RESEARCH ARTICLE

Differences in Motor Features of *C9orf72*, *MAPT*, or *GRN* Variant Carriers With Familial Frontotemporal Lobar Degeneration

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Abstract

Background and Objectives

Familial frontotemporal lobar degeneration (f-FTLD) is a phenotypically heterogeneous spectrum of neurodegenerative disorders most often caused by variants within chromosome 9 open reading frame 72 (*C9orf72*), microtubule-associated protein tau (*MAPT*), or granulin (*GRN*). The phenotypic association with each of these genes is incompletely understood. We hypothesized that the frequency of specific clinical features would correspond with different genes.

Methods

We screened the Advancing Research and Treatment in Frontotemporal Lobar Degeneration (ARTFL)/Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS)/ARTFL LEFFTDS Longitudinal Frontotemporal Lobar Degeneration Consortium for symptomatic carriers of pathogenic variants in *C9orf72*, *MAPT*, or *GRN*. We assessed for clinical differences among these 3 groups based on data recorded as part of a detailed neurologic examination, the Progressive Supranuclear Palsy Rating Scale, Progressive Supranuclear Palsy–Quality of Life Rating Scale, Unified Parkinson's Disease Rating Scale Part III (motor items), and the Amyotrophic Lateral Sclerosis Functional Rating Scale, revised version. Data were analyzed using Kruskal-Wallis and Wilcoxon rank-sum tests and Fisher exact test.

Results

We identified 184 symptomatic participants who had a single pathogenic variant in *C9orf72* (n = 88), *MAPT* (n = 53), or *GRN* (n = 43). Motor symptom age at onset was earliest in the *MAPT* participants followed by *C9orf72*, whereas the *GRN* pathogenic variant carriers developed symptoms later. *C9orf72* participants more often had fasciculations, muscle atrophy, and weakness, whereas parkinsonism was less frequent. Vertical oculomotor abnormalities were more common in the *MAPT* cohort, whereas apraxia and focal limb dystonia occurred more often in participants with *GRN* variants.

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Coinvestigators are listed at links.lww.com/WNL/C317

Glossary

AAO = age at onset; **ALS** = amyotrophic lateral sclerosis; **ARTFL** = Advancing Research and Treatment in Frontotemporal Lobar Degeneration; **ALLFTD** = ARTFL LEFFTDS Longitudinal Frontotemporal Lobar Degeneration Consortium; **ALSFRS** = Amyotrophic Lateral Sclerosis Rating Scale; **bvFTD** = behavioral variant FTD; ***C9orf72*** = chromosome 9 open reading frame 72; **CBS** = corticobasal syndrome; **FTD** = frontotemporal dementia; **FTLD** = frontotemporal lobar degeneration; ***GRN*** = granulin; **HRE** = hexanucleotide repeat expansion; **LEFFTDS** = Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects; **MAPT** = microtubule-associated protein tau; **NACC** = National Alzheimer's Coordinating Center; **nfvPPA** = nonfluent/agrammatic variant PPA; **PD** = Parkinson disease; **PPA** = primary progressive aphasia; **PSP** = progressive supranuclear palsy; **PSP-QoL** = Progressive Supranuclear Palsy–Quality of Life Rating Scale; **PSPRS** = Progressive Supranuclear Palsy Rating Scale; **svPPA** = semantic PPA; **UPDRS** = Unified Parkinson's Disease Rating Scale.

Discussion

We present a large comparative study of motor features in *C9orf72*, *MAPT*, and *GRN* pathogenic variant carriers with symptomatic f-FTLD. Our findings demonstrate characteristic phenotypic differences corresponding with specific gene variants that increase our understanding of the genotype-phenotype relationship in this complex spectrum of neurodegenerative disorders.

Trial Registration Information

NCT02365922, NCT02372773, and NCT04363684.

Frontotemporal lobar degeneration (FTLD) is a group of phenotypically heterogeneous neurodegenerative disorders affecting cognitive, behavioral, and motor systems. Historically, 3 clinical syndromes were defined: behavioral variant frontotemporal dementia (bvFTD), progressive nonfluent aphasia, and semantic dementia.[1] The latter syndromes are now classified as 2 of the 3 primary progressive aphasias (PPAs): nonfluent/agrammatic PPA (nfvPPA) and semantic PPA (svPPA).[2] Motor involvement is common in FTLD and more often present with bvFTD than PPAs.[3] Both typical parkinsonism and atypical parkinsonian syndromes, most commonly corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP), comprise part of the FTLD phenotypic spectrum. Amyotrophic lateral sclerosis (ALS) is diagnosed in 5%–10% of patients with FTLD, and subclinical motor neuron degeneration approaches 50%.[4-10]

