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# Mechanisms of disease in frontotemporal lobar degeneration: gain of function versus loss of function effects

**Glenda Halliday**,
Neuroscience Research Australia, University of New South Wales, Sydney, Australia

**Eileen H. Bigio**,
Alzheimer Disease Center, Department of Pathology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

**Nigel J. Cairns**,
Department of Neurology, Washington University School of Medicine, St. Louis, Missouri, USA

**Manuela Neumann**,
Department of Neuropathology, German Center for Neurodegenerative Diseases Tuebingen, University of Tuebingen, Tuebingen, Germany

**Ian R. A. Mackenzie**, and
Department of Pathology, University of British Columbia, Vancouver, Canada

**David M. A. Mann**
Institute of Brain, Behaviour and Mental Health, School of Community Based Medicine, University of Manchester, Manchester, UK

Salford Royal Hospital, University of Manchester, Stott Lane, Salford M6 8HD, UK

David M. A. Mann: david.mann@manchester.ac.uk

## Abstract

Frontotemporal lobar degeneration (FTLD) is clinically, pathologically and genetically heterogeneous. Three major proteins are implicated in its pathogenesis. About half of cases are characterized by depositions of the microtubule associated protein, tau (FTLD-tau). In most of the remaining cases, deposits of the transactive response (TAR) DNA-binding protein with Mw of 43 kDa, known as TDP-43 (FTLD-TDP), are seen. Lastly, about 5–10 % of cases are characterized by abnormal accumulations of a third protein, fused in sarcoma (FTLD-FUS). Depending on the protein concerned, the signature accumulations can take the form of inclusion bodies (neuronal cytoplasmic inclusions and neuronal intranuclear inclusions) or dystrophic neurites, in the cerebral cortex, hippocampus and subcortex. In some instances, glial cells are also affected by inclusion body formation. In motor neurone disease (MND), TDP-43 or FUS inclusions can present within motor neurons of the brain stem and spinal cord. This present paper attempts to critically examine the role of such proteins in the pathogenesis of FTLD and MND as to whether they might exert a direct pathogenetic effect (gain of function), or simply act as relatively innocent witnesses to a more fundamental loss of function effect. We conclude that although there is strong evidence for both gain and loss of function effects in respect of each of the proteins concerned, in reality, it is likely that each is a single face of either side of the coin, and that both will play separate, though



Correspondence to: David M. A. Mann, david.mann@manchester.ac.uk.

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complementary, roles in driving the damage which ultimately leads to the downfall of neurons and clinical expression of disease.

**Keywords**

Frontotemporal lobar degeneration; Motor neurone disease; Microtubule associated protein; Tau; TDP-43; FUS; Gain of function; Loss of function

## Introduction

Frontotemporal lobar degeneration (FTLD) is clinically, pathologically and genetically heterogeneous. The prototypical clinical syndromes are behavioural variant frontotemporal dementia (bvFTD), a disorder of behaviour and executive impairments, progressive non-fluent aphasia (PNFA), a disorder of expressive language, and semantic dementia (SD), a disorder of conceptual knowledge [54]. A proportion of patients with any of these syndromes of FTLD can develop the amyotrophic form of motor neurone disease (MND) [53, 78], further emphasising clinical heterogeneity within FTLD, and highlighting the long known association with, and suspected pathogenetic links between, FTLD and MND.

Extensive tissue research over the past decade has not only defined the pathological proteins involved in disease pathology, and has characterized their morphological form and topographical distribution within the brain, but most importantly has enabled a rational nomenclature and classification scheme to be introduced, which can now be employed to characterize virtually all but a handful of cases in a logical and consistent manner [13, 45]. Such a scheme had been lacking for many years, and this led to an unhelpful plethora of confusing, and sometimes conflicting, terminologies.

It was known from the 1980s that one of the major proteins involved in FTLD is the microtubule-associated protein, tau, which can accumulate in both nerve cells and glial cells. In sporadic disease, the signature accumulations take the form of neuronal Pick bodies (known as FTLD-tau PiD), tufted astrocytes (FTLD-tau PSP), or astrocytic plaques (FTLD-tau CBD), whereas in inherited cases, these can present as inclusions similar to any of these or with unique tau pathology, such cases being defined as FTLD-tau *MAPT*. Collectively, FTLD-tau accounts for about half of all cases of FTLD [5, 70]. The second major protein is the transactive response (TAR) DNA-binding protein with Mw of 43 kDa, known as TDP-43 [2, 55]. Pathologically, this is seen as inclusion bodies [neuronal cytoplasmic inclusions (NCI) and neuronal intranuclear inclusions (NII)] or dystrophic neurites (DN) in the cerebral cortex, hippocampus and subcortex. In many instances, the relative proportions of NCI, NII and DN within the tissue may permit subclassification into histological subtypes, A, B, C and D [45], which can aid diagnostic precision, but not all cases always show clear-cut distinctions, and further studies are needed to fully corroborate these entities [3]. In MND similar TDP-43 inclusions are present within motor neurons of the brain stem and spinal cord [2, 55]. Lastly, about 5–10 % of cases of FTLD [5, 46, 51, 57, 58, 68, 73], and a few familial MND cases [39, 82] are characterized by the abnormal accumulation, as cellular inclusions, of a third protein, fused in sarcoma (FUS). Other ubiquitinated, but as yet unidentified, target proteins characterize FTLD cases with *CHMP2B* mutations [33], and there may still be other rare cases where the hallmark of FTLD is present as microvacuolar change, but no NCI has been detected [13, 44, 45, 72].

