

Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis



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Summary

Background Frontotemporal dementia is a highly heritable neurodegenerative disorder. In about a third of patients, the disease is caused by autosomal dominant genetic mutations usually in one of three genes: progranulin (*GRN*), microtubule-associated protein tau (*MAPT*), or chromosome 9 open reading frame 72 (*C9orf72*). Findings from studies of other genetic dementias have shown neuroimaging and cognitive changes before symptoms onset, and we aimed to identify whether such changes could be shown in frontotemporal dementia.

Methods We recruited participants to this multicentre study who either were known carriers of a pathogenic mutation in *GRN*, *MAPT*, or *C9orf72*, or were at risk of carrying a mutation because a first-degree relative was a known symptomatic carrier. We calculated time to expected onset as the difference between age at assessment and mean age at onset within the family. Participants underwent a standardised clinical assessment and neuropsychological battery. We did MRI and generated cortical and subcortical volumes using a parcellation of the volumetric T1-weighted scan. We used linear mixed-effects models to examine whether the association of neuropsychology and imaging measures with time to expected onset of symptoms differed between mutation carriers and non-carriers.

Findings Between Jan 30, 2012, and Sept 15, 2013, we recruited participants from 11 research sites in the UK, Italy, the Netherlands, Sweden, and Canada. We analysed data from 220 participants: 118 mutation carriers (40 symptomatic and 78 asymptomatic) and 102 non-carriers. For neuropsychology measures, we noted the earliest significant differences between mutation carriers and non-carriers 5 years before expected onset, when differences were significant for all measures except for tests of immediate recall and verbal fluency. We noted the largest Z score differences between carriers and non-carriers 5 years before expected onset in tests of naming (Boston Naming Test -0.7 ; SE 0.3) and executive function (Trail Making Test Part B, Digit Span backwards, and Digit Symbol Task, all -0.5 , SE 0.2). For imaging measures, we noted differences earliest for the insula (at 10 years before expected symptom onset, mean volume as a percentage of total intracranial volume was 0.80% in mutation carriers and 0.84% in non-carriers; difference -0.04 , SE 0.02) followed by the temporal lobe (at 10 years before expected symptom onset, mean volume as a percentage of total intracranial volume 8.1% in mutation carriers and 8.3% in non-carriers; difference -0.2 , SE 0.1).

Interpretation Structural imaging and cognitive changes can be identified 5–10 years before expected onset of symptoms in asymptomatic adults at risk of genetic frontotemporal dementia. These findings could help to define biomarkers that can stage presymptomatic disease and track disease progression, which will be important for future therapeutic trials.

Funding Centres of Excellence in Neurodegeneration.

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Introduction

Frontotemporal dementia is a neurodegenerative disorder characterised by focal neuronal loss in the frontal and temporal lobes.¹ It is a common cause of early-onset

dementia, but can also present in old age and has an estimated prevalence of between 15 and 22 per 100 000 individuals in the population.² It presents clinically with either behavioural symptoms (behavioural variant

Lancet Neurol 2015; 14: 253–62

Published Online
February 4, 2015
[http://dx.doi.org/10.1016/S1474-4422\(14\)70324-2](http://dx.doi.org/10.1016/S1474-4422(14)70324-2)

This online publication has been corrected.

The corrected version first appeared at thelancet.com/neurology on November 9, 2015

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frontotemporal dementia) or language disturbance (primary progressive aphasia), but patients can also develop symptoms of motor neuron disease, progressive supranuclear palsy, or corticobasal syndrome.¹ It is highly heritable, with an autosomal dominant family history reported in around a third of people with the disease.³ Mutations in three genes are proven major causes of genetic frontotemporal dementia: microtubule-associated protein tau (*MAPT*), progranulin (*GRN*), and chromosome 9 open reading frame 72 (*C9orf72*).⁴ Frequencies of mutations of these three genes vary by geography, but together they account for 10–20% of all cases of frontotemporal dementia.⁴

The study of autosomal dominant frontotemporal dementia in its presymptomatic period provides a window into the earliest stages of the disease process.⁵ Evidence from familial Alzheimer's disease and Huntington's disease shows that changes in some biomarkers occur many years before symptom onset,^{6–8} suggesting that the ideal time to treat neurodegenerative disease could be before clinical presentation, at a point when the minimum of irreversible neuronal loss has occurred and cognitive function is still preserved. To optimise therapeutic opportunities, biomarkers of frontotemporal dementia are therefore needed that signify disease onset and can measure changes in disease trajectory in the presymptomatic period. Furthermore, biomarkers that allow accurate staging of the disease process will be important to identify individuals most suitable for particular trials, to reduce heterogeneity, and increase the statistical power.

Few studies of mutation carriers at risk of frontotemporal dementia have been done, and investigators of these studies have reported inconsistent findings (appendix).^{9–26} Although findings from some studies have shown presymptomatic changes in neuropsychometric testing near to disease onset,^{9,11,15–17,22} others have not shown any changes.^{13,19,21,23–25} Similarly, findings from a few case studies^{9,11,17} and small case series^{12,13,18} have shown evidence of grey matter volume loss before symptoms onset with structural MRI, but other studies have reported no abnormalities.^{19–22} In this study, we compared clinical, behavioural, and structural imaging measures between mutation carriers and non-carriers in a large international cohort of families with autosomal dominant frontotemporal dementia. Our hypothesis was that we would see presymptomatic changes in structural imaging measures initially and then behavioural and cognitive measures before onset of symptoms.

Methods

Participants

The Genetic Frontotemporal dementia Initiative (GENFI) consists of 11 research sites, in the UK, Italy, the Netherlands, Sweden, and Canada. We recruited participants who were either known carriers of a pathogenic mutation in *MAPT*, *GRN*, or *C9orf72*, or at

risk of carrying a mutation because a first-degree relative was a known symptomatic carrier. We genotyped all participants at their local site, with a pathogenic expansion in *C9orf72* being defined as the presence of greater than 30 repeats. We enrolled 220 participants between Jan 30, 2012, and Sept 15, 2013. Local ethics committees at each site approved the study and all participants provided written informed consent at enrolment.