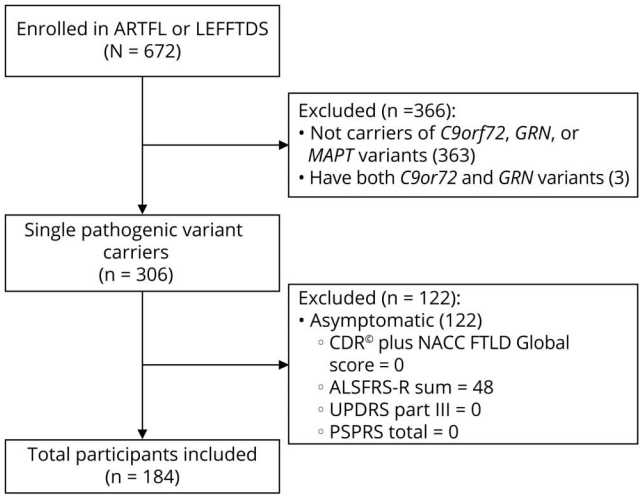
The complexity of FTLD genetics rivals that of the disease's phenotypic spectrum. Approximately 30% of FTLD is genetic, and those with bvFTD are 4 times more likely to have a strong family history compared with those with PPA.[10-12] Pathogenic variants (hereafter referred to as variants) in chromosome 9 open reading frame 72 (*C9orf72*), microtubule-associated protein tau (*MAPT*), and granulin (*GRN*) account for most familial FTLD.[13,14] Variants in these genes have been associated with various motor phenotypes, but correlations between genotype and phenotype are imperfect making patient-level predictions unreliable. For instance, the *MAPT* N279K variant was described in 2 Japanese brothers with memory impairment, parkinsonism, and corticospinal disturbances with poor levodopa response, whereas others have observed Richardson syndrome (PSP-RS) with this variant.[15,16] The unreliability of probabilistic phenotypic-genotype associations is likely due to clinical heterogeneity, small study sample sizes, and the limited use (and precision) of standardized clinical assessments. These findings highlight the need for detailed phenotypic assessments of large samples of genetic variant carriers to understand the frequency of phenotypic elements with respect to genetic alterations. This understanding may assist in the diagnostic pursuit and provide reliable clinical indicators for disease progression or response to therapy. Our study addresses the need for better understanding these phenotype-genotype associations by characterizing the motor phenotype of patients with FTLD and variants within *C9orf72*, *MAPT*, or *GRN*.

Methods

Participants

We screened participants in the Advancing Research and Treatment in Frontotemporal Lobar Degeneration (ARTFL)/Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS)/ARTFL LEFFTDS Longitudinal Frontotemporal Lobar Degeneration Consortium (ALLFTD), from 14 study centers, for individuals with a single pathogenic variant in the *C9orf72*, *MAPT*, or *GRN* genes (Figure). Study participants ranged between the ages of 22 and 85 years at the time of evaluation and had no structural brain lesion or other known neurologic disorder. Inclusion criteria consisted only of pathogenic variant carriers who were symptomatic defined by CDR Dementia Staging Instrument PLUS National Alzheimer's Coordinating Center (NACC) Behavior and Language Domains (CDR plus NACC FTLD) >0, Amyotrophic Lateral Sclerosis Rating Scale (ALSFRS-R) sum score <48, Unified Parkinson's Disease Rating Scale (UPDRS) Part III >0, or Progressive Supranuclear Palsy Rating Scale (PSPRS) total >0. The ALSFRS-R, UPDRS Part III, and PSPRS allow for symptom quantification of ALS, Parkinson disease (PD), and

Figure Participant Screening Flow Diagram



CDR Dementia Staging Instrument PLUS National Alzheimer's Coordinating Center (NACC) Behavior and Language Domains (CDR plus NACC FTLD), Amyotrophic Lateral Sclerosis Rating Scale (ALSFRS-R), Unified Parkinson's Disease Rating Scale (UPDRS), and Progressive Supranuclear Palsy Rating Scale (PSPRS).

Table 1 Clinical Phenotype

Variable	Total (N = 184) n (%)
AD	3 (1.6)
ALS	9 (4.9)
bvFTD	87 (47.3)
Clinically normal[a]	15 (8.2)
CBS: typical or variant	4 (2.2)
FTD/ALS	6 (3.3)
MCI: behavior	11 (6.0)
MCI: cognitive variants	26 (14.1)
Other[b]	10 (5.4)
Parkinson disease	1 (0.5)
PPA: agrammatic/nonfluent variant subtype	5 (2.7)
PPA: semantic variant subtype	1 (0.5)
Primary psychiatric disorder: mood	3 (1.6)
Progressive supranuclear palsy/ Richardson syndrome	3 (1.6)

Abbreviations: AD = Alzheimer disease; ALS = amyotrophic lateral sclerosis; bvFTD = behavioral variant FTD; CBS = corticobasal syndrome; FTD = frontotemporal dementia; MCI = mild cognitive impairment; PPA = primary progressive aphasia.
[a] Clinically normal was applied to those participants without sufficient clinical features or findings to warrant an alternative diagnosis.
[b] Other included parkinsonism-NOS, PPA-other, encephalitis, developmental, multiple sclerosis, cognitive impairment due to heroin abuse, subjective cognitive impairment, and obsessive compulsive disorder.

PSP, which encompass anticipated FTLD motor phenotypes. The CDR plus NACC FTLD scale has 2 additional domains compared with the CDR, language and behavior, comportment and personality, making it more sensitive for detecting FTD.[17,18] Participants were defined to have motor features if motor signs were documented on the detailed neurologic examination. Syndromic diagnoses were made using published criteria for bvFTD,[19] svPPA, lvPPA, nfvPPA,[2] CBS,[20] PSP,[21] Alzheimer disease,[22] PD,[23] and ALS/FTD-ALS (Table 1).[24] Participants were classified as clinically normal in the absence of sufficient clinical features or findings to warrant an alternative diagnosis.

