ORIGINAL CONTRIBUTION

Distinct Clinical Characteristics of *C9orf72* Expansion Carriers Compared With *GRN*, *MAPT*, and Nonmutation Carriers in a Flanders-Belgian FTLD Cohort

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Objective: To characterize patients with frontotemporal lobar degeneration (FTLD) with a repeat expansion mutation in the gene *C9orf72*, and to determine whether there are differences in the clinical presentation compared with FTLD carriers of a mutation in *GRN* or *MAPT* or with patients with FTLD without mutation.

Design: Patient series.

Setting: Dementia clinics in Flanders, Belgium.

Patients: Two hundred seventy-five genetically and phenotypically thoroughly characterized patients with FTLD.

Main Outcome Measures: Clinical and demographic characteristics of 26 *C9orf72* expansion carriers compared with patients with a *GRN* or *MAPT* mutation, as well as patients with familial and sporadic FTLD without mutation.

Results: *C9orf72* expansion carriers developed FTLD at an early age (average, 55.3 years; range, 42-69 years), significantly earlier than in *GRN* mutation carriers or patients with FTLD without mutation. Mean survival (6.2 years; range, 1.5-17.0 years) was similar to other patient groups. Most developed behavioral variant frontotemporal dementia (85%), with disinhibited behavior as the prominent feature. Concomitant amyotrophic lateral sclerosis is a strong distinguishing feature for *C9orf72*-associated FTLD. However, in most patients (73%), amyotrophic lateral sclerosis symptoms were absent. Compared with *C9orf72* expansion carriers, nonfluent aphasia and limb apraxia were significantly more common in *GRN* mutation carriers.

Conclusions: *C9orf72*-associated FTLD most often presents with early-onset behavioral variant frontotemporal dementia with disinhibition as the prominent feature, with or without amyotrophic lateral sclerosis. Based on the observed genotype-phenotype correlations between the different FTLD syndromes and different genetic causes, we propose a decision tree to guide clinical genetic testing in patients clinically diagnosed as having FTLD.

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FRONTOTEMPORAL LOBAR DEgeneration (FTLD) is a collective term for a group of neurodegenerative disorders with predominant atrophy of the frontal and/or the temporal lobes of the brain. Despite similar gross pathologic features, FTLD is markedly heterogeneous in clinical presentation, microscopic characteristics, and underlying genetic causes. Clinically, FTLD presents with either changes in personality and social conduct (behavioral variant frontotemporal dementia [bvFTD]) or with language problems (primary progressive aphasias including semantic dementia [SD] and progressive nonfluent aphasia [PNFA]).[1-3] The pathology of FTLD can, in turn, be subdivided according to the identity of the major inclusion protein that is found in protein depositions in degenerating neurons, those being TAR DNA-binding protein 43 (TDP-43; pathologic subclass, FTLD-TDP), tau (FTLD-tau), and FUS (FTLD-FUS).[4]

Approximately 10% to 15% of patients with FTLD also develop amyotrophic lateral sclerosis (ALS), characterized by progressive muscle weakness, atrophy, and spasticity.[5] Furthermore,

TDP-43 and FUS are also key pathologic proteins in ALS, suggesting that FTLD and ALS represent a continuum of neurodegenerative diseases and share common pathogenic mechanisms.[6] Frontotemporal lobar degeneration also shows clinical overlap with the atypical parkinsonian disorders corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP).[7]

As much as 40% of patients with FTLD report a first-degree relative with a similar neurodegenerative disorder. Despite the progress in identification of causal genes for FTLD (*GRN*, *MAPT*, and rarely *VCP* and *CHMP2B*), a significant fraction of familial FTLD remained unexplained, particularly among patients who had a familial history of both FTLD and ALS. Very recently, we and others[8-10] independently demonstrated that a pathologic expansion of a hexanucleotide repeat GGGGCC, located within the regulatory region of *C9orf72* is at the basis of chromosome 9p–linked FTLD and ALS. Extensive screenings for this expansion mutation have now been performed in several large patient cohorts of different geographic background, which revealed a *C9orf72* expansion in 7% to 9% of all patients with FTLD (12%-18% of familial FTLD) and in 7% to 11% of all patients with ALS (24%-38% of familial ALS).[8-19] In nearly all patients with FTLD, the associated molecular pathology was characterized by cellular inclusion bodies of TDP-43. However, the observed TDP-43 load was variable, and ubiquitin-positive, TDP-43–negative inclusions were also observed, suggesting that other unidentified proteins were also accumulating.[9,20,21] The exact length of the pathogenic repeat expansion in *C9orf72* has proven difficult to determine but was in 1 family roughly estimated at 700 to 1600 repeat units.[8]

Here, we describe the detailed clinical characteristics of a large number of *C9orf72* expansion carriers. Genotype-phenotype correlations were performed to investigate whether *C9orf72* expansion carriers showed distinctive phenotypic features compared with *GRN* or *MAPT* mutation carriers or patients with FTLD with no mutation in any of the known FTLD genes. The results of these detailed comparative clinical genetic studies may guide neurology practice in the diagnosis and prognosis of these patients.

