

# Phenotypic signatures of genetic frontotemporal dementia

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## Purpose of review

Frontotemporal dementia (FTD) is a clinically, pathologically and genetically heterogeneous disorder. Mutations in a number of genes are associated with FTD, although until recently only two [progranulin (*GRN*) and microtubule-associated protein tau (*MAPT*)] were known to be major causes of the disease. This review describes recent progress in identifying clinical and neuroanatomical phenotypes associated with autosomal-dominant FTD.

## Recent findings

Around a third to a half of FTD patients have an autosomal dominant pattern of inheritance. Up to 10% of patients have a mutation in *GRN* and a similar proportion have a mutation in *MAPT*. Recently a group of patients have been shown to have a hexanucleotide repeat expansion in the noncoding region of chromosome 9 open reading frame 72 (*C9ORF72*). A further group of patients have an autosomal dominant family history but no mutations in any of the known genes including a group of patients who have the same pathology as *GRN* mutations (type A TDP-43 pathology) but are negative for *GRN* mutations. Clinical phenotypes vary across the different mutations. Neuroimaging studies show that *GRN* and *MAPT* mutations have distinct patterns of atrophy – asymmetric fronto-temporo-parietal atrophy with *GRN* versus relatively symmetric medial temporal and orbitofrontal lobe atrophy with *MAPT* mutations. Neuroimaging of patients with an expansion in *C9ORF72* has yet to be studied in detail.

## Summary

Genetic FTD is heterogeneous but certain phenotypic signatures of the major causative genes can be identified.

## Keywords

amyotrophic lateral sclerosis, *C9ORF72*, frontotemporal dementia, motor neurone disease, progranulin, tau

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## Introduction

The term frontotemporal dementia (FTD) refers to a group of neurodegenerative disorders characterized by atrophy of the frontal and temporal lobes [1]. The canonical clinical presentations comprise a behavioural syndrome (behavioural variant FTD, bvFTD) and at least two language syndromes, semantic dementia and progressive nonfluent aphasia (PNFA). However, these presentations overlap with motor neurone disease/amyotrophic lateral sclerosis (FTD-MND/ALS) and with the atypical parkinsonian disorders corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP). Neuro-pathologically, FTD is highly heterogeneous but most cases are characterized by inclusions containing abnormal forms of one of three different proteins: tau, transactive response DNA binding protein 43 (TDP-43) or fused-in-sarcoma (FUS) [2]. Genetic factors have emerged as an important theme underpinning the pathological and clinical diversity of FTD [3], and there is currently

considerable interest in identifying phenotypic signatures that might help predict molecular pathology in these disorders.

## The heritability of frontotemporal dementia

Around a third to a half of patients with FTD will have a family history with an autosomal dominant mode of inheritance, although heritability varies across the different clinical subtypes, bvFTD being the most heritable [3,4]. Two genes have been shown to be major causes of FTD, microtubule-associated protein tau (*MAPT*) and progranulin (*GRN*). Mutations in four other genes [valosin-containing protein (*VCP*), chromatin-modifying protein 2B (*CHMP2B*), transactive DNA-binding protein (*TARDP*) and fused-in-sarcoma (*FUS*)] have been identified in a minority of cases. Single case reports have also described FTD associated with mutations in dynactin (*DCTN1*). In large series of FTD patients, mutations in *MAPT* account for between 2 and 11% of all cases, whilst mutations in *GRN* account for between

5 and 11%. This variation appears to be attributable mainly to geographical differences, with some regions having a relatively higher prevalence of mutations in *GRN* or *MAPT* (Table 1) [3–8]. In each of these large series mutations in other genes are rarely seen and information about the phenotypic features of these other genes is accordingly limited. Each of the FTD cohorts reported also included a substantial proportion (~10%) of cases with autosomal dominant inheritance without mutations in any of the genes so far identified as causes of FTD. In two series which have looked at the pathology of these cases two major groups emerged: those with type B TDP-43 pathology [9<sup>\*</sup>] with or without a clinical FTD-MND/ALS syndrome and those with type A TDP-43 pathology (the same pathology as *GRN* mutations) [3,4]. It has been shown recently that the former group have a hexanucleotide repeat expansion in the noncoding region of the gene *C9ORF72* [10<sup>\*\*</sup>,11<sup>\*\*</sup>].

