Age at symptom onset and death and disease duration in genetic frontotemporal dementia: an international retrospective cohort study

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Summary

Background Frontotemporal dementia is a heterogenous neurodegenerative disorder, with about a third of cases being genetic. Most of this genetic component is accounted for by mutations in *GRN*, *MAPT*, and *C9orf72*. In this study, we aimed to complement previous phenotypic studies by doing an international study of age at symptom onset, age at death, and disease duration in individuals with mutations in *GRN*, *MAPT*, and *C9orf72*.

Methods In this international, retrospective cohort study, we collected data on age at symptom onset, age at death, and disease duration for patients with pathogenic mutations in the *GRN* and *MAPT* genes and pathological expansions in the *C9orf72* gene through the Frontotemporal Dementia Prevention Initiative and from published papers. We used mixed effects models to explore differences in age at onset, age at death, and disease duration between genetic groups and individual mutations. We also assessed correlations between the age at onset and at death of each individual and the age at onset and at death of their parents and the mean age at onset and at death of their family members. Lastly, we used mixed effects models to investigate the extent to which variability in age at onset and at death could be accounted for by family membership and the specific mutation carried.

Findings Data were available from 3403 individuals from 1492 families: 1433 with *C9orf72* expansions (755 families), 1179 with *GRN* mutations (483 families, 130 different mutations), and 791 with *MAPT* mutations (254 families, 67 different mutations). Mean age at symptom onset and at death was 49·5 years (SD 10·0; onset) and 58·5 years (11·3; death) in the *MAPT* group, 58·2 years (9·8; onset) and 65·3 years (10·9; death) in the *C9orf72* group, and 61·3 years (8·8; onset) and 68·8 years (9·7; death) in the *GRN* group. Mean disease duration was 6·4 years (SD 4·9) in the *C9orf72* group, 7·1 years (3·9) in the *GRN* group, and 9·3 years (6·4) in the *MAPT* group. Individual age at onset and at death was significantly correlated with both parental age at onset and at death and with mean family age at onset and at death in all three groups, with a stronger correlation observed in the *MAPT* group (r=0·45 between individual and parental age at onset, r=0·63 between individual and mean family age at onset, r=0·58 between individual and parental age at death, and r=0·69 between individual and mean family age at death) than in either the *C9orf72* group (r=0·32 individual and parental age at onset, r=0·36 individual and mean family age at onset, r=0·38 individual and parental age at death, and r=0·40 individual and mean family age at death) or the *GRN* group (r=0·22 individual and parental age at onset, r=0·18 individual and mean family age at onset, r=0·22 individual and parental age at death, and r=0·32 individual and mean family age at death). Modelling showed that the variability in age at onset and at death in the *MAPT* group was explained partly by the specific mutation (48%, 95% CI 35–62, for age at onset; 61%, 47–73, for age at death), and even more by family membership (66%, 56–75, for age at onset; 74%, 65–82, for age at death). In the *GRN* group, only 2% (0–10) of the variability of age at onset and 9% (3–21) of that of age of death was explained by the specific mutation, whereas 14% (9–22) of the variability of age at onset and 20% (12–30) of that of age at death was explained by family membership. In the *C9orf72* group, family membership explained 17% (11–26) of the variability of age at onset and 19% (12–29) of that of age at death.

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Interpretation **Our study showed that age at symptom onset and at death of people with genetic frontotemporal dementia is influenced by genetic group and, particularly for *MAPT* mutations, by the specific mutation carried and by family membership. Although estimation of age at onset will be an important factor in future pre-symptomatic therapeutic trials for all three genetic groups, our study suggests that data from other members of the family will be particularly helpful only for individuals with *MAPT* mutations. Further work in identifying both genetic and environmental factors that modify phenotype in all groups will be important to improve such estimates.**

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Introduction

Frontotemporal dementia is a genetically and pathologically heterogeneous neurodegenerative disease.[1] The most common clinical subtypes of this disease are behavioural variant frontotemporal dementia, presenting with changes in personality and executive dysfunction, and primary progressive aphasia, in which individuals develop impairment of language processing. Three forms of primary progressive aphasia have been described: semantic, non-fluent or agrammatic, and logopenic; however, up to 20% of people do not fit the criteria for any of these variants and are categorised as having primary progressive aphasia not otherwise specified.[2] Both behavioural variant frontotemporal dementia and primary progressive aphasia overlap with amyotrophic lateral sclerosis and with the atypical parkinsonian syndromes corticobasal syndrome and progressive supranuclear palsy.[1]

Research in context

Evidence before this study

We searched PubMed for articles on genetic frontotemporal dementia with no language restrictions from database inception up to July 1, 2017, using the following terms: "frontotemporal dementia AND genetics", "progranulin OR *GRN*", "tau OR *MAPT*", and "chromosome 9 open reading frame 72 OR *C9orf72*", focusing on studies that reported age at symptom onset, age at death or disease duration of individuals with symptoms. No studies were found that had systematically investigated age at symptom onset, age at death, or disease duration across all the different genetic groups and the different mutations found within the groups. However, evidence from cohort studies and individual case series suggested that the age at symptom onset, age at death, and disease duration were highly variable across the genes implicated in frontotemporal dementia. Age-related penetrance was described in individuals with *GRN* and *C9orf72* mutations, with *MAPT* mutations usually being fully penetrant. We found a generational difference in age at symptom onset, with an earlier onset in later generations occurring in individuals with *GRN* or *C9orf72* mutations. Phenotypic differences in age at symptom onset have not been studied in detail yet, but one study showed a shorter disease duration in individuals with a diagnosis of amyotrophic lateral sclerosis in the *C9orf72* group compared with those with other diagnoses, and another study showed an earlier age at symptom onset in this group compared with that of other diagnoses.

Added value of this study

To our knowledge, this is the largest international study to date investigating individual age at symptom onset, age at death, and disease duration in patients with genetic frontotemporal dementia, across all the three main genetic groups (*C9orf72*, *GRN*, and *MAPT*), and all known mutations within the *GRN* and *MAPT* groups. Our study provides important evidence about the factors underlying age at symptom onset, age at death, and disease duration in the different groups. We showed that only in the *MAPT* mutation group were age at symptom onset and at death highly correlated with both parental and mean family ages at symptom onset and at death, with variability in these ages explained partly by the specific mutation and more so by family membership. Such correlations were weaker in the other two groups, with the variability in age at symptom onset and age at death for individuals with *GRN* mutations and *C9orf72* expansions not accounted for particularly by family membership or, for individuals with *GRN* mutations, by the specific mutation. This is the first time that such key differences between genetic frontotemporal dementia groups have been shown.

