Neurodevelopmental effects of genetic frontotemporal dementia in young adult mutation carriers

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Abstract

While frontotemporal dementia (frontotemporal dementia) has been considered a neurodegenerative disease that starts in mid-life or later, it is now clearly established that cortical and subcortical volume loss is observed more than a decade prior to symptom onset and progresses with aging. To test the hypothesis that genetic mutations causing frontotemporal dementia have neurodevelopmental consequences, we have examined the youngest adults in the GENFI cohort of pre-symptomatic frontotemporal dementia mutation carriers who are between the ages of 19 and 30y. Structural brain differences and improved performance on some cognitive tests was found for *MAPT* and *GRN* mutation carriers relative to familial non-carriers, while smaller volumes were observed in *C9orf72* repeat expansion carriers at a mean age of 26y. The detection of such early differences supports potential advantageous neurodevelopmental consequences of some frontotemporal dementia causing genetic mutations. These results have implications for design of therapeutic interventions for frontotemporal dementia. Future studies at younger ages are needed to identify specific early pathophysiologic or compensatory processes in the neurodevelopmental period.

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Abbreviations: ANCOVA = analyses of covariance; CBI-R = Cambridge Behavioural Inventory Questionnaire-Revised; *C9orf72* = chromosome 9 open reading frame 72; GENFI = Genetic Frontotemporal dementia Initiative; *GRN* = granulin gene; *MAPT* = microtubule associated protein tau gene; ROI = region of interest; TBV = total brain volume; TIV = total intracranial volume

Introduction

Frontotemporal dementia is a devastating progressive neurodegenerative disease that is highly heritable and currently incurable. Frontotemporal dementia is the second most common young-onset neurodegenerative dementia, most commonly diagnosed in individuals in their 40s to 60s. However, symptoms can start decades before full clinical diagnostic criteria are met, with some

individuals diagnosed as young as in their 20s.[1] Nearly a decade ago the first international cohort studies of patients with genetic frontotemporal dementia and their adult biological family members were launched which have enabled detailed study of the pre-symptomatic window comparing at-risk frontotemporal dementia mutation carriers to their biologically related non-carriers. These studies have delineated the symptom onset and main features of the course of the most common genetic causes of frontotemporal dementia: *MAPT*, *C9orf72* and *GRN*.[2-4] Several symptoms and biomarkers that change as pre-clinical mutation carriers approach their age of expected onset have also been identified, including apathy,[5] brain atrophy and connectivity,[6] and rising CSF NFL levels.[7] Interestingly, several of these recent studies have observed group differences between pre-symptomatic mutation carriers vs. non-carriers in brain structure even at the time of first assessment.[8] While frontotemporal dementia has been considered a neurodegenerative disease that starts in mid-life or later, it is now clearly established that cortical and subcortical volume loss is observed more than a decade prior to symptom onset[2,3] and progresses with aging.[9] These emergent findings raise a major question for the field of frontotemporal dementia: is genetic frontotemporal dementia a neurodevelopmental disorder?

Neurodevelopmental disorders refer to conditions that affect the development of the nervous system with manifestations in childhood. The brain is known to have a long and complex development and maturation period, extending up to the third decade of life.[10] Several lines of research point in the direction of a possible neurodevelopmental effect of frontotemporal dementia-causing mutations. *MAPT*, *C9ORF72* and *GRN* genes all have high penetrance and are expressed in the prenatal period.[11-15] While studies using knockout and transgenic mouse models to study *GRN*, *MAPT* and *C9orf72* have typically normal or only subtle phenotypes in the neurodevelopmental period and early life stages, each of these three main genes associated with FTD have roles that are likely active during neurodevelopment including microtubule stabilization, neurite outgrowth and stabilization (*MAPT*),[16,17] lysosomal function and regulation of inflammation (*GRN, C9orf72*).[18-20] Moreover, there are scattered clues in the human literature pointing towards potential neurodevelopmental consequences. Higher rates of childhood dyslexia and other language related learning disabilities were observed in patients who develop Primary Progressive Aphasias (the majority of which are language subtypes of frontotemporal dementia), and their first-degree relatives.[21] In a small series of pre-symptomatic carriers of *MAPT* mutations, impairments in performance on frontal executive tasks were observed several

decades before expected symptom onset, prompting the authors to raise a neurodevelopmental hypothesis for this form of genetic frontotemporal dementia.[22] In pre-symptomatic *MAPT* mutation carriers, mesial temporal lobe atrophy was observed in 20% of participants in their 30s.[23] In a family carrying a *GRN* mutation, abnormal white matter connectivity was detected in *GRN* presymptomatic mutation carriers whose average age was 37y compared to non-carriers (mean age 43y).[24] Furthermore, increased prevalence of psychotic disorders, including typical age-of-onset schizophrenia (teens to 20s), has been reported in offspring of *C9orf72* repeat expansion carriers.[25]

Clues from other neurodegenerative diseases further support the hypothesis that pathophysiologic changes in some mid and late-life neurodegenerative diseases may occur decades before the appearance of clinical symptoms and diagnosis, and possibly during early brain development. In Huntington's disease, another neurodegenerative disorder with mid-life symptom onset, the KIDS-HD and CHANGE-HD studies have identified multiple differences in brain structure in youth mutation carriers at 6 and 7 years of age, who have CAG repeat lengths predictive of adult-onset disease.[25] Some of these effects are likely a direct result of the pathogenic effects of the mutation, including smaller intracranial volumes, while others which may represent compensatory changes, such as striatal hypertrophy and increased basal ganglia functional connectivity.[26,27] Intriguing questions have been raised of whether genetic mutations causing some mid-life onset disorders like Huntington's disease or spinocerebellar ataxia persist not only because their deleterious effects occur after the age of reproduction, but also because they may confer early life advantages.[28,29] This hypothesis is further supported by study of young carriers of the Huntington gene expansions who show enhanced cognitive performance[30] and reduced anxiety and depression compared to familial non-carriers.[31] Neurodevelopmental effects of the Huntington's gene CAG repeat expansion recently have been confirmed during human embryonic brain development as early as 13 weeks gestation.[32] These included mislocalized junctional complexes and of the mutant protein huntingtin, abnormal neuroprogenitor cell polarity and differentiation, and altered mitosis and cell cycle progression.[32] This represents perhaps the strongest evidence to date of the neurodevelopmental effects of a hereditary adult-onset neurodegenerative disorder.

In the Genetic Frontotemporal dementia Initiative (GENFI) cohort, in comparison to non-carriers from the same families, mutation carriers reported subtle changes in mood and behaviour at the

time of the baseline assessments, independent of age.[33] In the absence of pediatric research data on mutation carriers, we evaluated data from the youngest adult GENFI participants, those between the ages of 19 and 29y, to explore whether changes in symptoms, cognition or brain structure may be present during neurodevelopment (up through the third decade of life). In this age range, we consider neurodegenerative changes to be unlikely to confound findings as the mean expected years to disease onset is approximately 30 years, a time-frame well before the two years prior to phenotype conversion when increases in biomarkers of neurodegeneration such as neurofilament light chain are elevated in mutation carriers.[7] The objectives of the present study were to determine whether young adults between the ages of 19 and 29 who carry frontotemporal dementia causing gene mutations show differences compared to familial age-matched non-carriers in: 1) brain structure as measured by cortical and subcortical volumes and cortical thickness and 2) functional outcomes as indexed by behavioural and cognitive assessments.

