Phenotypic signatures of genetic frontotemporal dementia
Jonathan D. Rohrer and Jason D. Warren

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

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). Neurologically, 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...
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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] 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**,11**].

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*]. 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**,18].

Interestingly, in the study of Chen-Plotkin et al. [13*], 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-MND/ALS (whether familial or apparently sporadic) was much more commonly (26.3% of cases) GRN-negative with FTLD-TDP pathology.

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.

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

<table>
<thead>
<tr>
<th>Geographic area</th>
<th>No in series</th>
<th>% MAPT mutations</th>
<th>% GRN mutations</th>
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<tr>
<td>Cruts et al. [5]</td>
<td>Belgium</td>
<td>103</td>
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<td>Gass et al. [6]</td>
<td>USA</td>
<td>167</td>
<td>4</td>
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<td>Le Ber et al. [7]</td>
<td>France</td>
<td>210</td>
<td>3</td>
</tr>
<tr>
<td>Pickering-Brown et al. [8]</td>
<td>UK</td>
<td>223</td>
<td>8</td>
</tr>
<tr>
<td>Seelaar et al. [4]</td>
<td>The Netherlands</td>
<td>364</td>
<td>2</td>
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<td>Rohrer et al. [3]</td>
<td>UK</td>
<td>225</td>
<td>9</td>
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Adapted from [3].
It is difficult to propose a rational policy for screening \textit{GRN} mutations in the face of this wide phenotypic variation. There are over 70 \textit{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 \textit{GRN} mutations). Low plasma \textit{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 \textit{GRN}-associated FTD that are also associated with TDP-43 type A pathology and with an apparently autosomal dominant family history, but without \textit{GRN} mutations [23]; such cases suggest that other causative genes feeding into the \textit{GRN} pathogenetic pathway still await discovery.

\textbf{MAPT} mutations

Over 45 mutations are currently described in the \textit{MAPT} gene. As with \textit{GRN} the most common phenotype is bvFTD [23]. However, other phenotypes can be seen less frequently. Semantic impairment can develop in patients with \textit{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 \textit{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 \textit{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 \textit{MAPT} mutations, CBS more frequently than PSP. A review of \textit{MAPT} mutations and PSP-like syndromes was recently published in conjunction with a case report of a family with a novel L284R \textit{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 \textit{GRN} mutations, episodic memory impairment is occasionally the first and most prominent symptom of \textit{MAPT} mutations leading to a clinical diagnosis of Alzheimer’s disease. In one recent study the R406W mutation in \textit{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 \textit{MAPT} gene, although these patients presented initially with behavioural symptoms characteristic of bvFTD [31*].

\textbf{VCP mutations}

Over 15 probably pathogenic mutations in \textit{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 \textit{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 \textit{VCP} mutations account for approximately 1–2% of familial MND/ALS. \textit{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 \textit{VCP} mutations although members of a recently described Korean family presented with early language deficits and semantic impairment [32].

\textbf{TARDP mutations}

Mutations in \textit{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 FTLD spectrum included five patients with possibly pathogenic variants in the \textit{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. Parkinonism 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...
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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**].

**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
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<th>Gene</th>
<th>bvFTD</th>
<th>MND/ALS</th>
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*In pure form.*

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.

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<th>Gene</th>
<th>bvFTD</th>
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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 nontau-associated forms of genetic FTD; 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.
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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 FTLD 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.

Acknowledgements
The work was undertaken at UCLH/UCL who received a proportion of funding from the Department of Health’s NIHR Biomedical Research Centres funding scheme. The Dementia Research Centre is an Alzheimer’s Research Trust Co-ordinating Centre. This work was also funded by the Medical Research Council UK. JDW is supported by a Wellcome Trust Senior Clinical Fellowship.

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).


9 Mackenzie IRA, Neumann M, Babione A, et al. A harmonized classification system for FTLD-TDP pathology. Acta Neuropathol 2011; 122:111–113. This study describes a harmonized classification for FTLD-TDP pathology using A to D as classifiers. Previously two discordant numbered systems were being used causing confusion in the field.

• hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-Linked FTD and ALS. Neuron 2011 [Epub ahead of print].


13 Chen-Plotkin AS, Martinez-Lage M, Steinman PMA, et al. Genetic and clinical features of progranulin-associated frontotemporal lobar degeneration. Arch Neuro 2011; 68:488–497. This study arose from a large international collaborative effort in the FTD field to bring together samples from patients with FTLD-TDP pathology. It highlights important points about the phenotype of GRN mutations including the presence although rarity of the FTD-MND phenotype.


34 Johnson JO, Mandiri J, Benatar M, et al. Exome sequencing reveals VCP mutations as a cause of familial ALS. Neuro 2010; 22:857–864. In this study, the relatively novel technique of exome sequencing revealed that VCP mutations are a cause of MND/ALS as well as the rare syndromic combination of IBM/PFD.


39 Blair IP, Williams KL, Warracch ST, et al. FUS mutations in amyotrophic lateral sclerosis: clinical, pathological, neurophysiological and genetic analysis. J Neurol Neurosurg Psychiatry 2010; 81:639–645. This study screened a large series of patients with familial and sporadic ALS for FUS mutations finding mutations in 3.2% of the familial cases. Importantly, a FUS mutation was seen in a family in which FTD was the presenting feature in one member.

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