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Mapping the progression of progranulin-associated frontotemporal lobar degeneration

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SUMMARY

Background A 55-year-old woman was followed over a 13-year period as part of a longitudinal study of people at risk for familial dementia. She was a member of a family with an autosomal dominant familial dementia that fulfilled consensus criteria for frontotemporal lobar degeneration. The patient was initially asymptomatic but developed progressive behavioral and cognitive decline characterized by apathy, impaired emotion recognition, mixed aphasia and parietal lobe dysfunction.

Investigations Clinical assessments, neuropsychometry, volumetric brain MRI, and genetic mutation screening.

Diagnosis Progranulin-associated frontotemporal lobar degeneration.

Management Explanation of the patient's condition and genetic counseling for her family.

KEYWORDS dementia, frontotemporal lobar degeneration, progranulin, progressive aphasia

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THE CASE

A 55-year-old right-handed woman was seen in a specialist cognitive disorders research unit as part of a prospective, longitudinal study of asymptomatic individuals at risk for developing dementia. She was a member of a family that had a history of an autosomal dominant dementia that met consensus criteria for frontotemporal lobar degeneration (FTLD); the average age of symptom onset in the family was 57.8 years (range 54–67 years).[1,2] Supplementary Figure 1 provides a pedigree of the family.

The patient was assessed at eight visits over a 13-year period (Figure 1), with each assessment involving detailed clinical and neuropsychological evaluation and volumetric brain MRI. On the first five visits the patient was well, displaying no cognitive symptoms and scoring normally on neuropsychological assessment, apart from a slightly reduced verbal fluency score (9 'S' words in 1 min, where normal is ≥10) on the Frontal Assessment Battery at visit five. At visit six the patient still had no cognitive complaints; neuropsychometry revealed a decline in naming and calculation skills, but her scores remained above the 5th percentile of the distribution within the general population (Supplementary Table 1).

At visit seven the patient complained of cognitive symptoms for the first time and reported having word-finding difficulties during the previous 6 months. Verbal fluency on the Frontal Assessment Battery was further reduced (6 'S' words in 1 min). Although the patient's score on the Mini Mental State Examination remained in the normal range (28 out of 30), her score on a graded naming test was now below the 5th percentile (10 out of 30) and further cognitive decline was evident on testing of calculation (Supplementary Table 1). Her performance had now deteriorated on a test of verbal comprehension but remained normal on tests of executive function and visuoperceptual skills. Imitation of meaningless hand positions was a little clumsy, but neurological examination at this time was otherwise normal.