### Clinical features

We now consider phenotypic features described in association with each of the genes so far identified as causing autosomal-dominant FTD.

#### *GRN* mutations

Two recent large series of patients have explored the clinical presentation of patients with *GRN* mutations [12,13<sup>\*</sup>]. As with previous studies, the most common clinical diagnosis was bvFTD with PNFA and CBS seen less frequently. Other recent case series continue to show that these three syndromes can be seen within the same family [14]. The aphasia phenotype of *GRN* mutations has been recently investigated and there are some suggestions that this syndrome is distinct from the PNFA with apraxia of speech seen (usually sporadically) in association with tau pathology [15,16]. Both of these two aphasia syndromes can be distinguished from the logopenic aphasia syndrome seen most commonly as an atypical presentation of Alzheimer's disease pathology [17<sup>\*\*</sup>,18].

Interestingly, in the study of Chen-Plotkin *et al.* [13<sup>\*</sup>], five patients (5.4% of cases) had a diagnosis of FTD-MND/ALS previously reported only rarely in association with *GRN* mutations. This study also found that FTD-

### Key points

- Frontotemporal dementia is a highly heritable disorder with up to a third to a half of patients having an autosomal dominant pattern of inheritance.
- The most common genetic causes are mutations in progranulin or the microtubule-associated protein tau, or a hexanucleotide repeat expansion in *C9ORF72*.
- A number of frontotemporal dementia (FTD) patients have an autosomal dominant pattern of inheritance but do not have a mutation in one of the known disease-causing genes including those with type A TDP-43 pathology (but negative for mutations in progranulin).
- Clinical phenotypes vary across the different mutations but certain phenotypic signatures can be identified.

MND/ALS (whether familial or apparently sporadic) was much more commonly (26.3% of cases) *GRN*-negative with FTLD-TDP pathology.

In both the series of Yu *et al.* [12] and Chen-Plotkin *et al.* [13<sup>\*</sup>] a small number of patients were initially diagnosed with either Parkinson's disease or Alzheimer's disease. There are few detailed studies of Parkinson's disease or Alzheimer's disease phenotypes in association with *GRN* mutations and it is therefore unclear how closely the phenotype corresponds to a typical Parkinson's disease or Alzheimer's disease syndrome. Certainly parkinsonism has been reported relatively frequently (41% of cases in the Yu *et al.* study) although usually developing after the onset of behavioural or language symptoms rather than as the primary feature. Individual case reports suggest that parkinsonism may initially respond to levodopa (e.g. [19,20]). As some patients with *GRN* mutations can have visual hallucinations a diagnosis of dementia with Lewy bodies may be entertained [12,21]. One case series identified a family in which some individuals presented with amnesic symptoms, which remained the most prominent feature for a number of years, leading to a diagnosis of Alzheimer's disease in life [21]. As is the case for parkinsonism, however, episodic memory impairment is more usually a later feature.

**Table 1 Percentage of cases with *MAPT* and *GRN* mutations in large series of frontotemporal dementia patients**

	Geographic area	No in series	% <i>MAPT</i> mutations	% <i>GRN</i> mutations
Cruts <i>et al.</i> [5]	Belgium	103	2	11
Gass <i>et al.</i> [6]	USA	167	4	5
Le Ber <i>et al.</i> [7]	France	210	3	5
Pickering-Brown <i>et al.</i> [8]	UK	223	8	6
Seelaar <i>et al.</i> [4]	The Netherlands	364	11	6
Rohrer <i>et al.</i> [3]	UK	225	9	8

Adapted from [3].