Materials and methods

Participants

Young adults between the ages of 18 and 29 years inclusive who enrolled in the GENFI multi-centre cohort study were included. The GENFI consortium includes research centres across Europe and Canada (http://genfi.org.uk/) and enrolls adults with known pathogenic mutations in the *GRN* or *MAPT* genes or with a pathogenic expansion in the *C9orf72* gene (greater than 30 repeats). The cohort is comprised of symptomatic mutation carriers, pre-symptomatic mutation carriers, and non-mutation carriers from the same families. The majority (~71%) of at-risk family members in the GENFI study were not aware of their genetic status at the time of the assessments. Baseline data from the presymptomatic young adults' first GENFI assessments were included, including participant and informant clinical scales of behavioural and cognitive symptoms and magnetic resonance imaging. Presymptomatic (unaffected) designation was made by the local GENFI site physicians based on participants considered not to be showing signs of frontotemporal dementia and not meeting consensus criteria for behavioural variant frontotemporal dementia, amyotrophic lateral sclerosis, nonfluent primary progressive aphasia, semantic variant primary progressive aphasia, corticobasal syndrome or other dementia. The data

analyzed below represent that available from GENFI data freeze #5 (2012-2019). This includes participants from Phase 1 (GENFI1; 2012-2015), and phase 2 (GENFI2; 2015-2019) of GENFI. Data are presented in ways to ensure continued blinding of participants' genetic status. Mutation carriers were compared with non-carriers of the same gene group (e.g. *MAPT* mutation carriers vs. non-carriers from *MAPT* mutation families) for all analysis to reduce potential confounds related to language and family differences.

Written informed consent was obtained from all participants. The study was approved by the local ethics committee for each of the GENFI sites.

Neuroimaging

Participants completed volumetric T1-weighted MRI acquired with the GENFI protocol with a 1.1-mm isotropic resolution on a 3T scanner (Siemens Trio, Siemens Skyra, Siemens Prisma, Philips Achieva, GE Discovery MR750) or 1.5T scanner (Siemens, GE). Pre-processing of volumetric MRI scans was performed as previously reported,[34] including visual QC checks, bias field correction and whole brain parcellated using the geodesic information flow algorithm.[35] We combined regions of interest to calculate the volumes of the whole brain (total brain volume which includes all gray and white matter), lobes or regions (gray matter in frontal, temporal, parietal, occipital, cingulate and insula), subcortical structures including the amygdala, hippocampus, thalamus, and basal ganglia (caudate + pallidum + putamen), as well as cerebellum[36] and total CSF (ventricles and non-ventricular CSF). The cingulate and insula were included as specific regions as they are known to be amongst the earliest regions affected in many forms of FTD.[2,37] Left and right volumes were summed, and total intracranial volume (TIV), which includes all gray matter, white matter and CSF, was computed with SPM12 v6470 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, London, UK) running under Matlab R2014b (Math Works, Natick, MA, USA) (Malone et al., 2015). T1-weighted MRI were also processed for vertex-wide cortical thickness analysis with Civet 2.1 (http://www.bic.mni.mcgill.ca/ServicesSoftware/CIVET-2-1-0-Introduction) through the Cbrain platform.[38] All outputs were visually inspected for quality control.

Behavioural and Cognitive Measures

Symptoms

Clinicians completed the GENFI Symptom Scales with participants and their study informant to evaluate the presence of symptoms across the following five domains: behavioural, neuropsychiatric, cognitive, language, and motor. The presence and severity of each symptom was indicated using a 5-point Likert scale (0=absent, 0.5=questionable/very mild, 1=mild, 2=moderate, 3=severe). Symptom ratings of questionable/very mild, mild, moderate, severe were coded as *symptom endorsement* and absent coded as *symptom absent*.

Cambridge Behavioural Inventory Questionnaire-Revised (CBI-R)[39]: Study informants use a 5-point Likert scale to indicate whether participants demonstrate symptoms in the following domains: memory and orientation, everyday skills, self-care, abnormal behaviour, mood, beliefs, eating habits, sleep, stereotypic and motor behaviours, and motivation. Symptom reports reflect endorsement 4 weeks prior to the assessment, with higher scores indicate greater frequency of symptoms.

GENFI Neuropsychology Battery

The GENFI Neuropsychology Battery, comprised of tests as previously reported,[2] was administered to all participants. This included the following tests and indices: Digit Span Forward (maximum number of consecutive digits correctly produced, Digit Span Backward (maximum), Digit symbol (from the Wechsler Adult Intelligence Scale), Boston Naming Test (30 item), Verbal Fluency (Animals), Verbal fluency (Letter), Block design (correct trials, timed), Free and Cued Selective Reminding Test (FCSRT), D-KEFS Color-Word Interference Task (CWIT: total *errors* and *time* to completion), Mini-Social Cognition and Emotion Assessment (MiniSEA) comprised of the Faux-pas Test and Facial Recognition Task, Benson Figure Copy, Recall, and Recognition, Logical Memory Tests (subset of Wechsler Memory Scale).

Statistical Analysis

Neuroimaging

ANCOVAs examining interactions and main effects of genetic status (carrier vs. non-carrier) x sex x scanner type (vendor, model and field strength), with age at time of scan and TIV as

covariates were conducted on global and regional brain volumes. Given the sample sizes available, only main effects of genetic status significant after controlling for sex, scanner type, age and TIV are reported. Benjamini-Hochberg correction for multiple tests was used to control for multiple comparisons using $p<0.05$ for the false discovery rate.[40] For regions showing main effects of genetic status and genetic status x scanner type interactions, the potential impact of scanner specific effects was examined and results qualified as detailed below. Additional sensitivity analysis including only patients with 3T MRI scans were performed for all contrasts. Voxel-wise cortical thickness analyses were performed in SurfStat using general linear models, controlling for the effects of age, sex and scanner site. We tested for group contrasts (genetic carriers versus controls - $Y = intercept + b_1Sex + b_2Scanner + b_3Age + b_4GeneticStatus + error$) and for the age by genetic status interaction ($Y = intercept + b_1Sex + b_2Scanner + b_3Age + b_4GeneticStatus + b_5Age*GeneticStatus + error$). Analyses were performed separately for each genetic group and results were corrected with false discovery rate <0.05.

GENFI Symptom Scales

Due to skewing of scores, as most symptoms were not endorsed by many participants, chi-squared tests were used to examine mutation group level differences in each of the five symptom domains. Specifically, separate tests were used to detect differences in frequency of symptoms for each domain between carriers versus non-carriers for each of the three gene groups.

GENFI Neuropsychology Battery and Cambridge Behavioural Inventory-Revised

A series of one-way analyses of covariance (ANCOVAs) with genetic status (carrier, non-carriers) as the independent variable, and age and sex as covariates were used to detect differences between mutation carriers and non-carriers on neuropsychology measures common in GENFI 1 and GENFI 2. For variables unique to the GENFI 1 and GENFI 2 cohorts, separate GENFI 1 or GENFI 2 analyses were performed and are presented in Supplementary Table 1. Years of education was not included in the main analysis to avoid obscuration of potential neurodevelopmental effects on cognition that could have also affected scholastic achievement,

but, where applicable, secondary sensitivity analyses were conducted with years of education as an additional covariate. The dependent measures included scores on Digit Span Forward, Digit Span Backward, Digit Symbol, Boston Naming Test, Verbal Fluency Animals, Verbal Fluency Letter, Block Design, and CBI-R. The dependent variables unique to GENFI1 included immediate and delayed scores on the logical memory tests, and for GENFI 2 included Benson Figure Recall, Benson Figure Recognition, FCSRT Free Recall, FCSRT Total, FCSRT Delayed Free Recall, CWIT Errors, CWIT Time, and MiniSEA Total. Given the available sample sizes, only main effects of genetic status, after controlling for sex and age, are reported. Observations greater than +/- 3 standard deviations were deemed outliers. One outlier was detected on the Block Design measure and one on the verbal fluency task; removal of these outliers did not affect the statistical results.

Data availability

The raw data of this project is part of GENFI. De-identified participant data can be accessed on reasonable request to Elizabeth.Finger@lhsc.on.ca and genfi@ucl.ac.uk.