METHODS

STUDY POPULATION

Patients with FTLD (n=275) were recruited from 1998 as part of an ongoing multicenter collaboration of specialized memory clinics in Flanders, Belgium.[9] Index patients were evaluated using a standard protocol, which included a detailed clinical and family history, neurologic examination, neuropsychologic testing, biochemical analyses, and neuroimaging. Additional relatives of mutation carriers of whom detailed neurologic records were available were included in the current study. The diagnosis of FTLD was made according to the international consensus criteria.[1] A small number of patients (n=8) had symptoms of different FTLD subtypes at presentation (denoted as mixed FTLD). Diagnosis of FTLD-ALS was made for 20 patients who also met the criteria for clinical possible ALS according to the revised El Escorial criteria.[22] Ten patients with prominent behavioral changes and/or speech impairment received a clinical diagnosis of CBS[23] and 4 of PSP.[24] Brain autopsy was performed for 4 *C9orf72* expansion carriers, as published.[9] All data records, medical records, neuroimaging studies, and autopsy reports were reviewed, and the demographic, clinical, and pathologic characteristics of each patient were summarized in a standardized format.

For molecular genetic studies, index patients and relatives were contacted by trained research nurses. Detailed information on family history of dementia was gathered, and additional patients and unaffected family members were asked to participate in genetic studies.

All participants or their legal guardian gave written informed consent for participation in the clinical and genetic studies, as well as for brain autopsy if appropriate. The clinical study protocol and the informed consent forms for patient ascertainment were approved by the local ethics committees of the collaborating medical centers. The genetic and pathologic study protocols and informed consent forms were approved by the ethics committee of the University Hospital of Antwerp and the University of Antwerp, Belgium.

MUTATION ANALYSIS

All patients in this cohort were analyzed for mutations in the 5 known FTLD genes (ie, *C9orf72*, *GRN*, *MAPT*, *VCP*, and *CHMP2B*). Genomic DNA was isolated from whole blood using standard protocols. Patients were analyzed for the *C9orf72* repeat expansion by a repeat-primed polymerase chain reaction, as described.[9] Sequencing of *GRN*, *MAPT*, *VCP*, and *CHMP2B* was performed as described.[25-28] Mutation carriers were included in the clinical analysis if DNA was available for testing or if we could show segregation of the mutation to their offspring. Genetic and clinical characteristics of *GRN*, *MAPT*, *VCP*, and *CHMP2B* mutation carriers are summarized in the eTable (http://www.jamaneuro.com).

STATISTICAL ANALYSIS

Average age at onset was compared using an independent-sample *t* test and median age at onset using a Mann-Whitney *U* test. Disease durations were analyzed using Cox regression, with sex and age at onset as covariables, as well as censoring at the time of last contact. Clinical characteristics were compared using a Fisher exact test.

RESULTS

DEMOGRAPHIC CHARACTERISTICS

Demographic data of 26 *C9orf72* expansion carriers and patients with and without mutations in *GRN* or *MAPT* are summarized in **Table 1**. The mean age at onset of FTLD in *C9orf72* expansion carriers was 55.3 years (range, 42-69 years). The age at onset was significantly earlier compared with patients with a *GRN* mutation (59.6 years; $P=.03$), as well as patients with sporadic FTLD (63.1 years; $P<.001$) and familial FTLD without a mutation (63.9 years; $P<.001$). We produced a liability risk curve by using age at onset or age at last evaluation of all expansion carriers in the *C9orf72* families (n=51), which showed that 47% of the expansion carriers were affected by the age of 60 years, whereas 91% were affected by the age of 70 years (**Figure 1**). Notably, 3 expansion carriers are still asymptomatic at ages older than 70 years (1 at age 73 years and 2 at age 76 years). The average du-

Table 1. Characteristics of *C9orf72* Expansion Carriers Compared With Other Patients With FTLD With and Without Mutations