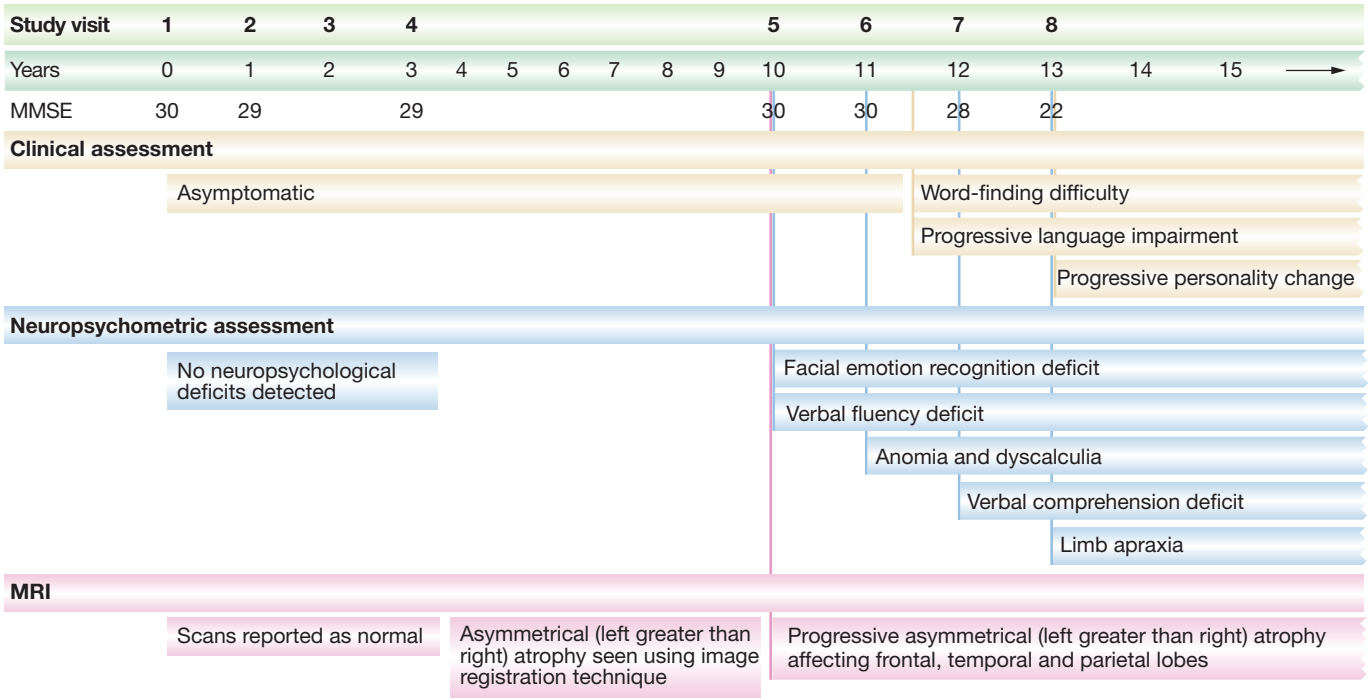

Figure 1 Timeline showing clinical assessments and progression of neuropsychological and neuroimaging deficits in a person at risk for frontotemporal lobar degeneration.

By visit eight the patient's word-finding ability had continued to deteriorate and she had developed speech production impairment with phonemic paraphasias and agrammatism. Her family reported that the patient had become more apathetic over the previous year and spent most of the time in her house. Her Mini Mental State Examination score was now 22 out of 30 and verbal fluency was again reduced. Mild bilateral ideomotor and ideational limb apraxia were also now evident, although the rest of the neurological examination remained normal. Naming skills had further deteriorated and difficulties in verbal memory had now become apparent.

In order to delineate the patient's language difficulties more precisely, she underwent more detailed neurolinguistic assessment 6 months after visit eight (2 years after symptom onset; Supplementary Table 2). Her speech contained grammatical and phonemic errors, but the flow of speech was relatively fluent without evidence of apraxia of speech or dysarthria. The patient had severe word-finding difficulty, with occasional circumlocutions and semantic errors. Deterioration was evident on a test of single-word comprehension, and sentence comprehension was also impaired. The patient had difficulties with both single-word and sentence repetition, and her reading portrayed phonological dyslexia (difficulty reading non-words). Writing showed evidence of agrammatism but spelling ability was relatively intact. These features are consistent with a progressive mixed aphasia. At this assessment, the patient was also noted to have a decreased forward digit span of 4 (normal >5), consistent with dominant parietal lobe involvement. There was now mild orofacial apraxia and moderate bilateral limb apraxia.

From the fifth visit onwards the patient was tested on her ability to recognize simple and complex facial emotions. On a test of basic facial emotion recognition, based on the Ekman emotional faces stimulus set,[3] the patient scored 19 out of 24 (age-matched and sex-matched normal range 20–24) and her score continued to deteriorate over the next three visits (Supplementary Table 1). At 18 months after symptom onset the patient scored only 11 out of 24 on this test; her performance was at chance level (3 out of 16) for recognizing negative emotions (fear, disgust, anger, sadness) but was normal (8 out of 8) for recognizing positive emotions (happiness, surprise). On a task that evaluated complex facial emotion recognition,[4] the patient's performance fell from an initial score of 26 out of 36 (age-matched and

sex-matched normal range 24–34) to a score of 22 at visit six (Supplementary Table 1). Eighteen months after symptom onset her score on this task had fallen to 18 out of 36.

