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Characterization of Movement Disorder Phenomenology in Genetically Proven, Familial Frontotemporal Lobar Degeneration: A Systematic Review and Meta-Analysis

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Abstract

Background

Mutations in granulin (*PGRN*) and tau (*MAPT*), and hexanucleotide repeat expansions near the *C9orf72* genes are the most prevalent genetic causes of frontotemporal lobar degeneration. Although behavior, language and movement presentations are common, the relationship between genetic subgroup and movement disorder phenomenology is unclear.

Objective

We conducted a systematic review and meta-analysis of the literature characterizing the spectrum and prevalence of movement disorders in genetic frontotemporal lobar degeneration.

Methods

Electronic databases were searched using terms related to frontotemporal lobar degeneration and movement disorders. Articles were included when cases had a proven genetic cause. Study-specific prevalence estimates for clinical features were transformed using Freeman-Tukey arcsine transformation, allowing for pooled estimates of prevalence to be generated using random-effects models.

Results

The mean age at onset was earlier in those with *MAPT* mutations compared to *PGRN* ($p<0.001$) and *C9orf72* ($p = 0.024$). 66.5% of subjects had an initial non-movement

presentation that was most likely a behavioral syndrome (35.7%). At any point during the disease, parkinsonism was the most common movement syndrome reported in 79.8% followed by progressive supranuclear palsy (PSPS) and corticobasal (CBS) syndromes in 12.2% and 10.7%, respectively. The prevalence of movement disorder as initial presentation was higher in *MAPT* subjects (35.8%) compared to *PGRN* subjects (10.1). In those with a non-movement presentation, language disorder was more common in PGRN subjects (18.7%) compared to MAPT subjects (5.4%).

Summary

This represents the first systematic review and meta-analysis of the occurrence of movement disorder phenomenology in genetic frontotemporal lobar degeneration. Standardized prospective collection of clinical information in conjunction with genetic characterization will be crucial for accurate clinico-genetic correlation.

Introduction

Frontotemporal lobar degeneration (FTLD) is a clinically, genetically and pathologically heterogeneous group of neurodegenerative disorders. Clinical presentation is characterized by variable but progressive disturbances in behavior, cognition and language [1]. It is the fourth most common cause of dementia in people over age 65, after Alzheimer´s disease (AD), Dementia with Lewy Bodies (DLB) and vascular cognitive impairment [2], and the second most common cause of young-onset dementia after AD [3]. There is a positive family history in 30–50% of FTLD patients with at least one family member presenting with similar symptomatology. ~10–20% of FTLD cases have an autosomal dominant pattern of inheritance [1, 4, 5]. While cognitive and behavioral features have been well described, movement disorder phenomenologies have been poorly and inconsistently characterized as part of the clinical spectrum of FTLD. Despite this, the association between Parkinsonism and other movement disorder phenomenologies have been recognized since the first part of the 20th century [von Braunmuhl 1930; Akeliatis 1944]. with movement features presenting prior to, in conjunction with, or following cognitive and psychiatric symptoms [6].

Since the identification of FTLD-disease causing mutations in *MAPT* in 1998 [7], *PGRN* in 2006 [8], and hexanucleotide repeat expansions in *C9orf72* genes in 2011 [9], literature regarding clinico-genetic correlates has emerged. However, clinical descriptions are often disparate, of variable quality and detail, and in the form of single case reports or case series. Given the wide spectrum of presentations and lack of consistent reliable reporting, we examined the literature in its entirety in the form of a systematic review and meta-analysis to synthesize available data.

The objective of this work was to estimate the prevalence of clinical syndromes, and to identify trends in demographic characteristics and clinical presentations that may correlate with known genetic FTLD subgroups. Given the quest for biologic and clinical markers that could theoretically provide ante-mortem diagnosis and possibly disease modifying therapies, [10] precise clinical characterization may help identify candidates appropriate for further testing.

The results of this meta-analysis have been, in part presented in poster form at the 19th international congress of Parkinson´s disease and Movement Disorders (June 2015, San Diego, USA) and published as an abstract (http://onlinelibrary.wiley.com/doi/10.1002/mds.26295/full)

Methods

Selection of studies

A systematic review of the literature was performed searching PubMed and EMBASE databases and included all English language articles published from January 1, 1998 (the year of the identification of the first FTLD gene, *MAPT*) up to September 1, 2013 to identify all reports of genetically confirmed FTLD with a movement disorder spanning this time interval.

The search was restricted to the three most common FTLD pathogenic genes; *MAPT*, *PGRN* and *C9orf72*. Definition of "pathogenic" included: segregation of the gene mutation with an FTLD phenotype and/ or with pathologically-proven FTLD within a family; prediction that the mutation would be damaging to protein function consistent with the known mechanism of genetic disease; and/ or the mutation is already known to be causative of disease.

Since mutations in other FTLD-associated genes, *CHMP2B*, *VCP*, *TARDBP*, and *FUS*, are extremely rare and represent a minority of familial FTLD cases accounting for less that 1% each [11], they were excluded from analysis. Subjects with clinically typical Parkinson's disease [12] identified to have *C9orf72* expansions that were deemed of unclear significance or incidental and not clearly causal, were excluded from analysis[13–15]. We did not stratify based on specific mutation genotype in *PRGN* or length of *C9orf72* hexanucleotide repeats for the following reasons: 1) *PRGN* mutations have a uniform pathogenic mechanism of haploinsufficiency [8], and 2) there appears to be no association between hexanucleotide repeat expansion length in *C9orf72* and clinical syndrome [12]. Since it is known that the majority of pathogenic mutations in *MAPT* occur in exons 9 through 13, we examined only cases with these exonic mutations; power issues prevented us from analyzing individual *MAPT* mutations [4]. In addition, insufficient power prevented us from analyzing in a meaningful way the prevalence of the movement disorder phenomenology observed in any of the specific genotype sub-groups for each of the three genes.

In summary, we examined the occurrence of specific movement disorder phenomenology in individuals or patient series that confirmed any mutation in *PGRN* or *MAPT* determined to be pathogenic, or in those with *C9orf72* repeat expansions greater than 30.

The search engines were queried using the terms illustrated in **Table 1** including a combination of every "A" + every "B" term. Titles and abstracts that described movement disorder features in the context of genetically proven FTLD were flagged and the full articles were reviewed.

Table 1. Search terms used for PubMed and EMBASE searches.

A	B
Frontotemporal lobar degeneration	Parkinsonism
Frontotemporal dementia	Dystonia
Motor neuron disease	Stereotypy/stereotypical movements
Semantic dementia	Tic
Progressive nonfluent aphasia	Myoclonus
Progranulin	Gait
PGRN	Corticobasal syndrome/disease
GRN	Tremor
(FTDP-17/FTDP17)	Progressive supranuclear palsy
(FTD-U)	Chorea
(MAPT)	Movement disorder
(C9orf72)	

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Inclusion criteria included: (i) movement disorder at some point in disease course; (ii) detailed clinical description of movement disorder phenomenology; (iii) FTLD proven genetically (*MAPT*, *PRGN*, *C9orf72* causative variants); (iv) human subjects; (v) papers published in English; and (vi) inclusion and presentation of data sufficient for estimation of the proportion of patients presenting with outcome of interest. Exclusion criteria included: (i) lack of movement disorder as part of clinical presentation; (ii) lack of description of movement disorder phenomenology; (iii) clinical information not presented individually or in ratios (i.e. data must have been presented in a way that showed frequency of clinical features); (iv) absence of genetic confirmation of FTLD; (v) animal or in vitro data without human subjects; (vi) previously reported data.

Abstracts were verified by two independent reviewers (BBS, CG). In cases where insufficient information was provided to determine eligibility for inclusion, the full article was reviewed. Some subjects were reported more than once in different publications and when uncertainty existed, the authors were contacted to ensure duplication of reporting did not occur. A manual search of references from included publications was performed. Those studies that met inclusion criteria and that were not already identified through the database query were included in the meta-analysis.

Data extraction

Data extraction was performed in duplicate using a standard assessment form by two investigators (BBS, CG). Any differences among results were discussed among co-authors (GKF, MM, AEL) until consensus was achieved. In addition to genetic data, demographic and disease specific clinical characteristics of movement disorder and other features were collected. These included:

1. Average age of symptom onset, gender, and duration of symptoms
2. Initial presentation (movement, non-movement or both)
    a. Non-movement syndromes included behavioral, language or other cognitive disorder or any combination of these
3. Prevalence of MD "syndromes"
    a. Parkinsonism defined as bradykinesia and rigidity
    b. Progressive supranuclear palsy syndrome (PSPS) syndrome defined as vertical gaze abnormality, and either axial rigidity, OR postural instability.
    c. Corticobasal syndrome (CBS) defined as asymmetry (any one of dystonia, rigidity, bradykinesia) AND at least one cortical feature including myoclonus, cortical sensory loss, limb apraxia or aphasia.
4. Levodopa-response classified as absent, partial or good.