Results

Participants

Ninety-two young adults in GENFI met the inclusion criteria for the study and were designated as presymptomatic (unaffected) by their local site physicians. The FTLD-CDR global rating was 0 for all but 5 who had ratings of 0.5, two of whom were mutation carriers and three were non-carriers. MRI scans passing quality checks were available from 85 of the 92 young adult GENFI participants from Data Freeze 5 (Table 1). Fifty-two percent were mutation carriers (41 non-carriers, 44 carriers). Amongst the mutation carriers, there were 17 *C9orf72*, nine *MAPT*, and 16 *GRN* carriers. The mean age at time of participation was 25 years (range 19-29), and mean level of education was 14 years (range 8-18). All of these young adults were designated as unaffected/ presymptomatic participants by the site physicians. The FTLD-CDR global rating for all was 0 for except for five participants with ratings of 0.5, three were mutation carriers and two were non-carriers. There were no significant differences in age at time of scan or sex distribution

comparing the mutation carriers vs. non-carriers for each of the three gene groups. *MAPT* carriers had more years of education than the *MAPT* non-carriers ($M_{carriers}$=15.5 y (SD 1.5) $M_{non\text{-}carriers}$ 14.1y (SD 1.7), $P<$ 0.05).

Behavioural and cognitive data were available from 91 young adult GENFI participants from data freeze 5 (Table 2), of which 49% were mutation carriers, and 51% were mutation non-carriers. Again it was observed that the *MAPT* carriers had more years of education than the *MAPT* non-carriers ($M_{carriers}$=15.2 y (SD 2.0) $M_{non\text{-}carriers}$ 143.6y (SD 1.9), P = 0.05). There were no other statistically significant differences in age, years of education, handedness, or sex between carriers and non-carriers within, and collapsed across, the three genetic groups.

C9orf72

MRI Analysis

Young adult *C9orf72* repeat expansion carriers had significantly smaller total brain volumes ($P <$ 0.005; partial eta squared (η^2p) =0.50) and thalamic volumes ($P <$ 0.005; η^2p =0.45) in comparison to *C9orf72* non-carriers (Table 1). No differences were observed for TIV or total CSF volumes. Mean volumes were non-significantly lower in carriers relative to non-carriers in all of the remaining regions apart from the caudate. There were no significant genetic status x scanner or genetic status x sex interactions. There was no significant difference in vertex-wide cortical thickness between expansion carriers and non-carriers.

Behavioural and Cognitive Assessments

No statistically significant differences between carriers and non-carriers were found in symptom frequencies across all domains (Supplementary Table 1). No significant differences between *C9orf72* repeat expansion carriers vs. non-carriers were observed in the other behavioural scales or cognitive tasks (Table 2 and Supplementary Tables 1-3).

MAPT

MRI Analysis

Young adult MAPT mutation carriers had larger TIV than non-carriers. There were no significant differences in brain or CSF volumes between young adult *MAPT* carriers and non-carriers when TIV was adjusted for. There was no significant difference in vertex-wide cortical thickness between *MAPT* mutation carriers and non-carriers.

Behavioural and Cognitive Assessments

MAPT mutation carriers performed better than non-carriers on verbal fluency (letter) performance (F18.6, $P < 0.001$) and digit span forward (F=5.8, $P < 0.05$) (Figure 1). Sensitivity analyses, adding education as a covariate and adding site as a variable retained the significant main effect of genetic status on both verbal fluency ($P < 0.001$) and digit span forward ($P < 0.05$).

No statistically significant differences between carriers and non-carriers were found for the CBI-R or in GENFI symptom list endorsement frequencies across all domains (Table 2 and Supplementary Tables 2 and 3).

GRN

MRI Analysis

GRN mutation carriers were found to have significantly larger TIV and cingulate volume ($P < 0.01$; $\eta^2p = 0.48$) relative to non-carriers when adjusted for TIV (Table 1). There were no other significant differences once scanner type interactions were accounted for, including no significant difference in vertex-wide cortical thickness between *GRN* mutation carriers and non-carriers.

Behavioural and Cognitive Assessments

GRN mutation carriers performed better on the digit symbol task than non-carriers (F=4.459, $P < 0.05$) (Figure 2). Sensitivity analyses adding education covariate and adding site as a variable supported the pattern of findings ($P = 0.07$). No statistically significant differences in symptom frequencies across all domains were found between *GRN* mutation carriers and non-carriers. No statistically significant differences between carriers and non-carriers were found in symptom frequencies across all domains (Table 2 and Supplementary Tables 2 and 3).

MRI sensitivity analyses

Sensitivity analyses conducted for all three gene groups including only participants with 3T MRI scans (n = 82) demonstrated the same pattern of significant and non-significant imaging findings as reported above.

Discussion

These data demonstrate early effects of *MAPT, C9orf72* and *GRN* mutations on brain structure and function, detectable in the third decade of life. The presence of structural differences nearly 30 years prior to expected symptom onset, at ages when the frontal lobes are still maturing suggests there are neurodevelopmental consequences of some forms of genetic frontotemporal dementia. The regions and patterns of volumetric differences varied according to the gene, with hints of potentially advantageous consequences early in life for *MAPT* and *GRN* mutations.

Patients with FTD due to *C9orf72* repeat expansions most commonly develop behavioural variant frontotemporal dementia or amyotrophic lateral sclerosis, though can present with a non-fluent primary progressive aphasia or corticobasal syndrome phenotype.[2] In young adult *C9orf72* repeat expansion carriers, the findings of reduced total brain and thalamic volumes are in line with studies of older symptomatic and presymptomatic frontotemporal dementia cohorts. Thalamic atrophy is a predominant structural change in symptomatic patients with *C9orf72* associated frontotemporal dementia, amyotrophic lateral sclerosis, or frontotemporal dementia/amyotrophic lateral sclerosis.[41-45] The current findings extend prior findings in older presymptomatic *C9orf72* expansion carriers of expanded 3rd ventricular volumes approximately 14 years prior to expected symptom onset[8] and a subgroup analysis of *C9orf72* repeat expansion carriers 40 years of age or younger that identified differences in thalamic volumes.[46] Indications that an alternate pathophysiologic process could drive these early structural differences is found in non-human models of *C9orf72* during the neurodevelopmental period, where the repeat expansion is associated with multiple cellular level effects including impaired axonal genesis, cellular motility and increased neuronal apoptosis.[47] Whether the smaller thalamic and total brain volumes are due to early hallmark frontotemporal dementia pathology causing atrophy or due to neurodevelopmental effects of *C9orf72* on other critical processes is not yet known given the lack of brain tissue evaluations available at these younger ages. However, the preserved TIV

with smaller total brain volumes and smaller thalamic volumes would favor volume loss and early neurodegeneration.

While informants' reports of neuropsychiatric symptoms in *C9orf72* expansion carriers vs. non-carriers did not reach significance, a prior family history study identified a higher prevalence of what are traditionally considered neurodevelopmental disorders including autism and schizophrenia (hazard ratios of 2.7 and 4.9 respectively).[25] In other another cohort, a retrospective inquiry and chart review of *C9orf72* expansion carriers vs. non-carriers reported some increase in behavioural traits, including a fixed pattern of behaviours, excessive buying and obsessive physical exercise in the years prior to frontotemporal dementia conversion,[48] though Lee at al.[49] found no differences in behavior or psychiatric histories between carriers and non-carriers at a mean age of 43y. The lack of neuropsychiatric symptom differences in the present study relative to these prior reports may be due to the prospective symptom ascertainment in our sample, at a time when the majority of participants and their informants were unaware of their genetic status. Other potential reasons for the lack of detection of reported behavioural symptoms in the current study in comparison to findings from Devenney et al.[25] and Gossink et al.[48] may reflect differences between a clinical sample vs. research sample. Specifically, participants who enroll in ongoing clinical research studies requiring multiple assessments and MRI scans are less likely to have significant psychiatric disorders at time of participation. Finally, the neuropsychiatric symptom rating scales used were broad, but did not probe each domain in detail, and thus a more detailed elicitation of potentially relevant symptoms using tools sensitive to subclinical phenomenon such prodromal psychosis or autistic traits may be more sensitive in pre-symptomatic states. These measures, as well as assessment of potential enrollment biases and differences within GENFI families between research participants and non-participants have been added to the GENFI-3 protocol.