It is difficult to propose a rational policy for screening *GRN* mutations in the face of this wide phenotypic variation. There are over 70 *GRN* mutations currently described, and the most common mutations account for only a small proportion of cases (e.g. in the Chen-Plotkin *et al.* series R493X accounted for 19% and A9D for 6% of all cases with *GRN* mutations). Low plasma *GRN* levels correlate with the presence of a mutation and have been used in some centres to guide genetic screening, as well as identifying patients with atypical phenotypes [20,22•].

A further issue is the existence of clinical phenotypes similar to *GRN*-associated FTD that are also associated with TDP-43 type A pathology and with an apparently autosomal dominant family history, but without *GRN* mutations [23]; such cases suggest that other causative genes feeding into the *GRN* pathogenetic pathway still await discovery.

### ***MAPT* mutations**

Over 45 mutations are currently described in the *MAPT* gene. As with *GRN* the most common phenotype is bvFTD [23]. However, other phenotypes can be seen less frequently. Semantic impairment can develop in patients with *MAPT* mutations but is usually not a presenting feature [4,24]. One recent case report described a family with the P301L mutation in which three members all presented with impaired single word comprehension suggestive of verbal semantic impairment although without detailed neuropsychological assessment [25]. It would be of interest to assess such cases for the development of multimodal semantic impairment as typically occurs in the (usually sporadic) semantic dementia syndrome associated with type C TDP-43 pathology. PNFA has not been described in large series of patients with *MAPT* mutations, but has recently been reported in association with V363I and G304S variations [26,27]. Further studies with pathological confirmation will be needed to determine whether these variants are truly pathogenic mutations [28].

As with *GRN* mutations, patients may present with parkinsonism. This can rarely be a sole presenting feature but more commonly develops in association with bvFTD. Atypical parkinsonian syndromes are also described in association with *MAPT* mutations, CBS more frequently than PSP. A review of *MAPT* mutations and PSP-like syndromes was recently published in conjunction with a case report of a family with a novel L284R *MAPT* mutation [29]: many of these cases in fact had an atypical PSP syndrome, the diagnosis being based on the presence of a supranuclear gaze palsy. However, a small number of cases have a more typical PSP syndrome often in association with behavioural symptoms. As is the case for *GRN* mutations, episodic memory impairment is occasionally the first and most prominent symptom of

*MAPT* mutations leading to a clinical diagnosis of Alzheimer's disease. In one recent study the R406W mutation in *MAPT* was discovered following a negative PIB-PET scan [30] in a family who had been included in a study of familial Alzheimer's disease. Prominent episodic memory impairment has also been described in association with the recently described duplication of the *MAPT* gene, although these patients presented initially with behavioural symptoms characteristic of bvFTD [31•].

### ***VCP* mutations**

Over 15 probably pathogenic mutations in *VCP* have been described. The association originally reported was a rare syndromic combination of frontotemporal dementia (usually bvFTD) with inclusion body myopathy and Paget's disease of bone (known as IBMPFD). Pathologically, patients have type D TDP-43 pathology. There is wide phenotypic variation even within families and although patients appear more likely to present with myopathy than with cognitive or other features this may partly reflect ascertainment bias [32]. Some cases were described as having atypical findings for IBMPFD, particularly pyramidal tract dysfunction (e.g. [33]), and it has now been shown in an exome sequencing study that *VCP* mutations can also cause an MND/ALS phenotype [34••]. Most of the patients in the study had a pure MND/ALS picture but some had FTD-MND/ALS. This study suggests that *VCP* mutations account for approximately 1–2% of familial MND/ALS. *VCP* mutations have not been described in previously studied series of familial FTD-MND, suggesting that they represent a relatively rare cause of this syndrome. Progressive aphasia has not been described in most series of patients with *VCP* mutations although members of a recently described Korean family presented with early language deficits and semantic impairment [32].

