Frequency and Longitudinal Course of Motor Signs In Genetic Frontotemporal Dementia

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Background and Objectives: Frontotemporal dementia (FTD) is a highly heritable disorder. The majority of genetic cases are caused by autosomal dominant pathogenic variants in the c9orf72, GRN and MAPT gene. As motor disorders are increasingly recognized as part of the clinical spectrum the current study aimed to describe motor phenotypes caused by genetic FTD, quantify their temporal association, and investigate their regional association with brain atrophy.

Methods: We analyzed baseline visit data of known carriers of a pathogenic variant in the c9orf72, GRN or MAPT gene from the Genetic Frontotemporal dementia Initiative cohort study. Principal component analysis with varimax rotation was performed to identify motor sign clusters that were compared with respect to frequency and severity between groups. Associations with cross-sectional atrophy patterns were determined using voxel-wise regression. We applied linear mixed effects models to assess whether groups differed in the association between motor signs and estimated time to symptom onset.

Results: 322 pathogenic variant carriers were included in the analysis: 122 c9orf72 (79 presymptomatic), 143 GRN (112 presymptomatic) and 57 MAPT (43 presymptomatic)
pathogenic variant carriers. Principal component analysis revealed five motor clusters, which we call progressive supranuclear palsy like (PSP-like), bulbar amyotrophic lateral sclerosis (ALS) like, mixed/ALS-like, Parkinson’s disease like (PD-like), and corticobasal syndrome like motor phenotypes. There was no significant group difference in the frequency of signs of different motor phenotypes. However, mixed/ALS-like motor signs were most frequent, followed by PD-like motor signs. While the PSP-like phenotype was associated with mesencephalic atrophy, the mixed/ALS-like phenotype was associated with motor cortex and corticospinal tract atrophy. The PD-like phenotype was associated with widespread cortical and subcortical atrophy. Estimated time to onset, genetic group and their interaction, influenced motor signs. In c9orf72 pathogenic variant carriers, motor signs could be detected up to 25 years prior to expected symptom onset.

Discussion: These results indicate the presence of multiple natural clusters of motor signs in genetic FTD, each correlated with specific atrophy patterns. Their motor severity depends on time and the affected gene. These clinico-genetic associations can guide diagnostic evaluations and the design of clinical trials for new disease-modifying and preventive treatments.

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Abbreviations: ALS = amyotrophic lateral sclerosis, c9orf72 = chromosome 9 open reading frame 72, CBS = corticobasal syndrome, EYO = estimated years to symptom onset, FTD = frontotemporal dementia, GENFI = Genetic Frontotemporal dementia Initiative, GRN = progranulin, LME = linear mixed effects model, MAPT = microtubule-associated protein tau, MDS = multidimensional scaling, MP = motor phenotype, PCA = principal component analysis, PD = Parkinson’s disease, PSP = progressive supranuclear palsy

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Introduction

Frontotemporal dementia (FTD) refers to a heterogeneous group of neurodegenerative disorders. The associated clinical syndromes classically affect personality and social behaviour or language. They are a common cause of early-onset dementia and are highly heritable. The majority of genetic cases are caused by pathogenic variants in one of three genes: chromosome 9 open reading frame 72 (c9orf72), progranulin (GRN) and microtubule-associated protein tau (MAPT). C9orf72 pathogenic variants are most common.

Because of the clinical heterogeneity, a precise knowledge of clinical presentations correlated with genetic subgroups is essential to guide diagnostic workup and assist decisions regarding genetic testing. It will also become increasingly important as disease-modifying drug trials are underway in each of the three genetic FTD groups.

Patients can also present with a wide range of motor signs, including those commonly associated with amyotrophic lateral sclerosis (ALS), Parkinson’s disease (PD), progressive supranuclear palsy (PSP) or corticobasal syndrome (CBS). We propose that the anatomical distribution of pathological brain changes determines the clinical phenotype. This distribution can be defined in terms of brain regions, or functionally in terms of degeneration of the first and second motor neuron and basal ganglia. The identification of motor structure-function relationships in sporadic FTD is hindered by uncertainty of the molecular pathology. This challenge is addressed by the analysis of genetic FTD.

While there is a wide literature covering behavioural and linguistic features in FTD, detailed phenotypic characterization of motor disorders is mostly in sporadic cases or in the form of case reports or case series. Longitudinal data on motor phenotypes are lacking. We aimed to describe motor phenotypes in genetic FTD, from the Genetic frontotemporal dementia initiative (GENFI). We examined motor sign occurrence in the course of the disease, including the presymptomatic phase, and tested whether structural brain changes are associated with particular motor phenotypes.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents
The study was performed according to the declaration of Helsinki (1991). Ethical approval for conduction of the study has been obtained at the coordinating site at University College London and all participating centers. Written informed consent was obtained from every participant.