At each visit, T1-weighted volumetric MRI brain scans were acquired on a 1.5 T scanner (General Electric, Milwaukee, WI). A semi-automated technique of brain segmentation was performed for each scan, followed by an affine (12 degrees of freedom) registration in order to align the repeat scan onto the baseline image (Figure 2 and Supplementary video 1). On the first four scans there were no clinically significant brain volume changes beyond those associated with normal ageing. In the period between the fourth and fifth scans, however, there was a marked decrease in brain volume (Figures 2 and 3). The fifth scan (18 months before symptom onset) showed asymmetrical frontal, temporal and parietal lobe atrophy that predominantly affected the left cerebral hemisphere (Figure 2B). Progressive atrophy of a similar distribution was present on the sixth scan (6 months before the onset of symptoms; Figure 2C). The distribution of volume change in the left hemisphere that occurred between the sixth and seventh scans (spanning the onset of symptoms) was further analyzed by use of a fluid registration technique in order to produce a voxel compression map.[5] Progressive regional atrophy during this time period again involved the left frontal, temporal and parietal lobes (Figure 3A). In the frontal lobes there was atrophy of the medial superior frontal and frontopolar regions, and involvement of the anterior cingulate gyrus. There was marked atrophy of the left temporal pole. The left middle and inferior temporal and fusiform gyri were particularly affected, with some atrophy of the left amygdala, hippocampus and superior temporal gyrus. In the parietal lobes there was relatively selective atrophy of the left angular gyrus. There was also evidence of left caudate, pallidal and thalamic atrophy. Registration of the seventh and eighth scans showed a similar pattern of atrophy but also involvement of the right hemisphere (Figure 3B). The most severe change across the scans involved prefrontal and inferior parietal areas, as well as orbitofrontal and inferior temporal areas, in the left hemisphere. Quantification of longitudinal regional atrophy confirmed that involvement of the left hemisphere preceded that of the right by a number of years. Supplementary Figure 2 shows in graphical form the volume changes in the whole brain, the left and right hemispheres, and the ventricles.