Data Collection

Demographic and detailed clinical information was collected for each individual. A complete detailed semiquantitative neurologic examination was performed. Age at onset (AAO) was estimated by the evaluating clinician. Rating scales were administered including the PSPRS, Progressive Supranuclear Palsy–Quality of Life Rating Scale (PSP-QoL), UPDRS Part III (motor items), and ALSFRS-R. Here, we report data from the most recent study visits for each participant as of the latest data freeze on October 7, 2020 (n = 184) including 62 baseline and 122 follow-up evaluations. Written consent was obtained from all participants or their proxies before study enrollment. All procedures received ethics approval from a central review board at Johns Hopkins University, as well as local review at all sites.

Genetic Analysis

For each family member from *MAPT* and *GRN* kindreds, the exon harboring the known variant observed was sequenced as published previously.[25,26] For individuals from *C9orf72* kindreds, GGGGCC repeat lengths were determined using an established 2-step PCR assay; these participants had repeat lengths >30 repeats.[27]

Statistical Analyses

Continuous variables were summarized as medians and ranges. Categorical variables were summarized as counts and percentages. Only explicitly scored examination findings and rating scale items were included for analysis, and omitted items were not presumed to be normal. Comparisons of characteristics between the *C9orf72*, *MAPT*, and *GRN* groups were made using Kruskal-Wallis rank-sum tests (continuous and ordinal characteristics) or Fisher exact tests (categorical characteristics) in tests of overall difference between the 3 groups. For characteristics that differed among the 3 groups with a p value ≤0.05, subsequent pairwise comparisons between groups were made using Wilcoxon rank-sum tests (continuous/ordinal characteristics) or Fisher exact tests (categorical characteristics); p values ≤0.0167 were considered statistically significant after applying a Bonferroni correction for multiple testing. All statistical tests were 2 sided. Statistical analyses were performed using SAS (version 9.4; SAS Institute, Inc., Cary, NC).

Results

Demographic Characteristics

A total of 184 participants met the inclusion criteria for this study (Table 2). Patients with *MAPT* variants had the lowest age at visit compared with other variants (median: *C9orf72:* 61; *GRN:* 64; *MAPT*: 54 years, overall $p < 0.001$), and there was a statistically significant difference in disease duration (overall $p = 0.019$); however, pairwise comparison was only significant for *C9*orf72 vs *GRN* ($p = 0.004$). The overall AAO of cognitive and behavioral symptoms was recorded earlier in participants with *MAPT* variants (all overall $p < 0.001$). The AAO of motor signs was earliest for participants with *MAPT* variants and latest for those with *C9orf72* repeat expansion (median, *MAPT*: 49 vs *C9orf72*: 59 years, overall $p = 0.007$). There were no significant differences regarding sex, race, years of education, or handedness across groups.

Genetic Data

Participants had pathogenic *C9orf72* hexanucleotide repeat expansions (HREs) of GGGGCC (n = 88), *GRN* variants (n = 43), or *MAPT* variants (n = 53). Among *GRN* variants, 19 were unique, and 3 were novel (eTable 1, links.lww.com/WNL/C170). Among *MAPT* variants, 10 were unique (eTable 1).

Table 2 Comparison of Demographics Among *C9orf72*, *GRN*, and *MAPT* Groups

					p Value			
	N[a]	*C9orf72* (N = 88)	*GRN* (N = 43)	*MAPT* (N = 53)	Overall test of difference	*C9* vs *GRN*	*C9* vs *MAPT*	*GRN* vs *MAPT*
Age at visit, y, median (IQR)	184	61 (22–85)	64 (32–82)	54 (31–70)	<0.001	0.029	0.005	<0.001
Disease duration, median (IQR)	163	6 (0–30)	4 (0–31)	4 (0–34)	0.019	0.004	0.27	0.16
Sex, n (%)	184				0.25	N/A	N/A	N/A
Male		42 (47.7)	15 (34.9)	27 (50.9)				
Female		46 (52.3)	28 (65.1)	26 (49.1)				
Race (White)	183	85 (97.7)	39 (90.7)	51 (96.2)	0.18	N/A	N/A	N/A
Years of education, median (IQR)	184	16 (10–20)	14 (6–20)	16 (12–22)	0.29	N/A	N/A	N/A
Handedness, n (%)	184				0.13	N/A	N/A	N/A
Left		8 (9.1)	5 (11.6)	1 (1.9)				
Right		76 (86.4)	37 (86.0)	52 (98.1)				
Ambidextrous		4 (4.5)	1 (2.3)	0 (0.0)				
Age at onset, y, median (IQR)	163	55 (12–81)	60 (30–73)	47 (29–66)	<0.001	0.009	1.00	1.00
Age at onset for decline in cognition, y, median (IQR)	144	55 (22–81)	60 (30–81)	49 (29–66)	<0.001	0.018	0.001	<0.001
Age at onset for behavioral symptoms, y, median (IQR)	139	56 (12–71)	61 (30–81)	50 (30–65)	<0.001	0.011	0.002	<0.001
Age at onset for motor symptoms, y, median (IQR)	78	59 (22–81)	64 (43–75)	49 (35–70)	0.007	0.15	0.025	0.003
Changes in motor function suggestive of parkinsonism? n (%)	76	12 (31.6)	14 (87.5)	21 (95.5)	<0.001	<0.001	<0.001	0.56
Changes in motor function suggestive of ALS? n (%)	73	19 (54.3)	0 (0.0)	0 (0.0)	<0.001	<0.001	<0.001	1.00
Predominant domain that was first recognized as changed in the participant, n (%)	152				0.009	0.006	0.82	0.003
Cognition		18 (26.1)	20 (55.6)	10 (21.3)				
Behavior		41 (59.4)	15 (41.7)	31 (66.0)				
Motor function		10 (14.5)	1 (2.8)	6 (12.8)				

Abbreviations: ALS = amyotrophic lateral sclerosis; *C9orf72* = chromosome 9 open reading frame 72; *GRN* = granulin; *MAPT* = microtubule-associated protein tau. The sample median (minimum, maximum) is given for continuous variables. *p* Values for overall tests of difference result from a Kruskal-Wallis rank-sum test (continuous variables) or Fisher exact test (categorical variables). *p* Values for pairwise comparisons between the 3 groups were only made given a *p* value <0.05 for the overall test of difference and result from a Wilcoxon rank-sum test (continuous variables) or Fisher exact test (categorical variables).
[a] Only for applicable patients, that is, patients without motor symptoms do not have a motor symptom onset.