Participants

To assess motor findings in genetic FTD we used Data Freeze three (DF3) from the GENFI multicentre cohort study, gathered between Jan 30, 2012, and Jan 31, 2017. GENFI consists of research centres across Europe and Canada (http://genfi.org.uk/) and enrolls participants who are known carriers of a pathogenic variant in c9orf72, GRN or MAPT or are at risk of carrying a pathogenic variant because a first-degree relative was a known carrier. A pathogenic c9orf72 expansion was defined as more than 30 repeats. Participants were genotyped at their local site. All eligible and interested participants were enrolled. 322 pathogenic variant carriers, including 122 c9orf72 (79 presymptomatic), 143 GRN (112 presymptomatic) and 57 MAPT pathogenic variant carriers (43 presymptomatic) were included in the analysis. Baseline visit data were used.

Participants underwent a standardized clinical assessment consisting of medical history, family history, and physical examination. Participants not yet demonstrating clear evidence of progressive cognitive, behavioural or motor symptoms were classified as presymptomatic. Estimated years to symptom onset (EYO) was defined as the difference between the participants’ current age and the mean age at onset within the participants’ family. Estimated years to symptom onset (EYO) was defined as the difference between the participants’ current age and the mean age at onset within the participants’ family.17

Assessment of motor impairment

The presence and severity of the following signs was assessed: supranuclear gaze palsy, impaired eyelid function, facial weakness, bulbar palsy, pseudobulbar palsy, neck weakness, neck rigidity, respiratory muscle weakness, myoclonus, rest tremor, postural tremor, dystonia, chorea, bradykinesia, rigidity, limb apraxia, alien limb phenomenon, cortical sensory loss, limb fasciculations, spasticity, limb weakness, hyperreflexia, ataxia, arising from chair, sitting down and postural instability. Severity of signs was scored as follows: score 0 = no impairment, score 0.5 = very mild impairment, score 1 = mild impairment, score 2 = moderate impairment, score 3 = severe impairment (Supplementary Table 1). For motor signs affecting different limbs, the score of the most severely affected limb was used. To assess limb motor asymmetry, laterality indices (LI) defined as the difference of left and right were calculated.
For motor signs scoring 4 extremities the mean of side differences was calculated. To assess overall asymmetry the amount of the sum of all LIs was used.

MRI acquisition and analysis

MRI data were available in 286/322 patients. MR images were acquired on a 3T scanner with a 1.1 mm isotropic resolution (GE, Philips, Siemens Prisma, Siemens Skyra, Siemens Trio). Acquisition protocols were synchronized across scanners and sites to achieve the best possible match.

Voxel based morphometry was performed using the Statistical Parametric Mapping toolbox (SPM12)\textsuperscript{18} in MATLAB (MathWorks, USA). Images were segmented into probability maps of gray matter, white matter and cerebrospinal fluid, non-linearly transformed using DARTEL\textsuperscript{19} to create a study specific template for white and gray matter and normalized to the Montreal Neurological Institute space with Jacobian modulation. Spatial smoothing was applied using a full width at half max 6 mm Gaussian Kernel. An estimate of total intracranial volume for each subject was computed by summing the 3 tissue class volumes\textsuperscript{20}.

Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows (Version 25.0. Armonk, NY: IBM Corp.). Non-dichotomized mean scores of demographic data were compared via Kruskal-Wallis test and \textit{post-hoc} Bonferroni corrected Mann-Whitney tests. Chi-square analysis was used to check for significant differences in sex. Standard statistical significance level was set at $p < 0.05$.

To identify groups of similar clinical variables, our set of motor scores as well as overall LI were subjected to a principal component analysis (PCA) with varimax rotation. Variables with factor loadings below 0.4 were eliminated from the analysis and the PCA run anew. Components were labeled \textit{post-hoc} according to the pattern of signs. No a priori assumptions regarding the clustering of motor signs were applied. To visualize the similarity of variables assigned to a specific component during PCA multidimensional scaling (MDS) was performed. Furthermore, to visualize possible gene-clustering between phenotype-clusters a between-cases MDS was performed. For each group, the variance in each dimension was calculated and a Levene’s test was performed to assess possible inequality of variances.

To test for differences of motor signs depending on the affected gene we calculated for each participant a sum score from the variables of each component. As overall LI has a different
scale than the other variables, it was analyzed separately. Sum scores were compared via Kruskal-Wallis and post-hoc Bonferroni corrected Mann-Whitney-tests between groups.

To assess the proportion of the predominant phenotype of patients with motor signs depending on the affected gene, cases were assigned to the component with the highest PCA-based sum score. In addition, the frequency of signs of different components was determined for each group. Chi-square analysis was used to check for significant differences in frequency of signs.

