Longitudinal Cognitive Changes in Genetic Frontotemporal Dementia Within the GENFI Cohort

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Abstract

Background and Objectives
Disease-modifying therapeutic trials for genetic frontotemporal dementia (FTD) are underway, but sensitive cognitive outcome measures are lacking. The aim of this study was to identify such cognitive tests in early stage FTD by investigating cognitive decline in a large cohort of genetic FTD pathogenic variant carriers and by investigating whether gene-specific differences are moderated by disease stage (asymptomatic, prodromal, and symptomatic).

Methods
C9orf72, GRN, and MAPT pathogenic variant carriers as well as controls underwent a yearly neuropsychological assessment covering 8 cognitive domains as part of the Genetic FTD Initiative, a prospective multicenter cohort study. Pathogenic variant carriers were stratified according to disease stage using the global Clinical Dementia Rating (CDR) plus National Alzheimer’s Coordinating Center (NACC) FTLD score (0, 0.5, or ≥1). Linear mixed-effects models were used to investigate differences between genetic groups and disease stages as well as the 3-way interaction between time, genetic group, and disease stage.

Results
A total of 207 C9orf72, 206 GRN, and 86 MAPT pathogenic variant carriers and 255 controls were included. C9orf72 pathogenic variant carriers performed lower on attention, executive function, and verbal fluency from CDR plus NACC FTLD 0 onwards, with...
relatively minimal decline over time regardless of the CDR plus NACC FTLD score (i.e., disease progression). The cognitive profile in MAPT pathogenic variant carriers was characterized by lower memory performance at CDR plus NACC FTLD 0.5, with decline over time in language from the CDR plus NACC FTLD 0.5 stage onwards, and executive dysfunction rapidly developing at CDR plus NACC FTLD ≥1. GRN pathogenic variant carriers declined on verbal fluency and visuconstruction in the CDR plus NACC FTLD 0.5 stage, with progressive decline in other cognitive domains starting at CDR plus NACC FTLD ≥1.

Discussion
We confirmed cognitive decline in the asymptomatic and prodromal stage of genetic FTD. Specifically, tests for attention, executive function, language, and memory showed clear differences between genetic groups and controls at baseline, but the speed of change over time differed depending on genetic group and disease stage. This confirms the value of neuropsychological assessment in tracking clinical onset and progression and could inform clinical trials in selecting sensitive end points for measuring treatment effects as well as characterizing the best time window for starting treatment.

Frontotemporal dementia (FTD) is a common cause of dementia, often presenting at a young age, with devastating effects on daily living.4 The typical case of FTD is neurodegeneration of the frontal and temporal lobes resulting in behavioral disturbances (behavioral variant FTD [bvFTD]) or language impairment (primary progressive aphasia [PPA]).2,3 FTD is highly heritable and is autosomal dominantly inherited in up to ~30% of cases. The most common causes are pathogenic variants in the microtubule-associated protein tau (MAPT), progranulin (GRN), or chromosome 9 open reading frame 72 (C9orf72) genes.4 Deficits in executive function, language, and social cognition are often predominant, but may vary in severity and progression due to the heterogeneous nature of the disease.1,3,5

Research into genetic FTD has shown that disease pathology emerges years before symptom onset.6-13 Initiating disease-modifying interventions at this early stage of the disease may have the most profound effect because neuronal loss is minimal and cognitive functions are preserved.14 It is therefore important to identify sensitive clinical instruments that can signal disease onset and track disease progression. Identifying such instruments for this early stage of the disease is also important because they can be used as clinical end points in therapeutic trials.

Gene-specific cognitive decline during the presymptomatic period has been demonstrated by both cross-sectional and longitudinal studies.6,10,15-26 For example, previous reports have shown decline in memory,17,19,20,26 language,17,20,23 and social cognition17,19,20 in MAPT pathogenic variant carriers, decline in attention15,16,19,20 and executive function15,16,18,20 in GRN pathogenic variant carriers, and a decline in social cognition in C9orf72 pathogenic variant carriers.22,24,25 However, other studies on genetic FTD failed to find these results.13,21,26,27

Most studies investigating cognitive decline in presymptomatic genetic FTD have had a small sample size, a limited number of yearly follow-ups, or did not include all 3 major causes of genetic FTD. Furthermore, most studies split their sample of pathogenic variant carriers either according to the artificial boundary of presymptomatic vs symptomatic or according to estimated years to symptomatic onset. As a result, none of the studies fully highlights the complexity of the disease trajectory.28

Larger international cohort studies with longer follow-up time are crucial to identify cognitive markers that signify disease onset at the earliest stage and can measure changes during disease progression. In addition, clinical instruments for disease severity, such as the Clinical Dementia Rating scale plus National Alzheimer’s Coordinating Center frontotemporal lobar degeneration module,29 could stratify pathogenic variant carriers and provide valuable insight into cognitive decline during the different stages of the disease per genetic group.