Table 3 Clinical Differences Among *C9orf72*, *GRN*, and *MAPT* Groups Based on Neurologic Examination Information[a]

	N	*C9orf72* (N = 88) n (%)	*GRN* (N = 43) n (%)	*MAPT* (N = 53) n (%)	*p* Value			
					Overall test of difference	*C9* vs *GRN*	*C9* vs *MAPT*	*GRN* vs *MAPT*
Higher cortical visual problem suggesting posterior cortical atrophy or apraxia of gaze	182	0 (0.0)	3 (7.1)	0 (0.0)	0.012	0.033	1.00	0.083
Findings suggestive of PSP, corticobasal syndrome, or other related disorder	182	7 (8.0)	12 (28.6)	9 (17.0)	0.010	0.003	0.17	0.22
Findings suggesting ALS	182	23 (26.4)	0 (0.0)	1 (1.9)	<0.001	<0.001	<0.001	1.00
Motor: fasciculations	179	12 (14.0)	0 (0.0)	0 (0.0)	0.001	0.010	0.004	1.00
Motor: fasciculations: cranial nerves	176	10 (11.6)	0 (0.0)	0 (0.0)	0.004	0.030	0.014	1.00
Motor: fasciculations: UE dominant	174				0.004	0.030	0.012	1.00
No		73 (89.0)	40 (100.0)	52 (100.0)				
Yes		9 (11.0)	0 (0.0)	0 (0.0)				
Motor: muscle bulk	180				<0.001	0.012	0.001	0.44
Abnormal		16 (18.4)	1 (2.4)	0 (0.0)				
Normal		71 (81.6)	40 (97.6)	52 (100.0)				
Motor: atrophy: cranial nerves	176	9 (10.5)	0 (0.0)	0 (0.0)	0.008	0.056	0.026	1.00
Motor: atrophy: LE dominant	174				0.046	0.18	0.081	1.00
No		76 (92.7)	40 (100.0)	52 (100.0)				
Yes		6 (7.3)	0 (0.0)	0 (0.0)				
Motor: atrophy: UE dominant	174				0.001	0.009	0.003	1.00
No		70 (85.4)	40 (100.0)	52 (100.0)				
Yes		12 (14.6)	0 (0.0)	0 (0.0)				
Motor: power	175				0.001	0.011	0.003	1.00
Abnormal		20 (23.5)	2 (5.0)	2 (4.0)				
Normal		65 (76.5)	38 (95.0)	48 (96.0)				
Motor: power: lower left extremities	174				0.003	0.061	0.004	0.44
Normal		73 (85.9)	38 (97.4)	50 (100.0)				
Weakness		12 (14.1)	1 (2.6)	0 (0.0)				
Motor: power: lower right extremities	175				0.008	0.057	0.026	1.00
Normal		76 (89.4)	40 (100.0)	50 (100.0)				
Weakness		9 (10.6)	0 (0.0)	0 (0.0)				
Coordination: apraxia present	168				0.009	0.015	0.51	0.012
Absent		75 (92.6)	31 (77.5)	45 (95.7)				
Present (not impairing most functions)		6 (7.4)	6 (15.0)	1 (2.1)				
Present (impairing most functions)		0 (0.0)	3 (7.5)	1 (2.1)				
Coordination: tremor at rest, face	181				0.036	0.013	0.21	0.21

Continued

Table 3 Clinical Differences Among *C9orf72*, *GRN*, and *MAPT* Groups Based on Neurologic Examination Information[a] *(continued)*

	N	*C9orf72* (N = 88) n (%)	*GRN* (N = 43) n (%)	*MAPT* (N = 53) n (%)	*p* Value			
					Overall test of difference	*C9* vs *GRN*	*C9* vs *MAPT*	*GRN* vs *MAPT*
Absent		86 (100.0)	39 (92.9)	52 (98.1)				
Slight and infrequently present		0 (0.0)	3 (7.1)	1 (1.9)				
Tremor: rest LE dominant	176				0.030	1.00	0.031	0.13
Absent		82 (100.0)	41 (100.0)	50 (94.3)				
Slight and infrequently present		0 (0.0)	0 (0.0)	2 (3.8)				
Mild in amplitude and persistent or moderate in amplitude but only intermittently present		0 (0.0)	0 (0.0)	1 (1.9)				
Reflexes: grasp dominant	157				0.030	0.012	0.54	0.082
Absent		66 (93.0)	28 (75.7)	44 (89.8)				
Present		5 (7.0)	9 (24.3)	5 (10.2)				

Abbreviations: ALS = amyotrophic lateral sclerosis; *C9orf72* = chromosome 9 open reading frame 72; *GRN* = granulin; LE = lower extremity; *MAPT* = microtubule-associated protein tau; PSP = progressive supranuclear palsy; UE = upper extremity.
p Values for overall tests of difference result from a Kruskal-Wallis rank-sum test (ordinal variables) or Fisher exact test (categorical variables). *p* Values for pairwise comparisons between the 3 groups result from a Wilcoxon rank-sum test (ordinal variables) or Fisher exact test (categorical variables).
[a] Only statistical significant variables were reported.