	Mutation			No Mutation	
	C9orf72 Expansion	*GRN*	*MAPT*	Familial	Sporadic
Patients (index patients), No.	26 (20)	27 (19)	8 (4)	69	145
Male, No. (%)	17 (65)	11 (41)	5 (63)	42 (61)	79 (54)
Age at onset, y					
Mean (SD)	55.3 (7.8)	59.6 (7.3)[a]	56.9 (4.4)	63.1 (9.6)[c]	63.9 (10.5)[c]
Median (range)	53.5 (42-69)	62.0 (45-70)[b]	56.5 (49-65)	64.0 (40-82)[c]	65.0 (29-85)[c]
Disease duration, y					
Mean (SD)	6.2 (4.8)	5.8 (1.9)	9.4 (5.0)	6.3 (3.5)	6.0 (3.9)
Median (range)	5.0 (1.5-17.0)	5.5 (3.0-9.1)	8.0 (3.1-18.0)	6.8 (0.8-12.6)	5.6 (0.5-22.0)

Abbreviation: FTLD, frontotemporal lobar degeneration.
[a]Standard deviation differs significantly from *C9orf72* carrier group with $P < .05$.
[b]Standard deviation differs significantly from *C9orf72* carrier group with $P < .01$.
[c]Standard deviation differs significantly from *C9orf72* carrier group with $P < .001$.

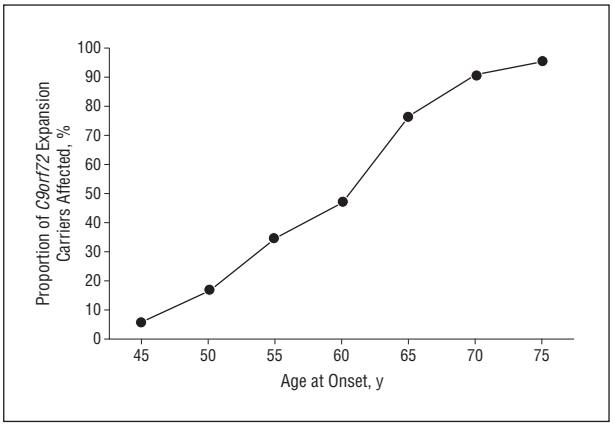

Figure 1. Liability risk curve for *C9orf72* expansion carriers. The age-related penetrance of a *C9orf72* expansion is shown using the age at onset or age at last evaluation for 42 affected and 9 unaffected expansion carriers.

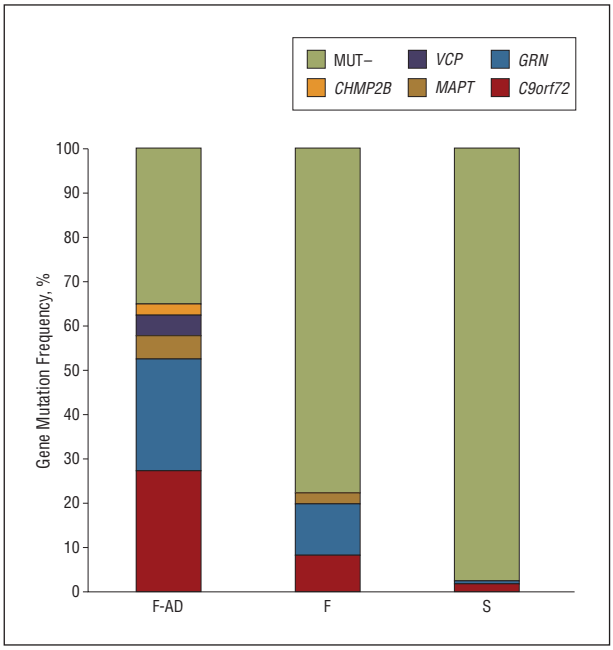

Figure 2. Gene mutation frequencies in the Flanders-Belgian frontotemporal lobar degeneration cohort. Indicated by F-AD, familial consistent with autosomal dominant means there were at least 3 affected individuals with dementia or amyotrophic lateral sclerosis in the pedigree in 2 or more generations. Familial (F) patients are those with at least 1 affected relative but the criteria used for F-AD were not met. Sporadic (S) patients are those patients without known affected relatives. MUT− indicates mutation negative.

ration of survival in 17 *C9orf72* expansion carriers who died during follow-up was 6.2 years (range, 1.5-17.0 years), which was similar to that observed in the other patient groups. Once the first symptoms of ALS appeared, patients survived on average 1.8 years (range, 1.0-3.2 years). Thirteen index patients with a *C9orf72* expansion mutation had a familial history compatible with autosomal dominant inheritance, while 4 had at least 1 affected relative but the criteria used for autosomal dominant inheritance were not met (**Figure 2**). Three expansion carriers had no familial history of the disease. In 64% of the *C9orf72* families, the disease presentation included both FTLD and ALS phenotypes, while in the remainder, this was FTLD only.