We assessed for each component the association between the sum scores and the patterns of atrophy using linear regression models. Data of patients with a sum score of 0 were excluded. The estimate of total intracranial volume was included as a covariate. Probability maps of gray matter and white matter were analyzed separately. T-maps were merged for visualization purposes. Images of the association between the sum scores of component 5 and cross-sectional atrophy patterns, were partly flipped according to the expected atrophy pattern. The hemisphere with the expected atrophy (based on lateralization of motor symptoms) was arranged to the left. Absolute threshold masking was set at 0.1 to prevent interference by non-brain voxels ($p < 0.001$, cluster threshold $k = 20$ voxel).

Additionally, we applied Linear Mixed Effects (LME) models\textsuperscript{21} to assess differences between genetic groups in function of the calculated sum scores. LME performs a modelling of the predictor variables as a linear model combining fixed and random effects; the former accounting for known sources of variation such as groups or time, the later accounting for the variance contribution of clusters in the data and correlations within members of each cluster.

We tested several models including random intercepts per family and site\textsuperscript{17}. Fixed effect variables included EYO, genetic group and sex, along with interactions between genetic group and EYO. Non-linear time dependence was expected, so a second order contribution of EYO, including an interaction with genetic group, was added to the model. Higher order contributions and logarithmic transformations were tested with no significant improvement of the model.

We applied a type II Wald Chi-square test to the model, to estimate the relationship between the fixed variables and the sum scores. Afterwards, the three-way empirical significance was estimated from a Monte-Carlo sampling of the models for each sum score\textsuperscript{22} every 5 years in the EYO range from -25 to +10 in order to identify each sign’s degree of differentiation. As indicator of the point in time at which motor signs of each component and genetic group start
to increase, the time at which the lower 95% confidence interval crosses zero on the x-axis was used. These analyses were performed using R 3.6.3.

Data availability

Data will be shared according to the GENFI data sharing agreement, after review by the GENFI data access committee with final approval granted by the GENFI steering committee.

Results

Demographics

Demographics of the study sample are provided in Table 1. MAPT pathogenic variant carriers were younger compared to the other groups. The proportion of presymptomatic participants was lower in c9orf72 compared to GRN pathogenic variant carriers. Groups did not differ in terms of education, sex and EYO\textsuperscript{17,23}.

Principal component analysis and multidimensional scaling

Both the Bartlett test (Chi-square (351) 7662.23, $p < 0.001$) and the Kaiser-Meyer-Olkin Measure of Sampling Adequacy (KMO = 0.766) indicated that variables were suitable for PCA with varimax rotation, which revealed the presence of 7 components with eigenvalues above 1. As 2 of these components contained only 2 variables these were excluded from the analysis, leaving a 5-component solution explaining 67.3% of variance. The motor sign chorea was excluded as its factor loadings were below 0.4.

The variables group in the components as follows (details in Table 2):

1. neck rigidity, impaired eyelid function, supranuclear gaze palsy, dystonia, pseudobulbar palsy and ataxia: we call this the PSP-like motor phenotype (PSP-MP).
2. respiratory muscle weakness, neck weakness, bulbar palsy, facial weakness and myoclonus: we call this the bulbar ALS-like motor phenotype (bulbar ALS-MP).
3. spasticity, limb weakness, limb fasciculations, arising from chair, bradykinesia, sitting down, postural instability and hyperreflexia: we call this the mixed/ALS-like motor phenotype (mixed/ALS-MP), as this phenotype contains both non-specific motor signs like bradykinesia as well as typical ALS features like spasticity, limb weakness, fasciculations and hyperreflexia.
4. rest tremor, postural tremor, overall LI and rigidity: we call this the PD-like motor phenotype (PD-MP).
5. cortical sensory loss, limb apraxia and alien limb phenomenon: we call this the CBS-like motor phenotype (CBS-MP).

Of note, high scores on a certain component do not make a specific diagnosis, the names given are but a simplified label for a cluster of signs. MDS confirmed the grouping of variables as reasonable (normalized raw stress 0.040) (Fig. 1A). Additionally, a between cases MDS (normalized raw stress 0.002) was performed (Fig. 1B). Levene’s test detected significant inequality of variances in dimension 1 between groups ($p = 0.039$) with highest variances in $c9orf72$ pathogenic variant carriers. No significant group differences were detected in dimension 2.

**Severity of motor signs**

Kruskal-Wallis test detected significant group differences of sum scores of the bulbar ALS-MP, mixed/ALS-MP and PD-MP with highest sum scores in $c9orf72$ pathogenic variant carriers (Fig. 2A). Sum scores of the mixed/ALS-MP and PD-MP were lowest in MAPT pathogenic variant carriers while sum scores of the bulbar ALS-MP were lowest in GRN pathogenic variant carriers. Sum scores of the PSP-MP and CBS-MP were highest in $c9orf72$ and lowest in MAPT pathogenic variant carriers, however, statistical significance was not reached. As presymptomatic participants were largely normal on their clinical exam, differences of sum scores between groups at baseline examination were mainly driven by symptomatic participants.