Implications of all the available evidence

Optimal therapeutic trial design will be important in genetic frontotemporal dementia, and particularly because many trials will aim to include presymptomatic individuals who are expected to be in proximity to symptom onset. Our study suggests that in individuals with *MAPT* mutations data from other family members will be particularly helpful in estimating time from symptom onset. Further work is needed to understand the variability in the other genetic groups, and other proximity markers, either individually or in combination, are likely to be required to refine the estimation of time to symptom onset in individuals with *GRN* or *C9orf72* mutations. In the meantime, the available data will provide clinicians and family members with a better understanding of the individual risk of probable symptom onset and time to death in each genetic group and within individual mutations.

About a third of frontotemporal dementia cases are genetic,[3] with mutations in multiple genes shown to be causative of this disease. However, most of the heritability of frontotemporal dementia is accounted for by mutations in three genes: progranulin (*GRN*), microtubule-associated protein tau (*MAPT*), and chromosome 9 open reading frame 72 (*C9orf72*; also known as *C9orf72*-SMCR8 complex subunit). Although much has been learned over the past decade about the clinical features of these genetic forms of frontotemporal dementia, most studies exploring age at symptom onset and disease duration have been small and geographically restricted.[4–6] In particular, although individual case series have suggested that such phenotypic characteristics can be quite variable, no studies have systematically investigated these factors across all the different genetic groups and the different mutations found within these groups.

Therefore, in this large international study, we aimed to analyse phenotypic characteristics of the main three forms of genetic frontotemporal dementia, including ages at symptom onset and death and disease duration, as well as examining the effect of mutation type and family membership on these factors.

Methods

Study design and participants

In this international retrospective cohort study, we collected data from centres that are part of the Frontotemporal Dementia Prevention Initiative (FPI) and through a literature review of publications. The FPI is a group connecting natural history cohort studies of genetic frontotemporal dementia: the Genetic Frontotemporal Dementia Initiative (GENFI),[7] Advancing Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL), Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS), and the Dominantly Inherited Non-Alzheimer's Dementias (DINAD) studies. These research studies include most of the centres investigating genetic frontotemporal dementia in Europe and eastern Canada (GENFI), USA and western Canada (ARTFL and LEFFTDS), and Australia (DINAD). In total, 33 centres across the world (12 countries; appendix p 20) provided participant data for our study. We included all known pathogenic mutations in the *GRN, MAPT*, and *C9orf72* genes in our study. Families with intermediate length expansions of *C9orf72* were not included in the study. All mutations were reviewed by two geneticists (RG and JB) to examine pathogenicity and were only included if both agreed on their probable pathogenic nature (full inclusion and exclusion criteria are in the appendix, p 2). Local ethics committees at each of the sites approved the study and data from participants was provided through informed written consent.

Procedures

Participant data collected from FPI centres included genetic group, individual mutation (for participants with mutations in *GRN* and *MAPT*), sex, clinical phenotype, age at symptom onset (defined by the onset of progressive behavioural, cognitive, or motor symptoms reported either by an informant [usually a family member] or, for non-behavioural symptoms, by the patient themselves), age at death, and relationship to other affected family members.

For the literature review, we assessed publications cited in the Alzheimer Disease & Frontotemporal Dementia Mutation database, and supplemented this by a detailed search of PubMed (done between Jan 1, 2015, and July 1, 2017) for other publications with data for age at symptom onset, age at death, or disease duration in people with genetic frontotemporal dementia: this identified 308 journal articles. To avoid potential double reporting, centres were asked to provide a list of publications relevant to their dataset. These lists were then manually examined for possible duplicates, which were removed when identified.

Statistical analysis

We grouped participants into a *GRN*, *MAPT*, or *C9orf72* group according to the mutation present. We calculated the numbers and percentages of participants within each genetic group by geographic location and clinical phenotype. We used a χ^2 test to compare sex distribution in each of the genetic groups. We calculated means and SDs for age at symptom onset, age at death, and disease duration in each genetic group and in the most common mutations in the *MAPT* and *GRN* groups (defined as those identified in the greatest number of individuals in the study). We used mixed effects models to examine differences in age at symptom onset, age at death, and disease duration between genetic groups (*GRN, MAPT*, and *C9orf72*), between the most common mutations in the *GRN* and *MAPT* groups, between an earlier (first) and later (second) generation of family members in all genetic groups, between men and women within each genetic group, and between the main clinical phenotypes within each genetic group. Analyses accounted for relatedness by including family membership as a random effect. We calculated Pearson correlation coefficients to explore the relationship between an individual's age at symptom onset (or death) and the age at symptom onset (or death) of their affected parent and the association between an individual's age at symptom onset (or death) and the average age at symptom onset (or death) of other members of the same family. Lastly, we also used mixed effects models to explore the extent to which variability in age at symptom onset and at death were explained by family membership (exploring variability both within and between families) and the specific mutation carried (in *GRN* and *MAPT* groups). Detailed statistical methods are shown in the appendix (pp 15–19). All statistical analyses were done with Stata (v.14 or later).