Procedures

Participants underwent a standardised clinical assessment consisting of a medical history, family history, and physical examination. We based symptomatic status on this assessment, which included a collateral history from a family member or close friend. We measured functional status using the Frontotemporal Dementia Rating Scale²⁷ and assessed behavioural symptoms using the Cambridge Behavioural Inventory Revised version (CBI-R).²⁸ Patients underwent a neuropsychological battery consisting of tests from the Uniform Data Set:²⁹ the Logical Memory subtest of the Wechsler Memory Scale-Revised with Immediate and Delayed Recall scores, Digit Span forwards and backwards from the Wechsler Memory Scale-Revised, a Digit Symbol Task, Parts A and B of the Trail Making Test, the short version of the Boston Naming Test, and Category Fluency (animals). We also tested Letter Fluency and did the Wechsler Abbreviated Scale of Intelligence Block Design task, and the Mini-Mental State Examination (MMSE). For each test, apart from the MMSE and CBI-R, we calculated Z scores based on language-specific norms. Most at-risk participants (158 [88%] of 180) had not undergone presymptomatic genetic testing and were therefore not aware of their mutation status, and for these participants the clinicians and neuropsychologists who did the assessments were masked to mutation status.

We did volumetric T1-weighted MRI on 3T and 1.5T scanners at sites where 3T scanning was not available. We designed scan protocols at the outset of the study to match across scanners as much as possible. For the volumetric analysis, we did a cortical parcellation using a multiatlas segmentation propagation approach following the brainCOLOR protocol,^{30,31} combining regions of interest to calculate grey matter volumes of the entire cortex, separated into the frontal, temporal, parietal, occipital, cingulate, and insula cortices. We also did a subcortical parcellation using the Neuromorphometrics protocol^{32,33} for the hippocampus, amygdala, striatum, and thalamus, and a parcellation of the cerebellum using the Diedrichsen cerebellar atlas,^{33,34} producing a measure for the entire cerebellum by combining regions of interest. We measured whole-brain volumes using a semi-automated segmentation method.³⁵ We expressed all measures as a percentage of total intracranial volume (measured with SPM12 with a combination of grey matter, white matter, and CSF segmentations). In view of

previous evidence for asymmetrical atrophy in *GRN* mutation carriers compared with *MAPT* and *C9orf72* carriers,^{4,5} we also assessed differences between left and right hemisphere volumes using a laterality index, calculated as the absolute difference between left and right cortical volumes divided by total cortical volume.

Findings from individual case series of individuals with dementia with a known genetic cause suggest that variability of age at symptom onset exists within families. However, authors of a large study of familial Alzheimer's disease³⁶ suggest that a strong relation exists between individual age at symptoms onset and both parental age at onset and mean age at onset within the family. To our knowledge, no similar studies have been done in frontotemporal dementia. We therefore did an initial analysis on the basis of the symptomatic carriers within our cohort, investigating the relation between their age at symptoms onset and parental age at onset, their age at onset and mean age at onset for other members of the same family, and their age at onset and median age at onset for other members of the same family (excluding the symptomatic individual from mean and median calculations). Parental age at onset did not show a significant correlation with age at symptoms onset of the symptomatic carriers (Pearson correlation coefficient 0.39; $p=0.0685$), but we found both mean and median ages at onset within the family to be significantly correlated with the symptomatic carriers' age at onset (Pearson correlation coefficient 0.53, $p=0.0019$ for the mean and 0.50, $p=0.0036$ for the median). Furthermore, in addition to being correlated with mean age of onset within their families, age at symptoms onset of symptomatic carriers did not significantly differ from mean age at onset within their families ($p=0.3216$ Wilcoxon signed

rank). On the basis of this analysis, we decided to use mean familial age at onset to estimate time to expected symptom onset—ie, someone aged 50 years old at the time of assessment with a mean age at onset of 55 years old in their family would be given an expected time from symptoms onset of -5 years. Data were available for this calculation from one family member in 35 families, from two in 15 families, from three in ten families, from four in four families, from five in five families, from six in two families, and from seven in two families; 12, 16, and 30 family members were available in a further three families.

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	Non-carriers (n=102)	Mutation carriers (n=118)
Male	60 (59%)	57 (48%)
Mutated gene		
<i>MAPT</i>	18 (18%)	26 (22%)
<i>GRN</i>	60 (59%)	58 (49%)
<i>C9orf72</i>	24 (24%)	34 (29%)
Clinical status		
Asymptomatic	102 (100%)	78 (66%)
Symptomatic	0	40 (34%)
Right-handed	94 (92%)	106 (90%)
Age (years)	49.2 (36.3-61.7)	53.3 (41.4-62.7)
Education (years)	13 (11-16)	13 (10-16)
Years from expected onset		
-20 or longer	32 (31%)	21 (18%)
-20 up to -10	18 (18%)	21 (18%)
-10 up to 0	23 (23%)	24 (20%)
0 and beyond expected onset	29 (28%)	52 (44%)

Data are n (%) or median (IQR).