BEHAVIORAL AND LANGUAGE DYSFUNCTION

Twenty-two *C9orf72* expansion carriers (85%) were diagnosed as having bvFTD (**Tables 2**, **3**, **4**, and **5**). Details on the behavioral, cognitive, and clinical characteristics are further shown in Tables 2-4. Social inappropriate, disinhibited behavior, with or without restlessness and hyperactivity, were the presenting and most prominent symptoms in most patients. Apathetic forms of bvFTD without disinhibition were infrequent (14%). Other frequent features of patients with bvFTD with a *C9orf72* expansion included compulsive or stereotyped behavior and impaired insight. Psychotic features were recorded in 12%. Memory impairment was also a relatively frequent complaint (42%); however, an early isolated episodic memory disorder, typical for Alzheimer disease, did not occur. Neuropsychologic evaluation usually demonstrated remarkable impairment on frontal executive tasks. In 2 patients, the initial symptoms consisted mainly of nonfluent speech and agrammatism with spared single-word comprehension consistent with the diagnosis of PNFA. In contrast, the third patient was diagnosed as having SD; her initial symptoms consisted of severe anomia, with comprehension deficits, surface dyslexia, spared sentence

Table 2. Clinical Phenotypes and Demographic Characteristics of Patients With *C9orf72* Repeat Expansion

Pedigree, Individual	Sex	Familial History	Age at Onset, y	Age at Death, y	Disease Duration, y	Initial Clinical Diagnosis	Final Clinical Diagnosis
DR10.1	F	F-AD	55	65	10	bvFTD	bvFTD
DR14.1	M	F-AD	57	60	3	bvFTD	bvFTD
DR14.5	M		65	73	8	bvFTD	bvFTD/PPA
DR29.1	F	F-AD	51	55	4	bvFTD	bvFTD
DR29.12	F		64		>1	bvFTD	bvFTD
DR52.1	M	FA	53	58	5	bvFTD	bvFTD
DR55.1	F	S	42	48	6	bvFTD	bvFTD
DR194.1	M	S	49	66	17	bvFTD	bvFTD
DR389.1	F	F-AD	46		>13	bvFTD	bvFTD
DR393.1	M	F-AD	54	56	2	bvFTD-ALS	bvFTD-ALS
DR396.1	F	FA	60	62	2	bvFTD-ALS	bvFTD-ALS
DR439.1	M	F-AD	54	69	15	bvFTD	bvFTD
DR439.5	M		52		>8	bvFTD	bvFTD
DR439.6	M		69		>3	bvFTD	bvFTD
DR454.1	F	F-AD	69	72	3	bvFTD-ALS	bvFTD-ALS
DR489.1	F	F-AD	45		>4	bvFTD/PPA	bvFTD/PPA
DR489.4	M		53		>1	bvFTD-ALS	bvFTD-ALS
DR575.1	M	F-AD	45	51	6	bvFTD	bvFTD
DR598.1	M	F-AD	66	68	2	PNFA	PNFA-ALS
DR659.1	M	F-AD	45		>3	bvFTD	bvFTD
DR659.2	M		65		>6	bvFTD	bvFTD
DR660.1	M	S	58	66	8	bvFTD	bvFTD
DR673.1	F	F-AD	57		>6.4	SD	SD/bvFTD
DR677.1	M	F-AD	62		>3	bvFTD	bvFTD
DR679.1	M	FA	53	55	1.5	PNFA	PNFA-ALS
DR681.1	M	FA	50	53	3.5	bvFTD	bvFTD-ALS

Abbreviations: ALS, amyotrophic lateral sclerosis; bvFTD, behavioral variant frontotemporal dementia; F, female; FA, familial; F-AD, autosomal dominant inheritance; M, male; PNFA, progressive nonfluent aphasia; PPA, primary progressive aphasias; S, sporadic; SD, semantic dementia.