**Frequency of motor signs**

When looking at the group of pathogenic variant carriers showing motor signs no significant group differences could be detected regarding the frequency of signs of different motor phenotypes (Fig. 2B). This was similar when looking at the whole group (Supplementary Fig. 1), chi-square analysis detected only significant group differences regarding the frequency of signs of the bulbar ALS-MP with highest frequency of signs in $c9orf72$ pathogenic variant carriers.

Signs of the mixed/ALS-MP were most frequent across groups (63.3% – 76.9%), followed by signs of the PD-MP (51.0% – 61.5%). Signs of the CBS-MP (26.5% and 38.5% respectively) were slightly more frequent than signs of the PSP-MP (20.4% and 30.8% respectively) in
GRN and MAPT pathogenic variant carriers. In contrast in c9orf72 pathogenic variant carriers signs of the PSP-MP (34.7%) occurred more frequently than signs of the CBS-MP (30.8%). The least common signs were those of the bulbar ALS-MP (7.7% – 13.5%). This was the case in all genetic groups, regardless of whether the cohort of patients showing motor signs or the whole cohort was analysed.

Predominance phenotype

In c9orf72 pathogenic variant carriers the most frequent predominant phenotype was the mixed/ALS-MP (44%), followed by signs of the PD-MP (33%) (Fig. 3) while this was the other way round in GRN and MAPT pathogenic variant carriers (PD-MP: 43% and 54% respectively, mixed/ALS-MP: 35% and 38% respectively). While 21.7% of c9orf72 pathogenic variant carriers with a predominant mixed/ALS-MP had confirmed motor neuron disease, in none of the patients with a GRN or MAPT pathogenic variant motor neuron disease was diagnosed. The third most common predominant phenotype was the CBS-MP in all genetic groups, which was equally frequent in c9orf72 and GRN (≈ 15%) and slightly less frequent in MAPT pathogenic variant carriers (8%). In c9orf72 pathogenic variant carriers the PSP-MP (4%) was slightly more frequent than the bulbar ALS-MP (2%). All c9orf72 pathogenic variant carriers with a predominant bulbar ALS-MP had confirmed motor neuron disease. None of the GRN pathogenic variant carriers showed a predominant bulbar ALS-MP and no MAPT pathogenic variant carrier showed a predominant PSP-MP or mixed/ALS-MP.

Atrophy patterns

Voxel-wise regression revealed sum scores of the PSP-MP to be highly correlated with mesencephalic atrophy (Fig. 4, Supplementary Fig. 3, Supplementary Table 2). Atrophy clusters correlating with sum scores of the bulbar ALS-MP were rather small and distributed over all lobes with a focus on the frontal and temporal lobe. For the mixed/ALS-MP the clusters of white matter atrophy were mainly located in extra-nuclear and brain stem white matter as well as in subcortical white matter of the medial frontal and precentral gyrus. Clusters of gray matter atrophy were located in the precentral, medial frontal and superior frontal gyrus (Fig. 4C). Additionally, clusters of gray matter atrophy could be detected in both cerebellar tonsils, the left declive, insula and posterior cingulate. Sum scores of the PD-MP showed a high correlation with diffuse cerebral and cerebellar cortical and subcortical atrophy (Fig. 4B). Only small atrophy clusters correlating with the sum scores of the CBS-MP mainly located in the temporal, occipital and parietal lobes could be detected.
Linear mixed effects (LME) models

The visual distribution of sum scores and overall laterality over EYO is depicted in Fig. 5. Type II Wald Chi-square test revealed a significant effect of EYO on the sum scores of the PSP-MP \((p < 0.001)\), mixed/ALS-MP \((p = 0.030)\) and PD-MP \((p < 0.001)\) and a significant effect of genetic group on the sum scores of the mixed/ALS-MP \((p < 0.001)\) and PD-MP \((p = 0.016)\). The interaction of EYO and genetic group had a significant effect on the sum scores of the PD-MP \((p = 0.027)\). None of the variables included in the model reached statistical significance when evaluating the sum scores of the bulbar ALS-MP and CBS-MP.

As a possible indicator of signs starting to emerge, we determined for each component and genetic group the point in time at which the lower 95% confidence interval of the model crosses the x-axis. While no clear onset of signs could be detected for the bulbar ALS-MP, in \(c9orf72\) and \(GRN\) pathogenic variant carriers an increase of signs of the PSP-MP could be detected already shortly prior to estimated onset (Fig. 5). In \(c9orf72\) pathogenic variant carriers an increase of signs of the mixed/ALS-MP was detectable already 25 years prior to the estimated onset. Signs of the PD-MP started to increase more than 15 years prior to estimated onset in \(c9orf72\) and \(GRN\) pathogenic variant carriers, and around 5 years prior to estimated onset in \(MAPT\) pathogenic variant carriers, while signs of the CBS-MP increased 10 years prior to estimated onset in \(c9orf72\) pathogenic variant carriers and more than 5 years prior to estimated onset in \(GRN\) pathogenic variant carriers.