Affected patients with *GRN* mutations most commonly present with behavioural variant frontotemporal dementia, though the other frontotemporal dementia clinical subtypes including nonfluent primary progressive aphasia and corticobasal syndrome have been reported.[50] In contrast to the smaller brain volumes observed in the young adult *C9orf72* expansion carriers, larger total intracranial and cingulate cortex volumes were observed in *GRN* mutation carriers vs familial non-carriers, the latter in particular a region commonly atrophied early in the course of symptomatic *GRN* frontotemporal dementia.[3,51] Cognition was generally preserved in the *GRN*

young adult carriers and was better than non-carriers on the digit-symbol task, one measure of processing speed. While larger brain volumes in young adult *GRN* mutation carriers may appear unexpected, youth carrying the Huntingtin gene mutation have larger volumes of the striatum relative to familial non-carriers, prior to accelerated atrophy.[52] We cannot yet comment on rates of change from this cross-sectional analysis, but delineation of the trajectories of these regions will be possible with further longitudinal data collection in the young adult GENFI participants. Of note, given that in this age range gray matter structures undergo a normative period of volume reduction as part of the maturation process,[53] a finding of larger volume can reflect abnormal maturational processes that are advantageous or disadvantageous. Larger brain volumes have been reported prior to atrophy in *presenilin 1* mutation carriers.[54] The findings of generally preserved cognitive performance and the lack of atrophy in young adult *GRN* mutation carriers fit with recent data from large international cohorts that indicate changes in brain volume and NFL levels start within a few years' proximity to overt conversion to symptomatic genetic frontotemporal dementia,[6,7,55,56] in which the average age of diagnosis is ~61 years.[1] Our findings of preserved cognition and brain volumes in *GRN* carriers support optimism that a window of opportunity exists in adult pre-symptomatic participants in which potential mitigation of low *GRN* levels in *GRN* carriers might delay or prevent subsequent neurodegeneration. The identification of hypertrophy of the relevant cingulate region in young adult *GRN* carriers suggests examination of such regions for potential early advantageous or compensatory cellular responses during neurodevelopmental phases may hold promise to identify new critical pathways and therapeutic targets.

Like *GRN* mutation carriers, *MAPT* mutation carriers also had larger TIV relative to non-carriers. While symptomatic and older presymptomatic *MAPT* carriers commonly show behavioural or language-related deficits and atrophy in anterior temporal regions,[2,3,57-60] the young adult *MAPT* mutation carriers showed no other structural brain differences and performed as well or better than familial non-carriers on cognitive tests and informant-based symptom ratings. These findings are generally consistent with those from the entire GENFI cohort and from independent cohorts of *MAPT* carriers where mean brain volumes did not differ between pre-symptomatic mutation carriers vs. controls,[61] though in some a small subset of presymptomatic carriers had lower volumes. Specifically, in an independent cohort of *MAPT* presymptomatic carriers with a mean age 40y, mean brain volumes did not differ from those of non-carriers, though frequency

maps identified 20% of *MAPT* carriers in their 30s as having lower mesial temporal volumes.[23] Similarly, in a GENFI study examining different atrophy patterns in *MAPT* mutation carriers, 84% of presymptomatic *MAPT* carriers were categorized as normal brain volume (mean age of 38 y), while ~16 percent were assigned to temporal or frontotemporal atrophy subtype.[62] Notably, group assignment was highly stable during longitudinal follow up (range 1-5 years). In a subset analysis, 6 presymptomatic mutation carriers with CDR 0, mean age 39y, showed smaller volumes in anterior temporal and frontal regions.[63] Longitudinal observations of young *MAPT* carriers are required to examine whether higher brain volumes may be present at younger ages, as observed in Huntingtin mutation carriers,[52] and in this study in young adult *GRN* mutation carriers. Additionally, larger cohorts that enable modeling of the different *MAPT* mutation types during neurodevelopmental periods are needed given the heterogeneous clinical presentations and neuroimaging patterns associated with different *MAPT* variants.[23,62]

The finding that *MAPT* carriers were rated as having more education and better cognitive performance than *MAPT* non-carriers was an unpredicted finding, though the Tau-4R-P301L *MAPT* mouse transgenic shows early life enhanced memory performance and increased long term potentiation in the hippocampus.[64] The higher educational attainment with aspects of improved cognitive performance, coupled with larger TIV in young *MAPT* carriers, suggests the possibility of antagonistic pleiotropy, where early advantageous consequences of a mutation come with later adverse effects such as poorer repair capacity in middle and old age.[28,65] In two small cohorts of *MAPT* presymptomatic mutation carriers with different mutation types, elevated tau tracer binding was observed in most of the pre-symptomatic patients in their 40s-60s.[66,67] However, the youngest carrier, who was ~ 30 years prior to estimated disease onset, showed no tau tracer binding. We suggest that together the evidence supports the likely presence of cellular advantageous or compensatory processes which delay such accumulation of pathologic tau aggregations early in neurodevelopmental periods and which represent an understudied opportunity for new therapeutic development. Given the limited sample size, this intriguing result of potential early life advantages with gradual accumulation of pathology only reaching a threshold to cause atrophy or functional changes close to mid-life requires replication before further interpretation.

Limitations of the present study include the relatively small sample size for comparison of cognitive performance, particularly given differences in language and education levels. Due to

the relatively small number of participants per family for the majority of GENFI participants, including some with no other participating family members, the study lacked power to include family and site as variables in the primary analysis, though site related variance was included in post-hoc sensitivity analysis of cognitive findings. The finding of total brain volumetric differences in the *C9orf72* expansion carriers but lack of significant differences in cortical thickness may indicate that differences in both subcortical gray matter and white matter regions are present and contribute to the observed volumetric differences. In *GRN* carriers the absence of changes in cortical thickness in the cingulate cortex may reflect differential power of the ROI vs. voxel-wise approaches to detect differences or that volume is influenced by factors other than cortical thickness, such as surface area.

In summary, this examination of the youngest adults from families with genetic frontotemporal dementia identifies early brain volume loss in *C9orf72* mutation carriers <30 years of age, increased TIV and early hypertrophy of the anterior cingulate in young adult *GRN* carriers, and increased TIV with relatively normal brain structure and enhanced cognitive performance in young adult *MAPT* carriers. These results support long raised speculations and hypotheses about potential neurodevelopmental origins of some forms of frontotemporal dementia, and identify structural changes in young adult mutation carriers, some of which may have early advantages but deleterious consequences later in life. Longitudinal follow up and establishment of younger cohorts will enable further essential prospective comparison of structural and functional trajectories in mutation carriers with familial non-carriers, as well as examination of mutation specific effects, to uncover key neurodevelopmental changes that may set the stage for or delay the onset of frontotemporal dementia.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

Appendix 1

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References

1. Moore KM, Nicholas J, Grossman M, et al. Age at symptom onset and death and disease duration in genetic frontotemporal dementia: an international retrospective cohort study. *Lancet Neurol*. Feb 2020;19(2):145-156. doi:10.1016/S1474-4422(19)30394-1

2. Rohrer JD, Nicholas JM, Cash DM, et al. Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis. *Lancet Neurol*. Mar 2015;14(3):253-62. doi:10.1016/S1474-4422(14)70324-2

3. Cash DM, Bocchetta M, Thomas DL, et al. Patterns of gray matter atrophy in genetic frontotemporal dementia: results from the GENFI study. *Neurobiol Aging*. Feb 2018;62:191-196. doi:10.1016/j.neurobiolaging.2017.10.008

4. Rosen HJ, Boeve BF, Boxer AL. Tracking disease progression in familial and sporadic frontotemporal lobar degeneration: Recent findings from ARTFL and LEFFTDS. *Alzheimers Dement*. Jan 2020;16(1):71-78. doi:10.1002/alz.12004

5. Malpetti M, Jones PS, Tsvetanov KA, et al. Apathy in presymptomatic genetic frontotemporal dementia predicts cognitive decline and is driven by structural brain changes. *Alzheimers Dement*. Jun 2021;17(6):969-983. doi:10.1002/alz.12252

6. Jiskoot LC, Panman JL, Meeter LH, et al. Longitudinal multimodal MRI as prognostic and diagnostic biomarker in presymptomatic familial frontotemporal dementia. *Brain*. Jan 1 2019;142(1):193-208. doi:10.1093/brain/awy288