Table 3. Detailed Behavioral and Clinical Characteristics of Patients With *C9orf72* Repeat Expansion

Pedigree, Individual	BD	H	A	C/S	HO	PP	P	ML	EoS	OA/A	CD	FRS	RM	B	T	ILT	HR	BA	SD	PA	AT	F
DR10.1			+					+	+			+	+						+			
DR14.1	+	+		+		+						+										
DR14.5			+					+	+	+	+	+		+								
DR29.1	+	+				+		+														
DR29.12	+	+		+	+	+		+			+		+									
DR52.1	+	+	+						+		+			+		+						
DR55.1	+	+		+										+	+							
DR194.1	+	+		+				+				+	+	+	+							
DR389.1			+	+		+			+	+	+		+	+								
DR393.1	+		+	+		+			+	+		+		+		+	+		+	+	+	+
DR396.1	+					+		+	+	+		+		+		+	+	+	+	+	+	+
DR439.1	+							+				+										
DR439.5	+			+					+													
DR439.6	+		+	+	+	+			+													
DR454.1	+						+		+	+	+			+	+	+	+		+	+	+	+
DR489.1	+			+		+		+	+	+	+								+			
DR489.4	+					+			+	+		+		+		+	+	+		+		+
DR575.1	+		+		+	+		+	+	+		+		+								
DR598.1									+	+				+		+	+	+	+	+	+	+
DR659.1	+	+	+	+	+				+					+		+						
DR659.2	+					+				+												
DR660.1	+		+		+			+			+						+					
DR673.1	+	+	+				+		+	+	+	+	+									
DR677.1	+	+	+		+	+	+	+	+													
DR679.1			+	+					+	+				+		+	+		+	+	+	+
DR681.1	+			+					+	+				+					+	+	+	+

Abbreviations: A, apathy; AT, atrophy; B, bradykinesia; BA, Babinski; BD, behavioral disinhibition; C/S, compulsive or stereotyped; CD, comprehension deficits; EoS, economy of speech; F, fasciculations; FRS, frontal release signs; H, hyperactivity; HO, hyperorality; HR, hyperreflexia; ILT, increased limb tone; ML, memory loss; OA/A, oral apraxia or agrammatism; P, psychosis; PA, paresis; PP, prosopagnosia; RM, repetitive movements; SD, swallowing difficulties; T, tremor.

Table 4. Imaging and Other Investigation Findings in Patients With *C9orf72* Repeat Expansion

Pedigree, Individual	Structural Imaging		Functional Imaging		Electromyography	CSF Biomarker[a]	Pathology
	Localization	Symmetry	Localization	Symmetry			
DR10.1	G	Bil	FR	Bil			FTLD-U
DR14.1	FR	Bil	FR	Bil		AD−	FTLD-TDP
DR14.5	FR	L	FR	L		AD−	
DR29.1	N		N			AD−	FTLD-UPS
DR29.12	N		PT	L			
DR52.1	FR	L	FT	L			FTLD-TDP
DR55.1	G	Bil	FT	Bil		AD−	
DR194.1	G	Bil					
DR389.1			FT	Bil			
DR393.1	G	Bil			MND		
DR396.1	G	Bil			MND		
DR439.1	FT	Bil					
DR439.5	FR	Bil				AD−	
DR439.6	G	Bil	T	Bil			
DR454.1	N		FR	Bil	MND		
DR489.1	T	Bil	FT	Bil	N		
DR489.4							
DR575.1	G	Bil	FR	R	N		
DR598.1	FT	Bil					
DR659.1	FR	Bil					
DR659.2	G	Bil	FT	Bil			
DR660.1	FR	Bil	FT	L			
DR673.1	FR	Bil	FT	Bil			
DR677.1	FT	Bil	T	R			
DR679.1	G	Bil	FT	L	MND		
DR681.1			FT	L	MND		

Abbreviations: AD, Alzheimer disease; Bil, both brain hemispheres equally involved; CSF, cerebrospinal fluid; FR, frontal; FT, frontotemporal; FTLD, frontotemporal lobar degeneration; FTLD-TDP: FTLD pathology with TAR DNA–binding protein 43–positive inclusions; FTLD-U, FTLD pathology with ubiquitin-positive inclusions; FTLD-UPS, FTLD pathology with ubiquitin-positive, TAR DNA–binding protein 43–negative inclusions; G, global; L, left predominant involvement; MND, motor neuron disease (indicates results of electromyography compatible with MND); N, normal; PT, parietotemporal; R, right predominant involvement; T, temporal.

[a] CSF biomarker profile of β-amyloid, tau, and phospho-tau_{181} that was within normal range is indicated by AD−.