Sum scores of the PD-MP were significantly higher in \(c9orf72\) compared to \(GRN\) and \(MAPT\) pathogenic variant carriers 5 years before estimated onset (Fig. 5) and significantly higher in \(MAPT\) compared to \(GRN\) pathogenic variant carriers 15 years after estimated onset. Sum scores of the CBS-MP were significantly higher in \(c9orf72\) compared to \(MAPT\) pathogenic variant carriers 15 years before estimated onset and converged 15 years after estimated onset. Furthermore, they were significantly higher in \(GRN\) compared to \(MAPT\) pathogenic variant carriers 10 years before estimated onset and converged 10 years after estimated onset. The earliest point at which sum scores of the CBS-MP were significantly higher in \(c9orf72\) compared to \(GRN\) pathogenic variant carriers was 10 years after estimated onset. We noted no significant group differences of sum scores of the PSP-MP, bulbar ALS-MP and mixed/ALS-MP over time.

Discussion
We present a data driven approach to demonstrate the phenotypic range of motor signs, their association with time to expected onset as well as with specific atrophy patterns in genetic FTD. Principal component analysis confirmed the presence of natural clusters of motor phenotypes, a PSP-like, a bulbar ALS-like, a mixed/ALS-like, a PD-like and a CBS-like motor phenotype.

The prevalence of signs of these phenotypes in the overall cohort was similar across genetic groups. This is in line with a recent review and meta-analysis\textsuperscript{13}. However, in our cohort, signs of the mixed/ALS-MP were most frequent across groups, followed by signs of the PD-MP. The most common phenotype in \textit{GRN} and \textit{MAPT} pathogenic variant carriers was PD-MP, closely followed by mixed/ALS-MP: this was the other way round in \textit{c9orf72} pathogenic variant carriers. This was to be expected in \textit{c9orf72} pathogenic variant carriers but is rather unexpected in \textit{GRN} and \textit{MAPT} pathogenic variant carriers, as the occurrence of ALS-like signs has only rarely been described in these conditions\textsuperscript{4,24}. Interestingly, this was only in part due to the non-specific variables with high cross loadings on the PSP-MP and PD-MP contained in this phenotype cluster, as the frequency of the remaining signs of the third component was still 16.1\% in \textit{GRN} and 15.8\% in \textit{MAPT} pathogenic variant carriers, with the most frequent sign being hyperreflexia. However, typical ALS signs like limb weakness, fasciculations and spasticity were present as well.

In previous reports, parkinsonism and Richardson-syndrome have been described in association with \textit{MAPT} pathogenic variants\textsuperscript{25-27}, but in our overall cohort motor signs of a PSP-MP, PD-MP and CBS-MP occurred most frequently in \textit{c9orf72} followed by \textit{GRN} pathogenic variant carriers. Intriguingly, no \textit{MAPT} pathogenic variant carrier exhibited a predominant PSP-MP. This may be due to the small number of \textit{MAPT} pathogenic variant carriers showing motor signs (n=13). The fact that motor disorders and parkinsonism are typically brought into connection with a \textit{MAPT} pathogenic variant may be caused by the earlier discovery of \textit{MAPT} pathogenic variants in people with PSP-like phenotypes\textsuperscript{7}, eight years earlier than \textit{GRN}\textsuperscript{6} and 13 years earlier than \textit{c9orf72}\textsuperscript{5}. Therefore, a higher number of papers reporting \textit{MAPT} pathogenic variants may have skewed the perception of prevalence, leading to the impression that \textit{MAPT} has a higher proportion of motor disorders.

The more frequent occurrence of signs of the CBS-MP in \textit{c9orf72} compared to \textit{GRN} pathogenic variant carriers is surprising as previous reports have described CBS to be most often associated with \textit{GRN} pathogenic variants\textsuperscript{28-30}. This discrepancy may be due to the fact that most previous studies on motor disorders in genetic FTD have been case reports and case
series that have focused on the predominance phenotype without describing accompanying low-grade signs. In fact, when looking solely at patients showing motor signs, GRN pathogenic variant carriers were similarly likely to show a predominant CBS-MP compared to c9orf72 pathogenic variant carriers.

Signs of a bulbar ALS-MP were most frequent in c9orf72 pathogenic variant carriers and could rarely be detected in GRN and MAPT pathogenic variant carriers. None of the GRN and MAPT pathogenic variant carriers showing motor signs exhibited a predominant bulbar ALS-MP. The presence of manifest bulbar signs therefore effectively excludes the presence of GRN and MAPT pathogenic variants.