This study aims to investigate longitudinal cognitive decline in genetic FTD pathogenic variant carriers. We performed a 5-year follow-up study in which we investigated baseline and longitudinal differences on neuropsychological test performance between C9orf72, GRN, and MAPT pathogenic variant carriers and control participants and stratified pathogenic variant carriers according to the CDR NACC FTLD global score.
Methods

Participants
Data were included from the fifth Genetic FTD Initiative (GENFI) data freeze, in which participants from confirmed genetic FTD families were recruited in 24 centers across Europe and Canada between January 30, 2012, and May 31, 2019. Pathogenic variant carriers were included in this study if they performed at least 1 or more neuropsychological assessments. A total of 207 C9orf72, 206 GRN, and 86 MAPT pathogenic variant carriers and 255 pathogenic variant negative family members (who served as control group) were included. A total of 109 C9orf72, 112 GRN, and 60 MAPT pathogenic variant carriers and 154 controls had completed at least 1 follow-up visit (Table 1). Pathogenic variant carriers were divided into 3 categories based on the CDR plus NACC FTLD global score at baseline: 0, 0.5, or at least 1 follow-up visit (Table 1). Pathogenic variant carriers were included in this study if they performed at least 1 or more neuropsychological assessments. A total of 207 C9orf72, 206 GRN, and 86 MAPT pathogenic variant carriers and 255 pathogenic variant negative family members (who served as control group) were included. A total of 109 C9orf72, 112 GRN, and 60 MAPT pathogenic variant carriers and 154 controls had completed at least 1 follow-up visit (Table 1). Pathogenic variant carriers were divided into 3 categories based on the CDR plus NACC FTLD global score at baseline: 0, 0.5, or ≥1. Of those with a CDR plus NACC FTLD global score of ≥1, 51 C9orf72, 27 GRN, and 21 MAPT pathogenic variant carriers met diagnostic criteria for bvFTD, 16 GRN and 3 C9orf72 pathogenic variant carriers met criteria for PPA, and 8 C9orf72 pathogenic variant carriers met criteria for FTLD with amyotrophic lateral sclerosis. Ten percent of C9orf72, 8% of GRN, and 8% of MAPT pathogenic variant carriers progressed from CDR category 0 to 0.5, and 4% of C9orf72, 2% of GRN, and 4% of MAPT pathogenic variant carriers progressed to ≥1. Six percent of C9orf72, 16% of GRN, and 20% of MAPT pathogenic variant carriers progressed from CDR category 0.5 to ≥1 (eTable 1, links.lww.com/WNL/B987).

Table 1 Number of Participants at Each Yearly Follow-up

| Year | C9orf72 | GRN | MAPT | Controls |
|------|---------|-----|------|----------|
| 1    | 207     | 206 | 86   | 255      |
| 2    | 109     | 112 | 60   | 154      |
| 3    | 105     | 72  | 40   | 105      |
| 4    | 34      | 31  | 11   | 34       |
| 5    | 0       | 3   | 1    | 1        |

Abbreviations: C9orf72 = chromosome 9 open reading frame 72; GRN = progranulin; MAPT = microtubule-associated protein tau.

Standard Protocol Approvals, Registrations, and Patient Consents
All GENFI sites had local ethical approval for the study and all participants gave written informed consent.

Procedures
Participants underwent a yearly standardized clinical assessment including the CDR plus NACC FTLD and a comprehensive neuropsychological test battery covering attention and processing speed (Wechsler Memory Scale–Revised [WMS-R] digit span forward31; Trail-Making Test [TMT] part A32; Wechsler Adult Intelligence Scale–Revised Digit Symbol test31; Delis-Kaplan Executive Function System [D-KEFS] Color-Word Interference Test color and word naming33; executive function (WMS-R Digit span backward31; TMT part B32; D-KEFS Color-Word Interference Test ink naming33; language (modified Camel and Cactus Test33; Boston Naming Test [short 30-item version]31), verbal fluency (category fluency31; phonemic fluency34), memory encoding (Free and Cued Selective Reminding Test [FCSRT] immediate free and total recall23), memory recall (FCSRT delayed free and total recall; Benson Complex Figure recall), social cognition (Facial Emotion Recognition Test34), and visuoconstruction (Benson Complex Figure copy). Previous studies have shown that verbal fluency can involve both language and executive function processes and therefore we included it as a separate domain. Mental State Examination (MMSE)37 measured global cognitive functioning.

Statistical Analysis
Statistical analyses were performed using Stata version 14.2 and R version 4.0.4. We compared continuous demographic data between groups with 2-way analyses of variance and a χ2 test for sex. The significance level was set at p < 0.05 (2-tailed) across all comparisons.

All neuropsychological data were standardized to z scores (i.e., raw score – mean score controls at baseline/SD controls at baseline). z scores for tests with reaction times (i.e., TMT and D-KEFS Color-Word Interference Test) were inverted so that lower z scores indicate worse performance. Cognitive domains were calculated by averaging the mean z scores of the neuropsychological tests in that domain. Only the FCSRT total recall was included in the memory domains, as the free recall scores are a part of the total recall scores. The memory, social cognition, and visuoconstruction domains are represented by only 1 test.