On other fronts, more progress has been made in unravelling the genetic basis of FTLD, with mutations in *tau* (*MAPT*) [35, 63, 75] and *progranulin* (*GRN*) [6, 20, 50] genes on chromosome 17 being the first to be discovered. Elsewhere, mutations were identified in an

extended Danish pedigree with bvFTD in *CHMP2B* gene on chromosome 3 [71], and in rare families with FTD and inclusion body myositis and Paget's disease of bone (IBMPFD) in *VCP* on chromosome 9 [84]. Most recently, a hexanucleotide expansion in *C9ORF72* gene has been shown to be the most common cause of both FTD (with or without MND), and MND itself [24, 64]. In addition, it has been suggested that variations in *UBAP1* on chromosome 9p21 may act as a genetic risk factor for FTLD [65]. Interestingly mutations in *TARDBP* [30, 76] and *FUS* [39, 82] can cause MND, but are only rarely associated with FTLD [8].

Although FTLD is clinically, genetically, and neuropathologically heterogeneous, these recent advances allow for a logical classification according to molecular pathology and genetics [13, 14, 45] (see Fig. 1). While this heterogeneity may at first sight appear 'random', some clinical and/or genetic entities have been associated with particular pathological TDP-43 subtypes. For example, cases of FTD+MND generally show TDP-43 type B histology [13, 52], and familial cases are often associated with mutations in *C9ORF72* [24, 64]. Cases of SD most often show TDP-43 type C histology, and are usually sporadic [5]. Cases of PNFA commonly display TDP-43 type A histology [5, 13], and familial cases with this histology are often those which are associated with *GRN* mutations [5]. Cases of IBMPFD are associated with *VCP* mutation and show TDP-43 type D histology [56]. BvFTD, however, remains a 'mixed bag' with multiple histologies (FTLD-tau, FTLD-TDP and FTLD-FUS), and multiple genes (*MAPT, GRN, C9ORF72*), contributing to similar, but not always identical, clinical presentations. For example, cases of FTLD-FUS stand out according to their very early onset and the presence of bizarre stereotypic behaviours [68, 73], whereas cases with *C9ORF72* mutation may display pronounced psychoses [74].

Pathological and biochemical studies of TDP-43 and FUS show that patients with FTLD, and others with FTD+MND, as well as those with MND alone, may share a unifying pathogenetic basis for their disease, or at least have many molecular properties in common. However, it is still not clear whether the differing clinical, histological and genetic forms of FTLD represent variations on a common disease theme, or are, in fact, separate disorders in their own right, which coincidentally damage the same or overlapping key brain structures. Although the aggregated proteins that form NCI, NII or DN within the brain can be useful for diagnostic purposes, it is also unclear whether these are the real culprits of disease pathogenesis, directly triggering or causing damage to neurons (and glial cells), or are mere witnesses to, or products of, the disease process, with their presence, perhaps reflecting a compensatory or protective response within cells to, or against, potentially toxic forerunners. Nonetheless, their sequestration into 'pathological aggregates' may lead to loss of normal content of these key proteins, and with that their cellular functions.

This present paper attempts to critically examine the role of such proteins in relationship to whether they might evidence a direct pathogenetic effect (gain of function), or simply act as relatively innocent witnesses to a more fundamental loss of function effect.

## Tau: gain of function

Certain genetic forms of FTLD-tau are known to change the types of tau isoforms expressed [35, 63, 75], with recent studies showing differential gene expression in cells overexpressing different tau isoforms [15]. Compared with 3-repeat tau, 4-repeat tau increases transcripts involved in neurite outgrowth and cell death, and decreases transcripts involved in neuronal survival. Changes in tau isoform expression may therefore precipitate a toxic gain of function over time.

## Tau: loss of function

A substantive, and specific, focal loss of cortical projection neurons is a unifying feature of all cases of FTLD. While only around half of patients with FTLD have hyperphosphorylated tau inclusions within neurons and/or glial cells [70], substantial research has been focused on the underlying mechanisms involved. A major function of tau is microtubule binding, thereby stabilizing the axonal cytoskeleton and regulating axonal transport [49]. It is the loss of this normal function of tau, with bundling into tangle- or Pick body-type structures, that is considered key to FTLD-tau.