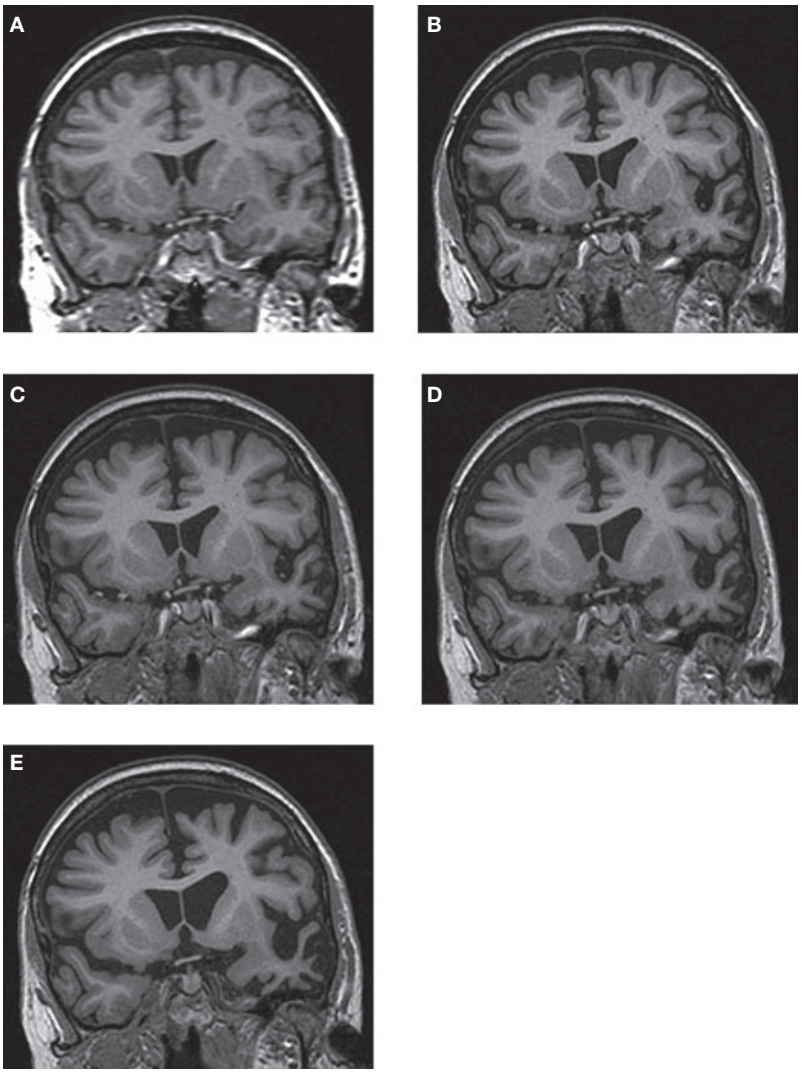

Figure 2 Series of five registered T1-weighted MRI scans of a patient with progranulin-associated frontotemporal lobar degeneration. (**A**) MRI scan 8.5 years before symptom onset. (**B**) MRI scan 18 months before symptom onset. (**C**) MRI scan 6 months before symptom onset. (**D**) MRI scan 6 months after symptom onset. (**E**) MRI scan 18 months after symptom onset.

Genetic screening of the patient revealed a c.90_91insCTGC (C31LfsX35) mutation in exon 2 of the progranulin gene (*GRN*). The mutation was also discovered in other symptomatic family members, confirming this mutation as the cause of dementia in the family.

DISCUSSION OF DIAGNOSIS

FTLD is a clinically, pathologically and genetically heterogeneous group of degenerative disorders that are characterized by atrophy of

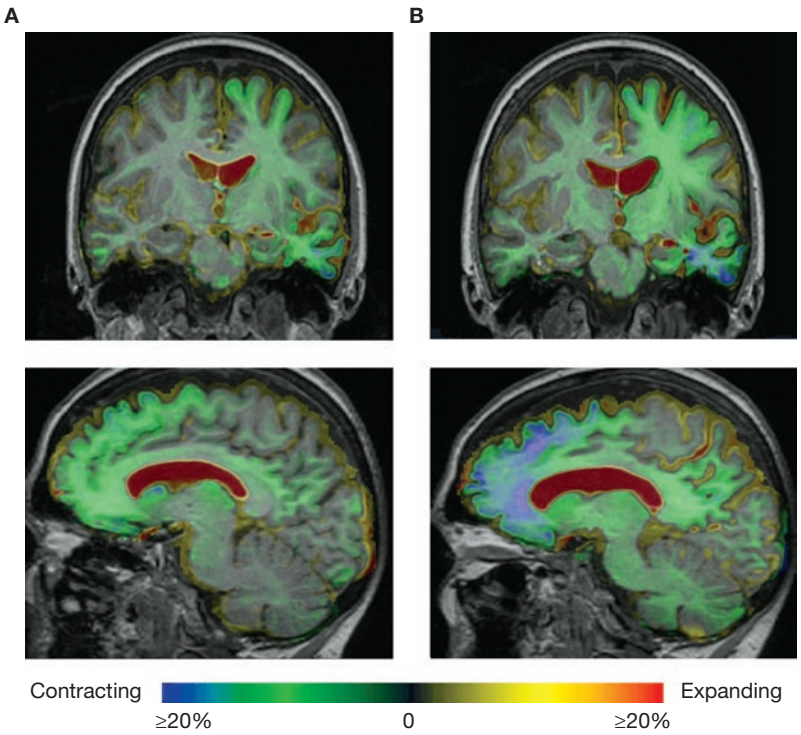

Figure 3 Coronal and sagittal MRI scans of a patient with progranulin-associated frontotemporal lobar degeneration, with voxel-compression-mapping overlay. (**A**) MRI scans showing changes between 6 months before and 6 months after symptom onset. (**B**) MRI scans showing changes 6–18 months after symptom onset. Red represents 20% or greater expansion of voxels and blue represents 20% or greater contraction of voxels.