As this is a prospective cohort study, not all pathogenic variant carriers had completed all study visits, which resulted in missing data. We used linear mixed-effects models for each cognitive domain to examine whether differences existed between C9orf72, GRN, and MAPT pathogenic variant carriers and controls in cognitive decline since baseline. This type of model allows for the analysis of longitudinal data with unbalanced time points and missing data.38 Age and years of education were included in all models as covariates. In each model, a different cognitive outcome was used as the dependent variable and we specified the following fixed effects: time since baseline in years, gene group, CDR category at baseline, age at baseline, years of education, the 2-way interactions between time and group, time and CDR category, and gene group and CDR category, and the 3-way interaction between time, group, and CDR category. We included random intercepts for participants who were nested within families, but not random slopes as this did not improve model fit. A natural cubic splines model did not improve model fit. We performed post hoc pairwise comparisons in intercepts and slopes between genetic groups within CDR categories. Results are shown as a difference between pathogenic variant group and the control group or a different pathogenic variant group if stated.
Table 2 Demographics and Neuropsychological Data per Genetic Group and CDR plus NACC FTLD Global Score Category at Baseline

| Neuropsychological data | C9orf72 | GRN | MAPT | Controls |
|-------------------------|--------|-----|------|----------|
| Language                | -0.2 (1.0) | -0.3 (1.3) | -3.1 (2.7) | 0.1 (0.6) |
| Attention               | -0.3 (0.8) | -0.3 (1.0) | -2.7 (1.7) | -0.0 (0.6) |
| Verbal fluency          | -0.2 (0.8) | -0.3 (0.9) | -2.0 (0.9) | 0.1 (0.8) |
| Executive function      | -0.4 (1.1) | -0.4 (1.2) | -3.3 (1.9) | -0.0 (0.7) |
| Memory: immediate recall | -0.5 (1.8) | -0.8 (2.3) | -3.3 (4.0) | 0.1 (0.7) |
| Memory: delayed recall  | -0.3 (0.9) | -0.1 (1.2) | -2.6 (2.6) | -0.0 (0.7) |
| Social cognition         | -0.1 (1.0) | -0.7 (1.3) | -3.1 (2.2) | 0.1 (1.1) |
| Visuconstruction         | -0.1 (1.2) | -0.2 (1.6) | -2.3 (2.9) | 0.2 (0.8) |

Abbreviations: C9orf72 = chromosome 9 open reading frame 72; CDR plus NACC FTLD = Clinical Dementia Rating scale plus National Alzheimer’s Coordinating Center Frontotemporal Lobar Degeneration; GRN = progranulin; MAPT = microtubule-associated protein tau; MMSE = Mini-Mental State Examination. Values are represented as mean ± standard deviation (SD) unless otherwise specified.

\( \beta \) indicates an estimated difference in z score at baseline; \( \beta_1 \) indicates a difference in change over time (slope). An example of the model and its outputs is shown in eAppendix 1 (links.lww.com/WNL/B987).

Data Availability
Anonymized data not published within this article will be made available upon reasonable request from any qualified investigator.

Results

Demographics
There were more female participants in CDR categories 0 and 0.5 and more male participants in CDR category \( \geq 1 \) for C9orf72 (\( \chi^2[2] = 9.8, p = 0.007 \)) and MAPT (\( \chi^2[2] = 6.6, p = 0.036 \)) pathogenic variant carriers (Table 2). We found differences in age at baseline between gene groups (\( F_{3,744} = 5.6, p < 0.001 \)) and between CDR categories (\( F_{2,744} = 91.4, p < 0.001 \)) (Table 2). Post hoc pairwise comparisons revealed that C9orf72 and GRN pathogenic variant carriers were older than MAPT pathogenic variant carriers (all \( p \leq 0.02 \)) and controls (all \( p < 0.001 \)) and each CDR category represented older pathogenic variant carriers than the categories with a lower CDR category (all \( p \leq 0.008 \)). We found differences between CDR categories in years of education at baseline (\( F_{3,744} = 8.8, p < 0.001 \)), with CDR category \( \geq 1 \) having had fewer years of education than the other categories (all \( p < 0.03 \)) (Table 2). There was an interaction effect between gene group and CDR category on MMSE at baseline (\( F_{3,742} = 4.3, p = 0.002 \)). Post hoc simple main effects illustrated a difference in MMSE at baseline between CDR categories in all 3 gene groups and a difference in MMSE at baseline between gene groups in CDR category \( \geq 1 \). Descriptive and neuropsychological data at baseline are reported in Table 2 and eTable 2 (links.lww.com/WNL/B987).

Baseline and longitudinal results for each cognitive domain are discussed in the following sections (Tables 2 and 3, Figures 1 and 2, and summarized in Figure 3).