Differential Motor Features Among Genetic Groups

All participants underwent a detailed neurologic examination (eTable 2, links.lww.com/WNL/C170), which revealed differences among the 3 groups (Table 3). Fasciculations were only observed in the *C9orf72* cohort (overall $p = 0.001$). Muscle bulk was more often abnormal in *C9orf72* patients (overall $p < 0.001$), and this is reflected by atrophy in cranial nerve distributions (overall $p = 0.008$), dominant lower extremity (overall $p = 0.046$), and dominant upper extremity (overall $p = 0.001$). Muscle strength was more often abnormal in *C9orf72* (overall $p = 0.001$), and this reached statistical significance in the left and right lower extremities (overall $p = 0.003$ and $p = 0.008$, respectively). Apraxia was more frequent in *GRN* participants compared with *C9orf72* ($p = 0.015$) and *MAPT* ($p = 0.012$). *C9orf72* participants had less rest tremor of the face compared with *GRN* ($p = 0.013$). *C9orf72* participants also had more rest tremor of the dominant lower extremity of *MAPT* patients (overall $p = 0.030$). Dominant-sided grasp reflexes were more frequent in the *GRN* group compared with *C9orf72* ($p = 0.012$).

PSPRS scores are summarized in Table 4. Neck rigidity/dystonia was less frequent in *C9orf72* patients (overall $p = 0.022$). Consistent with findings from the neurologic examination, the *GRN* group had more apraxia of hand movements (overall $p = 0.009$) and limb dystonia (overall $p = 0.013$). Vertical oculomotor abnormalities were more common in participants with *MAPT* variants compared with those with *GRN* variants ($p = 0.009$). The PSP-QoL motor scores showed differences in mobility impairments, falling, and difficulties with eyelid opening, communication, and reading (Table 5). Results from analysis of the PSP-QoL, including nonmotor items, are reported in eTable 3 (links.lww.com/WNL/C170). The *C9orf72* group had less difficulty moving compared with *GRN* patients ($p = 0.002$) and less difficulty communicating and reading than *MAPT* patients ($p = 0.006$ and $p = 0.003$, respectively).

The UPDRS Part III scores are summarized in Table 6. There were no statistically significant differences between *GRN* and *MAPT* participants. Compared with *C9orf72*, the *GRN* group had more rest tremor of facial musculature ($p = 0.013$) and the right hand ($p = 0.008$). Compared with *C9orf72*, the *MAPT* group more often had abnormal finger taps ($p = 0.011$), abnormal posture ($p = 0.003$), and rigidity of the left lower extremity ($p = 0.012$) and neck ($p = 0.012$).

Discussion

Motor phenomena are common in patients with FTLD who have variants in *C9orf72*, *MAPT*, and *GRN* genes, but the relationships between genes and clinical motor manifestations have not been firmly established. We assessed the motor disturbances in this large cohort of familial FTLD and found several differences between carriers of variants in *C9orf72*, *MAPT*, and *GRN* genes.

Hexanucleotide repeat expansions within *C9orf72* usually result in TDP-43 type B accumulation and are the most common genetic cause of FTD and ALS.[27-29] Although the

Table 4 Clinical Differences Among *C9orf72*, *GRN*, and *MAPT* Groups Based on PSPRS Information[a]

Variable	N	*C9orf72* (N = 88) n (%)	*GRN* (N = 43) n (%)	*MAPT* (N = 53) n (%)	*p* Value			
					Overall test of difference	*C9* vs *GRN*	*C9* vs *MAPT*	*GRN* vs *MAPT*
Gait and midline: neck rigidity or dystonia	175				0.022	0.019	0.010	0.86
Absent		80 (95.2)	34 (82.9)	41 (82.0)				
Slight or detectable only when activated by other movement		3 (3.6)	2 (4.9)	2 (4.0)				
Definitely abnormal, but full range of motion possible		1 (1.2)	3 (7.3)	2 (4.0)				
Only partial range of motion possible		0 (0.0)	1 (2.4)	4 (8.0)				
Little or no passive motion possible		0 (0.0)	1 (2.4)	1 (2.0)				
Limb motor: apraxia of hand movement	165				0.009	0.012	0.54	0.013
Absent		75 (92.6)	30 (76.9)	43 (95.6)				
Present, not impairing most functions		6 (7.4)	6 (15.4)	1 (2.2)				
Impairing most functions		0 (0.0)	3 (7.7)	1 (2.2)				
Limb motor: limb dystonia	177				0.013	0.049	0.18	0.010
Absent		83 (96.5)	35 (87.5)	51 (100.0)				
Subtle or present only when activated by other movement		3 (3.5)	2 (5.0)	0 (0.0)				
Obvious but not continuous		0 (0.0)	1 (2.5)	0 (0.0)				
Continuous but not disabling		0 (0.0)	1 (2.5)	0 (0.0)				
Continuous and disabling		0 (0.0)	1 (2.5)	0 (0.0)				
Ocular motor: voluntary downward command movement	167				0.011	0.13	0.044	0.009
Saccades not slow or hypometric; 86%–100% of normal excursion		78 (94.0)	37 (100.0)	39 (83.0)				
Saccades slow or hypometric; 86%–100% of normal excursion		1 (1.2)	0 (0.0)	3 (6.4)				
51%–85% of normal excursion		3 (3.6)	0 (0.0)	1 (2.1)				
15% of normal excursion or worse		1 (1.2)	0 (0.0)	4 (8.5)				
Ocular motor: voluntary upward command movement	167				0.011	0.13	0.047	0.009
Saccades not slow or hypometric; 86%–100% of normal excursion		78 (94.0)	37 (100.0)	39 (83.0)				
Saccades slow or hypometric; 86%–100% of normal excursion		1 (1.2)	0 (0.0)	3 (6.4)				
51%–85% of normal excursion		1 (1.2)	0 (0.0)	1 (2.1)				
16%–50% of normal excursion		1 (1.2)	0 (0.0)	0 (0.0)				
15% of normal excursion or worse		2 (2.4)	0 (0.0)	4 (8.5)				