### ***TARDP* mutations**

Mutations in *TARDP* were originally described in familial MND/ALS but most large series of FTD patients have not found mutations. However, a large Italian series of 252 patients with diagnoses in the FTL spectrum included five patients with possibly pathogenic variants in the *TARDP* gene, four with bvFTD and one with FTD-MND/ALS [35]. Although these variants were not found in a small series of controls there was no pathological confirmation in any of the cases. Parkinsonism was seen in some patients in this series and a recent screen of a cohort with a Parkinson's disease phenotype found the A382T mutation in eight patients and also in a family described as having FTD with parkinsonism [36]. This same mutation has been described as causing FTD-MND/ALS or MND/ALS alone [37]. A bvFTD syndrome (in association with a supranuclear gaze palsy

and chorea) has also recently been described in a patient with the novel K263E variant [38].

#### **FUS mutations**

As with *TARDP*, mutations in *FUS* were originally described in familial MND/ALS, accounting for 3% of cases in one recent series [39]. In this same series, one member of a genetic MND/ALS family presented with FTD, suggesting that *FUS* mutations may rarely cause an FTD syndrome. A further case of bvFTD with rapidly ensuing MND/ALS has also recently been described [40]. However, most FTD cases with *FUS* pathology are sporadic and do not have mutations in *FUS* [41–44]. Interestingly, one series of patients with *FUS* pathology included a family with a bvFTD phenotype and autosomal dominant inheritance without an identified mutation in *FUS* [43].

#### **CHMP2B mutations**

Mutations in *CHMP2B* are restricted to a large Danish family in Jutland and a few other case reports. The phenotype is usually a behavioural syndrome similar to bvFTD although one case with FTD-MND/ALS has been described. One recent screen for *CHMP2B* mutations in familial MND/ALS found probably pathogenic mutations in 1% of MND/ALS cases, although none of these patients had FTD [45].

#### **DCTN1 mutations**

There is a single case report linking mutations in the *DCTN1* gene encoding dynactin with a family with FTD and MND/ALS [46]. Few of the large genetic FTD series have investigated this gene. However, no mutations were found in a selected cohort with FTD-MND/ALS [4] or in another series of 286 patients with Parkinson's disease, FTD or MND/ALS [47]. More recently *DCTN1* mutations have been shown to cause Perry syndrome, an autosomal dominant disorder with parkinsonism, hypoventilation, dysautonomia, weight loss and behavioural symptoms (commonly depression and apathy) associated with TDP-43 pathology [48,49]. One recent case report described a patient presenting with features of bvFTD initially associated with parkinsonism who later developed hypoventilation and a vertical supranuclear gaze palsy [50].

#### **C9ORF72 repeat expansion**

A number of families have been described with FTD-MND/ALS linked to a locus on chromosome 9p21 and associated with type B TDP-43 pathology. Recently, new information about the clinical phenotype has emerged based on studies in two further families [51,52]. Ten members of the VSM-20 family [52] had available clinical data and showed a variable phenotype with mean age of onset around 45 years: three individuals had bvFTD without motor impairment, two had bvFTD