Table 1: Characteristics of study participants

	-25 years	-20 years	-15 years	-10 years	-5 years	0 years	5 years	10 years
Behavioural								
Cambridge Behavioural Inventory—Revised (/180)								
Non-carriers	1.9	4.6	7.6	10.6	13.2	14.9	15.4	14.2
Carriers	0.2	4.3	9.6	16.2	24.0	33.1	43.5	55.1
Difference	-1.7	-0.3	2.0	5.5	10.8	18.2	28.1	40.9
SE	2.8	2.2	2.7	4.0	4.9	5.3	5.8	8.7
p value	0.5611	0.8867	0.4748	0.1620	0.0269	0.0005	<0.0001	<0.0001
Cognitive								
Mini Mental State Examination (/30)								
Non-carriers	29.5	29.2	28.9	28.6	28.4	28.3	28.3	28.2
Carriers	30.3	29.6	28.8	28.0	27.1	26.1	25.0	23.9
Difference	0.7	0.4	<0.1	-0.6	-1.4	-2.2	-3.2	-4.4
SE	0.3	0.3	0.3	0.4	0.5	0.7	0.9	1.3
p value	0.0221	0.1683	0.9303	0.0922	0.0045	0.0008	0.0006	0.0007
Neuropsychological (Z score)								
Logical Memory—Immediate Recall								
Non-carriers	0.4	0.2	0.1	<0.1	-0.1	-0.2	-0.3	-0.4
Carriers	0.4	0.3	0.1	-0.1	-0.4	-0.8	-1.3	-1.9
Difference	<0.1	0.1	<0.1	-0.1	-0.3	-0.6	-1.0	-1.5
SE	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3
p value	0.8948	0.7183	0.8779	0.6136	0.0863	0.0005	<0.0001	<0.0001
Logical Memory—Delayed Recall								
Non-carriers	0.3	0.2	0.1	<0.1	-0.1	-0.2	-0.3	-0.5
Carriers	0.2	0.2	<0.1	-0.2	-0.5	-0.9	-1.3	-1.8
Difference	-0.1	-0.1	-0.1	-0.3	-0.4	-0.7	-1.0	-1.4
SE	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3
p value	0.6463	0.6767	0.4849	0.1696	0.0105	<0.0001	<0.0001	<0.0001
Digit Span forwards								
Non-carriers	0.1	0.1	0.1	<0.1	<0.1	-0.1	-0.1	-0.2
Carriers	0.5	0.3	0.1	-0.2	-0.4	-0.7	-1.0	-1.3
Difference	0.3	0.2	<0.1	-0.2	-0.4	-0.7	-0.9	-1.1
SE	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3
p value	0.1479	0.4366	0.9235	0.2847	0.0253	0.0005	0.0001	0.0003
Digit Span backwards								
Non-carriers	0.1	0.1	<0.1	<0.1	-0.1	-0.1	-0.2	-0.2
Carriers	0.1	<0.1	-0.2	-0.4	-0.6	-0.8	-1.1	-1.4
Difference	-0.1	-0.1	-0.2	-0.3	-0.5	-0.7	-0.9	-1.2
SE	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3
p value	0.8098	0.5866	0.3136	0.0933	0.0079	0.0001	<0.0001	0.0001

(Table 2 continues on next page)

	-25 years	-20 years	-15 years	-10 years	-5 years	0 years	5 years	10 years
(Continued from previous page)								
Digit Symbol Task								
Non-carriers	0.8	0.7	0.5	0.3	0.1	-0.2	-0.4	-0.7
Carriers	0.8	0.6	0.3	<0.1	-0.4	-0.9	-1.4	-1.9
Difference	<0.1	-0.2	-0.2	-0.3	-0.5	-0.7	-0.9	-1.2
SE	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3
p value	0.9036	0.7223	0.3033	0.0549	0.0017	<0.0001	<0.0001	<0.0001
Trail Making Test Part A								
Non-carriers	0.4	0.3	0.2	<0.1	-0.2	-0.4	-0.6	-0.8
Carriers	0.6	0.4	0.1	-0.2	-0.6	-1.0	-1.5	-2.0
Difference	0.2	0.1	-0.1	-0.2	-0.4	-0.6	-0.9	-1.2
SE	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3
p value	0.4662	0.7470	0.7716	0.2832	0.0355	0.0012	0.0002	0.0006
Trail Making Test Part B								
Non-carriers	0.6	0.4	0.3	0.2	<0.1	-0.2	-0.3	-0.5
Carriers	0.9	0.7	0.4	<0.1	-0.5	-1.0	-1.7	-2.5
Difference	0.3	0.2	0.1	-0.2	-0.5	-0.9	-1.4	-1.9
SE	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3
p value	0.1730	0.2639	0.7317	0.3799	0.0072	<0.0001	<0.0001	<0.0001
Letter Fluency								
Non-carriers	0.1	-0.1	-0.2	-0.3	-0.4	-0.5	-0.6	-0.6
Carriers	0.2	0.2	<0.1	-0.3	-0.6	-1.1	-1.7	-2.4
Difference	0.1	0.2	0.2	0.1	-0.2	-0.6	-1.1	-1.8
SE	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3
p value	0.6629	0.3280	0.3592	0.7952	0.2746	0.0015	<0.0001	<0.0001
Category Fluency								
Non-carriers	0.5	0.4	0.2	0.1	-0.1	-0.3	-0.4	-0.6
Carriers	0.6	0.5	0.3	<0.1	-0.4	-0.8	-1.3	-2.0
Difference	0.1	0.1	0.1	-0.1	-0.3	-0.5	-0.9	-1.4
SE	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3
p value	0.6632	0.4945	0.6544	0.7932	0.1226	0.0007	<0.0001	<0.0001
Boston Naming Test								
Non-carriers	<0.1	-0.1	-0.2	-0.3	-0.3	-0.3	-0.3	-0.3
Carriers	0.4	0.2	-0.2	-0.6	-1.0	-1.6	-2.2	-2.9
Difference	0.4	0.3	0.1	-0.3	-0.7	-1.2	-1.9	-2.6
SE	0.3	0.3	0.3	0.3	0.3	0.2	0.3	0.4
p value	0.1763	0.2871	0.7965	0.3202	0.0047	<0.0001	<0.0001	<0.0001
Block Design								
Non-carriers	0.4	0.3	0.2	<0.1	-0.2	-0.3	-0.5	-0.7
Carriers	0.7	0.5	0.2	-0.1	-0.5	-1.0	-1.4	-2.0
Difference	0.3	0.2	<0.1	-0.2	-0.4	-0.6	-0.9	-1.3
SE	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3
p value	0.2220	0.3911	0.8839	0.4029	0.0284	0.0001	<0.0001	<0.0001

Differences calculated from unrounded values.

Table 2: Behavioural and neuropsychological estimates in mutation carriers and non-carriers, by estimated time from expected symptoms onset

because of low numbers in each individual genetic group). This modelling framework allows estimation of fixed and random effects of predictor variables, including the intercept. Fixed effects represent non-random sources of variation, where the predictor variable has the same relation with the outcome in all observations. Random effects estimate the variance in the effect of a predictor between different clusters in the data and this estimation allows for correlation in the outcome between members of the same cluster.^{37,38}

For analysis of each measure, a random intercept for family allowed values of the marker to be correlated between family members. The fixed effect predictor variables of interest were mutation carrier status, time to expected onset, and terms for the interaction between mutation carrier status and time to expected onset. We expected a non-linear change in each measure over time, so models also included a quadratic term for time to expected onset and the interaction between this term and mutation carrier status. We included a more complex cubic relation association between the measure and time to expected onset only when significant ($p < 0.05$) evidence existed that addition of a cubic term and the interaction between the cubic term and mutation carrier status improved model fit. An example of the mixed effect model is given in the appendix for analysis of whole-brain volume to show the modelling framework that we used for analysis.