We attempted to extract information in isolation of specific MD syndromes, such as presence of dystonia, myoclonus, etc., but this was not possible since the calculated probabilities are derived from study-level data and there is no way to stratify these probabilities in isolation for an individual phenomenology. For example, if a study had 10 subjects and the probability of Parkinsonism was 0.4 and the probability of rigidity was 0.3 and the probability of bradykinesia was 0.2, there was no way to tell which of the 10 subjects only had one of the phenomenologies.

Similarly, we chose to identify the most common and recognized clinical PSPS syndrome ("Richardson syndrome") and were not able to stratify the other variant subtypes of PSPS [PSP-CBS, PSP with pure akinesia with gait freezing (PAGF)] for similar reasons.

Quality of the literature

A quality assessment was performed for each study based on criteria developed by the investigators. Studies were assigned one point for each question answered "Yes":

1. $\geq$ 5 subjects
2. Details of movement disorder phenomenology in the first 3 years of the disease in at least 50% of the sample. If the movement disorder phenomenology appeared after three years or if a study did not specify when the movement disorder occurred in the course of the illness, no point was assigned.
3. Longitudinal follow-up of $\geq$ 5 years

Statistical analysis

For descriptive statistics, one-way ANOVA was used to assess for statistical differences between genetic subgroups for continuous variables. Fisher's exact test was used for categorical variables. A p-value of $\leq$0.05 was considered statistically significant.

Case studies

To allow for inclusion of the large number of case studies (reports based on single patients) populating the current literature, case studies were combined to form a single patient population, which was treated as a publication for meta-analytic purposes. For each outcome of interest, the number of patients with and without the outcome within the artificial study was used to obtain the study-specific prevalence for the outcome.

Meta-analysis

Summary pooled estimates of the extracted prevalence data were obtained by conducting random-effects meta-analyses using the DerSimonian and Laird method [16]. Prevalence data for initial presentation (movement, non-movement or both), syndromes, and individual phenomenologies from individual studies were pooled together by first using the Freeman-Tukey arcsine transformation [17] The variance was calculated as $\frac{1}{(N_{total}+1)}$, where N_{total} was the number of patients in the study, and the transformed prevalence estimates were converted back as $\left(sin\left(\frac{N_{transformed}}{2}\right)\right)^2$, where $N_{transformed}$ was the transformed estimate [18]. Summary pooled estimates were presented as percentages. As a secondary outcome, the analysis was also stratified by *MAPT*, *PGRN*, and *C9orf72* genetic mutations to examine for potential trends.

Between-study heterogeneity was assessed using the and I^2 statistic. Confidence intervals (CIs) for I^2 statistic were also calculated to quantify the uncertainty in the heterogeneity estimates [19] Substantial heterogeneity was considered to be present if the I^2 statistic or confidence intervals were $\geq$ 50% (http://handbook.cochrane.org/chapter_9/9_5_2_identifying_and_measuring_heterogeneity.htm). Additionally, the H statistic and confidence intervals were also calculated to support the heterogeneity assessment, with a value of 1 indicating homogeneity [20]

In addition to quantifying the heterogeneity, summary pooled estimates for initial presentation, syndromes, and phenomenologies were recalculated under the assumption of substantial heterogeneity (I^2 = 90%) in order to assess the impact of undetected heterogeneity on estimates [21].

Publication bias was a concern due to the inclusion of case studies, which may represent the most extreme presentations of FTLD. Each outcome of interest was assessed graphically using

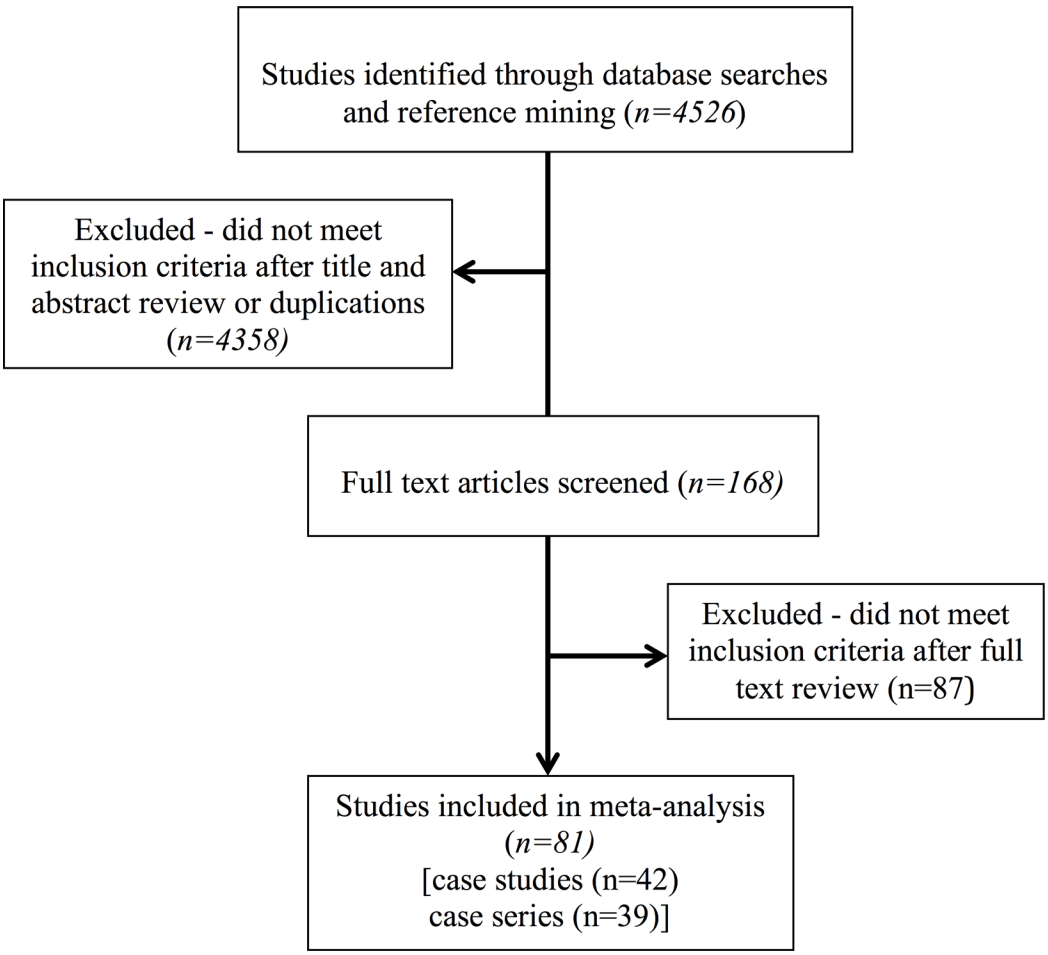

Fig 1. Flow diagram of the study selection process.

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funnel plots where the logit of the outcome was plotted against the study variance. Egger's test for funnel plot asymmetry was used to statistically assess for publication bias only where there were at least 10 studies [22]. A p-value of ≤ 0.05 was considered statistically significant.

We performed sensitivity analyses evaluating the impact of including the pooled case studies by repeating the main analysis without them. Values from the main analysis and the sensitivity analysis were compared to assess the influence of the inclusion/exclusion of the case studies.

All statistical analyses were conducted in Stata version 12.1 (Stata Corp., College Station, TX).

Results

The combined MEDLINE and EMBASE searches yielded 4526 original titles (**Fig 1**, Prisma Flow Diagram). 168 full text-articles were reviewed, including those that did not include an abstract and could not be excluded form reviewing the title; 87 articles were excluded due to insufficient clinical data (**S1 Table**). A total of 77 distinct studies were included in the meta-analysis [23–99].

However, for the purpose of data collection, in those studies that included mutations in more than one gene (4 studies), each mutation and clinical information related to that mutation, was treated as a separate study. Using this method, a total of 81 studies were included in

this systematic review. Of these 42 were case series ($n \geq 2$) and 39 were individual case studies ($n = 1$). There were a total of 376 patients included from all studies. The proportion of cases with mutations in *MAPT*, *PGRN*, and *C9orf72* expansions was 44.2%, 31.7%, and 24.2%, respectively.

Demographic Characteristics

Table 2 outlines the demographic characteristics of study subjects. The mean age at onset for all subjects with genetically confirmed FTLD and a movement disorder was 51.7 years old. Men and women were represented approximately equally with an average disease duration spanning the time from symptom onset till death of 7.1 years.

There was a significant difference between the age at onset stratified by genetic mutation ($p<0.001$). The age at onset was significantly earlier in patients with *MAPT* compared to *PGRN* ($p<0.001$) and *C9orf72* ($p = 0.024$). The age at onset was not statistically different between *PGRN* and *C9orf72* ($p = 0.126$). No other demographic characteristics differed significantly by genetic mutation.

Initial presentation

Characteristics of subjects upon initial presentation are outlined in Table 3. 27.1% (95% CI 17.4–37.9%) of subjects were identified to have their first manifestation of illness as a movement disorder (preceding cognitive or behavioral symptoms). Except for 4 subjects with *C9orf72* mutations presenting with motor neuron disease (MND) [37, 85] and another 2 subjects also with *C9orf72* mutations presenting with MD and MND [82, 85], all subjects with movement symptoms at onset presented with a movement disorder including clinical syndromes of Parkinsonism, CBS or PSPS. We will not comment further or present data on patients with a pure MND presentation.