with parkinsonism, 2 had limb-onset MND/ALS with only minimal behavioural or cognitive impairment and three had a combination of bvFTD and MND/ALS (one of whom presented initially with apraxia and parkinsonism consistent with CBS). In the Gwent family [52] nine members had clinical data with a mean age of onset of 42.7 years: as with the VSM-20 family a variable phenotype was seen with some patients presenting with MND/ALS (bulbar and/or limb-onset), bvFTD alone or a combination of FTD and MND/ALS. Parkinsonism was seen in four cases. Two cases had prominent psychosis, one with hallucinations and delusions – a feature that appears to develop more commonly in association with FTD-MND than in FTD without MND [53]. One case also had cerebellar ataxia, a phenotype not previously described in chromosome 9-linked FTD-MND families. In total there are now 14 families reported with chromosome 9-linked FTD-MND. In one of these families (Aus-14), the causative gene was reported as being *SIGMAR1* although in fact this family appears unique in having distinct pathological findings of both TDP-43 and *FUS* inclusions [54]. In the majority of chromosome 9-associated FTD-MND (including the VSM-20 and Gwent families), it has now been recognised that the cause of disease is an expanded GGGGCC hexanucleotide repeat in a noncoding region of chromosome 9 open reading frame 72 (*C9ORF72*) [10,11]. In the Mayo Clinic series of patients, 11.7% of familial FTD and 3.0% of sporadic FTD had the repeat expansion [10], making it the most common genetic abnormality in FTD (*GRN* mutations were found in 7.6% familial FTD and 3.0% sporadic FTD whilst *MAPT* mutations were found in 6.3% of familial FTD and 1.5% sporadic FTD). The FTD phenotype was bvFTD in 25 out of 26 patients, with 26.9% also having MND/ALS [10]. BvFTD was also the most common phenotype in a separately reported Finnish cohort (64.0%) but a substantial proportion of patients also had a language phenotype (PNFA in 26.7% and semantic dementia in 9.3%) [11].

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#### **Neuroimaging studies**

There are relatively few detailed neuroimaging studies in genetic FTD and studies are mostly limited to single cases (see neuroimaging summary in Table 2) [32]. However, recently larger series have been described comparing *MAPT* and *GRN* mutations [23,24,55]. *GRN* mutations are more likely to show strongly asymmetrical atrophy affecting either the left or right hemispheres maximally and involving the inferior frontal, temporal and inferior parietal lobes as well as long intrahemispheric association white matter tracts. This is distinct from the patterns of atrophy seen with other TDP-43 pathologies [56,57]. *MAPT* mutations are associated with a more symmetrical pattern of atrophy localized predominantly to the anterior temporal lobes and also involving

**Table 2 Summary of clinical and neuroimaging features of genetic frontotemporal dementia**

Gene	Clinical										Neuroimaging				
	bvFTD	FTD-MND	MND/ALS <sup>a</sup>	PNFA	SD	CBS	PSPS	Park	Other	FL	TL	PL	Other	Asymm	
<i>GRN</i>	+	Rare	-	+	-	+	-	+	+	++	+	++	Basal ganglia	++	
<i>MAPT</i>	+	-	-	Unclear	Rare	+	Rare	+	+	+ <sup>b</sup>	++	- <sup>b</sup>		+	
<i>VCP</i>	Rare	Rare	+	-	Unclear	-	-	-	IBM, Paget's disease of bone	+ <sup>b</sup>	+/++ <sup>b</sup>	+ <sup>b</sup>		+/++ <sup>b</sup>	
<i>TARDP</i>	Rare	Rare	+	-	-	Unclear	+	+		++	+	+	Midbrain <sup>c</sup>	+	
<i>FUS</i>	Rare	Rare	+	-	-	-	-	-		+ <sup>c</sup>	+	+		+	
<i>CHMP2B</i>	Rare	Rare	Rare	-	-	-	Rare	Rare		+ <sup>c</sup>	+	+		+	
<i>DCTN1</i>	Rare	Unclear	Rare	-	-	-	Rare	Rare	Perry syndrome	+ <sup>c</sup>	+	+	Midbrain <sup>c</sup>	+	
<i>C9ORF72</i>	+	+	+	+	Rare	Rare	+	+		++	+	+		+	

ALS, amyotrophic lateral sclerosis; Asymm, inter-hemispheric asymmetry; bvFTD, behavioural variant frontotemporal dementia; CBS, corticobasal syndrome; CHMP2B, chromatid modifying protein 2B; DCTN1, dynein 1; FL, frontal lobe; FUS, fused-in-sarcoma peptide; GRN, granulin; IBM, inclusion body myopathy; MAPT, microtubule-associated protein tau; MND, motor neuron disease; Park, parkinsonism; PL, parietal lobe; PNFA, progressive nonfluent aphasia; PSPS, progressive supranuclear palsy syndrome; SD, semantic dementia; TARDP, transactive DNA binding protein; TL, temporal lobe; VCP, valosin-containing peptide.