We also did exploratory analyses to assess whether differences between non-carriers and *MAPT*, *GRN*, and *C9orf72* mutation carriers existed in the association between values of each measure and time to expected onset of symptoms. Because of the small number of participants in each gene group, we considered only linear changes in markers over time in this analysis.

We did a Wald test for each model to assess whether the mean value of the measure differed between mutation carriers and non-carriers. We predicted average values from the mixed effects model for each group and differences between mutation carriers and non-carriers every 5 years between 25 years before expected onset and 10 years after expected onset. All analyses were adjusted for study site and sex. Model diagnostics for both MMSE and CBI-R suggested non-constant variance, so we used robust standard errors for these analyses.

In addition to the prespecified analysis of markers of disease progression, we did a post-hoc analysis to examine whether differences existed between non-carriers and *MAPT*, *GRN*, and *C9orf72* mutation carriers in the association between laterality of brain volume and time to expected onset of symptoms. Because of strong skew in laterality, we used a log transformation for this analysis, and results are presented as ratios of laterality between mutation carriers and non-carriers for ease of interpretation. We did all analyses with STATA (version 12.1 or later).

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Statistical analysis

We used linear mixed-effects models to examine whether differences existed between non-carriers and mutation carriers in the association between each clinical, behavioural, or structural imaging measure and the time to expected onset of symptoms (we combined all genes

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study except for the results of genetic mutation screening in presymptomatic participants. Only JM and DMC had access to all of the genetic results to avoid risk of disclosure of genetic status to at-risk participants who were unaware of whether they carried a mutation. All authors had final responsibility for the decision to submit for publication.

Results

We analysed data from 220 participants, consisting of 118 mutation carriers and 102 non-carriers (table 1). Of the 118 mutation carriers, 40 were symptomatic (11 with *MAPT*, 13 with *GRN*, and 16 with *C9orf72* mutations) and 78 were asymptomatic (15 with *MAPT*, 45 with *GRN*, and 18 with *C9orf72* mutations). Of the 102 non-carriers, 18 were from families with *MAPT* mutations, 60 were from families with *GRN* mutations, and 24 were from families with *C9orf72* mutations.

Participants came from 76 families (17 with *MAPT*, 32 with *GRN*, and 27 with *C9orf72* mutations), with the mean age at symptom onset across all individuals being 56.9 (SD 8.4) years. Mean age at symptom onset was 49.5 (5.6) years in the *MAPT* families, 57.8 (8.7) years in the *GRN* families, and 60.6 (6.7) years in the *C9orf72* families (appendix). We noted ten different *MAPT* mutations in the 17 families: Pro301Leu, intronic 10+16, Gly272Val, Val363Ile, Arg406Trp, Val337Met, Ser320Phe, Pro301Ser, Leu315Arg, and Gln351Arg (in order of number of participants in study). We found 13 different *GRN* mutations in the 32 families: Ser82fs, Thr272fs, Gln125X, Gln249X, Arg493X, Gln130fs, Cys416fs, Val411fs, Trp386X, Gly35fs, Cys31fs, Cys474fs, and Asp22fs.

In the symptomatic cohort, most participants had a diagnosis of behavioural variant frontotemporal dementia (meeting the Rascovsky diagnostic criteria),³⁹ except for six participants with *GRN* mutations who had diagnoses of the non-fluent variant of primary progressive aphasia (Gorno-Tempini diagnostic criteria)⁴⁰ and four participants with *C9orf72* mutations (one with the non-fluent variant of primary progressive aphasia, two with frontotemporal dementia with motor neuron disease, and one with a dementia syndrome not otherwise specified). Functionally, one participant (with a *MAPT* mutation) in the symptomatic cohort was very mildly affected (according to the Frontotemporal Dementia Rating Scale), three (one *GRN* and two *C9orf72*) were mildly affected, 16 (four *MAPT*, five *GRN*, and seven *C9orf72*) were moderately affected, 13 (four *MAPT*, four *GRN*, and five *C9orf72*) were severely affected, and seven (two *MAPT*, three *GRN*, and two *C9orf72*) were very severely affected.

MMSE, CBI-R, and all neuropsychology measures showed significant mean differences between mutation