the frontal and temporal lobes.[6] Three subtypes are described by consensus criteria:[1] frontotemporal dementia (also referred to as behavioral variant FTLD), in which patients have changes in personality and behavior; progressive nonfluent aphasia, a disorder involving speech production impairment; and semantic dementia, in which patients have loss of semantic knowledge and present with anomia, a fluent aphasia, and difficulties with single-word comprehension. However, these three syndromes may overlap with each other and with further degenerative disorders, namely motor neuron disease, corticobasal syndrome and progressive supranuclear palsy. There are few epidemiological studies of FTLD, but prevalence is probably between 3 and 15 people per 100,000.[7] The condition affects both sexes equally; symptom onset is usually between the ages of 45 years and 65 years.[7]

Patients presenting with a clinical FTLD phenotype that has an autosomal dominant pattern of inheritance should be screened for common disease-causing mutations, accompanied by appropriate genetic counseling. Around 30–50% of patients with FTLD have a family history of the disorder. However, until recently, only mutations in the microtubule-associated protein tau gene (*MAPT*) were known to cause familial FTLD; these mutations account for less than 5% of cases.[7] Patients with *MAPT* mutations commonly present with behavioral variant FTLD and/or with parkinsonism.[8] Patients who present with parkinsonism can have features of corticobasal syndrome or progressive supranuclear palsy. Although patients with *MAPT* mutations can become anomic or develop a paucity of speech output, true semantic dementia or progressive nonfluent aphasia syndromes have not been described in association with such mutations. Two other genes (encoding chromatin-modifying protein 2B and valosin-containing protein) are rare causes of FTLD, but a fourth gene (*GRN*) has been shown to account for 5–10% of all cases of FTLD and about a quarter of cases with a family history of FTLD.[9,10] Over 50 *GRN* mutations associated with FTLD have now been described.[11] Patients with such a mutation can present with behavioral variant FTLD, but, importantly (in contrast to other FTLD-causing mutations), *GRN* mutations can also produce familial progressive aphasia. Rarely, a corticobasal syndrome is seen.[12]

The present case illustrates the important roles of neuropsychology and brain imaging in guiding the differential diagnosis of patients presenting with cognitive impairment (Table 1). Neuropsychometric testing helps to better characterize the clinical syndrome, whereas brain imaging is useful to rule out treatable pathologies and to define a profile of atrophy. The current patient had a mixed aphasia with features of both semantic dementia and progressive nonfluent aphasia,[13] as well as early parietal lobe impairment. A mixed aphasia of this type and early parietal lobe impairment have both been shown to be associated with *GRN* mutations.[12] Furthermore brain imaging in this patient revealed early, strikingly asymmetric cerebral damage, a feature that often characterizes *GRN*-associated FTLD.[12] In individuals at risk for an inherited dementia, neuropsychometry can be useful in detecting presymptomatic cognitive and behavioral deficits that might not be apparent on routine clinical assessment. This patient had presymptomatic deficits on neuropsychological testing that included impairment of emotion processing,

Table 1 Comparison of features in familial dementias: frontotemporal lobar degeneration, Alzheimer's disease and prion disease.