Attention
We found strong evidence for differences in the attention domain between CDR categories (\( \chi^2[2] = 23.2, p < 0.001 \)) and between gene groups (\( \chi^2[3] = 26.0, p < 0.001 \)) at baseline. C9orf72 (\( \beta = -2.2, SE = 0.14, p < 0.001 \)), GRN (\( \beta = -2.2, SE = 0.16, p < 0.001 \)), and MAPT (\( \beta = -1.1, SE = 0.21, p < 0.001 \))
| CDR plus NACC FTLD | 0 | 95% CI | 0.5 | 95% CI | ≥1 | 95% CI |
|-------------------|---|--------|-----|--------|----|--------|
| **C9orf72**       |   |        |     |        |    |        |
| Language          | 0.02 | −0.09 to 0.14 | −0.03 | −0.37 to 0.32 | −0.50 | −0.70 to −0.30 |
| Attention         | −0.03 | −0.10 to 0.05 | 0.07 | −0.15 to 0.29 | −0.24 | −0.36 to −0.11 |
| Verbal fluency    | −0.01 | −0.07 to 0.04 | 0.03 | −0.14 to 0.19 | −0.13 | −0.22 to −0.04 |
| Executive function| −0.07 | −0.16 to 0.02 | −0.04 | −0.31 to 0.23 | −0.03 | −0.20 to 0.14 |
| Memory: immediate recall | 0.26 | 0.11 to 0.40 | 0.45 | 0.06 to 0.84 | −0.01 | −0.25 to 0.24 |
| Memory: delayed recall | 0.14 | 0.05 to 0.23 | 0.14 | −0.09 to 0.37 | 0.00 | −0.16 to 0.16 |
| Social cognition  | 0.06 | −0.06 to 0.17 | 0.14 | −0.15 to 0.43 | 0.20 | 0.00 to 0.40 |
| Visuoconstruction | −0.07 | −0.25 to 0.11 | −0.13 | −0.58 to 0.32 | 0.02 | −0.25 to 0.28 |
| **GRN**           |   |        |     |        |    |        |
| Language          | 0.05 | −0.04 to 0.14 | −0.08 | −0.39 to 0.23 | −1.24 | −1.51 to −0.97 |
| Attention         | 0.02 | −0.04 to 0.07 | −0.03 | −0.22 to 0.17 | −0.34 | −0.52 to −0.16 |
| Verbal fluency    | 0.00 | 0.04 to 0.05 | −0.18 | −0.33 to −0.03 | −0.15 | −0.28 to −0.02 |
| Executive function| −0.01 | −0.08 to 0.06 | 0.09 | −0.16 to 0.33 | −0.09 | −0.32 to 0.15 |
| Memory: immediate recall | 0.06 | −0.05 to 0.17 | 0.17 | −0.17 to 0.52 | −0.24 | −0.64 to 0.17 |
| Memory: delayed recall | 0.05 | −0.02 to 0.12 | −0.03 | −0.24 to 0.18 | −0.06 | −0.32 to 0.20 |
| Social cognition  | 0.09 | 0.00 to 0.18 | 0.11 | −0.16 to 0.39 | −0.47 | −0.70 to −0.23 |
| Visuoconstruction | −0.09 | −0.23 to 0.05 | −0.45 | −0.88 to −0.02 | −1.13 | −0.48 to 0.23 |
| **MAPT**          |   |        |     |        |    |        |
| Language          | 0.08 | −0.06 to 0.22 | −0.43 | −0.76 to −0.10 | −0.39 | −0.67 to −0.10 |
| Attention         | −0.01 | −0.09 to 0.08 | −0.08 | −0.28 to 0.13 | −0.21 | −0.39 to −0.04 |
| Verbal fluency    | 0.00 | −0.07 to 0.07 | 0.05 | −0.10 to 0.21 | −0.09 | −0.23 to 0.04 |
| Executive function| 0.07 | −0.04 to 0.17 | 0.14 | −0.12 to 0.41 | −0.55 | −0.77 to −0.33 |
| Memory: immediate recall | 0.02 | −0.15 to 0.18 | 0.19 | −0.20 to 0.57 | −0.06 | −0.46 to 0.34 |
| Memory: delayed recall | 0.03 | −0.07 to 0.13 | 0.07 | −0.16 to 0.31 | −0.16 | −0.41 to 0.09 |
| Social cognition  | 0.08 | −0.05 to 0.21 | 0.20 | −0.12 to 0.52 | −0.13 | −0.37 to 0.12 |
| Visuoconstruction | 0.04 | −0.17 to 0.25 | 0.11 | −0.36 to 0.58 | 0.20 | −0.17 to 0.58 |
| **Controls**      |   |        |     |        |    |        |
| Language          | 0.06 | −0.02 to 0.13 |     |        |    |        |
| Attention         | 0.05 | 0.00 to 0.10 |     |        |    |        |
| Verbal fluency    | 0.02 | −0.02 to 0.05 |     |        |    |        |
| Executive function| 0.02 | −0.03 to 0.08 |     |        |    |        |
| Memory: immediate recall | 0.00 | −0.11 to 0.22 |     |        |    |        |
| Memory: delayed recall | 0.05 | −0.01 to 0.10 |     |        |    |        |
| Social cognition  | 0.04 | −0.03 to 0.12 |     |        |    |        |
| Visuoconstruction | 0.13 | 0.04 to 0.12 |     |        |    |        |

Abbreviations: C9orf72 = chromosome 9 open reading frame 72; CDR plus NACC FTLD = Clinical Dementia Rating scale plus National Alzheimer’s Coordinating Center Frontotemporal Lobar Degeneration; GRN = progranulin; MAPT = microtubule-associated protein tau.
pathogenic variant carriers with CDR category ≥1 all performed worse than controls, with both C9orf72 (β = −1.1, SE 0.23, p < 0.001) and GRN (β = −1.2, SE 0.25, p < 0.001) pathogenic variant carriers performing worse than MAPT pathogenic variant carriers. C9orf72 pathogenic variant carriers with CDR category 0 also performed worse at baseline than GRN (β = −0.3, SE 0.13, p = 0.010) and MAPT (β = −0.4, SE 0.16, p = 0.030) pathogenic variant carriers and controls (β = −0.4, SE 0.11, p < 0.001; Figure 1A). In addition, we found an interaction effect between time and gene group (χ²[3] = 37.1, p < 0.001). All gene groups with CDR category ≥1 declined over time compared with controls (C9orf72: β₁ = −0.3, SE 0.07, p < 0.001; GRN: β₁ = −0.4, SE 0.10, p < 0.001; MAPT: β₁ = −0.3, SE 0.09, p = 0.004). There was some weak evidence that C9orf72 pathogenic variant carriers with CDR category 0 declined over time compared with controls (β₁ = −0.4, SE 0.11, p = 0.086; Figure 1A).