	-25 years	-20 years	-15 years	-10 years	-5 years	0 years	5 years	10 years
Whole-brain volume (% of TIV)								
Whole brain								
Non-carriers	86.1%	84.8%	83.7%	82.6%	81.6%	80.7%	79.8%	79.0%
Carriers	87.0%	85.7%	84.0%	82.1%	79.8%	77.2%	74.3%	71.1%
Difference	0.9%	0.8%	0.3%	-0.5%	-1.8%	-3.5%	-5.5%	-8.0%
SE	0.9	0.8	0.8	0.8	0.7	0.7	0.9	1.2
p value	0.3184	0.3198	0.6738	0.5004	0.0157	<0.0001	<0.0001	<0.0001
Cortical volume (% of TIV)								
Frontal lobe								
Non-carriers	12.9%	12.7%	12.4%	12.2%	12.0%	11.8%	11.7%	11.5%
Carriers	13.1%	12.8%	12.4%	12.0%	11.5%	11.1%	10.5%	10.0%
Difference	0.2%	0.1%	<0.1%	-0.2%	-0.5%	-0.8%	-1.1%	-1.5%
SE	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3
p value	0.3208	0.5261	0.8689	0.1766	0.0023	<0.0001	<0.0001	<0.0001
Temporal lobe								
Non-carriers	8.8%	8.6%	8.5%	8.3%	8.2%	8.1%	8.0%	7.9%
Carriers	8.7%	8.6%	8.4%	8.1%	7.9%	7.6%	7.3%	6.9%
Difference	<0.1%	<0.1%	-0.1%	-0.2%	-0.3%	-0.5%	-0.7%	1.0%
SE	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2
p value	0.8944	0.7049	0.3287	0.0483	0.0005	<0.0001	<0.0001	<0.0001
Parietal lobe								
Non-carriers	7.1%	7.0%	6.8%	6.7%	6.6%	6.4%	6.4%	6.3%
Carriers	7.0%	6.9%	6.7%	6.6%	6.4%	6.2%	5.9%	5.6%
Difference	-0.1%	-0.1%	-0.1%	-0.1%	-0.2%	-0.3%	-0.5%	-0.6%
SE	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2
p value	0.2818	0.4546	0.4800	0.2820	0.0510	0.0010	<0.0001	<0.0001
Occipital lobe								
Non-carriers	5.6%	5.6%	5.5%	5.4%	5.4%	5.3%	5.2%	5.1%
Carriers	5.6%	5.5%	5.5%	5.4%	5.3%	5.2%	5.0%	4.9%
Difference	-0.1%	-0.1%	<0.1%	-0.1%	-0.1%	-0.1%	-0.2%	-0.3%
SE	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
p value	0.4022	0.5072	0.5377	0.4311	0.2181	0.0554	0.0166	0.0175
Insula								
Non-carriers	0.86%	0.85%	0.85%	0.84%	0.83%	0.82%	0.80%	0.79%
Carriers	0.85%	0.84%	0.82%	0.80%	0.77%	0.74%	0.71%	0.67%
Difference	-0.01%	-0.02%	-0.03%	-0.04%	-0.05%	-0.07%	-0.10%	-0.12%
SE	0.02	0.02	0.02	0.02	0.02	0.01	0.02	0.02
p value	0.5379	0.2992	0.1028	0.0131	0.0002	<0.0001	<0.0001	<0.0001
Cingulate								
Non-carriers	1.95%	1.91%	1.89%	1.86%	1.84%	1.82%	1.81%	1.79%
Carriers	1.98%	1.95%	1.91%	1.86%	1.80%	1.74%	1.67%	1.59%
Difference	0.04%	0.03%	0.02%	<0.01%	-0.04%	-0.08%	-0.14%	-0.20%
SE	0.04	0.03	0.03	0.03	0.03	0.03	0.03	0.05
p value	0.3386	0.3246	0.5478	0.8934	0.1935	0.0036	<0.0001	<0.0001
Subcortical volume (% of TIV)								
Hippocampus								
Non-carriers	0.70%	0.69%	0.68%	0.68%	0.67%	0.66%	0.65%	0.64%
Carriers	0.69%	0.69%	0.68%	0.66%	0.64%	0.62%	0.59%	0.55%
Difference	-0.01%	-0.01%	-0.01%	-0.01%	-0.02%	-0.04%	-0.06%	-0.09%
SE	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.02
p value	0.4421	0.6667	0.6464	0.3408	0.0441	0.0003	<0.0001	<0.0001

(Table 3 continues on next page)

	-25 years	-20 years	-15 years	-10 years	-5 years	0 years	5 years	10 years
(Continued from previous page)								
Amygdala								
Non-carriers	0.14%	0.14%	0.14%	0.14%	0.14%	0.14%	0.14%	0.14%
Carriers	0.14%	0.14%	0.14%	0.14%	0.13%	0.13%	0.12%	0.12%
Difference	<0.01%	<0.01%	<0.01%	<0.01%	-0.01%	-0.01%	-0.01%	-0.02%
SE	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.005
p value	0.7016	0.7182	0.5451	0.2397	0.0302	0.0005	<0.0001	<0.0001
Striatum								
Non-carriers	1.28%	1.26%	1.25%	1.24%	1.23%	1.23%	1.22%	1.22%
Carriers	1.29%	1.26%	1.23%	1.21%	1.18%	1.16%	1.13%	1.11%
Difference	0.01%	<0.01%	-0.01%	-0.03%	-0.05%	-0.07%	-0.09%	-0.11%
SE	0.03	0.02	0.02	0.02	0.02	0.02	0.02	0.03
p value	0.6840	0.9889	0.5552	0.1928	0.0255	0.0010	0.0002	0.0008
Thalamus								
Non-carriers	0.95%	0.93%	0.92%	0.90%	0.89%	0.88%	0.87%	0.85%
Carriers	0.94%	0.92%	0.91%	0.89%	0.86%	0.83%	0.80%	0.76%
Difference	-0.02%	-0.01%	-0.01%	-0.02%	-0.03%	-0.04%	-0.07%	-0.09%
SE	0.02	0.02	0.02	0.01	0.01	0.01	0.02	0.02
p value	0.3630	0.4977	0.4688	0.2472	0.0385	0.0007	<0.0001	<0.0001
Cerebellar volume (% of TIV)								
Cerebellar								
Non-carriers	7.6%	7.5%	7.4%	7.3%	7.2%	7.1%	7.1%	7.0%
Carriers	7.6%	7.6%	7.5%	7.4%	7.3%	7.1%	6.9%	6.6%
Difference	0.1%	0.1%	0.2%	0.1%	0.1%	<0.1%	-0.2%	-0.4%
SE	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
p value	0.5840	0.1865	0.1070	0.1478	0.4216	0.6560	0.0604	0.0071

Differences calculated from unrounded values. TIV=total intracranial volume.

Table 3: Imaging estimates in mutation carriers and non-carriers, by estimated time from expected symptoms onset

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carriers as a whole group and non-carriers ($p \leq 0.0028$ for all markers). MMSE, CBI-R, and all neuropsychology measures except the Logical Memory Immediate Recall and verbal fluency tasks showed significant mean differences between mutation carriers as a whole group and non-carriers 5 years before expected onset (table 2 and appendix). We noted no significant differences at timepoints earlier than 5 years before expected onset. The earliest point at which the Logical Memory Immediate Recall and verbal fluency tasks showed differences between mutation carriers and non-carriers was at the time of expected onset. In the exploratory analysis of individual genetic groups, the behavioural and neuropsychological tests that showed differences between mutation carriers and non-carriers at the earliest times before expected onset were different in each genetic group: the Boston Naming Test and the CBI-R for the *MAPT* group, the Digit Span backwards for the *GRN* group, and the CBI-R in the *C9orf72* group (appendix).