Table 5. Clinical Characteristics of FTLD Groups With and Without a Mutation in *C9orf72*, *GRN*, or *MAPT*

	No. (%)				
	Mutation			No Mutation	
	C9orf72 Expansion	*GRN*	*MAPT*	Familial	Sporadic
Total patients, No.	26	27	8	69	145
bvFTD	22 (85)	16 (59)	8 (100)	48 (70)	108 (75)
PNFA	2 (8)	11 (41)[a]	0	10 (14)	21 (14)
SD	1 (4)	0	0	11 (16)	10 (7)
Mixed FTLD	1 (4)	0	0	1 (1)	6 (4)
MND	7 (27)	0[a]	0	1 (1)[b]	12 (8)[a]
Parkinsonism	3 (12)	5 (19)	2 (25)	8 (12)	21 (14)
Limb apraxia	0	5 (19)	0	3 (4)	8 (6)
Oculomotor palsy	0	0	1 (13)	0	5 (3)
Psychosis	3 (12)	3 (12)	0	4 (6)	17 (12)

Abbreviations: bvFTD, behavioral variant frontotemporal dementia; FTLD, frontotemporal lobar degeneration; MND, motor neuron disease; PNFA, progressive nonfluent aphasia; SD, semantic dementia.

[a] Standard deviation differs significantly from *C9orf72* carrier group with $P < .01$.

[b] Standard deviation differs significantly from *C9orf72* carrier group with $P < .05$.

repetition, and fluent speech, although decreased in output. Behavioral abnormalities were absent at the time of diagnosis for 2 of the patients with primary progressive aphasia, while mild rigidity in thoughts was reported in the third. Some patients developed overlapping symptoms of different FTLD subtypes during their disease course (Tables 2-4). The patient with SD initially presenting with anomia developed typical symptoms of bvFTD 3 years after onset. Another patient (DR489.1; Tables 2-4) presented with both prominent behavioral changes; effortful, halting speech; and impaired language comprehension.

MOTOR NEURON DISEASE

Seven *C9orf72* expansion carriers with FTLD (27%) also developed signs of motor neuron disease in 2 or more anatomical regions (Tables 2-4). Nearly all patients with FTLD-ALS (86%) developed signs of both upper and lower motor neuron disease during the disease course, with one showing a lower motor neuron–predominant picture. Bulbar involvement at onset was seen in 5 patients with FTLD-ALS. In 4 patients, FTLD and ALS symptoms developed nearly simultaneously. In 3 other patients with FTLD-ALS, the maximum interval between onset of FTLD and ALS symptoms was 2.5 years. In the 19 patients with FTLD without ALS, neurologic examination results at onset were usually unremarkable, except for occasional frontal release signs or repetitive movements. Eight *C9orf72* expansion carriers without ALS with disease duration of 5 years or more were evaluated. Signs of parkinsonism, mostly consisting of bradykinesia and rigidity, were found in 4 patients. However, signs of lower motor neuron disease were not reported in these patients.

IMAGING AND OTHER INVESTIGATION FINDINGS

Functional neuroimaging was performed in 18 *C9orf72* expansion carriers, consisting of single-photon emission computed tomography in 13 individuals and positron emission tomography with ^{18}fluorodeoxyglucose in 5 individuals. Predominant hypoperfusion or glucose hypometabolism in the frontal and/or temporal regions was detected on visual inspection in 89% (Tables 2-4). One patient with bvFTD had normal single-photon emission computed tomography results 3 years after clinical onset, and another had hypoperfusion in the superior part of the parietal lobes and left anterior temporal lobe. Magnetic resonance imaging or computed tomographic imaging showed some degree of frontal and/or temporal lobe atrophy, but the topographic pattern was generally less specific than functional imaging abnormalities. Levels of β-amyloid, total tau, and phospho-tau$_{181P}$ were normal in the cerebrospinal fluid of 5 *C9orf72* mutation carriers. Nerve conduction studies and electromyography were performed in 5 patients with FTLD-ALS and confirmed the clinical diagnosis in all. Two patients with FTLD without clinical symptoms of ALS, of which 1 reported swallowing difficulties 3 years after onset of FTLD, had normal electromyography results. The diagnosis of FTLD was confirmed in 4 autopsied patients with bvFTD with the *C9orf72* expansion (Tables 2-4).[9] In 1 patient, DR29.1, the lower brainstem and spinal cord were also examined. No neuronal loss, ubiquitin-positive inclusions, or TDP-43–positive inclusions were observed in these regions.