Executive Function

We found strong evidence for differences on the executive function domain between CDR categories (χ²[2] = 27.2, p < 0.001) and between gene groups (χ²[3] = 23.3, p < 0.001) at baseline. A similar profile was seen in all gene groups with CDR category ≥1 performing worse at baseline than controls (C9orf72: β = −3.1, SE 0.25, p < 0.001; GRN: β = −3.2, SE 0.23, p < 0.001; MAPT: β = −1.7, SE 0.29, p < 0.001), and C9orf72 (β = −1.0, SE 0.32, p = 0.003) and GRN (β = −1.1, SE 0.35, p = 0.002) pathogenic variant carriers performing worse than MAPT pathogenic variant carriers (Figure 1B). C9orf72 pathogenic variant carriers with CDR category 0 also performed worse than GRN (β = −0.4, SE 0.17, p = 0.016) and MAPT (β = −0.6, SE 0.23, p = 0.012) pathogenic variant carriers, and controls (β = −0.5, SE 0.15, p < 0.001) and GRN pathogenic variant carriers with CDR category 0.5 performed worse than controls (β = −0.7, SE 0.25, p = 0.006). We found interaction effects between time and gene group (χ²[3] = 24.7, p < 0.001), time and CDR category (χ²[2] = 25.8, p < 0.001), and time, gene group, and CDR category (χ²[4] = 18.6, p = 0.001). MAPT pathogenic variant carriers with CDR category ≥1 demonstrated steeper decline over time than C9orf72 (β₁ = −0.5, SE 0.14, p = 0.002) and GRN pathogenic variant carriers (β₁ = −0.5, SE 0.17, p = 0.005) and controls (β₁ = −0.6, SE 0.12, p < 0.001) (Figure 1B).

Language

Language differed between CDR categories (χ²[2] = 96.7, p < 0.001) and between gene groups (χ²[3] = 21.5, p < 0.001) at baseline. Again, all gene groups with CDR category ≥1 performed worse than controls (C9orf72: β = −3.2, SE 0.28, p < 0.001; GRN: β = −2.9, SE 0.31, p < 0.001; MAPT: β = −5.0, SE 0.41, p < 0.001) at baseline, but in this case MAPT pathogenic variant carriers performed worse than C9orf72 (β = −1.7, SE 0.34, p = 0.002) and GRN (β = −1.3, SE 0.33, p = 0.009) pathogenic variant carriers (Figure 1C). We also found interaction effects between time and gene group (χ²[3] = 104.8, p < 0.001), time and CDR category (χ²[2] = 14.0, p = 0.001), and time, gene group, and CDR category (χ²[4] = 25.5, p < 0.001). MAPT pathogenic variant carriers with CDR category 0.5 (β₁ = −0.5, SE 0.17, p = 0.004) or ≥1 (β₁ = −0.5, SE 0.15, p = 0.003) as well as C9orf72 (β₁ = −0.6, SE 0.11, p < 0.001) and GRN (β₁ = −1.3, SE 0.14, p < 0.001) pathogenic variant carriers with CDR category ≥1 declined over time compared with controls. In CDR category ≥1, GRN pathogenic variant carriers demonstrated steeper decline over time than C9orf72 (β₁ = −0.7, SE 0.17, p < 0.001) and MAPT (β₁ = −0.9, SE 0.20, p < 0.001) pathogenic variant carriers (Figure 1C).

Verbal Fluency

For verbal fluency, we found strong evidence for differences between CDR categories (χ²[2] = 40.0, p < 0.001) at baseline. All gene groups with CDR category ≥1 performed worse than controls (C9orf72: β = −1.8, SE 0.12, p < 0.001; GRN: β = −1.6, SE 0.14, p < 0.001; MAPT: β = −1.3, SE 0.18, p < 0.001), with C9orf72 performing worse than MAPT pathogenic variant carriers (β = −0.5, SE 0.19, p = 0.018; Figure 1D). In CDR category 0, C9orf72 pathogenic variant carriers performed worse than controls (β = −0.3, SE 0.09, p = 0.003) and GRN pathogenic variant carriers (β = −0.3, SE 0.11, p = 0.002). We found an interaction effect between time and gene group (χ²[3] = 14.5, p < 0.002). C9orf72 pathogenic variant carriers with CDR category ≥1 (β₁ = −0.2, SE 0.05, p = 0.004) and GRN pathogenic variant carriers with CDR categories 0.5 (β₁ = −0.2, SE 0.08, p = 0.013) and ≥1 (β₁ = −0.2, SE 0.07, p = 0.015) declined over time compared with controls (Figure 1D).

Memory: Immediate Recall

For immediate recall, we found strong evidence for differences between CDR categories (χ²[2] = 51.4, p < 0.001) and between gene groups (χ²[3] = 40.2, p < 0.001) at baseline. All gene groups with CDR category ≥1 performed worse than controls (C9orf72: β = −2.7, SE 0.32, p < 0.001; GRN: β = −5.5, SE 0.40, p < 0.001; MAPT: β = −4.3, SE 0.51, p < 0.001), with MAPT performing worse than C9orf72 pathogenic variant carriers (β = −1.7, SE 0.56, p = 0.003) and GRN pathogenic variant carriers performing worse than C9orf72 (β = −3.0, SE 0.47, p < 0.001) and MAPT pathogenic variant carriers (β = −1.2, SE 0.62, p = 0.032; Figure 2A).