However, tau knockout mice are viable without overt phenotype when young, as microtubule-associated protein (MAP)-1 can perform the same functions, at least during this developmental period [37, 49]. Only very old tau knockout mice display some behavioural and motor deficits [49]. Additional functions, identified using tau knockout models, include the regulation of microtubule acetylation through the inhibition of histone deacetylase (HDAC)-6, with HDAC-6 activity being regulated by tau levels [18, 61]. A nuclear function has also been proposed for tau associated with histone deacetylase activity where it regulates BAF57 levels, a component of the neuron-restrictive silencing factor repressor complex (repressed genes are associated with hypoacetylation) [23]. Interestingly, knock in models of human tau have shown an increase in the numbers of neurons [69], perhaps via this mechanism.

## TDP-43: gain of function

TDP-43 is the major protein component of the abnormal inclusions in FTLD-TDP and most non-SOD1 ALS [2, 55]. TDP-43 is a multifunctional hnRNP protein involved in regulation of RNA splicing, translation, miRNA processing, and mRNA transport and stability [11]. There is evidence for TDP-43 autoregulation, participation in stress granule formation, and a protease-resistant prion-like domain in the C-terminal region [4, 17, 21, 28]. TDP-43 has more than 6,000 RNA targets [62].

Mutations in *TARDBP* occur predominantly in the C-terminal region, most causing ALS [30, 76], but some rarely causing FTLD [8]. Various cell, fly, and rodent models have shown evidence for either loss or gain of function, or both, in the pathogenesis of TDP-43 protein-opathy, but none has completely modelled human disease. Evidence for a toxic gain of function in model systems has included the following: in rodent models, overexpression of both wild type (WT) [86] and mutant TDP-43 are neurotoxic in a dose-dependent manner, and in some rodent models, C-terminal fragments (CTFs) correlate with disease progression; in cultured rodent neurons, one study showed that CTFs impair neurite outgrowth that is rescued by full-length TDP-43, while in another, neurotoxicity correlated with the amount of cytoplasmic TDP-43 expression; Drosophila studies have shown neurotoxicity with both expression of full-length WT and mutant TDP-43 [7, 42, 77, 80, 85, 87, 88, 91]. *TARDBP* mutations also increase stress granule formation in response to cellular stress, increase cleavage of TDP-43 and formation of CTFs, and increase the production of low molecular weight prion-like protease-resistant fragments [7, 17, 26, 31, 43, 47, 60, 66, 90]. The evidence for toxic gain of function due to overexpressed or mutant TDP-43 or cytoplasmic TDP-43/CTFs is compelling, but given the numerous crucial functions carried out by normal TDP-43, it is more than likely that a loss of function will also contribute to the pathogenesis of TDP-43 proteinopathy. Indeed, both a loss and a gain of function will most probably play a role in these diseases.

## TDP-43: loss of function

TDP-43 protein expression is tightly controlled within narrow limits by an auto-regulatory mechanism, and both over- and under-expression of TDP-43 result in impaired neuronal viability [38, 41, 89]. However, the precise mechanisms leading to cell death are not known. While TDP-43 loss-of-function mechanisms may contribute to neurodegeneration, especially in cases with mutations in the *TARDBP* gene, alternative etiologies may contribute to pathogenesis in sporadic cases. Cellular stress is an attractive precipitating factor, because it is a feature of most TDP-43 proteinopathies, including primary diseases where the principal molecular pathology is FTLD-TDP (including both sporadic forms of FTLD-TDP, and familial forms with *GRN, C9ORF72, TARDBP*, or *VCP* mutation), and those disorders such as Alzheimer's disease, Dementia with Lewy bodies, and Parkinson's disease where it is a secondary disease process or co-morbidity. Cellular stress likely causes redistribution of TDP-43 to the cytoplasm where its intrinsic self-aggregating property leads to inclusion body formation or trafficking to stress granules. Cytoplasmic, and less commonly nuclear, aggregation is accompanied by several post-translational modifications including phosphorylation, ubiquitination, and cleavage. These inclusion bodies may act as TDP-43 'sinks' and hinder translocation to the nucleus where TDP normally regulates mRNA processing. Alternatively, these inclusion bodies may have the effect of 'mopping up' soluble TDP-43 resulting in an overall depletion of nuclear and usable TDP-43 causing an increase in cellular stress and resulting in neurodegeneration.

Some cellular and animal models indicate that mutant TARDBP does not necessarily result in inclusion body formation, and so both under- and over-expression of TDP-43 is sufficient to cause neurodegeneration [86], but inclusion body formation is likely to contribute additionally to neurodegeneration.