<sup>a</sup> In pure form.

<sup>b</sup> One reported family with semantic-dementia-like phenotype and asymmetric temporo-parietal atrophy [32] although most cases reported to have diffuse atrophy with fronto-temporal emphasis.

<sup>c</sup> Limited information.

orbitofrontal cortices and fornix. This latter pattern of atrophy seems to be distinct from other patterns seen in patients with bvFTD [58]. *GRN* mutations are also associated with faster rates of brain atrophy than *MAPT* mutations. Examples of magnetic resonance (MR) images from patients with *GRN* and *MAPT* mutations are shown in Fig. 1.

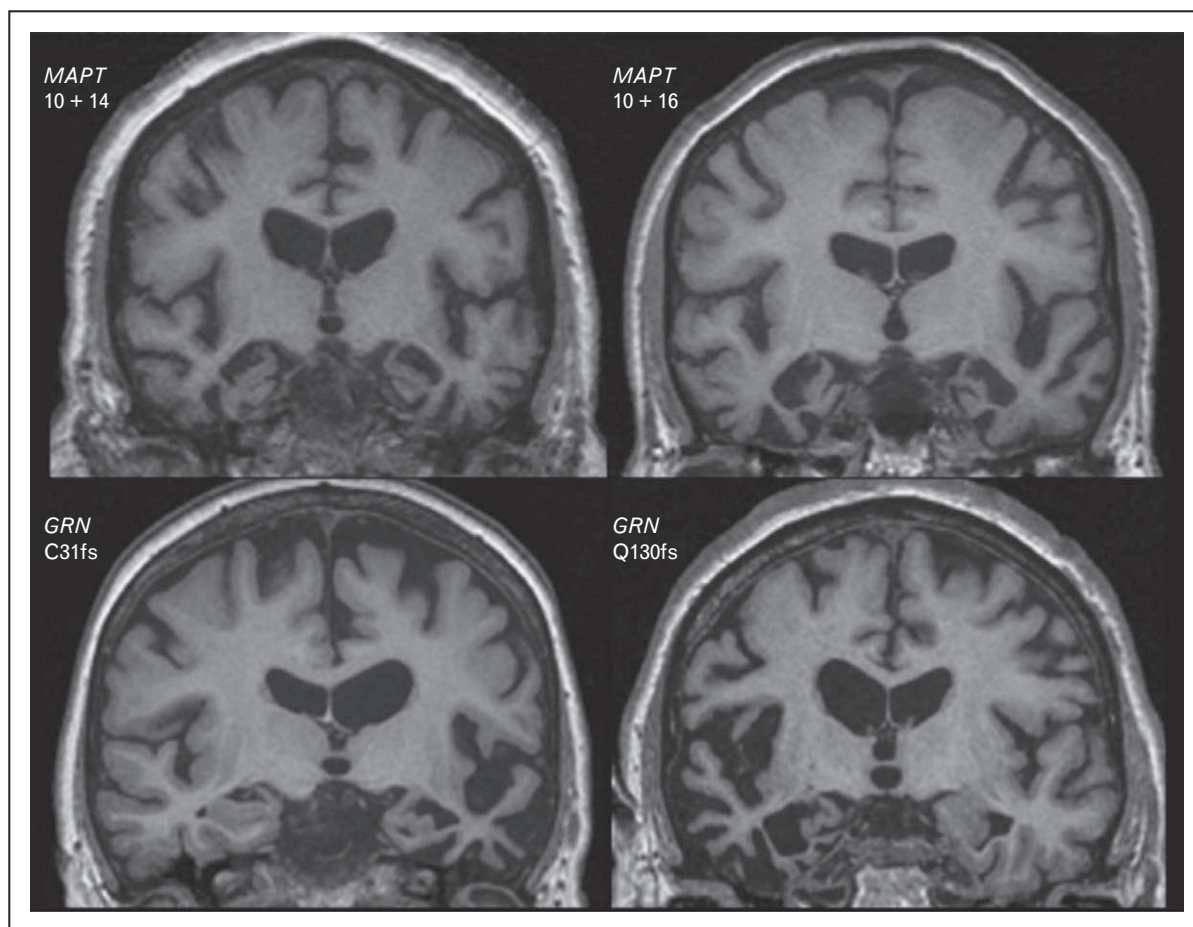
The question arises as to whether particular mutations in a given gene might show distinctive patterns of atrophy. A small study of *MAPT* mutations suggested that one such distinction may apply to mutations which affect the structure of the tau protein, for example P301L (with more lateral temporal lobe involvement and relative sparing of the medial temporal lobes) versus mutations which affect alternative splicing of tau, for example the 10 + 16 intronic mutation (with more medial temporal lobe involvement and relative sparing of the lateral temporal lobes) [59].