Genetic mutation	Presenting syndrome	Behavioral and cognitive features	Parkinsonism	Motor neuron disease	Other clinical features	Neuroimaging features
GRN	bvFTLD PNFA CBS	Behavioral syndrome (apathy, sweet tooth, etc.), executive dysfunction, episodic memory impairment, aphasia, parietal lobe dysfunction	+	Rare	Features of CBS can be present	Frontal, temporal and parietal lobe atrophy (often asymmetrical)
MAPT	bvFTLD CBS PSP Parkinsonism	Behavioral syndrome (disinhibition, inappropriate social behavior, etc.), executive dysfunction, decreased speech, anomia	+	–	Features of CBS or PSP can be present	Bilateral frontotemporal lobar atrophy
VCP	bvFTLD	Behavioral syndrome, executive dysfunction	–	–	Inclusion body myopathy and Paget's disease	A few reports of frontotemporal lobar atrophy
CHMP2B	bvFTLD	Behavioral syndrome (apathy, restlessness, aggression, etc.), executive dysfunction, decreased speech, possible early parietal impairment	–	Rare	None	Generalized atrophy
Chr 9 FTD-MND[a]	bvFTLD MND	Behavioral syndrome, executive dysfunction	–	+	None	Single report of frontal lobe atrophy sparing posterior regions
APP *PS1* *PS2*[15]	AD (i.e. amnestic presentation) Atypical AD[b]	Episodic memory impairment initially, then global impairment	Rare	–	Myoclonus or seizures can occur; spastic paraparesis is seen rarely in PS1	Presymptomatic medial temporal lobe atrophy spreading to diffuse neocortical areas
PRNP[16]	Dementia with neurological signs	Highly heterogeneous, ranging from rapidly progressive dementia with myoclonus and ataxia, similar to classical CJD, to much more slowly progressive syndromes involving episodic memory, executive dysfunction, dyspraxia	+	Rare	Ataxia, myoclonus, seizures, chorea or dystonia	Generalized cerebral and cerebellar atrophy typical; rapidly progressive clinical syndromes can be associated with high signal in the caudate and putamen on T2-weighted MRI

[a]A locus on chromosome 9p has been associated with FTD-MND, but the abnormal gene has yet to be found. [b]Rarely, a prominent behavioral phenotype similar to bvFTLD is seen in patients with PS1 mutations. Abbreviations: AD, Alzheimer's disease; *APP*, amyloid precursor protein gene; bvFTLD, behavioral variant frontotemporal lobar degeneration; CBS, corticobasal syndrome; *CHMP2B*, chromatin-modifying protein 2B gene; *Chr 9 FTD-MND*, chromosome 9-associated frontotemporal dementia with motor neuron disease gene; CJD, Creutzfeldt–Jakob disease; *GRN*, progranulin gene; *MAPT*, microtubule-associated protein tau gene; MND, motor neuron disease; PNFA, progressive nonfluent aphasia; *PRNP*, prion protein gene; *PS1*, presenilin 1 gene; *PS2*, presenilin 2 gene; PSP, progressive supranuclear palsy; *VCP*, valosin-containing protein gene; +, can be present; –, absent.

which is seldom evaluated in the clinic but can lead to substantial morbidity in FTLD.[14] The onset of disease can also be detected by brain imaging a number of years before clinical symptoms develop, as demonstrated by this case. This role of imaging will become more important if and when disease-modifying treatments become available for the dementias.

The neuroanatomical distribution of disease burden in this patient followed the pattern predicted from the neuropsychological profile: damage to dominant frontal lobe mechanisms, which mediate word retrieval and propositional speech; injury to parietal lobe mechanisms, which mediate praxis, speech repetition and calculation; and impairment of orbitofrontal–anterior temporal lobe mechanisms, which are involved in emotion processing. The affected areas form part of noncontiguous but anatomically and functionally linked intrahemispheric functional networks. The progressive spread of atrophy via such networks in *GRN*-associated FTLD could account both for the early involvement of anatomically remote (but linked) anterior and posterior areas within a hemisphere, and for the striking asymmetry of disease burden, which can remain largely restricted to a single hemisphere for many years.

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Competing interests
The authors declared no competing interests.

TREATMENT AND MANAGEMENT

There remains no curative treatment for any of the subtypes of FTLD. The current patient was referred for speech and language therapy, which can be useful for the development of communication strategies in patients with progressive aphasia. Family members were offered genetic counseling.

CONCLUSION

This case details the longitudinal analysis of a member of a family with a C31LfsX35 mutation in the *GRN* gene causing FTLD; the patient was followed up over a 13-year period from an initial asymptomatic phase through to the establishment of clinical disease. A syndrome of progressive mixed aphasia developed, heralded by presymptomatic clinical, neuropsychological and imaging changes. This case illustrates the importance of correlating neuropsychological and radiological findings for early detection and characterization of genetically mediated neurodegenerative diseases with multiple downstream effects.

Supplementary information in the form of two tables, two figures and a video is available on the *Nature Clinical Practice Neurology* website.

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