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	GRN (n=1179)	*MAPT* (n=791)	*C9orf72* (n=1433)	Difference *MAPT vs GRN*	Difference *C9orf72 vs GRN*	Difference *C9orf72 vs MAPT*	p value *MAPT vs GRN*	p value *C9orf72 vs GRN*	p value *C9orf72 vs MAPT*
Sex (n [%])	..	..	..	..	..	..	0·0015	<0·0001	0·18
Men	490 (41·6%)	386 (48·8%)	742 (51·8%)	..	..	..	..	..	..
Women	689 (58·4%)	405 (51·2%)	691 (48·2%)	..	..	..	..	..	..
Number of families	483	254	755	..	..	..	..	..	..
Age at symptom onset (years)	..	..	..	−11·8 (−13·0 to −10·6)	−2·8 (−3·8 to −1·9)	9·0 (7·8 to 10·1)	<0·0001	<0·0001	<0·0001
Mean (SD; n)	61·3 (8·8; n=967)	49·5 (10·0; n=609)	58·2 (9·8; n=1076)	..	..	..	..	..	..
Range	25–90	17–82	20–91	..	..	..	..	..	..
Age at death (years)	..	..	..	−10·7 (−12·3 to −9·1)	−3·5 (−4·9 to −2·2)	7·2 (5·7 to 8·6)	<0·0001	<0·0001	<0·0001
Mean (SD; n)	68·8 (9·7; n=656)	58·5 (11·3; n=485)	65·3 (10·9; n=839)	..	..	..	..	..	..
Range	42–98	24–93	26–97	..	..	..	..	..	..
Disease duration (years)	..	..	..	0·18 (0·08 to 0·29)	−0·26 (−0·35 to −0·17)	−0·44 (−0·54 to −0·34)	0·0005	<0·0001	<0·0001
Mean (SD; n)	7·1 (3·9; n=548)	9·3 (6·4; n=394)	6·4 (4·9; n=618)	..	..	..	..	..	..
Range	0–27	0–45	0–36	..	..	..	..	..	..

For age at symptom onset, age at death, and disease duration, differences are adjusted mean differences (natural log values for disease duration) with 95% CIs. For sex differences, p values calculated with a χ^2 test. For age at symptom onset, age at death, and disease duration, p values calculated with mixed effects models.

Table 1: **Patient demographics and age at symptom onset, age at death, and disease duration in each of the three genetic groups**

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Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Our combined dataset comprised 3403 symptomatic individuals from 1492 families who had data available for one or more of age at symptom onset, age at death, disease duration, and clinical phenotype (table 1): 1433 individuals with *C9orf72* expansions (from 755 families), 1179 with *GRN* mutations (483 families), and 791 with *MAPT* mutations (254 families).

In total, 130 *GRN* mutations and 67 *MAPT* mutations were identified and all were included in the study (appendix pp 5–10). We found 78 *GRN* and 45 *MAPT* pathogenic mutations through the Alzheimer Disease & Frontotemporal Dementia Mutation database, 35 *GRN* and 18 *MAPT* variants, which were not included in the database, through a PubMed search, and the FPI centres provided data on an additional 17 *GRN* and four *MAPT* variants not previously described in the literature (appendix p 2). The most common *GRN* mutations were Thr272fs (rs63749877; 201 individuals, 95 families), Arg493X (rs63751294; 55 individuals, 22 families), IVS7–1G→A (50 individuals, 18 families), Cys31fs (rs63751057, 47 individuals, 10 families), Gly35fs (rs63751073, 42 individuals, 10 families), and Ala9Asp (rs63751243, 37 individuals, four families). The most common *MAPT* mutations were Pro301Leu (rs63751273, 234 individuals, 59 families), IVS10+16C→T (rs63751011; 149 individuals, 48 families), Arg406Trp (rs63750424, 67 individuals, nine families), and Asn279Lys (rs63750756, 44 individuals, 17 families).

Overall, the most prevalent genetic group was that comprising individuals carrying a *C9orf72* expansion (1433 [42·1%] of 3403 individuals), followed by individuals with *GRN* mutations (1179 [34·6%]), with individuals carrying *MAPT* mutations comprising the least common group (791 [23·2%]; figure 1). However, we observed geographical variability in the distribution of these mutations, with a different spread of frequencies among the three genetic groups in some countries and regions: individuals with *GRN* mutations were more common than those of other groups in Italy (289 [66%] of 438 individuals) and, to a lesser extent, in Spain (76 [49%] of 155); whereas individuals with *MAPT* mutations were found more frequently in the Netherlands (81 [40%] of 204) and the US west coast (71 [47%] of 150; appendix pp 20–23).

Although behavioural variant frontotemporal dementia was the most common diagnosis in each genetic group, we observed phenotypic variability across the different mutations (table 2; appendix pp 24–32). Both *C9orf72* and *MAPT* groups contained approximately equal numbers of men and women (table 1, appendix pp 33–34). However, the *GRN* group had a significant overrepresentation of women compared with both the *C9orf72* group and the *MAPT* group.

The mean age at symptom onset was lowest for the *MAPT* group, which was significantly lower than those of the *GRN* and *C9orf72* groups (p<0·0001 for each