The number of studies used to calculate the summary pooled estimate for each outcome of interest can be seen in S2 Table**.** In ~66.5% (95% CI 54.0–78.0%) of subjects, the initial presentation was categorized as non-movement. Subjects whose initial presentation was non-movement most commonly manifested a behavioral syndrome (35.7%, 95% CI 24.4–47.9%), while cognitive (14.4%, 95% CI 8.7–21.2%) and language (9.9%, 95% CI 6.6–13.8%) presentations were less frequent. Some of the non-movement presentations were variable combinations of behavioral, cognitive and language symptoms (S3 Table).

Pooled estimates for movement disorder presentation differed between *MAPT* and *PGRN* mutations. 35.8% (95% CI 18.9–54.8%) of subjects with *MAPT* presented with an initial

Table 2. Demographic characteristics of study subjects stratified based on genetic subgroup.

	MAPT	PGRN	C9ORF72	Overall
No. of patients: *Frequency* (%) [A]	166 (44.1)	119 (31.7)	91 (24.2)	376 (100.0)
No. of patients per study: *mean* (min, max) [B]	7.2 (2.0, 25.0)	10.0 (2.0, 34.0)	8.3 (2.0, 40.0)	8.6 (2.0, 40.0)
Age at onset: *Mean years* (min, max) [C]	45.8 (28.0, 63.5)	59.6 (54.8, 68.5)	54.7 (42.3, 70.5)	51.7 (28.0, 70.5)
Disease duration: *Mean years* (min, max) [D]	6.5 (0.7, 16.0)	6.9 (4.9, 10.0)	8.0 (2.1, 16.2)	7.1 (0.7, 16.2)
Proportion of males: % (95% CI) [E]	50.7 (38.0–63.4)	42.7 (31.8–54.0)	41.7 (25.1–59.3)	45.7 (37.9–53.7)

[A] Fischer's exact test: $p = 0.315$, therefore not statistically significant.

[B] Fischer's exact test: $p = 0.196$, therefore not statistically significant.

[C] One-way ANOVA: $p<0.001$; MAPT vs. PGRN: <0.001; MAPT vs. C9ORF72: 0.024; PGRN vs. C9ORF72: 0.126.

[D] One-way ANOVA: $p = 0.860$, therefore not statistically significant.

[E] Estimates from random-effects meta-analyses.

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Table 3. Initial Presentation stratified based on genetic subgroup.

	MAPT % (95% CI)	PGRN % (95% CI)	C9ORF72% (95% CI)	Overall % (95% CI)
Movement Disorder	35.8 (18.9–54.8)	10.1 (4.8–17.1)	34.0 (14.9–56.3)	27.1 (17.4–37.9)
Non-movement Disorder	62.7 (44.0–79.6)	83.6 (73.8–91.5)	46.2 (17.5–76.3)	66.5 (54.0–78.0)
Movement + Non-movement Disorder	5.8 (2.4–10.4)	7.2 (2.9–13.4)	15.1 (5.7–28.1)	7.7 (4.8–11.1)

Note: 13 studies missing data on initial presentation necessary to calculate percentage with each type of initial presentation. 3 studies with incomplete data on initial presentation.

Due to the random effects meta-analysis, the studies are being given different weights dependent on the sample size so the overall number of subjects do not sum to 100%. The studies with missing data are very small so they do not add much weight to the estimates.

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movement disorder, whereas 10.1% (95% CI 4.8–17.1%) of subjects with *PGRN* had an initial movement disorder. Additionally, 5.4% (95% CI 2.2–10.0%) of subjects with genetic mutation *MAPT* presented with a language disorder, in contrast to 18.7% (95% CI 11.5%-27.3%) of subjects with *PGRN*. For both of these outcomes, the 95% CIs for the estimates stratified by genetic mutation did not overlap, indicating a statistically significant difference (which cannot be ruled out when CIs overlap) [100].

Parkinsonism, Corticobasal (CBS) and Progressive Supranuclear Palsy Syndromes (PSPS)

Parkinsonism was the most common movement disorder syndrome reported in 79.8% of subjects (95% CI 69.7–88.2%) followed by PSPS (12.2%, 95% CI 6.2–19.7%) and CBS (10.7%, 95% CI 6.7–15.4%), respectively, at any given time during the course of the disease (**Table 4**).

Levodopa Responsiveness

Response to levodopa is summarized in **S1 Fig** comprising a total of 63 distinct subjects in 25 studies. Overall levodopa response was good in 15.3% (95% CI 4.2–31.6%) of patients reported, partial in 21.9% (95% CI 7.7–40.8%) and absent in 50.9% (95%CI 23.3–78.3%) (**S4 Table**).

Literature Quality

25.9% of the studies had 5 or more subjects (**S5 Table**); 69.1% of studies had detailed information regarding the movement disorder phenomenology in the first 3 years; 44.4% of studies reported clinical information for 5 or more years.

Heterogeneity and Publication Bias

The heterogeneity was quantified for overall outcomes and is presented in **S6 Table**. Based on an established threshold of $\geq$ 50% for the I^2 statistic, most estimates were found to have substantial heterogeneity. For movement disorder at initial presentation, the proportion of variation due to heterogeneity between studies was 73.8% (95% CI 63.7–81.1%). Initial presentation

Table 4. Movement disorder syndromes present at any point during the FTLD disease course stratified based on genetic subgroup.

	MAPT % (95% CI)	PGRN % (95% CI)	C9ORF72% (95% CI)	Overall % (95% CI)
PSPS	17.4 (5.8–33.5)	8.1 (1.8–18.3)	6.0 (2.1–11.9)	12.2 (6.2–19.7)
CBS	7.6 (3.7–12.8)	26.4 (10.6–46.3)	6.1 (2.3–11.6)	10.7 (6.7–15.4)
Parkinsonism	79.9 (63.8–92.1)	71.3 (54.7–85.4)	91.4 (81.3–97.8)	79.8 (69.7–88.2)

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as non-movement disorder had a similar result with the variation resulting from between-study heterogeneity being 75.4% (95% CI 65.8–82.3%). For the subset with non-movement disorder at initial presentation that manifested as a behavioral syndrome, the between study variation from heterogeneity was 73.2% (95%CI 62.4–80.9).

Parkinsonism and PSPS also both had I^2 statistics that were greater than 50% indicating substantial heterogeneity. Estimates for levodopa response that were absent or partial were 78.2% (95% CI 57.0–88.9%) and 58.3% (95% CI 8.8–81.0%) respectively. With the exception of partial levodopa response, the I^2 95% CIs were above 50% for the outcomes mentioned, indicating with high certainty that substantial heterogeneity was present for these outcomes. Performing the H statistic replicated these findings, with the H statistic and 95% CIs above 1.5.

The impact of the heterogeneity was assessed by repeating the main analysis under the assumption that the proportion of between study variation due to heterogeneity was 90%. The results are presented in **S7 Table**. The largest differences were found for levodopa response, CBS, and cognitive and language presentations. However, all of the differences were less than 2%, with the largest for levodopa response (present) being 1.9%.

Finally, meta-analyses of the main outcomes were conducted without the inclusion of pooled case studies. Pooled summary estimates along with the quantified heterogeneity are presented in **S8 Table**. When comparing the results from the main analysis with the sensitivity analysis, the 95% CIs for all the estimates overlapped. Similar to the analysis comparing genetic mutations, statistical significance cannot be ruled out when CIs overlap. However, none of the estimates were necessarily statistically different.

There was evidence of publication bias for two outcomes of interest where there were more than 10 studies included: behavioral + cognitive disorder at presentation and Parkinsonism with a larger number of smaller studies having a lower proportion of behavioural + cognitive disorder reported ($p<0.001$) (**S2 Fig**). With respect to Parkinsonism, there was a larger number of smaller studies having a higher proportion of Parkinsonism reported ($p<0.001$) (**S3 Fig**).

Discussion

The focus of this systematic review and meta-analysis was to determine prevalence of movement disorder phenomenology in people with genetically proven FTLD and manifesting a movement disorder during the disease course, and also to explore whether genetic mutation predicted clinical characteristics. It was not within the scope of this review to determine prevalence of movement disorders in all cases of genetically proven FTLD as those without movement disorders were not included in the cohort. We also chose to exclude studies that had only pathologically proven FTLD without genetic confirmation to manage the scope of our study, though pathological data was collected and will be the subject of a separate manuscript.

While the published literature is variable in quality and comprised mostly of retrospective case reports and small case series, this first comprehensive review synthesizes and summarizes trends in movement disorders occurring in genetically confirmed FTLD in the available literature.

Prevalence of genetic mutations

PGRN, *MAPT* and *C9orf72* gene variants account for at least 17% of total FTLD cases [101], and between 32–40% of all identified genetic causes of FTLD [9]. *PGRN and MAPT* are estimated to account for 5–20% of familial FTLD cases, and *C9orf72* mutations account for ~21% of familial FTLD cases [102] The genetic mutations thought to contribute to the remainder of familial FTLDs (~60%) confirmed by positive family history are rare or as yet undiscovered [103].