We did volumetric T1-weighted MRI in 212 participants (eight were unable to have a scan because of either contraindications to MRI scanning or claustrophobia). A further ten scans did not pass an

initial quality control process, usually owing to excessive motion during the scan. We therefore used 202 scans for analysis (175 from 3T scanners [55 Siemens, 99 Philips, and 21 General Electric scanners] and 27 from 1.5T scanners [19 Siemens and 8 General Electric scanners]). 93 scans were from non-carriers and 109 from mutation carriers (24 *MAPT*, 52 *GRN*, and 33 *C9orf72*). Whole-brain volume showed a significant difference between mutation carriers as a whole group and non-carriers ($p < 0.0001$), with strong evidence for a difference in all cortical and subcortical volumes ($p \leq 0.0030$), except for the occipital lobe, which was not significant ($p = 0.0598$). The cerebellum had a less significant difference than the cortical and subcortical volumes ($p = 0.0211$). We noted differences in group means between mutation carriers and non-carriers at the earliest timepoint for the insula (10 years before expected symptom onset) followed by the temporal lobe (also 10 years before expected symptom onset, but with a less significant difference; table 3 and figure). We noted differences in the frontal lobe, all subcortical volumes, and whole-brain volume between carriers and non-carriers at 5 years before expected onset, whereas we noted differences in the parietal lobe and cingulate only just before expected time of onset (table 3, figure, and appendix). Although we noted only weak evidence for a difference between mutation carriers and non-carriers, the results suggest that significant differences might exist in the occipital lobe at 5 years after symptoms onset and in the cerebellum at 10 years after symptoms onset.

When we analysed the individual genetic groups separately, we noted a different ordering of cortical and subcortical involvement in each group (appendix): in the *MAPT* group, we noted differences between mutation carriers and non-carriers in the hippocampus and amygdala at 15 years before expected onset, followed by the temporal lobe at 10 years before expected onset, and the insula at 5 years before expected onset; in the *GRN* group, we noted differences between carriers and non-carriers in the insula at 15 years before expected onset, then in the temporal and parietal lobes at 10 years before expected onset, with the earliest subcortical area affected being the striatum at 5 years before expected onset; and in the *C9orf72* group, subcortical areas including the thalamus, the insula, and posterior cortical areas differed between carriers and controls at 25 years before expected onset, followed by the frontal and temporal lobes at 20 years before expected onset. We noted significant differences in the cerebellum presymptomatically in the *C9orf72* group at 10 years before expected onset. Examination of the laterality index showed evidence for asymmetry between left and right cortical volumes in the *GRN* mutation carriers ($p = 0.0001$ vs non-carriers), but not in the *MAPT* carriers ($p = 0.3283$ vs non-carriers) or *C9orf72* carriers ($p = 0.2018$ vs non-carriers). *GRN* mutation carriers showed significantly greater asymmetry than non-carriers at 5 years before expected onset (appendix).

Discussion

We have shown that imaging changes can be identified at least 10 years before expected onset of symptoms in genetic frontotemporal dementia. Structural neuroimaging identifies a sequence of change in atrophy through cortical and subcortical regions, with the insular and temporal cortices affected initially (around 10 years before expected symptoms onset), followed by the frontal cortex and subcortical areas (around 5 years before expected onset), parietal and cingulate cortices (around time of expected onset), and, lastly, the occipital cortex (5 years after expected onset) and cerebellum (10 years after expected onset). We noted that neuropsychological measures were first different between carriers and non-carriers later than initial imaging measures, up to 5 years before expected symptoms onset. These findings suggest that the disease process significantly precedes onset of symptoms in genetic frontotemporal dementia. Whereas previous studies have shown inconsistent findings (panel), the value of investigation of a large cohort of presymptomatic participants is confirmed in this study, consistent with similar approaches previously done in patients with familial Alzheimer's disease⁸ and patients with Huntington's disease.⁷

The findings from this study are consistent with our understanding of the earliest structural changes in frontotemporal dementia. The insula is thought to act as a crucial hub in many key networks that become affected (particularly the so-called salience network connecting the insula, frontal lobe, and anterior cingulate, and frontoparietal networks).^{25,41,42} Here, we noted that the insula was the first cortical area to show evidence of atrophy in the mutation group as a whole, and was one of the earliest areas affected in the analyses of each individual genetic group, suggesting that it might be an early focus of pathology followed by connectivity-based spread of disease.

Our primary analysis focused on genetic frontotemporal dementia as a single group. The rationale for this decision lies in the shared clinical features and overlapping disease mechanisms seen in genetic frontotemporal dementia. However, differences have been shown between genetic subgroups in previous neuroimaging studies,^{43,44} and signatures of network disintegration with particular genetic proteinopathies are predicted on both empirical and theoretical grounds.⁴⁵ Our exploratory analyses are consistent with and extend this previous work. In the *MAPT* group, temporal lobe and medial temporal structures (the hippocampus and amygdala) were affected initially, consistent with previous findings suggesting that the disease is a temporal-predominant disorder.^{18,43,46} However, this study shows that significant changes can be seen in these areas much earlier than previously suggested. In the *GRN* group, the insula was the first area affected (around 15 years before expected onset), followed by the temporal and parietal lobes. Consistent with previous neuroimaging studies of symptomatic carriers