While the clinical phenotype is known to be highly heterogeneous across all pathogenic variants under investigation, the between cases MDS performed demonstrates tightly overlapping phenotype clusters, albeit with higher variance in c9orf72 pathogenic variant carriers and a more consistent syndrome for GRN and MAPT. This is reflected by the higher frequency and greater severity of signs across all phenotype clusters in c9orf72 compared to GRN and MAPT pathogenic variant carriers. In agreement with the concept that the anatomy determines the phenotype we were able to demonstrate strong clinico-anatomic correlations. This is reassuring about the validity of phenotype clusters defined by PCA. In agreement with previous studies on PSP-Richardson syndrome and PSP-like signs in sporadic FTD, the severity of the PSP-MP correlated with mesencephalic atrophy. The bulbar ALS-MP correlated with small areas of atrophy, mainly in the frontal and temporal lobe. This is consistent with previous studies reporting atrophy in frontotemporal regions especially in patients additionally displaying behavioural or language signs, which was the case in all of our patients showing signs of the bulbar ALS-MP.

As expected, mixed/ALS-MP signs correlated with bilateral atrophy of the motor and premotor cortex and the corticospinal tracts including the internal capsule and brainstem. As in previous reports on the FTD-ALS continuum clusters of atrophy in further frontotemporal regions and the cerebellum were also detectable.

Surprisingly, there was only a small correlation of the PD-MP with basal ganglia atrophy but widespread cortical and subcortical correlates. Recent studies have demonstrated a similar widespread pattern of subtle bilateral cortical thinning involving frontal, parietal, temporal and occipital lobes and extensive white matter damage already in early PD. However, our cases carry FTD pathogenic variants associated with TDP43 and Tau-pathology, not alpha-synucleinopathy. Dual pathology can occur but is very unlikely to be common across the
GENFI cohort sufficient to cause the correlations with atrophy. The absence of basal ganglia atrophy may reflect the different underlying molecular pathology of PD-like MP in genetic FTD, versus PD. The data suggest that mild PD-like signs in genetic FTD are rather due to diffuse cortical and subcortical atrophy than profound degeneration of the basal ganglia.

Even when flipping images according to the expected clinical atrophy pattern only small atrophy clusters correlated with the CBS-MP. These were in the parietal, temporal and occipital lobes. While the clinical presentation of CBS is typically asymmetric the variable overall laterality index (LI) was assigned to the PD-MP, not the CBS-MP by PCA which explains why atrophy clusters correlating with the CBS-MP are not asymmetrically distributed. The fact that the factor loading of the variable overall LI on the CBS-MP was comparatively low, may however be due to the small number of participants showing motor signs of the CBS-MP (n = 33).

Previous studies in CBS have demonstrated that atrophy patterns and cerebral glucose metabolism differ depending on the underlying pathology. While in patients with corticobasal degeneration the premotor cortex, supplemental motor area and insula are typically affected, those with TDP-43 pathology exhibit pronounced frontotemporal atrophy, and CBS patients with underlying Alzheimer’s pathology show more posterior atrophy, in parietal and temporal lobes. While small, the atrophy clusters detected in our cohort seem to correspond to the atrophy detected in CBS caused by Alzheimer’s pathology. However, a differing distribution of pathology and thus atrophy depending on the affected gene, which could have led to a mutual cancellation of atrophy patterns in our pooled analysis is also possible.

Previous studies in genetic FTD described changes in neuropsychological measures and structural imaging 5-10 years prior to expected onset. We show the emergence of motor signs, up to 25 years prior to expected onset. Furthermore, our results demonstrate that severity of signs depends on the affected gene and that its effect varies over time. Mixed/ALS-MP, PD-MP and CBS-MP signs occurred earliest in c9orf72 pathogenic variant carriers, in agreement with the early detectable structural imaging findings and slow progress described in some c9orf72 patients. In contrast, in MAPT pathogenic variant carriers that have been typically described in association with motor disorders, motor signs occurred later. While the severity of signs remained highest in c9orf72 pathogenic variant carriers, severity with GRN and MAPT pathogenic variant carriers converged over time.
As the majority of participants are alive no valid conclusion on the influence of motor signs on overall survival can be drawn. However, an impact of motor signs, especially of the bulbar and mixed/ALS-MP seems likely and should be investigated in future studies.

Besides the high number of genetic FTD patients and the prospective evaluation of signs, the identification of natural clusters of motor signs by PCA represents a key strength of our study. Applying a data driven approach allows for an objective analysis that does not follow classical clinical concepts and is not influenced by a priori assumptions.