PGRN is found causative in an additional 1–5% of sporadic FTLD cases. C9*orf*72 is also responsible for related syndromes occurring in 6% of sporadic FTLD cases, 37% of familial ALS cases, and 6% of sporadic ALS cases [102, 104]. In all series, the *C9orf72* repeat expansions have been the most common genetic cause of familial ALS (more frequent than *SOD1* mutations).

In our highly selected population (cases of *MAPT*, *PGRN* and *C9orf72* causing FTLD and a movement disorder), the most common gene involved was *MAPT* with a prevalence of 44% followed by *PGRN* (32%) and *C9orf72* (24%). Since *MAPT* mutations were first identified in 1998, 8 years before *PGRN* was discovered, and 13 years before *C9orf72* was discovered, the large number of papers dealing with *MAPT* mutations may have artificially skewed the prevalence findings to appear that MAPT has a significantly higher proportion of movement disorders in its clinical presentation.

Age at onset

Age at onset of familial FTLD has been reported to differ depending on genetic mutation with *PGRN* presenting on average at age 59 [105] and *C9orf72* at age 56 [52] whereas *MAPT* presents on average at age 49 [106]. Similarly, in our subset of patients with FTLD and a movement disorder, *MAPT* patients presented at age 46, *PGRN* at age 60, and *C9orf72* at age 55 (**Table 2**). Significant differences were found between *MAPT* and *PGRN* and between *MAPT* and *C9orf72*. There was no significant difference between *PGRN* and *C9orf72*.

Disease duration

Disease duration in FTLD has been reported to be approximately 7 years in *PGRN* and *MAPT* [106] and 5 years in *C9orf72*. This can be explained by the high frequency of MND/ALS reported among FTLD-*C9orf72* carriers (> 40%) [52]. In contrast, our cohort showed the opposite trend with *C9orf72* mutation carriers having an average disease duration of 8 years; though there were no statistically significant differences between genetic subgroup, the trend towards a longer disease duration in the *C9orf72* mutation carriers would seem counter intuitive and contrasts with other reports. One possible explanation is the fact that in this population of genetically-confirmed FTLD patients with a MD, there was a low frequency of MND in the *C9orf72* population (6/91~7% of the cohort). Still the lack of statistical difference between *C9orf72* subjects and *MAPT/PGRN* is likely artefactual and may represent a power issue. The number of *C9orf72* subjects was lower (though the difference was not statistically significant) than the subjects manifesting the other mutations and so may be too small to accurately reflect a real difference.

Initial presentation

FTLD has been reported to present as a primary language deficit [progressive non-fluent aphasia (PNFA), semantic dementia (SD)] or a behavioral variant (bvFTD); bvFTD has the highest prevalence representing 50–70% of all the FTLD cases [1,2,4]. The majority of subjects in our cohort also reported behavioral, cognitive or language abnormalities as a defining initial feature of illness (67%); an additional 8% of studies had combined non-movement and movement symptoms at initial presentation. 27% of subjects presented with a MD as the first manifestation of illness.

Movement disorder as initial presentation was higher in *MAPT* subjects (36%) compared to subjects with *PGRN* mutation (10%). In studies with non-movement manifestations as initial presentation, language disorder was less common in *MAPT* subjects (5%) compared to subjects

with *PGRN* mutation (19%). Other differences between genetic mutation could not be determined due to the 95% CIs overlapping between summary pooled outcomes.

Movement Disorders

Parkinsonism. The most common movement disorder syndrome associated with all FTLD is Parkinsonism. The prevalence of Parkinsonism in patients with FTLD reported in the literature varies widely between 6%-30% [6, 107, 108]. The phenomenology includes axial and limb rigidity, bradykinesia and postural instability. Resting tremor is usually absent [11], although other types of tremor are not unusual [52, 109]. Levodopa responsiveness is rare but does occur, generally with an initial good, but transient, or only partial response [11, 110]. Comparing these previous reports to our population is difficult given that all studies included in the meta-analysis, by definition had a movement disorder reported at some point in the disease course. In this context, Parkinsonism was also the most common syndrome reported in ~80% of studies; the prevalence of Parkinsonism appeared uniform across genetic mutations with no one gene being necessarily associated with a higher prevalence of Parkinsonism than the others due to the overlapping 95% CIs of the summary pooled estimates. In our cohort, ~37% of the patients receiving L-dopa had at least a partial response though this may be strongly influenced by reporting bias as many of the studies did not mention whether a trial of L-dopa was undertaken.

CBS and PSP-like syndromes. The prevalence of PSPS and CBS in the context of FTLD has not been well studied. One retrospective clinical study looking at the distribution of clinical syndromes in FTLD found that CBS and PSPS combined were present in 8.6% of the cohort representing only a small proportion of all FTLD syndromes [111]. PSPS is typically associated with tau pathology while CBS is recognized to be associated with variable underlying histopathology including tau, TDP-43 and Alzheimer's disease [112]. With respect to genetically defined FTLD, CBS has been most often associated with *PGRN* mutations though the prevalence of CBS due to *PGRN* is not known. In our meta-analysis, CBS was identified in ~11% of patients of genetic FTLD combined with MD. CBS appeared to occur more commonly with *PGRN* mutations compared to *MAPT* and *C9orf72* mutations, however the 95% CIs overlapped so conclusions are limited.

PSPS in our cohort was reported in ~12% of patients. We were unable to confirm differences in presentation of PSPS by genetic mutation due to the 95% CIs overlapping for summary pooled estimates between genetic subgroups. In previous literature, PSPS has been most often associated with *MAPT* mutations [51, 81, 113] and rarely reported due to *PGRN* mutations [63, 77, 88] or *C9orf72* expansions [59, 78].

Heterogeneity

Evidence of heterogeneity was found for some pooled estimates from the main analysis. Movement disorders, non-movement disorders, behavioral disorders, PSPS, Parkinsonism, and levodopa responsiveness (that was absent) all had I^2 statistics above 50%. Additionally, the 95% CIs for the statistic were also above 50% indicating that there was substantial variation in estimates between studies due to heterogeneity. Similarly, the H statistic, which is generally stable and independent of the number of studies included in the analysis, confirmed the heterogeneity for these outcomes with the 95% CIs being ≥ 1.5 [20].

When meta-analyses were conducted under the assumption of substantial heterogeneity ($I^2 = 90\%$), estimates were consistent with the main analysis. This indicates that any undetected heterogeneity in the main analysis seems to have a minimal impact on estimates. The biggest absolute percent difference was 1.9% for levodopa responsiveness that was present. As

expected, for the outcomes where high heterogeneity was detected in the main analysis, the percent difference was minimal when the I^2 was assumed to be 90%.

The impact of including the case studies (reports on single patients) was also assessed by excluding them and re-running the analyses. The estimates appeared to be similar without the case studies. Importantly, the same outcomes were found to have substantial heterogeneity as when the case studies were included. This indicates that the inclusion or exclusion of them alone is unlikely to explain the detected heterogeneity.

Further work is needed to explore and understand the detected heterogeneity in the outcomes examined in this paper. Genetic subgroup may be a potential factor, however this could not be firmly concluded in this analysis due to the small number of studies available stratifying by genetic mutation. While some outcomes such as movement disorder and language disorder at initial presentation were found to be statistically different between subjects with *MAPT* and *PGRN* mutations due to the non-overlapping 95% CIs, it is uncertain whether there are other statistical differences for the other outcomes by genetic mutation. More work is required to explore these outcomes by genetic subgroup as well as other possible factors that may explain the heterogeneity. The detected heterogeneity could reflect truly heterogeneous clinical features of genetic FTLD, variability in methods and measurement by investigators across studies, or heterogeneity that is attributable to some other study attribute that was not identified or recorded. It is important to interpret pooled estimates from multiple studies with caution where heterogeneity is present, as average effects across studies may provide a poor representation of the effects in individual subpopulations.

Quality of the literature

One variable we examined when assessing quality of the literature was description of movement disorder phenomenology within the first three years of the illness. It is well recognized that as neurodegenerative diseases advance, regardless of the underlying pathogenesis or causative genetic mutation there is a common later-stage syndrome of rigidity, immobility and eventually progression to the bed bound state [114] As such, we were primarily interested in how the illness presented in order to theoretically help direct evaluations for the purpose of diagnosis. Once a full blown cognitive syndrome manifested, a diagnosis was likely already determined.

Other factors we used to determine whether the literature was of good quality related to number of cases in a study; single case reports tend to report greater detail but often are unusual presentations and not necessarily representative of a population. Given the fact that advances in this field are relatively recent, prospective, large population studies outlining natural history, clinical features, genetic and pathologic studies are uncommon and therefore our results must be interpreted with caution. While this is the first systematic review and meta-analysis to synthesize available data regarding genetic subgroups and movement disorders in genetic FTLD, the conclusions are based on imperfect data.

Other limitations

We included standard criteria for definitions of the three syndromes of Parkinsonism, PSPS and CBS. While we were interested in analyzing the frequency of individual features such as tremor, dystonia and other movement disorder phenomenology when not part of a clinical syndrome (PSP/CBS/Parkinsonism), it was not possible to isolate the individual features from the clinical syndromes based on the data available from the literature. As such, documenting prevalence of phenomenology exclusive of reported syndromes was not possible.