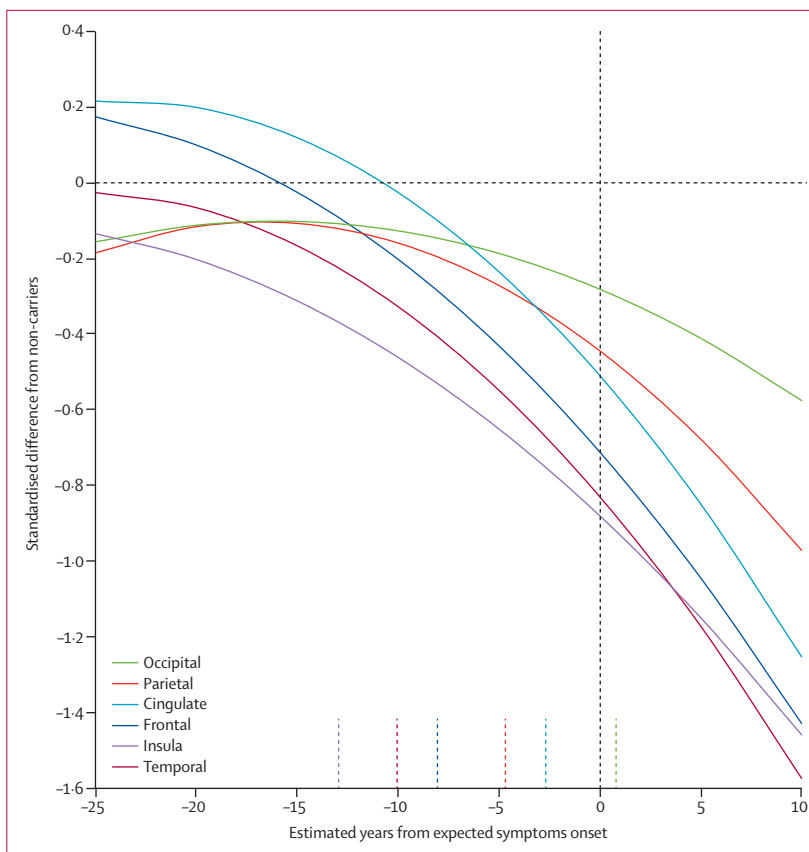


Figure: Standardised difference between all mutation carriers and non-carriers in cortical grey matter volumetric imaging measures versus estimated years from expected symptoms onset

Individual datapoints not plotted to prevent disclosure of genetic status. The time at which the upper 95% CI for each curve crosses zero on the y-axis (ie, the point at which a significant difference exists between mutation carriers and non-carriers) is shown on the x-axis. Individual curves with 95% CIs are shown in the appendix. Subcortical and cerebellar volumes are also shown in the appendix.

showing early temporal and parietal involvement in patients with *GRN* mutations,^{11,43,46} findings from this study identify the insula as the key region affected significantly earlier than other areas. Distinct from the other groups, the earliest subcortical involvement in the *GRN* group was in the striatum (around 5 years before expected onset), an area known to be involved in symptomatic *GRN* mutation cases, but not previously shown presymptomatically.⁴⁷ In the *C9orf72* group, the thalamus and more posterior cortical areas were affected early. No previous presymptomatic studies of this group have been done, but previous imaging analyses of symptomatic carriers suggest that the thalamus is a key area affected in people with *C9orf72* expansions and that posterior areas are more involved than in the other two genetic groups.^{43,44} Similarly, the cerebellum has been identified as an area affected in symptomatic *C9orf72* expansion carriers, and here we show evidence for presymptomatic involvement. The exploratory analysis suggested very early detectable structural imaging changes, particularly in the *C9orf72* group, more than 20 years before expected symptoms onset. The timing of

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See Online for appendix

For the Genetic Frontotemporal dementia Initiative see www.genfi.org.uk

Panel: Research in context**Systematic review**

We searched PubMed for articles on presymptomatic studies in genetic frontotemporal dementia up to Nov 16, 2014, using the following terms: “frontotemporal dementia AND genetics” and “frontotemporal dementia AND presymptomatic”. We identified one review article of presymptomatic studies in genetic frontotemporal dementia,⁵ and 18 original research studies that had investigated neuropsychology or neuroimaging, or both, in presymptomatic genetic frontotemporal dementia (appendix)^{9–21}. A few case studies^{9,11,16,17} and two other studies^{15,22} have shown evidence of presymptomatic abnormalities on neuropsychometry in asymptomatic mutation carriers, usually with tests of executive dysfunction. However, findings from some other studies have not shown any abnormalities before onset.^{13,19,21,23–25} In two single case studies^{9,11} and two small case series^{12,13} of presymptomatic *GRN* mutation carriers, focal brain atrophy has been shown a few years before symptoms onset using volumetric T1 MRI, with the prefrontal cortex being predominantly involved, often in an asymmetric pattern. *MAPT* carriers have been studied less than *GRN* carriers, with a single case study¹⁷ and a small case series¹⁸ showing presymptomatic atrophy, with hippocampal involvement predominating. We identified no presymptomatic studies of *C9orf72* mutation carriers. Some studies have focused on other types of MRI in *GRN* and *MAPT* carriers, particularly diffusion tensor imaging and resting-state functional MRI;^{19–26} however, Borroni and colleagues,^{19,21} Whitwell and colleagues,²⁰ and Dopper and colleagues²² also did voxel-based morphometry analyses using volumetric T1 imaging in their studies and did not find any differences between asymptomatic carriers and controls.

Interpretation

This work is the first multicentre study of presymptomatic genetic frontotemporal dementia and identifies structural imaging changes around 10 years before expected onset, and cognitive impairment around 5 years before expected onset, when the genetic group is investigated as a whole. Exploratory analyses suggest that different cortical and subcortical areas are affected earliest in each of the *MAPT*, *GRN*, and *C9orf72* groups, and that structural imaging changes can be seen 15 years or more before symptoms onset. Our results provide an insight into the early neuroanatomical changes in genetic frontotemporal dementia and suggest the potential for use of structural imaging measures as biomarkers in future therapeutic trials.

presymptomatic involvement before expected symptoms onset might, to some extent, result from limitations of the simple linear association used in modelling, but this intriguing finding needs further investigation and could be consistent with the very slow progressive change in symptoms seen in some patients with *C9orf72*-related frontotemporal dementia.^{48–50} Another possibility is that some of the very early differences between mutation carriers and non-carriers in the *C9orf72* group represent differences in brain volume that are, in fact, developmental and longstanding, with superimposed atrophy only late in the disease process.