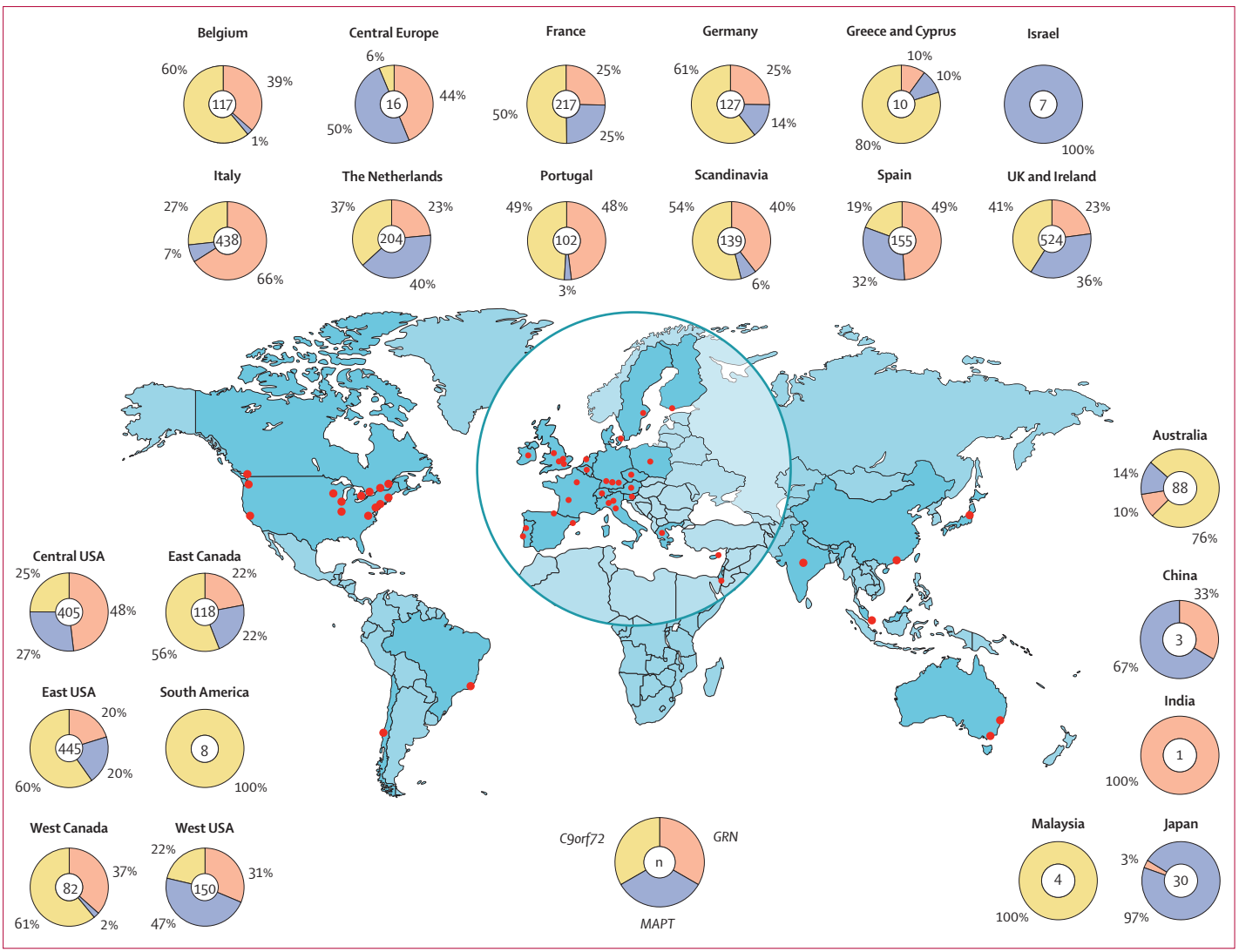

Figure 1: **Frequency of each of the three genetic groups by geographic location**
Countries with data included in the study are shown in dark blue (appendix p 20). Individual centres are shown as red dots on the map. Pie charts show relative frequency of each of the three genetic groups within a geographical area, with the number in the centre representing the number of cases included within that area.

comparison). The *C9orf72* group had the second lowest age, which was significantly lower than that of the *GRN* group (p<0·0001; table 1, appendix pp 35–36). However, we observed a wide range of age at symptom onset within each of the genetic groups, from the 20s to the 90s in the *GRN* and *C9orf72* groups and from age 17 years to the 80s in the *MAPT* group (figure 2, appendix pp 36). Cumulative probability curves for age at symptom onset in each of the genetic groups are shown in figure 3A (appendix p 39).

We also observed a wide range of age at symptom onset among *GRN* and *MAPT* mutations (appendix pp 6–10). We plotted cumulative probability curves for age at symptom onset for the most common *GRN* (figure 3B) and *MAPT* (figure 3C) mutations (appendix p 39). These curves largely overlapped for the *GRN* mutations, without any significant difference between groups. By contrast, we observed a significant difference between *MAPT* mutations, with the Asn279Lys mutation group having a lower age at symptom onset (mean 43·8 years, SD 6·7) than that of the other groups (p≤0·0026 for all comparisons; appendix p 40). The generational analysis showed a significantly lower age at symptom onset in the second (later) generation than the first (earlier generation) in all three groups: mean age was 65·5 years (SD 9·1) in *GRN* first generation and 60·7 years (8·9) in *GRN* second generation (p<0·0001); 62·3 years (10·9) in *C9orf72* first generation and 56·7 years (11·0) in *C9orf72* second generation (p<0·0001); and 51·4 years (9·5) in *MAPT* first generation and 49·6 years (10·0) in *MAPT* second generation (p=0·011; appendix pp 41–43).

We found no significant differences in age at symptom onset between men and women in the *MAPT* group

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	GRN (n=1179)	*MAPT* (n=791)	*C9orf72* (n=1433)
Diagnoses within the frontotemporal dementia spectrum			
Behavioural variant frontotemporal dementia	446 (37·8%)	354 (44·8%)	450 (31·4%)
Non-fluent variant primary progressive aphasia	107 (9·1%)	14 (1·8%)	26 (1·8%)
Semantic variant primary progressive aphasia	13 (1·1%)	14 (1·8%)	13 (0·9%)
Logopenic variant primary progressive aphasia	4 (0·3%)	0 (0%)	3 (0·2%)
Primary progressive aphasia not otherwise specified*	36 (3·1%)	2 (0·3%)	4 (0·3%)
Frontotemporal dementia with amyotrophic lateral sclerosis	7 (0·6%)	2 (0·3%)	157 (11·0%)
Amyotrophic lateral sclerosis	7 (0·6%)	1 (0·1%)	276 (19·3%)
Corticobasal syndrome	47 (4·0%)	14 (1·8%)	2 (0·1%)
Progressive supranuclear palsy†	0 (0%)	33 (4·2%)	1 (0·1%)
Diagnoses outside the frontotemporal dementia spectrum			
Alzheimer's disease	97 (8·2%)	24 (3·0%)	84 (5·9%)
Huntington's disease	0 (0%)	1 (0·1%)	4 (0·3%)
Parkinson's disease	16 (1·4%)	39 (4·9%)	15 (1·0%)
Dementia with Lewy Bodies	4 (0·3%)	1 (0·1%)	5 (0·3%)
Vascular dementia	9 (0·8%)	1 (0·1%)	7 (0·5%)
Dementia not otherwise specified*	361 (30·6%)	274 (34·6%)	362 (25·3%)
Other	25 (2·1%)	17 (2·1%)	24 (1·7%)

*Does not meet criteria for a specific subtype. †Richardson's syndrome.

Table 2: **Clinical diagnoses in each of the three genetic groups**

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(appendix p 44). However, in the *GRN* group, women were significantly older at symptom onset (61·8 years, SD 9·2) than men (60·5 years, 8·3; p=0·019), with the same observed in the *C9orf72* group (58·9 years, SD 9·6, in women, compared with 57·7 years, 10·0, in men [p=0·041]).