Finally, statistical adjustments for multiple tests were not used for this study; the Bonferroni adjustment was not used to assess the potential difference in onset age between different genetic mutations due to the fact that each outcome was assessed individually (not universally in combination with all others), and to avoid Type II error [115, 116].

This study is the first to systematically describe the clinical presentation of the commonest genetic forms of FTLD in the context of movement disorders though variability and heterogeneity of available literature prevents definitive conclusions.

Publication bias

Statistical testing and graphical exploration of the data found evidence of publication bias for behavioral + cognitive disorder at presentation and Parkinsonism. Due to this, pooled estimates for these outcomes should be interpreted with caution as the data gathered for these outcomes may not be accurate. The explanation for this may be due to the selection criteria applied for this review. We identified and reviewed more papers relating to our systematic search on *MAPT* mutations followed closely by those on *PGRN* mutations and then less frequently *C9orf72* hexanucleotide expansions. This likely represents a publication bias relating to time of discovery and publication of the specific mutations. Additionally, this review was restricted to studies published in English, which may have systematically excluded studies from this review.

Conclusions

In conclusion, this is the first systematic review and meta-analysis of the occurrence of movement disorder phenomenology in genetic FTLD. We found that Parkinsonism was the most common, whereas CBS and PSPS were much less frequent. Subjects with MAPT more commonly presented with a movement disorder compared to those with PGRN mutation.

Standardized prospective collection of clinical information in conjunction with genetic characterization will be crucial for more accurate clinic-genetic correlation in future studies.

Supporting Information

S1 Fig. Number of studies and patients where L-dopa responsiveness was assessed. Flow chart describes the number of studies that did and did not assess L-dopa responsiveness along with the number of patients that was assessed. Complete information means enough data was available to determine the percentage of patients whose response was absent, partial, and good. Missing information means that only some information on patients was available or no information on L-dopa responsiveness was available.
(PDF)

S2 Fig. Publication bias for behavioural + cognitive onset.
(PDF)

S3 Fig. Publication bias for parkinsonism.
(PDF)

S1 Table. Eighty-seven full-text excluded articles and the reasons for exclusión.
(DOCX)

S2 Table. Number of studies for each outcome.
(DOCX)

S3 Table. Non-motor presentations.
(DOCX)

S4 Table. Levodopa responsiveness.
(DOCX)

S5 Table. Quality of studies.
(DOCX)

S6 Table. Quantifying heterogeneity of pooled estimates.
(DOCX)

S7 Table. Examining impact of substantial heterogeneity on pooled estimates.
(DOCX)

S8 Table. Examining impact of removing pooled case studies.
(DOCX)

Author Contributions

Conceived and designed the experiments: GK MM. Performed the experiments: CG MM BS EK AEL DF GK. Analyzed the data: EK DF. Contributed reagents/materials/analysis tools: CG BS. Wrote the paper: CG MM EK AEL DF GK.

References

1. Warren JD, Rohrer JD, Rossor MN. Clinical review. Frontotemporal dementia. BMJ. 2013; 347:f4827. doi: 10.1136/bmj.f4827 PMID: 23920254
2. Pan XD, Chen XC. Clinic, neuropathology and molecular genetics of frontotemporal dementia: a mini-review. Transl Neurodegener. 2013; 2:8. doi: 10.1186/2047-9158-2-8 PMID: 23597030
3. Cairns NJ, Neumann M, Bigio EH, Holm IE, Troost D, Hatanpaa KJ, et al. TDP-43 in familial and sporadic frontotemporal lobar degeneration with ubiquitin inclusions. Am J Pathol. 2007; 171:227–240. PMID: 17591968
4. Sieben A, Van Langenhove T, Engelborghs S, Martin JJ, Boon P, Cras P, et al. The genetics and neuropathology of frontotemporal lobar degeneration. Acta Neuropathol. 2012; 124:353–372. doi: 10.1007/s00401-012-1029-x PMID: 22890575
5. Chow TW, Miller BL, Hayashi VN, Geschwind DH. Inheritance of frontotemporal dementia. Arch Neurol. 1999; 56:817–822. PMID: 10404983
6. Kertesz A, McMonagle P, Jesso S. Extrapyramidal syndromes in frontotemporal degeneration. J Mol Neurosci. 2011; 45:336–342. doi: 10.1007/s12031-011-9616-1 PMID: 21887521
7. Hutton M, Lendon CL, Rizzu P, Baker M, Froelich S, Houlden H, et al. Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. Nature. 1998; 393:702–705. PMID: 9641683
8. Baker M, Mackenzie IR, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, et al. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature. 2006; 442:916–919. PMID: 16862116
9. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, Rutherford NJ, et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron. 2011; 72:245–256. doi: 10.1016/j.neuron.2011.09.011 PMID: 21944778
10. Espay AJ, Litvan I. Parkinsonism and frontotemporal dementia: the clinical overlap. J Mol Neurosci. 2011; 45:343–349. doi: 10.1007/s12031-011-9632-1 PMID: 21892619
11. Siuda J, Fujioka S, Wszolek ZK. Parkinsonian syndrome in familial frontotemporal dementia. Parkinsonism Relat Disord. 2014; 20:957–964. doi: 10.1016/j.parkreldis.2014.06.004 PMID: 24998994
12. Dols-Icardo O, Garcia-Redondo A, Rojas-Garcia R, Sanchez-Valle R, Noguera A, Gomez-Tortosa E, et al. Characterization of the repeat expansion size in C9orf72 in amyotrophic lateral sclerosis and frontotemporal dementia. Hum Mol Genet. 2014; 23:749–754. doi: 10.1093/hmg/ddt460 PMID: 24057670

13. Theuns J, Verstraeten A, Sleegers K, Wauters E, Gijselinck I, Smolders S, et al. Global investigation and meta-analysis of the C9orf72 (G4C2)n repeat in Parkinson disease. Neurology. 2014; 83:1906–1913. doi: 10.1212/WNL.0000000000001012 PMID: 25326098

14. Nuytemans K, Inchausti V, Beecham GW, Wang L, Dickson DW, Trojanowski JQ, et al. Absence of C9ORF72 expanded or intermediate repeats in autopsy-confirmed Parkinson's disease. Mov Disord. 2014; 29:827–830. doi: 10.1002/mds.25838 PMID: 24573903

15. Xi Z, Zinman L, Grinberg Y, Moreno D, Sato C, Bilbao JM, et al. Investigation of c9orf72 in 4 neurodegenerative disorders. Arch Neurol. 2012; 69:1583–1590. doi: 10.1001/archneurol.2012.2016 PMID: 22964832

16. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials 1986; 7: 177–188. PMID: 3802833

17. Freeman MF,Tukey JW. Transformations related to the angular and the square root. The Annals of Mathematical Statistics. 1950: 607–611.

18. Rothman KJG S. Last TL. Measures of effect and measures of association: Philadelphia: Lippincott Williams and Wilkins; 2008.

19. Evangelou E, Ioannidis JP, Patsopoulos NA. Uncertainty in heterogeneity estimates in meta-analyses. BMJ: British Medical Journal, 2007; 335: 914–916. PMID: 17974687

20. Higgins J, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in medicine. 2002; 21: 1539–1558. PMID: 12111919

21. Kontopantelis E, Springate DA, Reeves D. A re-analysis of the Cochrane Library data: the dangers of unobserved heterogeneity in meta-analyses. PLoS One. 2013; 8: e69930. doi: 10.1371/journal.pone.0069930 PMID: 23922860

22. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315:629–634. PMID: 9310563

23. Le Ber I, van der Zee J, Hannequin D, Gijselinck I, Campion D, Puel M, et al. Progranulin null mutations in both sporadic and familial frontotemporal dementia. Hum Mutat. 2007; 28:846–855. PMID: 17436289

24. Masellis M, Momeni P, Meschino W, Heffner R Jr., Elder J, Sato C, et al. Novel splicing mutation in the progranulin gene causing familial corticobasal syndrome. Brain. 2006; 129:3115–3123. PMID: 17030534

25. Arvanitakis Z, Witte RJ, Dickson DW, Tsuboi Y, Uitti RJ, Slowinski J, et al. Clinical-pathologic study of biomarkers in FTDP-17 (PPND family with N279K tau mutation). Parkinsonism Relat Disord. 2007; 13:230–239. PMID: 17196872

26. Rademakers R, Baker M, Gass J, Adamson J, Huey ED, Momeni P, et al. Phenotypic variability associated with progranulin haploinsufficiency in patients with the common 1477C—>T (Arg493X) mutation: an international initiative. Lancet Neurol. 2007; 6:857–868. PMID: 17826340

27. Skoglund L, Viitanen M, Kalimo H, Lannfelt L, Jonhagen ME, Ingelsson M, et al. The tau S305S mutation causes frontotemporal dementia with parkinsonism. Eur J Neurol. 2008; 15:156–161. PMID: 18093153