Abbreviations: ALS = amyotrophic lateral sclerosis; *C9orf72* = chromosome 9 open reading frame 72; CBS = corticobasal syndrome; *GRN* = granulin; *MAPT* = microtubule-associated protein tau; PSPRS = Progressive Supranuclear Palsy Rating Scale.
p Values for overall tests of difference result from a Kruskal-Wallis rank-sum test. *p* Values for pairwise comparisons result from a Wilcoxon rank-sum test.
[a] Only statistical significant variables were reported.

Table 5 Motor Differences Among *C9orf72*, *GRN*, and *MAPT* Groups Based on PSP-QoL Information[a]

Variable	N	*C9orf72* (N = 88) n (%)	*GRN* (N = 43) n (%)	*MAPT* (N = 53) n (%)	*p* Value			
					Overall test of difference	*C9* vs *GRN*	*C9* vs *MAPT*	*GRN* vs *MAPT*
Had difficulty moving?	82				0.005	0.002	1.00	1.00
No problem		31 (81.6)	8 (40.0)	13 (54.2)				
Slight problem		2 (5.3)	4 (20.0)	8 (33.3)				
Moderate problem		4 (10.5)	5 (25.0)	1 (4.2)				
Marked problem		1 (2.6)	3 (15.0)	2 (8.3)				
Had falls?	82				0.028	0.068	1.00	1.00
No problem		31 (79.5)	12 (60.0)	11 (47.8)				
Slight problem		7 (17.9)	3 (15.0)	9 (39.1)				
Moderate problem		0 (0.0)	5 (25.0)	2 (8.7)				
Marked problem		1 (2.6)	0 (0.0)	1 (4.3)				
Had problems opening your eyes?	81				0.017	0.48	1.00	1.00
No problem		36 (94.7)	17 (89.5)	17 (70.8)				
Slight problem		2 (5.3)	2 (10.5)	2 (8.3)				
Moderate problem		0 (0.0)	0 (0.0)	1 (4.2)				
Marked problem		0 (0.0)	0 (0.0)	4 (16.7)				
Had problems communicating?	82				0.025	0.16	0.006	0.39
No problem		30 (78.9)	13 (65.0)	11 (45.8)				
Slight problem		4 (10.5)	1 (5.0)	5 (20.8)				
Moderate problem		2 (5.3)	3 (15.0)	3 (12.5)				
Marked problem		2 (5.3)	0 (0.0)	3 (12.5)				
Extreme problem		0 (0.0)	3 (15.0)	2 (8.3)				
Had difficulty reading?	80				0.009	0.018	0.003	0.72
No problem		36 (92.3)	14 (70.0)	13 (61.9)				
Slight problem		3 (7.7)	2 (10.0)	3 (14.3)				
Moderate problem		0 (0.0)	1 (5.0)	3 (14.3)				
Marked problem		0 (0.0)	1 (5.0)	1 (4.8)				
Extreme problem		0 (0.0)	2 (10.0)	1 (4.8)				

Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = granulin; *MAPT* = microtubule-associated protein tau; PSP-QoL = Progressive Supranuclear Palsy–Quality of Life Rating Scale.
p Values for overall tests of difference result from a Kruskal-Wallis rank-sum test. *p* Values for pairwise comparisons result from a Wilcoxon rank-sum test.
[a] Only statistical significant variables were reported.

motor manifestations of *C9orf72* variants are typically of motor neuron disease,[30] movement disorders may occur.[31-33] A recent retrospective study of 40 individuals with *C9orf72* variants identified a movement disorder in >40% of patients.[34] Among these, parkinsonism and tremor (resembling essential tremor) were the most common features, followed by myoclonus, dystonia, and chorea. An international study observing over 7,000 patients with PD identified *C9orf72* variants in 0.06% of study participants using a hexanucleotide repeat cutoff of >60.[35] Other studies have identified intermediate repeat expansions (usually defined as 20 to 30 repeats) as a risk factor for clinically diagnosed PD.[33] Two studies of pathologically proven PD combined for over 800 cases and identified only a single patient with a *C9orf72* HRE.[31,36] Our cohort of *C9orf72* repeat expansion carriers more often had features of motor neuron disease, for example,

Table 6 Clinical Differences Among *C9orf72*, *GRN*, and *MAPT* Groups Based on UPDRS Part III (Motor) Information[a]

