symptoms later than 65 years. We have to acknowledge, however, that presentation symptoms are

often subtle and a careful formal psychological assessment would be needed to raise suspicions of FTLD. Therefore, a delayed recognition and underestimation of first manifestations, either by family members or general practitioners, could be conceivable. Although a correlation of the number of repeats with the clinical phenotype would be very interesting to see whether repeat size correlates with disease severity, the method used does not allow to discriminate more than 30 to 50 repeats (24).

In accordance with previous observations (41), the presence of the *C9ORF72* repeat expansion was significantly associated with family history of FTLD or ALS.

Similar to previous observations in GRN carriers (34), the CSF profile of patients 3, 4, 5, 6, 9, and 21 were normal, making the concept of tau as a nonspecific marker of neurodegeneration and axonal loss questionable. In addition, no brain atrophy was observed at the time of symptom presentation in two patients, although, in one case, it appeared on MRI at a 1-year follow up. On the other hand, in 10 patients, imaging showed instead a diffuse atrophy, in accordance with Whitwell et al. (42), who observed a widespread pattern of gray matter loss in *C9ORF72* carriers compared with control subjects.

The histopathology, available for one case (patient 39), showed positivity for TDP-43 and p62, in accordance with previous observations in *C9ORF72* brains (9).

In conclusion, the description of these cases broadens the spectrum of clinical presentations of FTLD as a result of the *C9ORF72* hexanucleotide repeat expansion and suggests that genetic analysis of the expansion should be considered in patients presenting with late-onset pure psychotic symptoms (and exhibiting a normal CSF profile and/or normal imaging).

Acknowledgements

This research was supported by Fondazione Monzino, Italian Ministry of Health (Ricerca Corrente), Associazione per la Ricerca sulle Demenze - ARD Onlus, Associazione per la Ricerca Neurogenetica – ARN Onlus (Lamezia Terme), Cassa di Risparmio PT e Pescia (Grant n. 2011.0264), Ateneo ex60%, Ontario Research Fund, and Weston foundation (ER).

The authors report no biomedical financial interests or potential conflicts of interest.

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