28. Bugiani O, Murrell JR, Giaccone G, Hasegawa M, Ghigo G, Tabaton M, et al. Frontotemporal dementia and corticobasal degeneration in a family with a P301S mutation in tau. J Neuropathol Exp Neurol. 1999; 58:667–677. PMID: 10374757

29. Boeve BF, Baker M, Dickson DW, Parisi JE, Giannini C, Josephs KA, et al. Frontotemporal dementia and parkinsonism associated with the IVS1+1G->A mutation in progranulin: a clinicopathologic study. Brain. 2006; 129:3103–3114. PMID: 17030535

30. Zarranz JJ, Ferrer I, Lezcano E, Forcadas MI, Eizaguirre B, Atares B, et al. A novel mutation (K317M) in the MAPT gene causes FTDP and motor neuron disease. Neurology. 2005; 64:1578–1585. PMID: 15883319

31. Boeve BF, Tremont-Lukats IW, Waclawik AJ, Murrell JR, Hermann B, Jack CR Jr., et al. Longitudinal characterization of two siblings with frontotemporal dementia and parkinsonism linked to chromosome 17 associated with the S305N tau mutation. Brain. 2005; 128:752–772. PMID: 15615814

32. Soliveri P, Rossi G, Monza D, Tagliavini F, Piacentini S, Albanese A, et al. A case of dementia parkinsonism resembling progressive supranuclear palsy due to mutation in the tau protein gene. Arch Neurol. 2003; 60:1454–1456. PMID: 14568818

33. Lossos A, Reches A, Gal A, Newman JP, Soffer D, Gomori JM, et al. Frontotemporal dementia and parkinsonism with the P301S tau gene mutation in a Jewish family. J Neurol. 2003; 250:733–740. PMID: 12796837

34. Ferman TJ, McRae CA, Arvanitakis Z, Tsuboi Y, Vo A, Wszolek ZK. Early and pre-symptomatic neuropsychological dysfunction in the PPND family with the N279K tau mutation. Parkinsonism Relat Disord. 2003; 9:265–270. PMID: 12781592

35. Kobayashi T, Mori H, Okuma Y, Dickson DW, Cookson N, Tsuboi Y, et al. Contrasting genotypes of the tau gene in two phenotypically distinct patients with P301L mutation of frontotemporal dementia and parkinsonism linked to chromosome 17. J Neurol. 2002; 249:669–675. PMID: 12111297

36. Lippa CF, Zhukareva V, Kawarai T, Uryu K, Shafiq M, Nee LE, et al. Frontotemporal dementia with novel tau pathology and a Glu342Val tau mutation. Ann Neurol. 2000; 48:850–858. PMID: 11117541

37. Tolnay M, Grazia Spillantini M, Rizzini C, Eccles D, Lowe J, Ellison D. A new case of frontotemporal dementia and parkinsonism resulting from an intron 10 +3-splice site mutation in the tau gene: clinical and pathological features. Neuropathol Appl Neurobiol. 2000; 26:368–378. PMID: 10931371

38. Sperfeld AD, Collatz MB, Baier H, Palmbach M, Storch A, Schwarz J, et al. FTDP-17: an early-onset phenotype with parkinsonism and epileptic seizures caused by a novel mutation. Ann Neurol. 1999; 46:708–715. PMID: 10553987

39. Bermingham N, Cowie TF, Paine M, Storey E, McLean C. Frontotemporal dementia and Parkinsonism linked to chromosome 17 in a young Australian patient with the G389R Tau mutation. Neuropathol Appl Neurobiol. 2008; 34:366–370. PMID: 18067537

40. Neumann M, Mittelbronn M, Simon P, Vanmassenhove B, de Silva R, Lees A, et al. A new family with frontotemporal dementia with intronic 10+3 splice site mutation in the tau gene: neuropathology and molecular effects. Neuropathol Appl Neurobiol. 2005; 31:362–373. PMID: 16008820

41. Werber E, Klein C, Grunfeld J, Rabey JM. Phenotypic presentation of frontotemporal dementia with Parkinsonism-chromosome 17 type P301S in a patient of Jewish-Algerian origin. Mov Disord. 2003; 18:595–598. PMID: 12722177

42. Kowalska A, Hasegawa M, Miyamoto K, Akiguchi I, Ikemoto A, Takahashi K, et al. A novel mutation at position +11 in the intron following exon 10 of the tau gene in FTDP-17. J Appl Genet. 2002; 43:535–543. PMID: 12441638

43. Iseki E, Matsumura T, Marui W, Hino H, Odawara T, Sugiyama N, et al. Familial frontotemporal dementia and parkinsonism with a novel N296H mutation in exon 10 of the tau gene and a widespread tau accumulation in the glial cells. Acta Neuropathol. 2001; 102:285–292. PMID: 11585254

44. Hirano S, Shinotoh H, Kobayashi T, Tsuboi Y, Wszolek ZK, Aotsuka A, et al. Brain acetylcholinesterase activity in FTDP-17 studied by PET. Neurology. 2006; 66:1276–1277.

45. Yasuda M, Yokoyama K, Nakayasu T, Nishimura Y, Matsui M, Yokoyama T, et al. A Japanese patient with frontotemporal dementia and parkinsonism by a tau P301S mutation. Neurology. 2000; 55:1224–1227. PMID: 11071507

46. Mirra SS, Murrell JR, Gearing M, Spillantini MG, Goedert M, Crowther RA, et al. Tau pathology in a family with dementia and a P301L mutation in tau. J Neuropathol Exp Neurol. 1999; 58:335–345. PMID: 10218629

47. Fu YJ, Nishihira Y, Kuroda S, Toyoshima Y, Ishihara T, Shinozaki M, et al. Sporadic four-repeat tauopathy with frontotemporal lobar degeneration, Parkinsonism, and motor neuron disease: a distinct clinicopathological and biochemical disease entity. Acta Neuropathol. 2010; 120:21–32. doi: 10.1007/s00401-010-0649-2 PMID: 20140439

48. Di Fabio R, Tessa A, Simons EJ, Santorelli FM, Casali C, Serrao M, et al. Familial frontotemporal dementia with parkinsonism associated with the progranulin c.C1021T (p.Q341X) mutation. Parkinsonism Relat Disord. 2010; 16:484–485. doi: 10.1016/j.parkreldis.2010.05.001 PMID: 20570546

49. Sitek EJ, Narozanska E, Slawek J, Wieczorek D, Brockhuis B, Lass P, et al. Unilateral neglect in a patient diagnosed with frontotemporal dementia and parkinsonism linked to chromosome 17. Acta Neuropsychiatr. 2009; 21:209–210. doi: 10.1111/j.1601-5215.2009.00367.x PMID: 25384634

50. Narozanska E, Jasinska-Myga B, Sitek EJ, Robowski P, Brockhuis B, Lass P, et al. Frontotemporal dementia and parkinsonism linked to chromosome 17—the first Polish family. Eur J Neurol. 2011; 18:535–537. doi: 10.1111/j.1468-1331.2010.03107.x PMID: 20561037

51. Choumert A, Poisson A, Honnorat J, Le Ber I, Camuzat A, Broussolle E, et al. G303V tau mutation presenting with progressive supranuclear palsy-like features. Mov Disord. 2012; 27:581–583. doi: 10.1002/mds.24060 PMID: 22109955

52. Boeve BF, Boylan KB, Graff-Radford NR, DeJesus-Hernandez M, Knopman DS, Pedraza O, et al. Characterization of frontotemporal dementia and/or amyotrophic lateral sclerosis associated with the GGGGCC repeat expansion in C9ORF72. Brain. 2012; 135:765–783. doi: 10.1093/brain/aws004 PMID: 22366793

53. Luigetti M, Quaranta D, Conte A, Piccininni C, Lattante S, Romano A, et al. Frontotemporal dementia, Parkinsonism and lower motor neuron involvement in a patient with C9ORF72 expansion. Amyotroph

Lateral Scler Frontotemporal Degener. 2013; 14:66–69. doi: 10.3109/17482968.2012.692383 PMID: 22708871

54. Floris G, Borghero G, Cannas A, Di Stefano F, Costantino E, Murru MR, et al. Frontotemporal dementia with psychosis, parkinsonism, visuo-spatial dysfunction, upper motor neuron involvement associated to expansion of C9ORF72: a peculiar phenotype? J Neurol. 2012; 259:1749–1751. doi: 10.1007/s00415-012-6444-3 PMID: 22323211

55. Snowden JS, Rollinson S, Lafon C, Harris J, Thompson J, Richardson AM, et al. Psychosis, C9ORF72 and dementia with Lewy bodies. J Neurol Neurosurg Psychiatry. 2012; 83:1031–1032. doi: 10.1136/jnnp-2012-303032 PMID: 22832738

56. Chaunu MP, Deramecourt V, Buee-Scherrer V, Le Ber I, Brice A, Ehrle N, et al. Juvenile frontotemporal dementia with parkinsonism associated with tau mutation G389R. J Alzheimers Dis. 2013; 37:769–776. doi: 10.3233/JAD-130413 PMID: 23948919