A limitation of the current study that needs to be considered is the lack of a comparison to data from healthy controls. However, the primary aim was to compare motor disorders and their development over time between the genetic groups under investigation. We analysed only cross-sectional differences between different genetic groups at different times from estimated onset. Whether the progression of signs, especially in the presymptomatic phase when subtle signs may be challenging to measure, is followed within individuals has to be shown in future longitudinal studies. Furthermore, a replication of phenotypes in another cohort would be of interest but is difficult to pursue due to the rarity of genetic FTD. Another limitation is the method used for estimation of estimated years to symptom onset. There is a significant correlation between an individual’s age at onset and mean familial age at onset for MAPT pathogenic variants, this correlation is weak for c9orf72 and GRN, such that EYO becomes a surrogate of age\textsuperscript{23}.

Keeping these limitations in mind our data reveal the presence of natural clusters of motor signs in genetic FTD. Their severity increases over time and depends on the affected gene. The emergence of motor signs occurs early in the presymptomatic period, up to 25 years prior to estimated onset. Motor phenotypes have distinctive anatomical correlates. Given the heterogeneity of signs and symptoms and phenotypic overlap, these clinico-genetic associations of motor phenotypes in genetic FTD will help clinicians in their diagnostic work-up, assist in decision-making regarding genetic testing, and the design of preventive and disease-modifying treatments.

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http://links.lww.com/WNL/C157

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References


Tables

<p>| Tab. 1 Demographics of the study sample |</p>
<table>
<thead>
<tr>
<th></th>
<th>( C9orf72 )</th>
<th>( GRN )</th>
<th>( MAPT )</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>122</td>
<td>143</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Symptoms (Presymptomatic/Symptomatic)</td>
<td>79/43</td>
<td>112/31</td>
<td>43/14</td>
<td>0.041</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.2 (13.9)(^c)</td>
<td>50.0 (13.4)(^c)</td>
<td>45.1 (12.1)(^a,b)</td>
<td>0.003</td>
</tr>
<tr>
<td>Education (years)</td>
<td>13.9 (3.2)</td>
<td>13.9 (3.9)</td>
<td>14.3 (3.4)</td>
<td>0.571</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>66/56</td>
<td>88/55</td>
<td>34/23</td>
<td>0.462</td>
</tr>
<tr>
<td>EYO (years)</td>
<td>-8.0 (13.0)</td>
<td>-10.1 (13.1)</td>
<td>-7.8 (12.2)</td>
<td>0.224</td>
</tr>
</tbody>
</table>

Significantly different compared to \(^a\) \( C9orf72 \), \(^b\) \( GRN \), \(^c\) \( MAPT \).

\( C9orf72 \) chromosome 9 open reading frame 72, \( GRN \) progranulin, \( MAPT \) microtubule-associated protein tau, \( EYO \) estimated years to symptom onset.

Tab. 2 Rotated Component Matrix

<table>
<thead>
<tr>
<th>Component</th>
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</thead>
</table>