7. Rojas JC, Wang P, Staffaroni AM, et al. Plasma Neurofilament Light for Prediction of Disease Progression in Familial Frontotemporal Lobar Degeneration. *Neurology*. May 4 2021;96(18):e2296-e2312. doi:10.1212/WNL.0000000000011848

8. Tavares TP, Mitchell DGV, Coleman K, et al. Ventricular volume expansion in presymptomatic genetic frontotemporal dementia. *Neurology*. Oct 29 2019;93(18):e1699-e1706. doi:10.1212/WNL.0000000000008386

9. Le Blanc G, Jette Pomerleau V, McCarthy J, et al. Faster Cortical Thinning and Surface Area Loss in Presymptomatic and Symptomatic C9orf72 Repeat Expansion Adult Carriers. *Ann Neurol*. Jul 2020;88(1):113-122. doi:10.1002/ana.25748

10. Bethlehem RAI, Seidlitz J, White SR, et al. Brain charts for the human lifespan. *Nature*. Apr 2022;604(7906):525-533. doi:10.1038/s41586-022-04554-y

11. Caillet-Boudin ML, Buee L, Sergeant N, Lefebvre B. Regulation of human MAPT gene expression. *Mol Neurodegener*. Jul 14 2015;10:28. doi:10.1186/s13024-015-0025-8

12. Atkinson RA, Fernandez-Martos CM, Atkin JD, Vickers JC, King AE. C9ORF72 expression and cellular localization over mouse development. *Acta Neuropathol Commun*. Sep 25 2015;3:59. doi:10.1186/s40478-015-0238-7

13. Daniel R, Daniels E, He Z, Bateman A. Progranulin (acrogranin/PC cell-derived growth factor/granulin-epithelin precursor) is expressed in the placenta, epidermis, microvasculature, and brain during murine development. *Dev Dyn*. Aug 2003;227(4):593-9. doi:10.1002/dvdy.10341

14. Daniel R, He Z, Carmichael KP, Halper J, Bateman A. Cellular localization of gene expression for progranulin. *J Histochem Cytochem*. Jul 2000;48(7):999-1009. doi:10.1177/002215540004800713

15. Olszewska DA, Lonergan R, Fallon EM, Lynch T. Genetics of Frontotemporal Dementia. *Curr Neurol Neurosci Rep*. Dec 2016;16(12):107. doi:10.1007/s11910-016-0707-9

16. Denk F, Wade-Martins R. Knock-out and transgenic mouse models of tauopathies. *Neurobiol Aging*. Jan 2009;30(1):1-13. doi:10.1016/j.neurobiolaging.2007.05.010

17. Shahani N, Brandt R. Functions and malfunctions of the tau proteins. *Cell Mol Life Sci*. Oct 2002;59(10):1668-80. doi:10.1007/pl00012495

18. Yin F, Banerjee R, Thomas B, et al. Exaggerated inflammation, impaired host defense, and neuropathology in progranulin-deficient mice. *J Exp Med*. Jan 18 2010;207(1):117-28. doi:10.1084/jem.20091568

19. Huang M, Modeste E, Dammer E, et al. Network analysis of the progranulin-deficient mouse brain proteome reveals pathogenic mechanisms shared in human frontotemporal dementia

caused by GRN mutations. *Acta Neuropathol Commun*. Oct 7 2020;8(1):163. doi:10.1186/s40478-020-01037-x

20. Smeyers KM, Hutting KH. Congenital unilateral absence of the vas deferens with ipsilateral renal agenesis encountered during laparoscopic totally extraperitoneal inguinal hernia repair in an adult patient: A case report. *Ann Med Surg (Lond)*. Jun 2021;66:102449. doi:10.1016/j.amsu.2021.102449

21. Rogalski E, Johnson N, Weintraub S, Mesulam M. Increased frequency of learning disability in patients with primary progressive aphasia and their first-degree relatives. *Arch Neurol*. Feb 2008;65(2):244-8. doi:10.1001/archneurol.2007.34

22. Geschwind DH, Robidoux J, Alarcon M, et al. Dementia and neurodevelopmental predisposition: cognitive dysfunction in presymptomatic subjects precedes dementia by decades in frontotemporal dementia. *Ann Neurol*. Dec 2001;50(6):741-6. doi:10.1002/ana.10024

23. Chu SA, Flagan TM, Staffaroni AM, et al. Brain volumetric deficits in MAPT mutation carriers: a multisite study. *Ann Clin Transl Neurol*. Jan 2021;8(1):95-110. doi:10.1002/acn3.51249

24. Borroni B, Alberici A, Premi E, et al. Brain magnetic resonance imaging structural changes in a pedigree of asymptomatic progranulin mutation carriers. *Rejuvenation Res*. Jun 2008;11(3):585-95. doi:10.1089/rej.2007.0623

25. Devenney EM, Ahmed RM, Halliday G, Piguet O, Kiernan MC, Hodges JR. Psychiatric disorders in C9orf72 kindreds: Study of 1,414 family members. *Neurology*. Oct 16 2018;91(16):e1498-e1507. doi:10.1212/WNL.0000000000006344

26. Nopoulos PC, Aylward EH, Ross CA, et al. Smaller intracranial volume in prodromal Huntington's disease: evidence for abnormal neurodevelopment. *Brain*. Jan 2011;134(Pt 1):137-42. doi:10.1093/brain/awq280

27. Tereshchenko AV, Schultz JL, Bruss JE, Magnotta VA, Epping EA, Nopoulos PC. Abnormal development of cerebellar-striatal circuitry in Huntington disease. *Neurology*. May 5 2020;94(18):e1908-e1915. doi:10.1212/WNL.0000000000009364

28. Eskenazi BR, Wilson-Rich NS, Starks PT. A Darwinian approach to Huntington's disease: subtle health benefits of a neurological disorder. *Med Hypotheses*. 2007;69(6):1183-9. doi:10.1016/j.mehy.2007.02.046

29. Yu F, Sabeti PC, Hardenbol P, et al. Positive selection of a pre-expansion CAG repeat of the human SCA2 gene. *PLoS Genet*. Sep 2005;1(3):e41. doi:10.1371/journal.pgen.0010041

30. Schultz JL, Saft C, Nopoulos PC. Association of CAG Repeat Length in the Huntington Gene With Cognitive Performance in Young Adults. *Neurology*. May 11 2021;96(19):e2407-e2413. doi:10.1212/WNL.0000000000011823

31. Reasoner EE, van der Plas E, Al-Kaylani HM, et al. Behavioral features in child and adolescent huntingtin gene-mutation carriers. *Brain Behav*. Jul 2022;12(7):e2630. doi:10.1002/brb3.2630

32. Barnat M, Capizzi M, Aparicio E, et al. Huntington's disease alters human neurodevelopment. *Science*. Aug 14 2020;369(6505):787-793. doi:10.1126/science.aax3338

33. Tavares TP, Mitchell DGV, Coleman KK, et al. Early symptoms in symptomatic and preclinical genetic frontotemporal lobar degeneration. *J Neurol Neurosurg Psychiatry*. Sep 2020;91(9):975-984. doi:10.1136/jnnp-2020-322987

34. Bocchetta M, Todd EG, Peakman G, et al. Differential early subcortical involvement in genetic FTD within the GENFI cohort. *Neuroimage Clin*. 2021;30:102646. doi:10.1016/j.nicl.2021.102646

35. Cardoso MJ, Modat M, Wolz R, et al. Geodesic Information Flows: Spatially-Variant Graphs and Their Application to Segmentation and Fusion. *IEEE Trans Med Imaging*. Sep 2015;34(9):1976-88. doi:10.1109/TMI.2015.2418298

36. Diedrichsen J, Verstynen T, Schlerf J, Wiestler T. Advances in functional imaging of the human cerebellum. *Curr Opin Neurol*. Aug 2010;23(4):382-7. doi:10.1097/WCO.0b013e32833be837

37. Seeley WW, Crawford R, Rascovsky K, et al. Frontal paralimbic network atrophy in very mild behavioral variant frontotemporal dementia. *Arch Neurol*. Feb 2008;65(2):249-55. doi:10.1001/archneurol.2007.38

38. Sherif T, Rioux P, Rousseau ME, et al. CBRAIN: a web-based, distributed computing platform for collaborative neuroimaging research. *Front Neuroinform*. 2014;8:54. doi:10.3389/fninf.2014.00054

39. Wear HJ, Wedderburn CJ, Mioshi E, et al. The Cambridge Behavioural Inventory revised. *Dementia and Neuropsychologia*. 2008;2(2):102-107.

40. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society: Series B (Methodological)*. 1995;57(1):289-300. doi:https://doi.org/10.1111/j.2517-6161.1995.tb02031.x

41. Bocchetta M, Gordon E, Cardoso MJ, et al. Thalamic atrophy in frontotemporal dementia - Not just a C9orf72 problem. *Neuroimage Clin*. 2018;18:675-681. doi:10.1016/j.nicl.2018.02.019

42. Bocchetta M, Iglesias JE, Neason M, Cash DM, Warren JD, Rohrer JD. Thalamic nuclei in frontotemporal dementia: Mediodorsal nucleus involvement is universal but pulvinar atrophy is unique to C9orf72. *Hum Brain Mapp*. Mar 2020;41(4):1006-1016. doi:10.1002/hbm.24856

43. Floeter MK, Bageac D, Danielian LE, Braun LE, Traynor BJ, Kwan JY. Longitudinal imaging in C9orf72 mutation carriers: Relationship to phenotype. *Neuroimage Clin*. 2016;12:1035-1043. doi:10.1016/j.nicl.2016.10.014

44. Sha SJ, Takada LT, Rankin KP, et al. Frontotemporal dementia due to C9ORF72 mutations: clinical and imaging features. *Neurology*. Sep 4 2012;79(10):1002-11. doi:10.1212/WNL.0b013e318268452e

45. Schonecker S, Neuhofer C, Otto M, et al. Atrophy in the Thalamus But Not Cerebellum Is Specific for C9orf72 FTD and ALS Patients - An Atlas-Based Volumetric MRI Study. *Front Aging Neurosci*. 2018;10:45. doi:10.3389/fnagi.2018.00045

46. Bertrand A, Wen J, Rinaldi D, et al. Early Cognitive, Structural, and Microstructural Changes in Presymptomatic C9orf72 Carriers Younger Than 40 Years. *JAMA Neurol*. Feb 1 2018;75(2):236-245. doi:10.1001/jamaneurol.2017.4266

47. Yeh TH, Liu HF, Li YW, et al. C9orf72 is essential for neurodevelopment and motility mediated by Cyclin G1. *Exp Neurol*. Jun 2018;304:114-124. doi:10.1016/j.expneurol.2018.03.002

48. Gossink F, Dols A, Stek ML, et al. Early life involvement in C9orf72 repeat expansion carriers. *J Neurol Neurosurg Psychiatry*. Jan 2022;93(1):93-100. doi:10.1136/jnnp-2020-325994

49. Lee SE, Sias AC, Mandelli ML, et al. Network degeneration and dysfunction in presymptomatic C9ORF72 expansion carriers. *Neuroimage Clin*. 2017;14:286-297. doi:10.1016/j.nicl.2016.12.006

50. Le Ber I, Camuzat A, Hannequin D, et al. Phenotype variability in progranulin mutation carriers: a clinical, neuropsychological, imaging and genetic study. *Brain*. Mar 2008;131(Pt 3):732-46. doi:10.1093/brain/awn012

51. Whitwell JL, Boeve BF, Weigand SD, et al. Brain atrophy over time in genetic and sporadic frontotemporal dementia: a study of 198 serial magnetic resonance images. *Eur J Neurol*. May 2015;22(5):745-52. doi:10.1111/ene.12675

52. van der Plas E, Langbehn DR, Conrad AL, et al. Abnormal brain development in child and adolescent carriers of mutant huntingtin. *Neurology*. Sep 3 2019;93(10):e1021-e1030. doi:10.1212/WNL.0000000000008066

53. Coupe P, Catheline G, Lanuza E, Manjon JV, Alzheimer's Disease Neuroimaging I. Towards a unified analysis of brain maturation and aging across the entire lifespan: A MRI analysis. *Hum Brain Mapp*. Nov 2017;38(11):5501-5518. doi:10.1002/hbm.23743

54. Fortea J, Sala-Llonch R, Bartres-Faz D, et al. Increased cortical thickness and caudate volume precede atrophy in PSEN1 mutation carriers. *J Alzheimers Dis*. 2010;22(3):909-22. doi:10.3233/JAD-2010-100678

55. Staffaroni AM, Cobigo Y, Goh SM, et al. Individualized atrophy scores predict dementia onset in familial frontotemporal lobar degeneration. *Alzheimers Dement*. Jan 2020;16(1):37-48. doi:10.1016/j.jalz.2019.04.007

56. Meeter LH, Dopper EG, Jiskoot LC, et al. Neurofilament light chain: a biomarker for genetic frontotemporal dementia. *Annals of Clinical and Translational Neurology*. 2016;3(8):623-636. doi:https://doi.org/10.1002/acn3.325

57. Hakkinen S, Chu SA, Lee SE. Neuroimaging in genetic frontotemporal dementia and amyotrophic lateral sclerosis. *Neurobiol Dis*. Nov 2020;145:105063. doi:10.1016/j.nbd.2020.105063

58. Whitwell JL, Jack CR, Jr., Boeve BF, et al. Voxel-based morphometry patterns of atrophy in FTLD with mutations in MAPT or PGRN. *Neurology*. Mar 3 2009;72(9):813-20. doi:10.1212/01.wnl.0000343851.46573.67

59. Staffaroni AM, Goh SM, Cobigo Y, et al. Rates of Brain Atrophy Across Disease Stages in Familial Frontotemporal Dementia Associated With MAPT, GRN, and C9orf72 Pathogenic Variants. *JAMA Netw Open*. Oct 1 2020;3(10):e2022847. doi:10.1001/jamanetworkopen.2020.22847

60. Seelaar H, Papma JM, Garraux G, et al. Brain perfusion patterns in familial frontotemporal lobar degeneration. *Neurology*. Jul 26 2011;77(4):384-92. doi:10.1212/WNL.0b013e3182270456

61. Panman JL, Jiskoot LC, Bouts M, et al. Gray and white matter changes in presymptomatic genetic frontotemporal dementia: a longitudinal MRI study. *Neurobiol Aging*. Apr 2019;76:115-124. doi:10.1016/j.neurobiolaging.2018.12.017

62. Young AL, Bocchetta M, Russell LL, et al. Characterizing the Clinical Features and Atrophy Patterns of MAPT-Related Frontotemporal Dementia With Disease Progression Modeling. *Neurology*. Aug 31 2021;97(9):e941-e952. doi:10.1212/WNL.0000000000012410

63. Dominguez-Vivero C, Wu L, Lee S, et al. Structural Brain Changes in Pre-Clinical FTD MAPT Mutation Carriers. *J Alzheimers Dis*. 2020;75(2):595-606. doi:10.3233/JAD-190820

64. Boekhoorn K, Terwel D, Biemans B, et al. Improved long-term potentiation and memory in young tau-P301L transgenic mice before onset of hyperphosphorylation and tauopathy. *J Neurosci*. Mar 29 2006;26(13):3514-23. doi:10.1523/JNEUROSCI.5425-05.2006

65. Jones JH. The Force of Selection on the Human Life Cycle. *Evol Hum Behav*. Sep 1 2009;30(5):305-314. doi:10.1016/j.evolhumbehav.2009.01.005

66. Levy JP, Bezgin G, Savard M, et al. 18F-MK-6240 tau-PET in genetic frontotemporal dementia. *Brain*. Oct 19 2021;doi:10.1093/brain/awab392

67. Wolters EE, Papma JM, Verfaillie SCJ, et al. [(18)F]Flortaucipir PET Across Various MAPT Mutations in Presymptomatic and Symptomatic Carriers. *Neurology*. Sep 7 2021;97(10):e1017-e1030. doi:10.1212/WNL.0000000000012448

Figure legends

Figure 1 Main effect of genetic status on cognitive performance in young adult *MAPT* mutation group. *MAPT* mutation carriers show enhanced performance on **A)** digit span forward and **B)** verbal fluency in comparison to non-carriers. Small black circles represent individual scores; large black circles represent group means.