57. Boxer AL, Mackenzie IR, Boeve BF, Baker M, Seeley WW, Crook R, et al. Clinical, neuroimaging and neuropathological features of a new chromosome 9p-linked FTD-ALS family. J Neurol Neurosurg Psychiatry. 2011; 82:196–203. doi: 10.1136/jnnp.2009.204081 PMID: 20562461

58. Coppola C, Rossi G, Barbarulo AM, Di Fede G, Foglia C, Piccoli E, et al. A progranulin mutation associated with cortico-basal syndrome in an Italian family expressing different phenotypes of fronto-temporal lobar degeneration. Neurol Sci. 2012; 33:93–97. doi: 10.1007/s10072-011-0655-8 PMID: 21695656

59. Origone P, Verdiani S, Ciotti P, Gulli R, Bellone E, Marchese R, et al. Enlarging the clinical spectrum associated with C9orf 72 repeat expansions: findings in an Italian cohort of patients with parkinsonian syndromes and relevance for genetic counselling. Amyotroph Lateral Scler Frontotemporal Degener. 2013; 14:479–480. doi: 10.3109/21678421.2013.774020 PMID: 23509957

60. Passov V, Gavrilova RH, Strand E, Cerhan JH, Josephs KA. Sporadic corticobasal syndrome with progranulin mutation presenting as progressive apraxic agraphia. Arch Neurol. 2011; 68:376–380. doi: 10.1001/archneurol.2011.26 PMID: 21403024

61. Arosio B, Abbate C, Galimberti D, Rossi PD, Inglese S, Fenoglio C, et al. GRN Thr272fs clinical heterogeneity: a case with atypical late onset presenting with a dementia with Lewy bodies phenotype. J Alzheimers Dis. 2013; 35:669–674. doi: 10.3233/JAD-130053 PMID: 23478307

62. Taipa R, Tuna A, Damasio J, Pinto PS, Cavaco S, Pereira S, et al. Clinical, neuropathological, and genetic characteristics of the novel IVS9+1delG GRN mutation in a patient with frontotemporal dementia. J Alzheimers Dis. 2012; 30:83–90. doi: 10.3233/JAD-2012-112084 PMID: 22366770

63. Rusina R, Kovacs GG, Fiala J, Hort J, Ridzon P, Holmerova I, et al. FTLD-TDP with motor neuron disease, visuospatial impairment and a progressive supranuclear palsy-like syndrome: broadening the clinical phenotype of TDP-43 proteinopathies. A report of three cases. BMC Neurol. 2011; 11:50. doi: 10.1186/1471-2377-11-50 PMID: 21569259

64. Rohrer JD, Paviour D, Vandrovcova J, Hodges J, de Silva R, Rossor MN. Novel L284R MAPT mutation in a family with an autosomal dominant progressive supranuclear palsy syndrome. Neurodegener Dis. 2011; 8:149–152. doi: 10.1159/000319454 PMID: 20838030

65. Momeni P, Wickremaratchi MM, Bell J, Arnold R, Beer R, Hardy J, et al. Familial early onset frontotemporal dementia caused by a novel S356T MAPT mutation, initially diagnosed as schizophrenia. Clin Neurol Neurosurg. 2010; 112:917–920. doi: 10.1016/j.clineuro.2010.07.015 PMID: 20708332

66. Savica R, Adeli A, Vemuri P, Knopman DS, Dejesus-Hernandez M, Rademakers R, et al. Characterization of a family with c9FTD/ALS associated with the GGGGCC repeat expansion in C9ORF72. Arch Neurol. 2012; 69:1164–1169. doi: 10.1001/archneurol.2012.772 PMID: 22637471

67. Pires C, Coelho M, Valadas A, Barroso C, Pimentel J, Martins M, et al. Phenotypic variability of familial and sporadic Progranulin p.Gln257Profs*27 mutation. J Alzheimers Dis. 2013; 37:335–342. doi: 10.3233/JAD-130146 PMID: 23813535

68. Dopper EG, Seelaar H, Chiu WZ, de Koning I, van Minkelen R, Baker MC, et al. Symmetrical corticobasal syndrome caused by a novel C.314dup progranulin mutation. J Mol Neurosci. 2011; 45:354–358. doi: 10.1007/s12031-011-9626-z PMID: 21863316

69. Lindquist SG, Duno M, Batbayli M, Puschmann A, Braendgaard H, Mardosiene S, et al. Corticobasal and ataxia syndromes widen the spectrum of C9ORF72 hexanucleotide expansion disease. Clin Genet. 2013; 83:279–283. doi: 10.1111/j.1399-0004.2012.01903.x PMID: 22650353

70. Chen-Plotkin AS, Martinez-Lage M, Sleiman PM, Hu W, Greene R, Wood EM, et al. Genetic and clinical features of progranulin-associated frontotemporal lobar degeneration. Arch Neurol. 2011; 68:488–497. doi: 10.1001/archneurol.2011.53 PMID: 21482928

71. Rohrer JD, Geser F, Zhou J, Gennatas ED, Sidhu M, Trojanowski JQ, et al. TDP-43 subtypes are associated with distinct atrophy patterns in frontotemporal dementia. Neurology. 2010; 75:2204–2211. doi: 10.1212/WNL.0b013e318202038c PMID: 21172843

72. Takada LT, Pimentel ML, Dejesus-Hernandez M, Fong JC, Yokoyama JS, Karydas A, et al. Frontotemporal dementia in a Brazilian kindred with the c9orf72 mutation. Arch Neurol. 2012; 69:1149–1153. doi: 10.1001/archneurol.2012.650 PMID: 22964910

73. Rohrer JD, Lashley T, Schott JM, Warren JE, Mead S, Isaacs AM, et al. Clinical and neuroanatomical signatures of tissue pathology in frontotemporal lobar degeneration. Brain. 2011; 134:2565–81. doi: 10.1093/brain/awr198 PMID: 21908872

74. Lee SE, Tartaglia MC, Yener G, Genc S, Seeley WW, Sanchez-Juan P, et al. Neurodegenerative disease phenotypes in carriers of MAPT p.A152T, a risk factor for frontotemporal dementia spectrum disorders and Alzheimer disease. Alzheimer Dis Assoc Disord. 2013; 27:302–309. doi: 10.1097/WAD.0b013e31828cc357 PMID: 23518664

75. Lesage S, Le Ber I, Condroyer C, Broussolle E, Gabelle A, Thobois S, et al. C9orf72 repeat expansions are a rare genetic cause of parkinsonism. Brain. 2013; 136:385–391. doi: 10.1093/brain/aws357 PMID: 23413259

76. Rodriguez-Rodriguez E, Vazquez-Higuera JL, Sanchez-Juan P, Gonzalez-Aramburu I, Pozueta A, Mateo I, et al. Screening for progranulin mutations by serum protein dosage in common neurodegenerative disorders. Parkinsonism Relat Disord. 2013; 19:768–769. doi: 10.1016/j.parkreldis.2013.04.008 PMID: 23684369

77. Antonell A, Gil S, Sanchez-Valle R, Balasa M, Bosch B, Prat MC, et al. Serum progranulin levels in patients with frontotemporal lobar degeneration and Alzheimer's disease: detection of GRN mutations in a Spanish cohort. J Alzheimers Dis. 2012; 31:581–591. doi: 10.3233/JAD-2012-112120 PMID: 22647257

78. Le Ber I, Camuzat A, Guillot-Noel L, Hannequin D, Lacomblez L, Golfier V, et al. C9ORF72 repeat expansions in the frontotemporal dementias spectrum of diseases: a flow-chart for genetic testing. J Alzheimers Dis. 2013; 34:485–499. doi: 10.3233/JAD-121456 PMID: 23254636

79. Spagnolo F, Ceppi D, Cardamone R, Falautano M, Martinelli V, Comi G, et al. Frontotemporal dementia with parkinsonism presenting as posterior cortical atrophy. Mov Disord. 2011; 26:2131–2132. doi: 10.1002/mds.23768 PMID: 21618283

80. Spector AR, Dugger BN, Wszolek ZK, Uitti RJ, Fredrickson P, Kaplan J, et al. Anatomy of disturbed sleep in pallido-ponto-nigral degeneration. Ann Neurol. 2011; 69:1014–1025. doi: 10.1002/ana.22340 PMID: 21681797

81. Ogaki K, Li Y, Takanashi M, Ishikawa K, Kobayashi T, Nonaka T, et al. Analyses of the MAPT, PGRN, and C9orf72 mutations in Japanese patients with FTLD, PSP, and CBS. Parkinsonism Relat Disord. 2013; 19:15–20. doi: 10.1016/j.parkreldis.2012.06.019 PMID: 22818528

82. O'Dowd S, Curtin D, Waite AJ, Roberts K, Pender N, Reid V, et al. C9ORF72 expansion in amyotrophic lateral sclerosis/frontotemporal dementia also causes parkinsonism. Mov Disord. 2012; 27:1072–1074. doi: 10.1002/mds.25022 PMID: 22807188