A key strength of this study is its ability to show robust presymptomatic differences in clinical and imaging biomarkers in genetic frontotemporal dementia. However, we analysed only cross-sectional differences between carriers and controls at different times from expected symptoms onset. Whether the apparent progression of atrophy through a sequence of cortical and subcortical regions is followed within individuals remains to be shown in a longitudinal study. A further

limitation of the study is the method used for estimation of age at onset in presymptomatic mutation carriers. Despite our initial analysis showing a significant correlation between actual age at onset in symptomatic carriers and mean familial age at onset, this measure is imperfect, with variability in age at onset within a family in all frontotemporal dementia mutations. This variability is greater for *C9orf72* and *GRN* mutations than for *MAPT* mutations, which could lead to greater error in estimated time to onset in these subtypes than in the *MAPT* subtype (and could therefore suggest that changes can be seen earlier than actually occur). Another limitation of the study is its ability to detect subtle neuropsychiatric or neuropsychological abnormalities. The behavioural and cognitive battery used in the study includes a series of standard validated tests, but these tests might not have sufficient sensitivity for diagnosis of subtle cognitive or neuropsychiatric dysfunction identified with experimental tests.

In further studies, imaging, genetic, biochemical, and cognitive measures might be able to be combined to identify changes even earlier than noted here. Findings from initial studies^{19–25} suggest that presymptomatic differences between carriers and non-carriers of mutations associated with frontotemporal dementia might be seen with other imaging methods, such as diffusion tensor imaging and resting-state functional MRI. Findings from presymptomatic studies of Alzheimer's disease⁸ also suggest earlier changes in ¹¹C Pittsburgh compound B PET and CSF measures than diffusion tensor imaging and resting-state functional MRI. Although no fluid biomarkers have been identified for frontotemporal dementia, tau PET scanning is now available⁵¹ and will be important to examine in this cohort as the GENFI study progresses. Our findings suggest that some readily measurable markers can show rates of decline before symptom onset in frontotemporal dementia; if confirmed in the longitudinal stages of the GENFI study, these measures could be suitable for use in clinical trials and, we hope, contribute to development of preventive strategies.

Contributors

JDR drafted the initial version of the report and the figures. JMN did the statistical analysis. RvM, SM, ER, HT, LB, GB, and BN did genetic analyses. All authors recruited patients, collected data, and contributed to reviewing and editing of the report.

Declaration of interests

JDR is funded by a National Institute for Health Research Rare Disease Translational Research Collaboration Fellowship. SAR is supported by a Vici grant from the Netherlands Organization for Scientific Research. MM is supported by the Department of Medicine, Sunnybrook Health Sciences Centre, and the Sunnybrook Foundation. He is funded by the Canadian Institutes of Health Research and the Ontario Research Fund. He reports consultancy fees from Novartis, Teva, Union Chimique Belge Canada, General Electric Healthcare, and Bioscape Medical Imaging CRO all outside the submitted work. He also holds a US patent of a pharmacogenetic test for Parkinson's disease. MF receives support from the Saul A Silverman Family Foundation as a Canada International Scientific Exchange Program and Morris Kerzner Memorial Fund, and is listed on a provisional patent related to methods and kits for differential

diagnosis of Alzheimer's disease versus frontotemporal dementia with blood biomarkers. ER is funded by the Weston Brain Institute and Ontario Research Fund. RL Jr is funded by Réseau de médecine génétique appliquée, Fonds de recherche du Québec—Santé (FRQS). FT, RG, and LB are funded by the Italian Ministry of Health. DG, ES, AA, and GF are supported by the Fondazione Monzino and Italian Ministry of Health, Ricerca Corrente. JBR is supported by a Wellcome Trust Senior Research Fellowship (088324). JBR and IC-G are supported by the National Institute for Health Cambridge Biomedical Research Centre and Biomedical Research Unit in Dementia. BN is funded by Cassa di Risparmio di Pistoia e Pescia (CRPT 2013/0347). SS is funded by Cassa di Risparmio di Firenze (CRF 2013/0199) and the Ministry of Health RF-2010-231972. JDW is funded by a Wellcome Trust Senior Clinical Fellowship (091673/Z/10/Z). NCF and MNR are National Institute for Health Research Senior Investigators. NCF also reports consultancy fees (all paid to University College London) from Janssen/Pfizer, General Electric Healthcare, IXICO, Johnson & Johnson, Genzyme (Sonofi company), Eisai, Janssen Alzheimer's Immunotherapy Research and Development, Lilly Research Laboratories (AVID), Eli Lilly, and Novartis Pharma AG all outside the submitted work. He also has a patent QA Box issued. The Dementia Research Centre at University College London is an Alzheimer's Research UK coordinating centre and has received equipment funded by Alzheimer's Research UK and Brain Research Trust. MNR also reports fees (paid to University College London) for serving on a Data Monitoring Committee for Servier outside the submitted work. SEB reports personal fees from Pfizer, GlaxoSmithKline, Novartis, Roche, Eli Lilly, Pfizer, Eisai, Boehringer Ingelheim, General Electric Healthcare, and Novartis, and grants from Pfizer, Elan/Transition Therapeutics Ireland Ltd, Roche, Eli Lilly, General Electric Healthcare, and Lundbeck all outside the submitted work. SO is funded by the Engineering and Physical Sciences Research Council (EP/H046410/1, EP/J020990/1, EP/K005278), the Medical Research Council (MR/J01107X/1), the EU-FP7 project VPH-DARE@IT (FP7-ICT-2011-9-601055), and the National Institute for Health Research University College London Hospitals Biomedical Research Centre (NIHR BRC UCLH/UCL High Impact Initiative BW.mn.BRC10269). All other authors declare no competing interests.

Acknowledgments

This work was funded by the UK Medical Research Council, the Italian Ministry of Health, and the Canadian Institutes of Health Research as part of a Centres of Excellence in Neurodegeneration grant. JDR, JDW, NCF, and MNR acknowledge the support of the National Institute for Health Research Queen Square Dementia Biomedical Research Unit, Leonard Wolfson Experimental Neurology Centre, the Brain Research Trust, and the University College London Hospitals NHS Trust Biomedical Research Centre. CG acknowledges the support of Swedish Brain Power. ME and SO acknowledge the support of VPH-DARE@IT. We thank Daniel Marcus and Rick Herrick of Radiologics for their support in setting up of the GENFI XNAT database. We would like to thank the participants and their families for taking part in the GENFI study.

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