Studies of presymptomatic genetic FTLD offer the opportunity of identifying very early imaging features of disease. A number of case reports have been published showing atrophy predating symptom onset by a number of years (e.g. [60]). Recently two studies have looked at presymptomatic *MAPT* mutation carriers. In a study of three patients, two showed presymptomatic hippocampal atrophy and all three showed dopaminergic dysfunction (using PET imaging) [61], whereas another cohort of 14 patients showed proton MRS abnormalities several years before the onset of symptoms [62\*].

**Conclusion**

This survey of genotype–phenotype relations in FTD leads to the initial conclusion that few clinical or neuroanatomical features have a specific molecular association (see Table 2). Both clinically and anatomically, there is substantial overlap amongst these diseases and (at first sight, even more problematically) substantial heterogeneity even within single families. Nevertheless, certain relatively specific markers do emerge. These include the predilection of MND-like features for the nontau-associated forms of genetic FTD; the association of inclusion body myopathy and Paget’s disease with *VCP* mutations; the association of hypoventilation and dysautonomia with *DCTN1* mutations; and neuroanatomically, the association of strongly asymmetric inter-hemispheric atrophy with *GRN* mutations and relatively symmetrical, relatively localized (predominantly anterior temporal lobe) atrophy with *MAPT* mutations. One recent synthesis [23] proposes that molecular signatures of FTD manifest not as specific clinical features or local anatomical associations, but as specific patterns of network breakdown directed by the interaction of the molecular lesion with network morphological characteristics

**Figure 1** Coronal sections of structural T1-weighted magnetic resonance brain images from clinically affected patients with mutations in *MAPT* (top) and *GRN* (bottom)



(e.g. *GRN*-associated toxicity with long intra-hemispheric pathways; *MAPT*-associated toxicity with local bi-hemispheric networks). The local mechanisms that translate molecular lesions to neural network dysfunction remain largely unknown but could include loss of regulatory or trophic factor support, propagation of toxic molecules, and disturbed network homeostasis. To test such hypotheses will require adequate sampling across the spectrum of genotypes and phenotypes that comprise genetic FTD, and with sufficient power to evaluate group-wise differences. As the genetic forms of FTD are individually uncommon, this will in turn require multicentre case ascertainment and collaboration based on uniform methods of disease phenotyping.

Identification of phenotypic signatures of genetic FTD is of high clinical as well as neurobiological importance. If robust, such signatures might help guide genetic screening or provide biomarkers of disease onset and evolution. Natural history studies of both presymptomatic and affected patients with genetic FTLT will

set the scene for future clinical trials of possible disease-modifying therapies. Potential compounds are already under investigation: one recent study showed that SAHA (Vorinostat) enhanced *GRN* expression in human cells [63], whilst another showed that alkalizing reagents rescued *GRN* deficiency in human cells [64]. Compounds that affect tau are also under investigation. It is likely that these or similar compounds will eventually enter into clinical trials and finally offer the hope of disease modification for patients with genetic FTD.

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### Conflicts of interest

There are no conflicts of interest.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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