83. Annan M, Beaufils E, Viola UC, Vourc'h P, Hommet C, Mondon K. Idiopathic Parkinson's disease phenotype related to C9ORF72 repeat expansions: contribution of the neuropsychological assessment. BMC Res Notes. 2013; 6:343. doi: 10.1186/1756-0500-6-343 PMID: 23987827

84. Galimberti D, Fenoglio C, Serpente M, Villa C, Bonsi R, Arighi A, et al. Autosomal dominant frontotemporal lobar degeneration due to the C9ORF72 hexanucleotide repeat expansion: late-onset psychotic clinical presentation. Biol Psychiatry. 2013; 74:384–391. doi: 10.1016/j.biopsych.2013.01.031 PMID: 23473366

85. Pearson JP, Williams NM, Majounie E, Waite A, Stott J, Newsway V, et al. Familial frontotemporal dementia with amyotrophic lateral sclerosis and a shared haplotype on chromosome 9p. J Neurol. 2011; 258:647–655. doi: 10.1007/s00415-010-5815-x PMID: 21072532

86. Snowden JS, Rollinson S, Thompson JC, Harris JM, Stopford CL, Richardson AM, et al. Distinct clinical and pathological characteristics of frontotemporal dementia associated with C9ORF72 mutations. Brain. 2012; 135:693–708. doi: 10.1093/brain/awr355 PMID: 22300873

87. O'Dowd S, Murray B, Roberts K, Cummins G, Magennis B, Lynch T. Pallidopontonigral degeneration: a deceptive familial tauopathy. Mov Disord. 2012; 27:817–819. doi: 10.1002/mds.24052 PMID: 22729984

88. Tremolizzo L, Bertola F, Casati G, Piperno A, Ferrarese C, Appollonio I. Progressive supranuclear palsy-like phenotype caused by progranulin p.Thr272fs mutation. Mov Disord. 2011; 26:1964–1966. doi: 10.1002/mds.23749 PMID: 21542024

89. Cannon A, Fujioka S, Rutherford NJ, Ferman TJ, Broderick DF, Boylan KB, et al. Clinicopathologic variability of the GRN A9D mutation, including amyotrophic lateral sclerosis. Neurology. 2013; 80:1771–1777. doi: 10.1212/WNL.0b013e3182919059 PMID: 23596077

90. Carney RM, Kohli MA, Kunkle BW, Naj AC, Gilbert JR, Zuchner S, et al. Parkinsonism and distinct dementia patterns in a family with the MAPT R406W mutation. Alzheimers Dement. 2014; 10:360–365. doi: 10.1016/j.jalz.2013.02.011 PMID: 23727082

91. Rossi G, Marelli C, Farina L, Laura M, Maria Basile A, Ciano C, et al. The G389R mutation in the MAPT gene presenting as sporadic corticobasal syndrome. Mov Disord. 2008; 23:892–895. doi: 10.1002/mds.21970 PMID: 18307268

92. Nasreddine ZS, Loginov M, Clark LN, Lamarche J, Miller BL, Lamontagne A, et al. From genotype to phenotype: a clinical pathological, and biochemical investigation of frontotemporal dementia and parkinsonism (FTDP-17) caused by the P301L tau mutation. Ann Neurol. 1999; 45:704–715. PMID: 10360762

93. Spina S, Murrell JR, Huey ED, Wassermann EM, Pietrini P, Grafman J, et al. Corticobasal syndrome associated with the A9D Progranulin mutation. J Neuropathol Exp Neurol. 2007; 66:892–900. PMID: 17917583

94. Spina S, Murrell JR, Yoshida H, Ghetti B, Bermingham N, Sweeney B, et al. The novel Tau mutation G335S: clinical, neuropathological and molecular characterization. Acta Neuropathol. 2007; 113:461–700. PMID: 17186252

95. Wider C, Uitti RJ, Wszolek ZK, Fang JY, Josephs KA, Baker MC, et al. Progranulin gene mutation with an unusual clinical and neuropathologic presentation. Mov Disord. 2008; 23:1168–1173. doi: 10.1002/mds.22065 PMID: 18442119

96. Ghetti B, Spina S, Murrell JR, Huey ED, Pietrini P, Sweeney B, et al. In vivo and postmortem clinicoanatomical correlations in frontotemporal dementia and parkinsonism linked to chromosome 17. Neurodegener Dis. 2008; 5:215–217. doi: 10.1159/000113706 PMID: 18322394

97. Le Ber I, Camuzat A, Hannequin D, Pasquier F, Guedj E, Rovelet-Lecrux A, et al. Phenotype variability in progranulin mutation carriers: a clinical, neuropsychological, imaging and genetic study. Brain. 2008; 131:732–746. doi: 10.1093/brain/awn012 PMID: 18245784

98. Kelley BJ, Haidar W, Boeve BF, Baker M, Graff-Radford NR, Krefft T, et al. Prominent phenotypic variability associated with mutations in Progranulin. Neurobiol Aging. 2009; 30:739–751. PMID: 17949857

99. Leverenz JB, Yu CE, Montine TJ, Steinbart E, Bekris LM, Zabetian C, et al. A novel progranulin mutation associated with variable clinical presentation and tau, TDP43 and alpha-synuclein pathology. Brain. 2007; 130:1360–1374. PMID: 17439980

100. Knezevic A. Overlapping confidence intervals and statistical significance. StatNews: Cornell University Statistical Consulting Unit. 2008, 73.

101. Majounie E, Renton AE, Mok K, Dopper EG, Waite A, Rollinson S, et al. Frequency of the C9orf72 hexanucleotide reeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. Lancet Neurol. 2012; 11:323–330. doi: 10.1016/S1474-4422(12)70043-1 PMID: 22406228

102. Rademakers R, Neumann M, Mackenzie IR. Advances in understanding the molecular basis of frontotemporal dementia. Nat Rev Neurol. 2012; 8:423–434. doi: 10.1038/nrneurol.2012.117 PMID: 22732773

103. Rohrer JD, Guerreiro R, Vandrovcova J, Uphill J, Reiman D, Beck J, et al. The heritability and genetics of frontotemporal lobar degeneration. Neurology. 2009; 73:1451–1456. doi: 10.1212/WNL.0b013e3181bf997a PMID: 19884572

104. Hardy J, Rogaeva E. Motor neuron disease and frontotemporal dementia: sometimes related, sometimes not. Exp Neurol. 2014; 262:75–83. doi: 10.1016/j.expneurol.2013.11.006 PMID: 24246281

105. Gass J, Cannon A, Mackenzie IR, Boeve B, Baker M, Adamson J, et al. Mutations in progranulin are a major cause of ubiquitin-positive frontotemporal lobar degeneration. Hum Mol Genet. 2006; 15:2988–3001. PMID: 16950801

106. Fujioka S, Wszolek ZK. Clinical aspects of familial forms of frontotemporal dementia associated with parkinsonism. J Mol Neurosci. 2011; 45:359–365. doi: 10.1007/s12031-011-9568-5 PMID: 21656039

107. Park HK, Chung SJ. New perspective on parkinsonism in frontotemporal lobar degeneration. J Mov Disord. 2013; 6:1–8. doi: 10.14802/jmd.13001 PMID: 24868417

108. Padovani A, Agosti C, Premi E, Bellelli G, Borroni B. Extrapyramidal symptoms in Frontotemporal Dementia: prevalence and clinical correlations. Neurosci Lett. 2007; 422:39–42. PMID: 17574750

109. Wszolek ZK, Tsuboi Y, Ghetti B, Pickering-Brown S, Baba Y, Cheshire WP. Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). Orphanet J Rare Dis. 2006; 1:30. PMID: 16899117

110. Tsai RM, Boxer AL. Treatment of frontotemporal dementia. Curr Treat Options Neurol. 2014; 16:319. doi: 10.1007/s11940-014-0319-0 PMID: 25238733

111. Ioannidis P, Konstantinopoulou E, Maiovis P, Karacostas D. The frontotemporal dementias in a tertiary referral center: classification and demographic characteristics in a series of 232 cases. J Neurol Sci. 2012; 318:171–173. doi: 10.1016/j.jns.2012.04.002 PMID: 22541253

112. Boeve BF, Lang AE, Litvan I. Corticobasal degeneration and its relationship to progressive supranuclear palsy and frontotemporal dementia. Ann Neurol. 2003; 54 Suppl 5:S15–9. PMID: 12833363

113. Rohrer JD, Paviour D, Bronstein AM, O'Sullivan SS, Lees A, Warren JD. Progressive supranuclear palsy syndrome presenting as progressive nonfluent aphasia: a neuropsychological and neuroimaging analysis. Mov Disord. 2010; 25:179–188. doi: 10.1002/mds.22946 PMID: 20077483

114. Grasbeck A, Englund E, Horstmann V, Passant U, Gustafson L. Predictors of mortality in frontotemporal dementia: a retrospective study of the prognostic influence of pre-diagnostic features. Int J Geriatr Psychiatry. 2003; 18:594–601. PMID: 12833303

115. Perneger TV. What's wrong with Bonferroni adjustments. BMJ. 1998; 316:1236–1238. PMID: 9553006

116. Tukey J W. Some thoughts on clinical trials, especially problems of multiplicity. Science. 1977; 198: 679–684. PMID: 333584