Memory: Delayed Recall

For delayed recall, we also found evidence for differences between CDR categories (χ²[2] = 36.9, p < 0.001) and between gene groups (χ²[3] = 10.4, p < 0.015) at baseline. Again, all gene groups with CDR category ≥1 performed worse than controls (C9orf72: β = −2.0, SE 0.21, p < 0.001; GRN: β = −2.8, SE 0.27, p < 0.001; MAPT: β = −2.7, SE 0.35, p < 0.001), with GRN (β = −0.9, SE 0.32, p = 0.007) and MAPT (β = −0.8, SE 0.38, p = 0.033) performing worse than C9orf72 pathogenic variant carriers. MAPT pathogenic variant carriers with CDR category 0.5 (β = −0.8, SE 0.36, p = 0.021) performed worse than controls and C9orf72 pathogenic variant carriers (β = −0.9, SE 0.42, p = 0.023). There was some weak evidence indicating that MAPT pathogenic variant carriers with CDR category 0 performed worse than controls (β = −0.4, SE 0.21, p = 0.081; Figure 2B). None of the groups declined significantly over time.
**Social Cognition**
We found strong evidence for differences between CDR categories ($\chi^2[2] = 35.7, p < 0.001$) at baseline on social cognition. All gene groups with CDR category $\geq 1$ performed worse than controls ($C9orf72$: $\beta = -2.6, SE 0.19, p < 0.001$; $GRN$: $\beta = -2.3, SE 0.23, p < 0.001$; $MAPT$: $\beta = -1.9, SE 0.28, p < 0.001$), with $GRN$ performing worse than $MAPT$ pathogenic variant carriers ($\beta = -0.7, SE 0.33, p = 0.001$; Figure 2C). $C9orf72$ ($\beta = -0.7, SE 0.24, p = 0.001$) and $GRN$ ($\beta = -0.7, SE 0.25, p = 0.001$) pathogenic variant carriers with CDR category 0.5 also performed worse at baseline than controls. We found interaction effects between time and gene group ($\chi^2[3] = 21.3, p < 0.001$) and time, CDR category, and gene group ($\chi^2[4] = 16.3, p < 0.003$). $GRN$ pathogenic variant carriers with CDR category $\geq 1$ showed steeper decline over time compared with controls ($\beta_1 = -0.5, SE 0.13, p < 0.001$), $C9orf72$ ($\beta_1 = -0.7, SE 0.16, p < 0.001$), and $MAPT$ ($\beta_1 = -0.3, SE 0.17, p = 0.049$) pathogenic variant carriers and $MAPT$ pathogenic variant carriers with CDR category $\geq 1$ showed steeper decline over time compared to $C9orf72$ pathogenic variant carriers ($\beta_1 = -0.3, SE 0.16, p = 0.047$; Figure 2C).

**Visuoconstruction**
We found differences between gene groups on visuoconstruction ($\chi^2[3] = 11.0, p = 0.012$) at baseline. All gene groups with CDR category $\geq 1$ performed worse than controls ($C9orf72$: $\beta = -2.0, SE 0.22, p < 0.001$; $GRN$: $\beta = -1.6, SE 0.26, p < 0.001$; $MAPT$: $\beta = -0.9, SE 0.32, p = 0.004$), with $C9orf72$ ($\beta = -1.2, SE 0.33, p = 0.002$) and $GRN$ ($\beta = -1.0, SE 0.36, p = 0.008$) performing worse than $MAPT$ pathogenic variant carriers. $GRN$ pathogenic variant carriers with CDR
category 0.5 (β₁ = −0.5, SE 0.23, p = 0.050) showed steeper decline over time than controls (Figure 2D).

**Discussion**

This study demonstrated gene-specific baseline differences and decline over a 5-year time period in a large cohort of genetic FTD pathogenic variant carriers that was moderated by the CDR plus NACC FTLD global score. C9orf72 pathogenic variant carriers performed lower on attention, executive function, and verbal fluency from CDR plus NACC FTLD 0 onwards, with relatively minimal decline over time compared with other genetic groups regardless of the CDR plus NACC FTLD score (i.e., disease progression). The cognitive profile in MAPT pathogenic variant carriers was characterized by early impaired memory (already at CDR plus NACC FTLD 0.5), with language decline starting at CDR plus NACC FTLD 0.5, and executive dysfunction developing rapidly at CDR plus NACC FTLD ≥1. GRN pathogenic variant carriers showed no differences or decline compared with controls at CDR plus NACC FTLD 0, but verbal fluency and visuoconstruction started to decline at CDR plus NACC FTLD 0.5. GRN pathogenic variant carriers showed the most rapid decline compared with the other groups in language and social cognition from CDR plus NACC FTLD ≥1 onwards. The results from this study confirm cognitive decline in the asymptomatic and prodromal stages of genetic FTD and hold potential for upcoming therapeutic trials by identifying (1) the most sensitive cognitive measures to track disease progression and treatment effects and (2) the speed of change over time, thereby providing insight into the best time window to start disease-modifying treatment.
Asymptomatic C9orf72 pathogenic variant carriers performed worse at baseline than controls on attention/mental processing speed, executive function, and verbal fluency. In the prodromal stage, social cognition was also lower at baseline, whereas at the fully symptomatic stage, all cognitive domains were lower at baseline. There was no decline over time in the asymptomatic stage or prodromal stage, but attention/mental processing speed, language, and verbal fluency declined over time in the symptomatic stage, although less rapidly than in other gene groups. The other cognitive domains remained relatively stable, and there were signs of possible practice effects for memory and social cognition. This is largely in line with previous studies demonstrating widespread cognitive impairment in C9orf72 pathogenic variant carriers with relatively minimal decline over time.\textsuperscript{5,39,40} It is further corroborated by the fact that the neurodegenerative process associated with the C9orf72 pathogenic variant is widespread, with neurodegeneration in the frontal and temporal cortices but also in more posterior cortical, subcortical, and cerebellar regions.\textsuperscript{39,41} This group performed lowest compared with the other groups on a wide range of neuropsychological tests, specifically tests for attention/mental processing speed and executive function, at the asymptomatic stage. Although these performances were not at an “impaired” level (i.e., z score $\leq-2$), these deficits might represent the earliest signs of neurodegeneration with very slow decline over time. Alternatively, the lack of decline over time in all 3 disease stages raises the intriguing possibility that these deficits are not merely preclinical signs of FTD as a result of early neurodegeneration, but might be indicative of a neurodevelopmental disorder in C9orf72, which at a certain age is superimposed by additional neurodegeneration. This hypothesis has been suggested by several previous studies that found gray and white matter deficits and connectivity disruption as well as psychiatric conditions and cognitive deficits many years before the estimated age at symptom onset without evidence of disease progression over time.\textsuperscript{42,43} Future studies should focus on ascertaining early-life radiologic and clinical assessments to test this hypothesis.