GENOTYPE-PHENOTYPE CORRELATIONS IN FTLD

The *C9orf72* expansion mutation accounted for most of the patients with familial FTLD-ALS (88%; Table 5). Amyotrophic lateral sclerosis was not found in *GRN* or *MAPT* mutation carriers and occurred less frequently in patients with unresolved familial FTLD (1%, $P < .001$) and sporadic FTLD (8%; $P = .01$). In contrast, *GRN* mutation carriers more often presented with PNFA (41%) compared with *C9orf72* expansion carriers (8%; $P = .009$) and patients without mutation (14% of familial FTLD, $P = .01$; 14% of sporadic FTLD, $P = .003$). Of the 23 index patients with familial PNFA in the study population, 48% had a mutation in *GRN*. Furthermore, 1 patient with PNFA had concomitant CBS symptoms at onset, with severe limb apraxia and asymmetrical parkinsonism; 4 other *GRN* mutation carriers developed limb apraxia in a later phase of the disease. Together, 19% of *GRN* mutation carriers developed limb apraxia compared with none of the *C9orf72* mutation carriers ($P = .05$), 3% of the patients with familial FTLD ($P = .04$), and 6% of those with sporadic FTLD ($P = .03$). The frequency of *GRN* mutations in familial FTLD with limb apraxia was 63%. All 8 studied *MAPT* mutation carriers had bvFTD presentations. One carrier of a p.R406W mutation in *MAPT* also developed vertical gaze palsy with postural instability, and parkinsonism 12 years after bvFTD onset, meeting the criteria for diagnosis of PSP.

COMMENT

To date, a pathogenic hexanucleotide repeat expansion in *C9orf72* is the most frequent genetic cause of FTLD in the Flanders-Belgian cohort, with mutation frequencies of 8% overall and 17% in familial patients.[9] In the present study, we studied in detail the clinical features of *C9orf72* expansion carriers and compared the data with other patient groups with FTLD with a mutation in *GRN* or *MAPT* or without, with the aim of identifying noticeable relationships between genes and clinical phenotype.

C9orf72 expansion carriers often develop FTLD at a young age (average, 55.3 years), earlier than in *GRN* mutation carriers or patients without a mutation. However, the age at onset is highly variable, and some mutation carriers live up to 75 years without significant signs of disease. By the age of 70 years, nearly 90% of *C9orf72* expansion carriers were affected. The mean disease survival in *C9orf72* expansion carriers (6.2 years) was similar to that in the other patient groups but was also highly variable (range, 1.5-17.0 years). Amyotrophic lateral sclerosis is a negative prognostic factor; once first signs of ALS developed, patients survived on average 1.8 years. The wide variability in age at onset and disease duration suggests that other modifying factors are also important for the clinical expression of a *C9orf72* expansion mutation.

Most *C9orf72* expansion carriers had a positive family history of disease, but in agreement with other studies, *C9orf72* expansions were also observed in a minor percentage of patients with sporadic FTLD (2%-5%).[8,9,11,17,18] It is likely that in some of these patients with sporadic FTLD, the positive familial history was obscured by nonpenetrance of the mutation in parents, given that expansion carriers can remain asymptomatic until advanced age. Notably, all 3 sporadic *C9orf72* expansion carriers had developed disease at a young age (42, 49, and 58 years).

In most of the *C9orf72* expansion carriers (85%), the phenotype of dementia was consistent with bvFTD. In more detail, expansion carriers with bvFTD often presented with inappropriate behavior and agitation. This is in contrast to patients with bvFTD with a *GRN* mutation, in whom apathy dominates the clinical picture.[29,30] One study reported that 38% of patients with FTLD with a *C9orf72* expansion mutation had severe psychotic features compared with 4% in patients without mutation, suggesting that this is a distinct clinical feature of *C9orf72*-associated FTLD.[18] In contrast, we observed delusions or hallucinations in 12% of the *C9orf72* expansion carriers, with a comparable frequency in the other patient groups. Similar low frequencies of hallucinations or delusions in *C9orf72* expansion carriers were also reported in other FTLD cohorts.[16,17]

A few *C9orf72* expansion carriers presented with isolated language dysfunction (12%), consistent with PNFA in 2 patients and SD in 1 patient. This is similar to the proportion of primary progressive aphasia phenotypes that have been reported in other FTLD cohorts (0%-34%).[11,15-18] The isolated language dysfunction in the patient with SD was followed by the development of typical symptoms of bvFTD after 3 years, which possibly reflects the diffuse spread of atrophy in the frontotemporal regions once the *C9orf72*-associated disease progresses.