	N	*C9orf72* (N = 88) n (%)	*GRN* (N = 43) n (%)	*MAPT* (N = 53) n (%)	*p* Value			
					Overall test of difference	*C9* vs *GRN*	*C9* vs *MAPT*	*GRN* vs *MAPT*
Does the participant have limb or torso fasciculations consistent with a diagnosis of SMA or ALS?[b]	183				0.017	0.059	0.027	1.00
Not enough for dx		75 (86.2)	43 (100.0)	53 (100.0)				
Yes: asymmetry L > R		1 (1.1)	0 (0.0)	0 (0.0)				
Yes: asymmetry R > L		4 (4.6)	0 (0.0)	0 (0.0)				
Yes: without major asymmetry		7 (8.0)	0 (0.0)	0 (0.0)				
Does the participant have limb weakness and/or hyperreflexia consistent with a diagnosis of PLS or ALS?[b]	183				0.029	0.026	0.093	1.00
Not enough for dx		71 (81.6)	43 (100.0)	51 (96.2)				
Yes: asymmetry L > R		4 (4.6)	0 (0.0)	1 (1.9)				
Yes: asymmetry R > L		5 (5.7)	0 (0.0)	0 (0.0)				
Yes: without major asymmetry		7 (8.0)	0 (0.0)	1 (1.9)				
Does the participant have bulbar weakness and/or fasciculations consistent with a diagnosis of ALS?[a,b]	183				0.003	0.030	0.014	1.00
Not enough for dx		77 (88.5)	43 (100.0)	53 (100.0)				
Yes: without major asymmetry		10 (11.5)	0 (0.0)	0 (0.0)				
Finger taps right hand	171				0.037	0.10	0.011	0.50
Normal		73 (89.0)	31 (77.5)	35 (71.4)				
Slight		4 (4.9)	5 (12.5)	7 (14.3)				
Mild		3 (3.7)	2 (5.0)	4 (8.2)				
Moderate		2 (2.4)	1 (2.5)	0 (0.0)				
Severe		0 (0.0)	1 (2.5)	3 (6.1)				
Posture	178				0.014	0.10	0.003	0.35
Normal		75 (89.3)	32 (78.0)	36 (67.9)				
Slight		5 (6.0)	5 (12.2)	12 (22.6)				
Mild		1 (1.2)	3 (7.3)	5 (9.4)				
Moderate		3 (3.6)	0 (0.0)	0 (0.0)				
Severe		0 (0.0)	1 (2.4)	0 (0.0)				
Rigidity: left lower extremity	178				0.040	0.055	0.012	0.74
Normal		80 (95.2)	36 (85.7)	43 (82.7)				
Slight		4 (4.8)	3 (7.1)	3 (5.8)				
Mild		0 (0.0)	0 (0.0)	3 (5.8)				
Moderate		0 (0.0)	0 (0.0)	3 (5.8)				
Severe		0 (0.0)	3 (7.1)	0 (0.0)				

Continued

Table 6 Clinical Differences Among *C9orf72*, *GRN*, and *MAPT* Groups Based on UPDRS Part III (Motor) Information[a] *(continued)*

	N	*C9orf72* (N = 88) n (%)	*GRN* (N = 43) n (%)	*MAPT* (N = 53) n (%)	*p* Value			
					Overall test of difference	*C9* vs *GRN*	*C9* vs *MAPT*	*GRN* vs *MAPT*
Rigidity: neck	178				0.028	0.022	0.012	0.88
Normal		80 (95.2)	35 (83.3)	43 (82.7)				
Slight		3 (3.6)	2 (4.8)	2 (3.8)				
Mild		1 (1.2)	3 (7.1)	2 (3.8)				
Moderate		0 (0.0)	1 (2.4)	4 (7.7)				
Severe		0 (0.0)	1 (2.4)	1 (1.9)				
Tremor at rest: face, lips, and chin	181				0.036	0.013	0.21	0.21
Normal		86 (100.0)	39 (92.9)	52 (98.1)				
Slight		0 (0.0)	3 (7.1)	1 (1.9)				
Tremor at rest: left foot	181				0.026	1.00	0.027	0.12
Normal		86 (100.0)	42 (100.0)	50 (94.3)				
Slight		0 (0.0)	0 (0.0)	2 (3.8)				
Severe		0 (0.0)	0 (0.0)	1 (1.9)				
Tremor at rest: right foot	181				0.026	1.00	0.027	0.12
Normal		86 (100.0)	42 (100.0)	50 (94.3)				
Slight		0 (0.0)	0 (0.0)	2 (3.8)				
Mild		0 (0.0)	0 (0.0)	1 (1.9)				
Tremor at rest: right hand	181				0.037	0.008	0.13	0.33
Normal		85 (98.8)	37 (88.1)	50 (94.3)				
Slight		0 (0.0)	3 (7.1)	0 (0.0)				
Mild		0 (0.0)	2 (4.8)	1 (1.9)				
Moderate		1 (1.2)	0 (0.0)	2 (3.8)				

Abbreviations: ALS = amyotrophic lateral sclerosis; *C9orf72* = chromosome 9 open reading frame 72; CBS = corticobasal syndrome; *GRN* = granulin; *MAPT* = microtubule-associated protein tau; PLS = primary lateral sclerosis; SMA = spinal muscular atrophy; UPDRS = Unified Parkinson's Disease Rating Scale.
p Values for overall tests of difference result from a Kruskal-Wallis rank-sum test (ordinal variables) or Fisher exact test (categorical variables). *p* Values for pairwise comparisons between the 3 groups result from a Wilcoxon rank-sum test (ordinal variables) or Fisher exact test (categorical variables).
[a] Only statistical significant variables were reported.
[b] Questions are part of the supplemental UPDRS with the National Alzheimer's Coordinating Center.

fasciculations, muscle atrophy, and weakness, and less often had parkinsonism compared with *GRN* and *MAPT* variant carriers.