In the *C9orf72* group, we found no significant differences in mean age at symptom onset between individuals with different clinical phenotypes, except for those with a diagnosis of Alzheimer's disease (appendix pp 45–46). These individuals were significantly older at symptom onset than individuals with other phenotypes (mean 65·1 years, SD 10·6; p<0·0001 for all comparisons except for that with primary progressive aphasia [p=0·010]). Similarly, we found no significant differences in age at symptom onset between individuals with different clinical phenotypes in the *GRN* group, except for those with a diagnosis of Alzheimer's disease, who were significantly older at symptom onset (mean 66·4 years, SD 8·1) than individuals with other phenotypes (p<0·0001 for all comparisons). In the *MAPT* group, we found no significant differences in age at symptom onset between individuals with behavioural variant frontotemporal dementia and those with primary progressive aphasia; however, individuals with Alzheimer's disease were significantly older at symptom onset (mean 56·7 years, SD 11·1) than those with behavioural variant frontotemporal dementia (p=0·0006), primary progressive aphasia (p=0·013), and a combined corticobasal syndrome and progressive supranuclear palsy (atypical parkinsonism; p<0·0001). Furthermore, individuals in the *MAPT* group with atypical parkinsonism were significantly younger at symptom onset (mean 44·9 years, SD 7·8) than those with other phenotypes (individuals with atypical parkinsonism *vs* those with behavioural variant frontotemporal dementia p=0·013; *vs* individuals with primary progressive aphasia p=0·037).

The mean age at death was lowest in individuals with *MAPT* mutations and highest in those with *GRN* mutations (p<0·0001 for all comparisons between groups; table 1). Age at death was variable within genetic groups (table 1, figure 2) and within individual mutations (appendix pp 6–10, 37). As with age at symptom onset, we found no significant differences in age at death between men and women in the *MAPT* group, but found significant differences between men and women in the *GRN* group (mean 69·4 years, SD 10·2, in women *vs* 67·8 years, 8·8, in men; p=0·029) and *C9orf72* group (66·1 years, 11·0, in women *vs* 64·6 years, 10·8, in men; p=0·034; appendix p 44).

As with age at symptom onset, individuals with a diagnosis of Alzheimer's disease in all three genetic groups were significantly older at death than individuals with other phenotypes (appendix pp 45–46). In the *C9orf72* group, individuals with a diagnosis of amyotrophic lateral sclerosis were significantly younger (mean 59·2 years, SD 9·7) at death compared with those with a diagnosis of frontotemporal dementia with amyotrophic lateral sclerosis (62·1 years, 8·9; p=0·014) and those with a diagnosis of behavioural variant frontotemporal dementia (64·6 years, 9·0; p<0·0001). In turn, individuals with a diagnosis of frontotemporal dementia with amyotrophic lateral sclerosis were younger at death than those with a diagnosis of behavioural variant frontotemporal dementia (p=0·014). In the *MAPT* group, individuals with a diagnosis of atypical parkinsonism were significantly younger at death (mean 52·8 years, SD 8·9) compared with those with a diagnosis of behavioural variant frontotemporal dementia (60·6 years, 9·9; p=0·030) and those with a diagnosis of primary progressive aphasia (60·9 years, 15·2; p=0·036).

The mean disease duration was lowest for individuals with *C9orf72* expansions, followed by those with *GRN* mutations, and those with *MAPT* mutations (p≤0·0005 for each comparison; table 1). However, within each genetic group, several individuals survived for many decades; the longest surviving individuals lived 27 years from symptom onset in the *GRN* group, 36 years in the *C9orf72* group, and 45 years in the *MAPT* group (table 1, figure 2, appendix p 38). Although variability within individual mutations existed (appendix pp 6–10, 38), mean disease duration was similar across the *GRN* group, except for a significantly longer disease duration in individuals with an Ala9Asp mutation compared with those with Gly35fs, Thr272fs, and Arg493X mutations (appendix p 40). We found a greater variability in the mean disease duration in the *MAPT* group than in the *GRN* group. Individuals with an Arg406Trp mutation had a significantly longer disease duration than those with Pro301Leu and Asn279Lys mutations, and individuals with an IVS10+16C→T

mutation had a significantly longer disease duration than those with Pro301Leu mutations (appendix pp 40, 47–48).

We found no significant differences in disease duration between men and women in any of the groups (appendix p 44). We observed no significant differences in disease duration between clinical phenotypes in the *GRN* and *MAPT* groups (appendix pp 45–46). However, individuals with *C9orf72* expansions and a diagnosis of amyotrophic lateral sclerosis had a significantly lower disease duration (mean 2·9 years, SD 2·8) than those of the other groups (p<0·0001 for all comparisons); individuals with *C9orf72* expansions and a diagnosis of frontotemporal dementia with amyotrophic lateral sclerosis also had a lower disease duration (5·0 years, 4·2) than that of those with *C9orf72* expansions and behavioural variant frontotemporal dementia (7·8 years, 4·4; p<0·0001), primary progressive aphasia (7·5 years, 4·8; p=0·0016), and Alzheimer's disease (10·4 years, 4·9; p<0·0001; appendix pp 45–46).

Individual age at symptom onset significantly correlated with both parental and mean family age at symptom onset in all three genetic groups (p<0·0001; figure 4); in each group, individual age at symptom onset either had a similar correlation with parental and mean family age or a stronger correlation with mean family age than with parental age. The strength of these correlations varied across the genetic groups, being strongest in the *MAPT* group and weakest in the *GRN* group (figure 4). As with age at symptom onset, individual age at death significantly correlated with both parental age at death and mean family age at death in all three genetic groups (p<0·0001). We observed a similar pattern to that of age at symptom onset in the three genetic groups: the *MAPT* group had the strongest correlation (r=0·69 for mean family age at death, r=0·58 for parental age at death), followed by the *C9orf72* group (r=0·40, r=0·38) and the *GRN* group (r=0·32, r=0·22).

We found significant differences between the three mutation groups in the inter-family and intra-family variability of age at symptom onset (both p<0·0001; appendix p 49). Family membership explained 66% (95% CI 56–75) of this variability in individuals with *MAPT* mutations, but only 14% (9–22) in those with *GRN* mutations and 17% (11–26) in those with *C9orf72* expansions. We observed a significant difference between the *GRN* and *MAPT* groups in the between-mutation variability in age at symptom onset (p<0·0001): in the *GRN* group, only 2% (95% CI 0–10) of the variability was explained by the specific mutation, whereas in the *MAPT* group, 48% (35–62) of the variability was explained by the specific mutation.