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<table>
<thead>
<tr>
<th></th>
<th>PSP-MP</th>
<th>Bulbar ALS-MP</th>
<th>Mixed/ALS-MP</th>
<th>PD-MP</th>
<th>CBS-MP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck rigidity</td>
<td>.833</td>
<td>.071</td>
<td>.219</td>
<td>.086</td>
<td>.007</td>
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<tr>
<td>Impaired eyelid function</td>
<td>.806</td>
<td>-.043</td>
<td>.135</td>
<td>-.120</td>
<td>-.072</td>
</tr>
<tr>
<td>Supranuclear gaze palsy</td>
<td>.783</td>
<td>-.026</td>
<td>.051</td>
<td>-.005</td>
<td>.149</td>
</tr>
<tr>
<td>Dystonia</td>
<td>.754</td>
<td>-.048</td>
<td>.058</td>
<td>-.026</td>
<td>.114</td>
</tr>
<tr>
<td>Pseudobulbar palsy</td>
<td>.723</td>
<td>.021</td>
<td>.020</td>
<td>.137</td>
<td>-.105</td>
</tr>
<tr>
<td>ataxia</td>
<td>.463</td>
<td>-.011</td>
<td>-.093</td>
<td>.271</td>
<td>.165</td>
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<tr>
<td>Respiratory muscle weakness</td>
<td>.002</td>
<td>.956</td>
<td>.038</td>
<td>-.051</td>
<td>-.006</td>
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<tr>
<td>Neck weakness</td>
<td>.007</td>
<td>.951</td>
<td>.062</td>
<td>-.048</td>
<td>-.012</td>
</tr>
<tr>
<td>Bulbar palsy</td>
<td>-.003</td>
<td>.843</td>
<td>.128</td>
<td>-.072</td>
<td>.007</td>
</tr>
<tr>
<td>Facial weakness</td>
<td>.027</td>
<td>.775</td>
<td>.276</td>
<td>.025</td>
<td>-.063</td>
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<tr>
<td>Myoclonus</td>
<td>.007</td>
<td>.720</td>
<td>-.048</td>
<td>.318</td>
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<td>Spasticity</td>
<td>.335</td>
<td>.130</td>
<td>.740</td>
<td>.049</td>
<td>.056</td>
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<tr>
<td>Limb weakness</td>
<td>-.049</td>
<td>.544</td>
<td>.687</td>
<td>.002</td>
<td>.004</td>
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<tr>
<td>Limb fasciculations</td>
<td>-.170</td>
<td>-.136</td>
<td>.669</td>
<td>.061</td>
<td>.081</td>
</tr>
<tr>
<td>Arising from chair</td>
<td>.562</td>
<td>.398</td>
<td>.613</td>
<td>.067</td>
<td>-.042</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>.493</td>
<td>-.004</td>
<td>.602</td>
<td>.423</td>
<td>.075</td>
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<tr>
<td>Sitting down</td>
<td>.580</td>
<td>.393</td>
<td>.581</td>
<td>.063</td>
<td>-.048</td>
</tr>
<tr>
<td>Postural instability</td>
<td>.562</td>
<td>.352</td>
<td>.576</td>
<td>.152</td>
<td>.119</td>
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<tr>
<td>Hyperreflexia</td>
<td>.218</td>
<td>.327</td>
<td>.501</td>
<td>.015</td>
<td>.198</td>
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<tr>
<td>Rest tremor</td>
<td>.051</td>
<td>.047</td>
<td>-.095</td>
<td>.856</td>
<td>.053</td>
</tr>
<tr>
<td>Postural tremor</td>
<td>-.011</td>
<td>.011</td>
<td>.121</td>
<td>.806</td>
<td>.020</td>
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<tr>
<td>overall LI</td>
<td>.098</td>
<td>.058</td>
<td>.425</td>
<td>.665</td>
<td>.384</td>
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<tr>
<td>rigidity</td>
<td>.418</td>
<td>-.045</td>
<td>.198</td>
<td>.469</td>
<td>.188</td>
</tr>
<tr>
<td>Cortical sensory loss</td>
<td>.041</td>
<td>.036</td>
<td>-.037</td>
<td>-.023</td>
<td>.798</td>
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<tr>
<td>Limb apraxia</td>
<td>.025</td>
<td>-.004</td>
<td>.090</td>
<td>.313</td>
<td>.774</td>
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<tr>
<td>Alien limb phenomenon</td>
<td>.062</td>
<td>-.009</td>
<td>.133</td>
<td>.051</td>
<td>.590</td>
</tr>
</tbody>
</table>

Factor loadings exceeding 0.4 are color-coded depending on the associated component.


Figure legends
Fig. 1 Multidimensional scaling of motor signs and genetic cases respectively. A) Two-dimensional spatial representation based on the similarity of clinical variables as revealed by MDS. Variables that have been assigned to a specific motor phenotype by PCA are colour-coded. B) Two-dimensional spatial representation based on the similarity of cases as revealed by MDS. Cases are colour-coded according to their affected gene.

Fig. 2 Severity and frequency of motor signs. A) Comparison of the severity of motor signs as defined by the sum scores of the individual motor phenotypes according to the affected gene; B) Comparison of the frequency of motor signs between pathogenic variant carriers showing motor signs. Patients may present motor signs of different phenotypes, therefore the sum of frequencies does not add up to 100%.

Fig. 3 Proportion of the dominant clinical phenotype of patients with motor signs depending on the affected gene. Cases were assigned to the component with the highest PCA-based sum
score. As patients may present motor signs of other motor phenotypes in addition to the signs of the predominating motor phenotype, this figure is not congruent with Figure 2B.

Fig. 4 Correlation of sum scores of motor phenotypes with cerebral atrophy using linear regression models. T-maps from the analysis of gray and white matter were merged for visualization purposes. A) PSP-like motor phenotype, arising from c9orf72, GRN and MAPT pathogenic variants not progressive supranuclear palsy pathology; B) PD-like motor phenotype, arising from c9orf72, GRN and MAPT pathogenic variants not Parkinson’s disease; C) Mixed/ALS-like motor phenotype, arising from c9orf72, GRN and MAPT pathogenic variants.
Fig. 5 Calculated sum scores and overall laterality index (with 95% confidence intervals) respectively versus estimated years to symptom onset (EYO). An early increase of motor signs, up to 25 years prior to the expected symptom onset, could be detected in $c9orf72$ pathogenic variant carriers. In $MAPT$ pathogenic variant carriers motor signs occurred latest. The point in time at which the lower 95% confidence interval of the model crosses the x-axis is marked by a vertical bar in the respective colour for each group. While the severity of motor signs remained highest in $c9orf72$ pathogenic variant carriers over time, severity of motor signs of $GRN$ and $MAPT$ pathogenic variant carriers progressively converged. Individual data points are not plotted to prevent disclosure of genetic status. However, the time of the examination is marked on the x-axis by a coloured dash.
Frequency and Longitudinal Course of Motor Signs In Genetic Frontotemporal Dementia
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