GRN variants are primarily associated with the TDP-43 type A neuropathologic subtype most commonly leading to a clinical phenotype of bvFTD or nfvPPA.[29] Although these phenotypes are most often sporadic, familial *GRN* variants may present with CBS.[37-41] Despite not having pathologic tau deposition, these patients may appear phenotypically indistinguishable from corticobasal degeneration. Our *GRN* cohort was characterized by features of CBS, for example, parkinsonism and apraxia. Analysis of UPDRS Part III assessments showed that parkinsonian features such as neck rigidity, facial rest tremor, and right-hand rest tremor were more common in these participants than in carriers of *C9orf72* variants. The frequency of these features was not significantly different from that observed for the *MAPT* cohort; however, apraxia was more common than was observed in the *MAPT* carriers. This is consistent with findings from a study that compared 13 *GRN* and 17 *MAPT* variant carriers with FTLD.[42] There have been a few reports of *GRN* variant carriers with CBS and dystonia.[37,39,43] Our *GRN* cohort also reported greater difficulty with movement, on the PSP-QoL, compared with the *C9orf72* cohort.

There were clinical features within our *MAPT* cohort that distinguished it from the other cohorts. *MAPT* variant carriers

had more PSPRS-defined abnormalities with voluntary vertical eye movement abnormalities than carriers of other variant types. This likely contributed to their higher levels of reading difficulties, relative to *C9orf72* carriers, identified in the PSP-QoL. These participants also had more parkinsonism than the *C9orf72* carriers. These findings suggest a PSP phenotype, more specifically the Richardson syndrome (PSP-RS) given significant oculomotor abnormalities. These findings can also be understood as reflecting the propensity of various *MAPT* variants to result in an increased 4R/3R tau ratio. A case-control genome wide association study of PSP showed that the *MAPT* locus has a very strong effect.[44,45] Notwithstanding phenotypic heterogeneity within mutation carrier class, considering the *MAPT* variants in aggregate facilitated differentiation of features from those of the *C9orf72* variant carriers. This approach also facilitated distinction of features from those of *GRN* variant carriers, based on oculomotor abnormalities manifested by participants carrying *MAPT* variants, and apraxias in those carrying *GRN* variants. These characteristics suggest that *MAPT* is more often associated with a PSP-like phenotype, whereas *GRN* tends toward a CBS. The primary syndromic diagnoses in our sample reflect this as 75% (n = 3) of participants diagnosed with CBS had *GRN* variants (the other was *MAPT*) and 67% (n = 2) of participants with PSP-RS had *MAPT* variants (the other was *C9orf72*).

Although an FTLD syndrome can suggest mutation type, the syndrome is typically not fully developed at illness onset, and early diagnosis is challenging.[46,47] Generally, the syndrome develops over a period of a few years, as abnormalities from various domains (of motor, cognitive, and behavioral function) accumulate. For example, a clinician cannot confidently predict the presence of a *GRN* variant on the basis of parkinsonism alone, but the clinical suspicion would substantially increase when apraxia develops. The temporal profile of clinical features is a key element for the clinician. We report a temporal relationship of overall AAO between variant groups (*MAPT* followed by *C9orf72* and then *GRN*) that is in accordance with previous reports.[48,49] We found that the mean AAO for cognitive symptoms was significantly different among cohorts beginning with *MAPT* (49 years) followed by *C9orf72* (55 years) and then *GRN* (60 years). The same relationship was present for behavioral and motor features (Table 2). More importantly, *GRN* variant carriers most often presented with cognitive impairment, whereas the *C9orf72* and *MAPT* usually presented with behavioral abnormalities. Motor features at onset were also more common in *C9orf72* and *MAPT* compared with *GRN* patients. These characteristics can serve as valuable patterns when determining the genetic underpinnings of a patient's clinical presentation at the bedside.

Limitations of this study primarily relate to study size. This is a large study comparing motor features of familial FTLD (n = 184), but our subgroup sizes are relatively small precluding comparison of different types of variants within the same gene. Within the *GRN* cohort, there were 19 different variants (16 exonic) of which 3 are novel (see eTable 1, links.lww.com/WNL/C170). The *MAPT* cohort included 10 different variants (8 exonic). We previously reported these variants in our assessment of the entire ARTFL/LEFFTDS series, which also included patients without motor features.[50] Some of our participants were from the same family, potentially skewing genotype-phenotype correlations. We do not have information on the temporal relationship between neurologic examinations and medication dosing. Finally, some patients may have received dopaminergic medication to address their parkinsonism. This may have diluted or even masked significant differences among the cohorts. It is unlikely that they benefitted from levodopa, although no conclusions on levodopa responsiveness in our subgroups can be made.

We present an analysis comparing the motor phenotypes of a large number of patients with symptomatic familial FTLD carrying a pathogenic variant in *C9orf72*, *GRN*, or *MAPT*. Our findings suggest that there are phenotypic elements that, while not specific, are more common with certain variant types. This study also highlights the importance of large prospective multicenter studies, which enable the collection of cohorts large enough to discern these types of phenotype-genotype relationships in complex neurodegenerative disorders in a standardized manner.

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Continued

Appendix *(continued)*

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Appendix *(continued)*

Name	Location	Contribution
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