In MAPT pathogenic variant carriers, there was a trend towards lower memory performance than in controls at baseline in the asymptomatic stage, which became significant at the prodromal stage. All cognitive domains were lower than in controls at baseline in the symptomatic stage. There was no decline over time in the asymptomatic stage, but language
declined from the prodromal stage onwards. In addition, attention/mental processing speed, executive function, and social cognition declined progressively during the symptomatic stage. These results confirm that the first changes for this group occur in cognitive functions that are strongly associated with the temporal lobe, an area that already shows early degeneration in presymptomatic MAPT pathogenic variant carriers. Several previous studies have demonstrated that episodic memory impairment is a distinct feature in MAPT-related FTD, even in presymptomatic pathogenic variant carriers. Strikingly, we demonstrated lower memory performance in prodromal pathogenic variant carriers but with practice effects over time that disappeared at the fully symptomatic stage only. A likely explanation for these practice effects is that the same items for memory tests were used at all time points, stressing the need for the use of tests that have multiple versions with different stimuli in longitudinal cohort studies. The lower performance and decline seen in the language domain was largely driven by the Boston Naming Test, a test that strongly depends on the semantic memory system. This is unsurprising given that semantic memory is strongly associated with the anteromedial temporal lobe, an area known to deteriorate early and progressively in MAPT-associated FTD. Deficits in semantic memory have been described as a key symptom in MAPT pathogenic variant carriers in a more progressed disease stage, but our results illustrate that the first changes occur at a much earlier stage, suggesting that semantic tests might be a good candidate to serve as a sensitive end point in upcoming therapeutic trials of MAPT-associated FTD. Only at a later progressed stage, when atrophy spreads from the temporal to frontal areas of the brain, does impairment in cognitive functions that are typically associated with bvFTD develop, such as executive function and social cognition.

There were no cross-sectional differences between asymptomatic GRN pathogenic variant carriers and controls at baseline and there was no decline over time in this stage. In the prodromal stage, pathogenic variant carriers performed worse than controls on executive function and social cognition, and they declined over time on verbal fluency and visuoconstruction. All cognitive domains were lower than in controls at baseline in the symptomatic stage, and they showed progressive decline over time on attention/mental processing speed, verbal fluency, language, and social cognition. This is in line with previous studies showing minimal changes in gray and white matter but also cognition in pre-symptomatic GRN pathogenic variant carriers, often with fast progressive decline after symptom onset. Although in our study no change over time was detected in the asymptomatic stage, GRN pathogenic variant carriers performed worse on executive function and social cognitive tasks at the prodromal stage, suggesting some decline between these stages. Possible explanations could be that the asymptomatic pathogenic variant carriers were too far from symptom onset or that the time window between these stages where these changes occur is relatively short. Interestingly, verbal fluency declined progressively in the prodromal period, indicating an early deficit in specifically verbal fluency. This could be interpreted as an early sign of pathogenic variant carriers developing nonfluent variant PPA, a clinical phenotype that is often seen in GRN pathogenic variant carriers. However, verbal fluency measures are also known to strongly depend on executive function, a cognitive domain known to deteriorate in bvFTD. Surprisingly, visuoconstruction also declined in the prodromal stage, whereas this is considered to be relatively spared in FTD. However, most visuoconstructive tasks also strongly depend on executive functions such as planning, organizing, and keeping overview. It seems, therefore, more likely that these tasks were influenced by impaired executive function rather than a pure impairment in language and visuoconstruction per se.