Despite *C9orf72* being a major causal gene for ALS, ALS was absent in most of the Flanders-Belgian *C9orf72* patients (27% had ALS). No signs of lower motor neuron disease were present on neurologic examination in several patients who were followed up for multiple years. Pathologic examination results of the brainstem and spinal cord in 1 of the patients we examined, as well as in other series of autopsied *C9orf72* expansion carriers, support this observation.[11,17,19] Parkinsonism, usually characterized by an akinetic-rigid syndrome later in the disease course, occurred in a similar proportion of *C9orf72* expansion carriers as in other patient groups, precluding clinical differentiation. It is notable that when ALS complicated FTLD (n = 7), this was usually early in the disease course, with a maximum delay of 2.5 years. However, this finding needs confirmation by other, longitudinal studies.

Mutations in known FTLD genes now account for 34% of the familial FTLD cases and 88% of the familial FTLD-ALS cases in the Flanders-Belgian cohort. In patients with sporadic FTLD and those with FTLD-ALS, who constitute the majority, mutations can be observed in 3% and 0%, respectively. Taken together, this indicates that other genes remain to be discovered that contribute to the FTLD-ALS disease spectrum.

Frontotemporal lobar degeneration is a clinically and genetically heterogeneous disorder. Although differentiation at the individual patient level is still challenging, we found notable differences in the presenting phenotype associated with mutations in the 3 major FTLD genes. Based on these genotype-phenotype correlations combined with the observed mutation frequencies of the different FTLD-associated genes in the Flanders-Belgian FTLD cohort, we propose a decision tree on the basis of which the FTLD genes can be tested in a clinical genetic diagnostic setting (**Figure 3**).

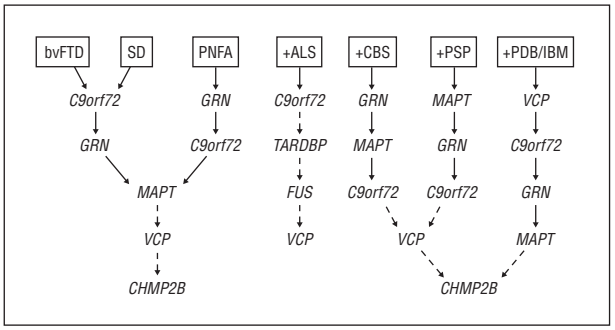

Figure 3. Decision tree for clinical genetic testing of patients clinically diagnosed as having frontotemporal lobar degeneration. +ALS indicates concomitant amyotrophic lateral sclerosis; bvFTD, behavioral variant frontotemporal dementia; +CBS, concomitant corticobasal degeneration syndrome; +PDB/IBM, concomitant Paget disease of the bone/inclusion body myopathy; PNFA, progressive nonfluent aphasia; +PSP, concomitant progressive supranuclear palsy syndrome; SD, semantic dementia. Dotted lines indicate rare genetic causes.

C9orf72 testing has priority in most patients with FTLD. To date, *C9orf72* expansion mutations are the only known genetic cause of FTLD-ALS and are the most frequent cause of bvFTD without ALS in the Flanders-Belgian cohort. In contrast, familial occurrence of PNFA, limb apraxia, and a CBS-like phenotype are more often associated with a *GRN* mutation, in line with previous reports.[29,30] The few *MAPT* mutation carriers in the Flanders-Belgian cohort complicated statistically robust comparison. Nonetheless, all *MAPT* mutation carriers presented with bvFTD, which is in keeping with results from literature.[29,31] *MAPT* mutations have also been associated with parkinsonism-predominant syndromes.[31,32] In the Flanders-Belgian cohort, 1 carrier of the p.R406W mutation in *MAPT* developed 12 years after bvFTD onset the cardinal clinical signs of PSP. So far, CBS or PSP phenotypes have not been associated with *C9orf72* expansion mutations, except for dystonic hand posturing being reported in 1 patient.[15] In the unusual case of FTLD or FTLD-ALS families also segregating inclusion body myopathy and/or Paget disease of the bone,[26] *VCP* testing should be prioritized.

In conclusion, patients with the *C9orf72* repeat mutation usually have an early onset, a familial history of FTLD and/or ALS, present with bvFTD (with disinhibition as the prominent feature), and more often develop ALS compared with other patient groups with FTLD. Yet, *C9orf72* expansion mutations also account for a small percentage of patients with FTLD with language difficulties at onset and patients without a familial history of the disease. Furthermore, we report genotype-phenotype correlations in FTLD that may provide important insights that are of particular relevance in the context of molecular diagnostics of FTLD.

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