Significant differences were also found between the three genetic groups in the variability of inter-family and intra-family age at death (both p<0·0001; appendix p 49). Family membership explained 74% (95% CI 65–82) of this variability in individuals with *MAPT* mutations, but only 20% (12–30) in those with *GRN* mutations and 19% (12–29) in those with *C9orf72* expansions. We also found a significant difference between the *GRN* and *MAPT* groups in the between-mutation variability in age at death (p<0·0001): in the *GRN* group, only 9% (95% CI 3–21) of the variability was explained by the specific mutation, whereas in the *MAPT* group, 61% (47–73) of the variability was explained by the specific mutation.

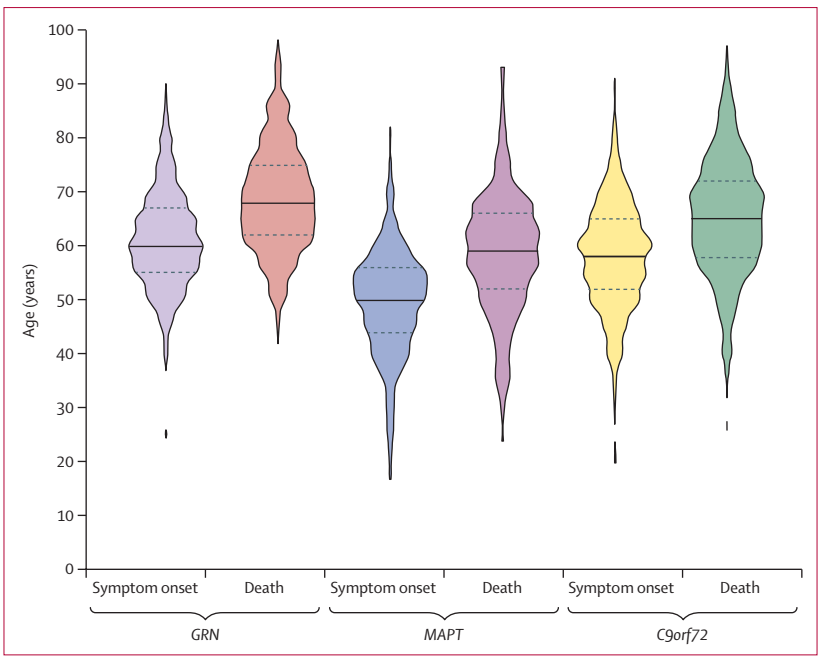

Figure 2: **Violin plots of age at symptom onset and at death for the three genetic groups**
Data are median (bold lines) with IQR (dashed lines).

Discussion

To our knowledge, we report in this study the largest dataset of age at onset, age at death, and disease duration in individuals with genetic frontotemporal dementia to date, incorporating data from across the world for the three main genetic groups and for all reported mutations in the *GRN* and *MAPT* groups. Our study provides evidence that an individual's age at symptom onset and death in genetic frontotemporal dementia is modulated by both the individual mutation carried and family membership and varies by clinical phenotype and sex, with the strongest effect of these factors seen in individuals with *MAPT* mutations.

Our study provides further evidence that genetic frontotemporal dementia is a disorder that can occur throughout adult life, with symptom onset occurring from as early as the late teens to age 90 years or older. Although we did not account for individuals with mutations who were unaffected in the analysis, our findings are consistent with previous studies showing age-related penetrance in the *GRN*[8] and *C9orf72*[9] groups, with individuals developing symptoms at age 90 years and older. A leftwards shift towards younger ages is evident in the penetrance curve in individuals with *MAPT* mutations (figure 3A) but

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For the **Frontotemporal Dementia Prevention Initiative** see http://www.genfi.org.uk/fpi.html

For the **Alzheimer Disease & Frontotemporal Dementia Mutation database** see www.molgen.ua.ac.be/FTDmutations

See **Online** for appendix

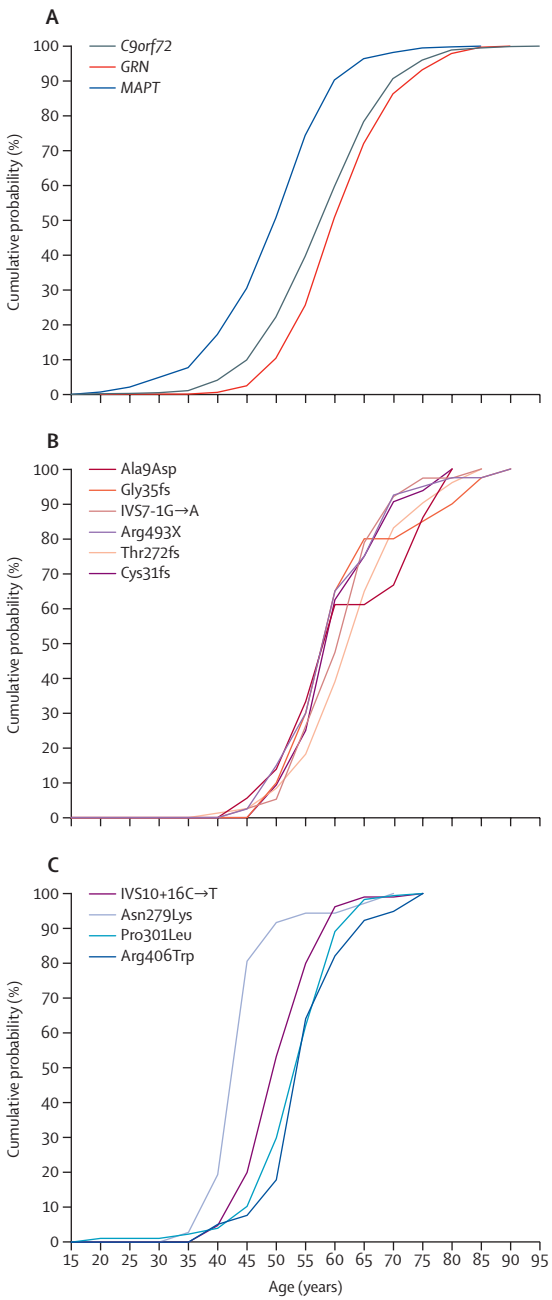

Figure 3: **Cumulative probability of symptom onset for each genetic group (A) and in the common *GRN* (B) and *MAPT* (C) mutations**
Data includes only individuals who have become symptomatic and does not account for family members who are not symptomatic.

nonetheless, the oldest age at symptom onset in this group was 82 years. Although usually considered a fully penetrant disorder, occasional incomplete penetrance might exist in some families with *MAPT* mutations (eg, Leu315Arg[10], Val363Ile[11,12], and Gly389Arg[13]), which might be age-related.