This is the first study to longitudinally investigate a large cohort of all 3 major causes of genetic FTD over a 5-year period. A major strength of this study is the use of the CDR plus NACC FTLD to stratify pathogenic variant carriers from asymptomatic to prodromal and fully symptomatic (i.e., 0, 0.5, ≥1). Most previous studies have stratified pathogenic variant carriers as either presymptomatic or symptomatic according to whether they fulfilled diagnostic criteria for FTD syndromes, but this does not fully grasp the clinical trajectory of FTLD. The cognitive profile between the presymptomatic and symptomatic phase has not been well-characterized. Some other studies have used estimated years to symptom onset based on mean family age at onset, but a recent article demonstrated that the correlations between age at symptom onset and mean family age at symptom onset were weak for C9orf72 and GRN pathogenic variant carriers, indicating that this might not be a reliable proxy. By stratifying according to CDR plus NACC FTLD, we have provided insight into cognitive decline during different disease stages.
high variability between individuals in each group. A possible explanation for this interindividual variability could be that some individuals with a CDR plus NACC FTLD global score of 0 might be closer to symptom onset than others. Similarly, individuals with a CDR plus NACC FTLD score of 0.5 or ≥1 at baseline might vary in time since progression to that CDR category (i.e., individuals who had a global score of 0.5 for several years at inclusion will likely progress faster than individuals who progressed to a score of 0.5 more recently). Validation in other cohorts such as ALLFTD or DINAD is warranted. Fourth, practice effects were strikingly visible for the FCSRT and Facial Emotion Recognition Test, stressing the need for different test versions in the former, but more sensitive tasks for emotion recognition (e.g., the use of morphed facial expressions) and social cognition in general. Lastly, in the interpretation of memory–immediate recall, social cognition, and visuoconstruction results, it should be taken into account that they were represented by only a single cognitive test, and those individual tests might not be a representation of the entire cognitive domain.

We provide evidence for gene-specific cognitive decline in the prodromal stage of genetic FTD. Specifically, tests for attention/mental processing speed, executive function, language, and memory showed clear differences between gene groups and controls at baseline, but the speed and nature of change over time differed depending on (1) the gene group and (2) the CDR plus NACC FTLD global score. These results confirm the value of neuropsychological assessment in tracking disease progression and could inform upcoming clinical trials in selecting sensitive end points for measuring treatment effects as well as in characterizing the best time window for starting treatment.

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Disclosure

J.D. Rohrer has received consulting fees from UCB, AC Immune, Astex Pharmaceuticals, Biogen, Takeda, and Eisai and is part of the Medical Advisory Board for Alector, Arkuda Therapeutics, Wave Life Sciences, and Prevail Therapeutics. R. Sanchez-Valle has received consulting fees from Wave Pharmaceuticals and Ionis-Biogen and from Roche Diagnostics and Janssen for educational activities and is member of the Data Safety Monitoring Board for Wave Pharmaceuticals and Ionis-Biogen. B. Borroni has received consulting fees from Alector and Wave Pharmaceuticals and has a pending patent on noninvasive brain stimulation. M. Masellis has received compensation for royalties from Henry Stewart Talks Ltd.; consulting fees from Arkuda Therapeutics, Ionis, Alector, Biogen, and Wave Life Sciences; personal fees for educational activities from Alector and Arkuda Therapeutics; and travel fees from Alector Pharmaceuticals. M.C. Tartaglia has received consulting fees from Roche. C. Graff has received consulting fees from Studentlitteratur 238 SEK 2020 and reimbursement for travel and lodging from University of Pennsylvania for attending KOL-meeting in October 2019. J. Rowe has received consulting fees from Asceneuron, Biogen, UCB, SV Health, and Astex; has provided expert testimony in private noncommercial medicolegal case reports; is part of an Advisory Board for several noncommercial academic institutions; and is Chief Scientific Advisor to Alzheimers Research UK, Guarantor of Brain, Trustee PSP Association, Trustee Darwin College, and Associate Director of the Dementias Platform UK. E. Finger has received consulting fees for the AAN annual meeting speaker and course director honorariums; is member of the Data Safety Monitoring Board for the Lithium trial, PI E. Huey (trial funded by peer reviewed grants from ADDF); and is a scientific advisory board member for Vigil Neuroscience, Denali Therapeutics, and on an advisory panel for Biogen. M. Synofzik has received consulting fees from Janssen Pharmaceuticals, Ionis Pharmaceuticals, and Orphazyme Pharmaceuticals and received support from the Movement Disorder Society for travel. R. Vandenberghhe has received consulting fees from CyTox and is a member of the Data Safety and Monitoring Board of AC Immune. I. Santanà has received consulting fees from Biogen and Roche Biogen, personal fees for presentations from Biogen, and is part of the Data Safety Monitoring Board for Novo Nordisk. S. Ducharme has received consulting fees from Innomed Neurosciences and personal fees from Sunovion Eisai. J. Levin has received consulting fees from Bayer Vital, Roche, and Biogen; is part of the Advisory Board for Axon Neurosciences; has received compensation for duty as part-time CMO from Modag; and has received author fees from Thieme publishing as well as nonfinancial support from AbbVie. A. Danek has received consulting fees from 3 hospitals in Switzerland and personal fees from the German court of law for medico-legal opinion. M. Otto has received consulting fees from Biogen, Axon, and Roche and is part of the Advisory Board for Axon. I. Le Ber has received consulting fees from Alector Prevail Therapeutics and personal fees from MDS and is also part of the Data Safety Monitoring Board for Alector Prevail Therapeutics. Go to Neurology.org/N for full disclosures.

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## Appendix 1 (continued)

| Name                  | Location                                      | Contribution                                                                 |
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Continued
Appendix 1 (continued)

| Name                  | Location                                      | Contribution                                      |
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Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/WNL/B988.

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