Figure 2 Main effects of genetic status on cognitive performance in the young adult *GRN* mutation group. *GRN* mutation carriers show enhanced performance on digit symbol in comparison to non-carriers. Small black circles represent individual scores; large black circles represent group means.

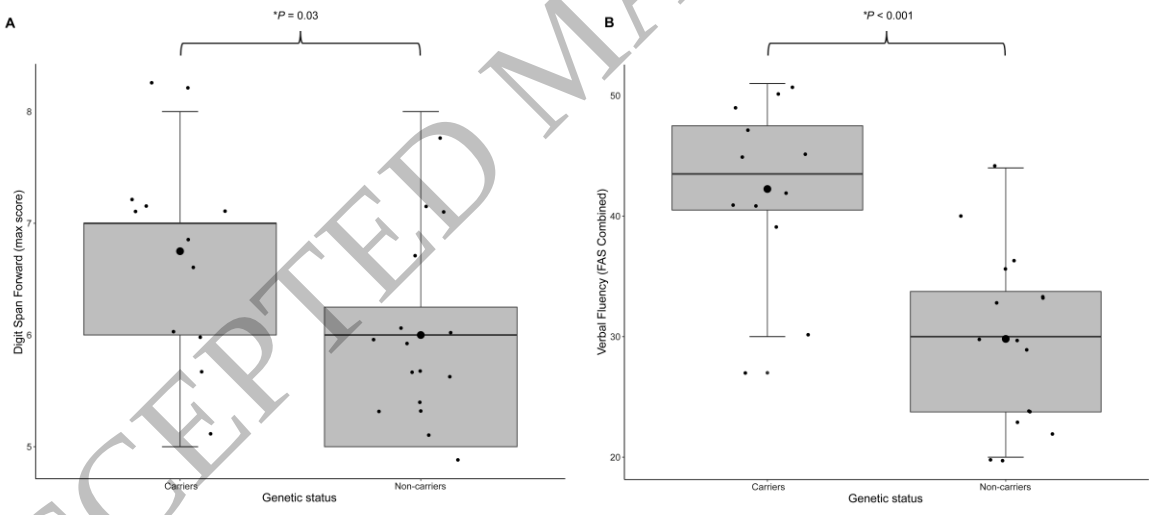

Figure 1
159x66 mm (5.5 x DPI)

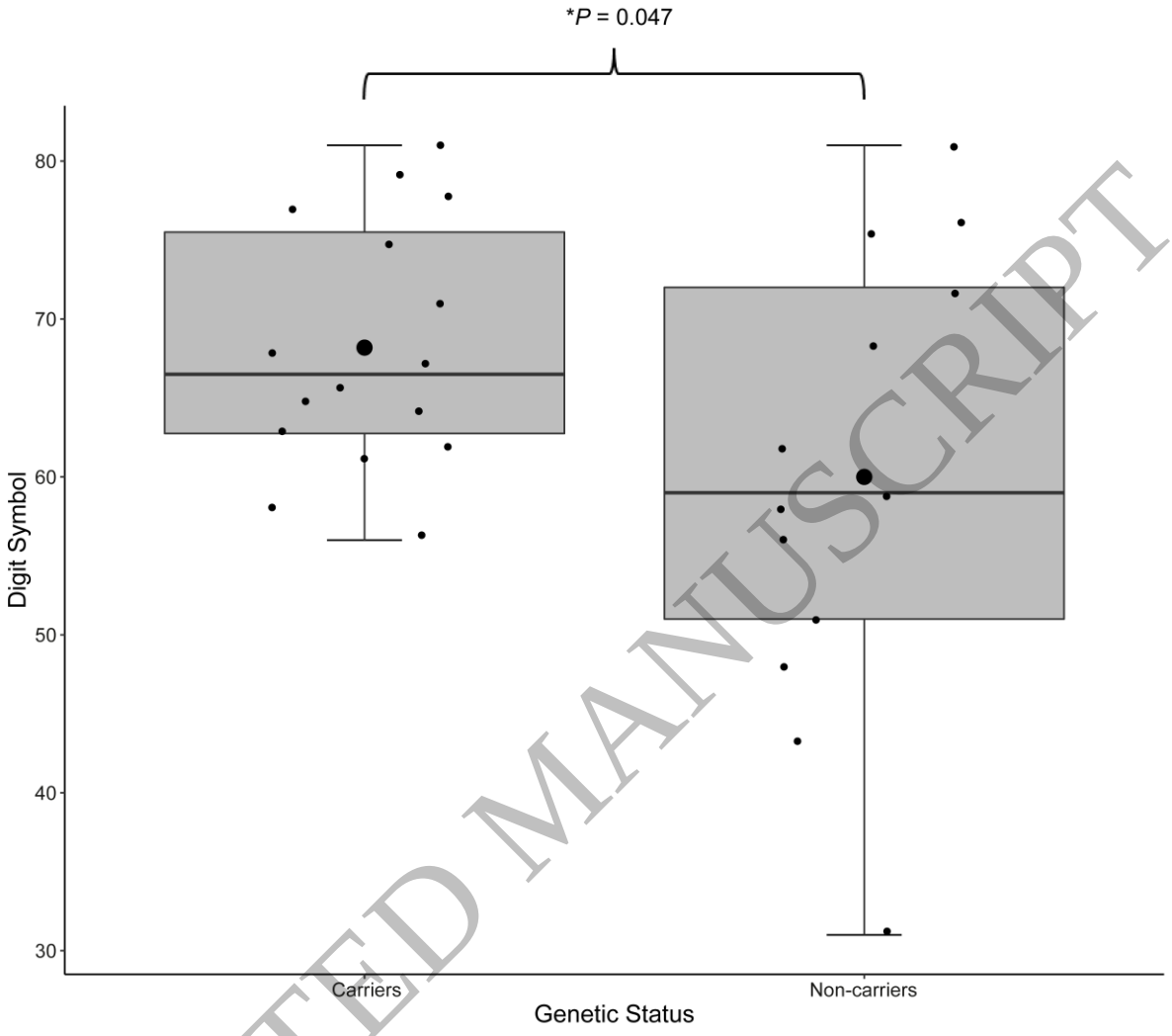

Figure 2
159x141 mm (5.5 x DPI)