The investigation of individual mutations within *GRN* revealed little difference between them in terms of age at symptom onset, age at death, or disease duration. These results are consistent with the underlying pathophysiological mechanism of progranulin haplo-insufficiency being the same in most *GRN* mutations.[14,15] By contrast, we found significant differences between individual *MAPT* mutations, with the mean symptom onset in the Asn279Lys mutation group occurring 12 years earlier than in the Arg406Trp mutation group. Along with the Val337Met mutation, the Arg406Trp mutation has a distinct pathological form compared with that of the other *MAPT* mutations, with the presence of tau pathology with paired helical filaments similar to that seen in Alzheimer's disease; this group had a significantly longer disease duration than that of the other mutations, as previously described in single case reports.[16]

The generational analysis revealed significant differences in all three genetic groups, consistent with previous studies,[4,17] with earlier age at symptom onset occurring in later (second) generations. These findings have been variably interpreted previously. One study has suggested that, in individuals with *C9orf72* expansions, this finding was evidence of genetic anticipation.[17] However, another research group interpreted this data as likely to be related to later generations recognising the disease earlier because of increased familiarity with symptoms and being more likely to be alert to the presence of such symptoms because of their awareness of being at-risk.[4] At a molecular level, studies have shown that although *C9orf72* expansions might be dynamic, they can both expand and contract across generations.[17] Furthermore, no clear evidence exists for a relationship between age at symptom onset and expansion length, with contradictory evidence of both a positive correlation in some studies[18–20] and an inverse correlation in another.[21] Evidence against anticipation being an explanation for the earlier age at symptom onset in later generations also comes from the similar results observed in the *GRN* (corroborated by another study[4]) and *MAPT* groups: these mutations are stable and do not change molecularly across generations, therefore no plausible mechanism exists for anticipation in *GRN* or *MAPT* mutations.

Few studies have compared whether age at symptom onset, age at death, or disease duration vary by clinical phenotype within genetic groups. In our study, individuals with a diagnosis of Alzheimer's disease within each group were significantly older at symptom onset than those with other diagnoses. Although it is possible that individuals with a true amnestic presentation of genetic frontotemporal dementia do present at an older age (and that an underlying biological explanation for this exists), this is more likely to be related to the misdiagnosis of individuals with late-onset dementia as having Alzheimer's disease. In the *MAPT* group, individuals with an atypical parkinsonian syndrome were significantly younger at symptom onset and at death and had a shorter disease duration than those of the other groups—this was not entirely driven by the presence of a specific mutation because the phenotype was

seen across multiple mutations (eg, only 13% of this group had an Asn279Lys mutation, which has an earlier mean age at symptom onset than that of other mutations). In the *C9orf72* group, the presence of amyotrophic lateral sclerosis was associated with a shorter disease duration than that of other phenotypes (with amyotrophic lateral sclerosis alone having a significantly shorter disease duration than the combined phenotype of frontotemporal dementia with amyotrophic lateral sclerosis), as previously reported.[22] A previous study compared a combined frontotemporal dementia group with an amyotrophic lateral sclerosis group in individuals with *C9orf72* expansions and found an earlier onset in the amyotrophic lateral sclerosis group.[9] In our *C9orf72* cohort, a significantly earlier onset was found in the amyotrophic lateral sclerosis group compared with that of a combined group of individuals with a cognitive presentation (appendix p 46), but this is partly driven by the Alzheimer's disease group and no differences were found between the amyotrophic lateral sclerosis group and either the behavioural variant frontotemporal dementia or primary progressive aphasia groups individually (appendix pp 45–46).

Individual age at symptom onset was significantly correlated with both parental age at symptom onset and mean family age at symptom onset in all three genetic groups. Similarly, individual age at death was significantly correlated with both parental age at death and mean family age at death in all three genetic groups. However, we found stronger correlations in the *MAPT* group than in the other two groups, similar to the results found in patients with familial Alzheimer's disease.[23] The variability in age at symptom onset and at death for individuals with *MAPT* mutations was partly explained by the specific mutation and more so by family membership. Unlike the other genetic groups, in the *MAPT* group, prediction of probable age at symptom onset and at death is therefore highly related to the presence of the *MAPT* mutation itself. Other genetic or environmental factors affecting age at symptom onset and at death in individuals with *MAPT* mutations have not yet been well studied.[24]

Despite being statistically significant, correlation coefficients were low in the *GRN* group for the comparisons between individual age at symptom onset and parental and mean family age at symptom onset. The variability in age at symptom onset and age at death for individuals with *GRN* mutations was not accounted for particularly by either the individual mutation or family membership. This finding is consistent with previous reports of large variability within families (and specific mutations), even within the same generation.[25–27] Genetic factors affecting age at symptom onset include polymorphisms in *TMEM106B*[28,29] and potentially also in *PRNP*,[30] but several recent studies suggest that environmental factors related to an altered neuroinflammatory response might also be important.[31–34]

The *C9orf72* group sits between the *GRN* and *MAPT* groups in terms of the strength of correlation of individual age at symptom onset and at death with parental and mean family age at symptom onset and at death. However, similar to *GRN* mutations, the variability in age at symptom onset and at death was not accounted for particularly by family membership. Although conflicting evidence exists about whether expansion length is relevant,[18–21] several studies have identified DNA methylation[21,35,36] and a locus on chromosome 6[37] as important factors in age at symptom onset, age at death, and disease duration in individuals with *C9orf72* expansions (see appendix for further discussion of potential modifiers of age at symptom onset and age at death [pp 49–50]).

Our study has several limitations. One such limitation was its focus on mainly retrospective data collection, with age at symptom onset recorded as the age at which an

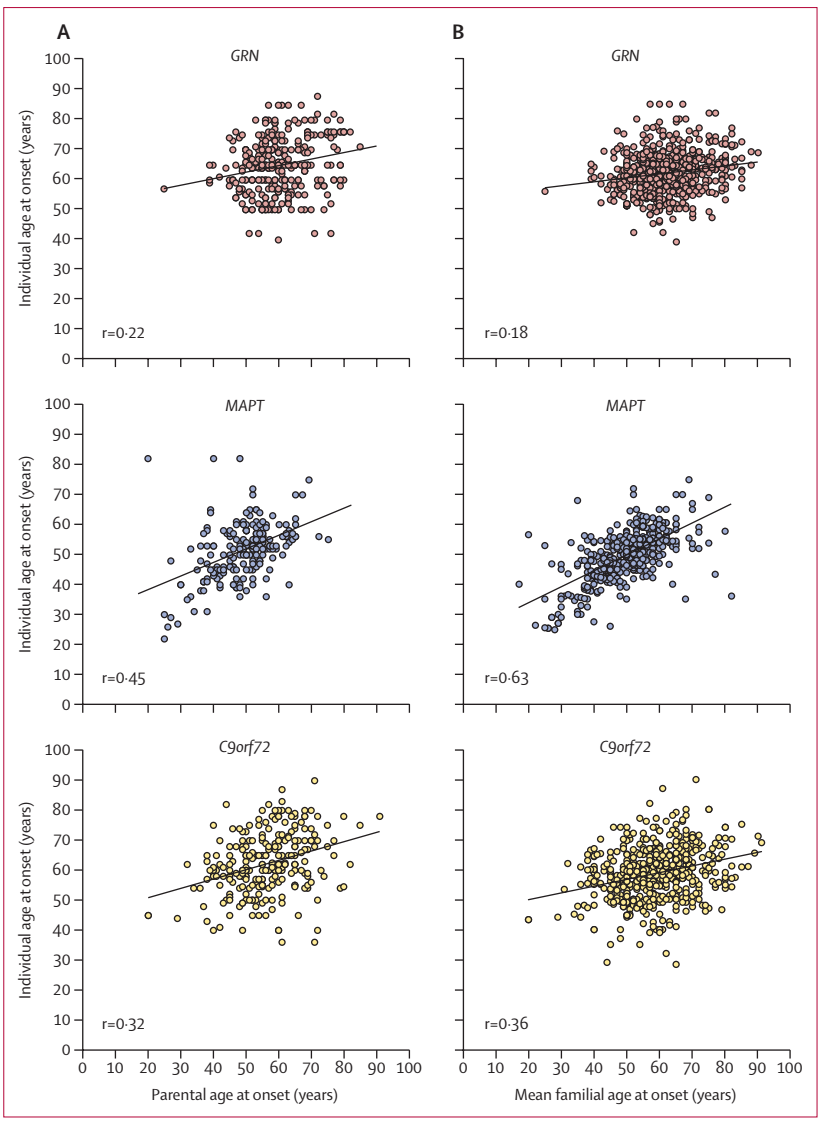

Figure 4: **Correlation of individual age at symptom onset with parental (A) and mean familial (B) ages at symptom onset for *GRN*, *MAPT*, and *C9orf72* genetic groups**
Pearson's correlation coefficient is shown on each graph.

individual was determined to have progressive cognitive, behavioural, or motor symptoms. As such, our data might be confounded by factors such as individual differences in interpreting symptom onset. This is a major issue in the study of frontotemporal dementia, for which objective measures of symptom onset are needed. A grey zone in proximity to symptom onset exists, in which subtle cognitive and behavioural deficits are present,[7] but have not yet been identified as symptoms by the patient themselves or family members. Work within the FPI aims to identify such proximity markers, which will be important for future stratification in clinical trials, particularly, as identified in this study, for individuals with *GRN* and *C9orf72* mutations, in whom prediction by age itself is poor.

Another limitation of the study is that we did not collect data on individuals with known mutations who did not develop symptoms of frontotemporal dementia. This is particularly important when assessing age-related penetrance in the *GRN* and *C9orf72* groups, although we did identify people older than 90 years developing symptoms of frontotemporal dementia in both these groups. Attainment of data from long-living individuals with mutations will be important to better understand the modifiers of age at symptom onset and this will require large, well characterised longitudinal cohort studies, such as those in the FPI.

Although many of the centres in our study saw patients and families with all phenotypes of frontotemporal dementia, amyotrophic lateral sclerosis, and movement disorders within their clinics, the focus on genetic frontotemporal dementia within our study might have led to an underrepresentation of patients with amyotrophic lateral sclerosis or parkinsonian disorders. However, many of the families had members with multiple different phenotypes (including cognitive, behavioural, and motor), and few families had only a single phenotype, suggesting that the data in our study is unlikely to lead to a major discrepancy in phenotypic frequency.

Lastly, we did not have any data on the *TMEM106B* genotype (which is a known modifier in individuals with *GRN* mutations) nor on other genetic modifiers, such as *APOE* genotype, to further investigate their effect. However, such data, along with various environmental and lifestyle factors, are now being collected within the FPI and will be investigated in future studies.

In summary, we showed that individuals with *MAPT* mutations are younger at symptom onset and at death than those of the other groups, with the observed variance largely accounted for by family membership and the specific mutation carried. Individuals with *GRN* mutations had the weakest association of age at symptom onset and at death with other family members, and most of the observed variance in age at symptom onset and at death was accounted for by neither family membership nor the specific mutation. However, we found a sex effect, with increased prevalence of symptomatic individuals and older age at onset in women than in men, probably driven by age-related penetrance seen in those with *GRN* mutations. *C9orf72* expansions were the overall most common cause of genetic frontotemporal dementia in our study. Phenotypical differences in disease duration exist, with the presence of amyotrophic lateral sclerosis leading to a shortened disease duration. As in the *GRN* group, little of the variance in age at symptom onset or at death was accounted for by family membership, with other genetic and environmental factors likely to be involved.

Our study highlights the strength of collaborative studies in rare diseases, bringing together data from across the world to better understand genetic frontotemporal dementia and to provide important data relevant to future trial designs. The prospective cohort studies within the FPI will hopefully provide solutions to some of the unanswered questions over the forthcoming years.

Contributors

KMM, JDR, MG, BFB, JCvS, BCD, CG, NG, BB, DG, IRM, ALB, HR, JL, JBR, MO, MM, RLJr, CUO, and JN contributed to the study design. KMM and JDR drafted the initial version and figures. JN and JDR did the statistical analysis. All authors were involved in data collection and interpretation and drafting of the manuscript. All authors critically reviewed the manuscript and approved the final draft.

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Declaration of interests

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