Table 1 MRI volumetric analysis of mutation carriers versus non-carriers

	Total	**Carrier**	**Non-carrier**	***C9orf72* carriers**	***C9orf72* non-carriers**	***C9orf72* contrasts**	***MAPT* carriers**	***MAPT* non-carriers**	***MAPT* contrasts**	***GRN* carriers**	***GRN* non-carriers**	***GRN* contrasts**
N	85	44	41	17	15	–	11	13	–	16	13	–
Age (SD)	25.7 (2.9)	25.7 (3.2)	25.8 (2.6)	25.9 (3.3)	25.8 (2.1)	F = 0.01, P = 0.95	24.8 (3.7)	25.8 (3.6)	F = 0.38, P = 0.54	25.9 (2.68)	25.9 (2.27)	F = 0.1, P = 0.9
Education, years (SD)	14.35 (2.23)	14.6 (2.1)	14.1 (2.3)	14.0 (2.45)	14.4 (2.20)	F = 0.23, P = 0.63	15.5 (1.5)	14.1 (1.7)	F = 4.9, P = 0.04*	14.6 (1.9)	13.6 (3.0)	F = 1.3, P = 0.26
Mean age of onset in family		56.1 (6.7)	55.4 (8.4)	55.3 (7.9)	58.2 (6.3)		54.3 (6.6)	52.7 (4.8)		58.1 (5.2)	54.9 (12.1)	
Handedness						X^2 = 1.4, P = 0.23			X^2 = 4.1, P = 0.04			X^2 = 0.06, P = 0.81
Right	73	37	36	16	12		8	13		13	11	
Left	12	7	5	1	3		3	0		3	2	
Sex						X^2 = 0.13, P = 0.72			X^2 = 0.24, P = 0.63			X^2 = 0.17 P = 0.68
Male	40	21	19	9	7		7	7		5	5	
Female	45	23	22	8	8		4	6		11	8	
Brain volumes												
TIV[a]				1390903	1450461	F = 1.73, P = 0.21	1501219	1375417	**F = 9.88, *P* = 0.01****	1437451	1373921	**F = 6.77, *P* = 0.03****
Total brain				1166301	1205228	**F = 15.02, *P* = 0.001****	1201246	1206018	F = 0.08, P = 0.79	1123944	1143427	F = 4.48, P = 0.06
Total CSF				249971	241656	F = 1.52, P = 0.23	250306	244399	F = 0.55, P = 0.47	232339	222586	F = 1.45, P = 0.24
Frontal lobes				185756	192530	F = 2.81, P = 0.11	192501	186598	F = 1.44, P = 0.26	180518	182866	F = 0.32, P = 0.58
Temporal lobes				125657	131026	F = 3.95, P = 0.07	132589	130117	F = 0.00, P = 0.98	123905	123288	F = 1.78, P = 0.21
Parietal lobes				95994	99841	F = 0.17, P = 0.69	99570	97354	F = 1.52, P = 0.25	93592	95352	F = 0.68, P = 0.43
Occipital lobes				73183	77445	F = 0.96, P = 0.34	75198	76833	F = 0.08, P = 0.78	72467	73832	F = 0.24, P = 0.64
Cingulate				30155	30789	F = 0.39, P = 0.54	31106	31461	F = 0.11, P = 0.75	29934	28600	**F = 9.91, *P* = 0.009****
Insula				11545	11838	F = 0.79, P = 0.39	12207	11332	F = 1.71, P = 0.23	11177	11694	F = 0.21, P = 0.65
Cerebellum				104739	107168	F = 0.03, P = 0.87	112314	115886	F = 0.16, P = 0.70	105285	106223	F = 0.82, P = 0.39
Amygdala				3471	3528	F = 0.12, P = 0.74	3678	3566	F = 0.46, P = 0.52	3499	3527	F = 16.41, P = 0.002
Hippocampus				7679	7902	F = 0.09, P = 0.77	8190	8199	F = 0.39, P = 0.55	7880	8036	F = .00 P = 0.98
Thalamus				10975	12045	**F = 12.3, *P* = 0.003****	11256	13011	F = 4.81, P = 0.06	11561	10838	F = 41.85, P < 0.001
Basal ganglia				20487	20650	F = 0.11, P = 0.74	19650	21116	F = 4.19, P = 0.08	19203	20015	F = 2.10, P = 0.18

TIV = total intracranial volume. Brain volume contrasts indicate main effect of genetic status when controlling for age, TIV, sex and scanner type. Mean volumes in mm^3, corrected for age at visit and TIV mm^3.

*P < 0.05.

**Bolded values significant after FDR correction and accounting for scanner effects. For non-bolded imaging contrasts with significant *P*-values, scanner effects preclude conclusion about group differences.
[a]TIV contrast controlled for age, sex and scanner type.

Table 2 Demographics, Behavioural and Cognitive Assessments of GENFI Young Adult Mutation Carriers versus Non-carriers

	Total	Carriers	Non-carriers	*C9orf72* Carriers	*C9orf72* non-Carriers	*C9orf72* contrasts	*MAPT* Carriers	*MAPT* non-carriers	*MAPT* contrasts	*GRN* carriers	*GRN* non-carriers	*GRN* contrasts
GENFI1 + GENFI2												
N	92	45	47	17	18	–	12	16	–	16	13	–
Age (SD)	25.5 (2.9)	25.7 (3.1)	25.4 (2.8)	25.8 (3.3)	25.9 (2.2)	t = 0.13, P = 0.90	24.9 (3.6)	25.0 (3.1)	t = 0.06, P = 0.95	25.8 (2.55)	25.0 (3.17)	t = 0.8, P = 0.46
Education, Yrs (SD)	14.2 (2.3)	14.6 (2.2)	13.8 (2.5)	14.0 (2.5)	14.1 (2.6)	t = 0.07, P = 0.95	15.2 (2.0)	13.6 (1.9)	**t = 2.01, P = 0.05**	14.7 (1.99)	13.6 (3.01)	t = 1.10, P = 0.28
Mean age of onset in family, Yrs (SD)	55.6 (7.7)	55.8 (6.9)	55.4 (8.4)	53.2 (13.3)	59.2 (6.3)	t = 1.7, P = 0.09	53.4 (7.1)	51.8 (4.9)	t = 0.73, P = 0.47	58.1 (5.2)	54.9 (12.1)	t = 1.0, P = 0.34
Handedness						t = 1.0, P = 0.33			t = 1.3, P = 0.21			t = 0.23, P = 0.82
Right	79	37	42	16	15	–	9	15	–	13	11	–
Left	13	7	6	1	3	–	3	1	–	3	2	–
Sex						t = 0.49, P = 0.63			t = 0.22, P = 0.83			t = 0.39, P = 0.70
Male	48	24	24	8	10	–	5	6	–	11	8	–
Female	44	21	23	9	8	–	7	10	–	5	5	–
Neuropsych, Mean (SD)												
Digit Span Forward				6.6 (1.1)	6.7 (1.1)	F = 0.04, P = 0.84	6.8 (0.9)	6.0 (0.9)	**F = 5.8, P = 0.03***	7.1 (0.1)	6.5 (1.1)	F = 2.5, P = 0.13
Digit Span Backward				5.1 (0.9)	5.1 (1.7)	F = 0.02, P = 0.90	5.4 (1.2)	4.8 (1.1)	F = 1.91, P = 0.18	5.2 (1.1)	4.9 (1.2)	F = 1.0, P = 0.32
Digit Symbol				60.3 (7.3)[a]	61.8 (15.2)	F = 0.2, P = 0.69	66.7 (11.0)	60.4 (10.9)	F = 1.81, P = 0.19	68.2 (7.8)	60.0 (14.5)	**F = 4.5, P = 0.047***
Boston Naming				27.4 (1.8)	27.5 (2.2)	F = 0.02, P = 0.90	27.5 (1.9)	27.9 (1.6)	F = 0.28, P = 0.60	27.4 (1.)	27.7 (1.6)	F = 0.3, P = 0.58
Verbal Fluency (Animals)				22.7 (4.5)	24.9 (7.3)	F = 1.5, P = 0.24	22.4 (4.7)	23.1 (8.9)	F = 0.06, P = 0.82	25.8 (5.14)	23.5 (5.2)	F = 1.4, P = 0.26
Verbal Fluency (FAS)				35.1 (10.5)	41.1 (12.1)	F = 2.1, P = 0.16	42.3 (7.5)	29.8 (7.2)	**F = 18.6, P = 0.0003***	37.4 (14.1)	42.8 (9.3)	F = 1.3, P = 0.26
Block Design				50.1 (17.7)[a]	56.0 (9.2)	F = 1.4, P = 0.25	57.4 (10.8)	54.0 (11.5)	F = 0.62, P = 0.44	57.6 (10.4)	52.7 (15.2)	F = 1.1, P = 0.31
CBI				3.2 (3.5)[b]	3.6[b] (5.2)	F = 0.1, P = 0.79	2.75 (5.4)	5.9 (8.3)	F = 1.6, P = 0.22	3.7 (4.2)[b]	3.5 (5.1)[b]	F = 0.01, P = 0.94

*P < 0.05. Significant results bolded. Independent sample t-tests or one-way analyses of covariance were used to discern group differences for relevant variables. F statistics indicate main effects of genetic status.
[a]One data-point missing (*C9orf72* expansion carrier).
[b]Data-points missing (*C9orf72*: 2 carriers, 2 non-carriers; *GRN*: 1 carrier, 1 non-carrier).