## FUS: gain of function

FUS is a ubiquitously expressed multifunctional DNA/RNA-binding protein that can bind to a large number of RNA targets [32, 79]. It is mainly localized to the nucleus [1], but under physiological conditions continuously shuttles between the nuclear and cytoplasmic compartments [92]. In about 5–10 % of FTLD patients (subsumed as FTLD-FUS) [5, 46, 51, 57, 58], and in familial forms of ALS associated with mutations in the *FUS* gene [39, 82], abnormal accumulation of FUS into cytoplasmic inclusions are the defining hallmark lesion.

The majority of *FUS* mutations have been shown to disrupt a region characterized as a non-classical nuclear localization sequence, and this disruption leads to impaired transportin-mediated nuclear import of FUS, with redistribution of the protein to the cytoplasm [27, 36]. However, the mechanisms leading to cytoplasmic FUS accumulation in FTLD-FUS in the absence of *FUS* mutations, and the processes of FUS-associated neurodegeneration, are not yet known. Model systems addressing the fundamental questions on the underlying mechanisms are just emerging with some inconsistent findings. However, there is evidence supporting the idea that neurodegeneration might be triggered through a neurotoxic/gain of function effect of cytoplasmic FUS rather than by a loss of function.

In human pathology, inclusion bearing cells often retain their physiological nuclear FUS staining, arguing against a loss of nuclear function mechanism [57, 58]. In yeast, FUS toxicity is closely related to its cytoplasmic localization [19]. In transgenic worm, fly and rat models, expression of cytoplasmic FUS is sufficient to induce motor defects and premature death, though no depletion of nuclear FUS is observed [16, 34, 81]. Moreover, the severity of phenotype nicely correlates with the level of cytoplasmic FUS, thereby supporting the idea of a neurotoxic effect of cytoplasmic FUS. This might be mediated by either abnormal interaction with cytoplasmic RNA targets or protein binding partners, resulting in

disturbance of RNA metabolism, or by a gain of novel function of disease-associated FUS isoforms unrelated to its native function.

## FUS: loss of function

Although the specific mechanisms of FUS-associated neurodegeneration are not known, several lines of evidence support a role for loss of FUS physiological function. *FUS* mutations that cause ALS primarily affect the C terminus that includes the nuclear localization signal. The degree to which these mutations interfere with transportin-mediated nuclear import correlates with the severity of clinical disease and neuropathology [27, 36]. Cases of FTLD-FUS, which are not associated with *FUS* mutations, also demonstrate reduced nuclear FUS staining of inclusion bearing neurons [51, 57, 58]. This strongly suggests that neurodegeneration is directly related to cellular redistribution of FUS, with one logical explanation being a reduced ability of FUS to perform its normal nuclear functions. Although the results from animal models have been inconsistent, knockdown of FUS or its homologues has been shown to result in abnormal development, reduced viability, motor deficits and abnormal neuronal morphology, with some of these deficits being rescued by expression of FUS transgenes [40, 67, 83]. Evidence against a toxic-gain-of-function mechanism includes the absence of abnormal molecular species in FTLD-FUS [57, 58], the lack of neurodegeneration in some anatomical regions with abundant cytoplasmic FUS inclusions [46] and the absence of FUS aggregates in some models of toxicity [40]. The fact that all FET proteins [22, 59], along with transportin-1 [9, 22], co-accumulate in the cellular inclusions of FTLD-FUS, indicate that dysregulation of several other RNA-binding proteins [29] is also associated with FTLD.

## Concluding remarks

The last decade has seen an extraordinary development in our understanding of FTLD. In recent years, the genetic causes of most cases of autosomal dominant FTLD have been discovered [6, 20, 24, 63, 64, 75], and the molecular pathologies associated with this group have largely been defined [13, 14, 45]. Thus, it is true to say the clinical, genetic, and neuropathological phenotypes that constitute FTLD have been characterized in large part. What remains to be determined is the elucidation of the mechanisms of neurodegeneration caused by different gene defects and different molecular pathologies. In the present article, evidence has been presented in support of whether the underlying pathogenetic mechanism appertaining to the major pathological proteins of FTLD can be best represented by a ‘gain’ or a ‘loss’ of function effect.

However, it is clear that the situation for each protein is unlikely to be an ‘either–or’ situation, but some combination of both. If it is postulated that there is a ‘gain of function’ of potentially toxic versions, or species, of each protein due to pathophysiological changes which favour aggregation, then it is clear that conversion of normal protein into an abnormal form must involve a loss of content of ‘wild-type’ protein, and along with that, a loss of function. For example, oligomerisation of phospho-tau may induce neurotoxicity prior to full aggregation into fibrillar tau. However, phosphorylation of tau will induce loss of microtubule binding capacity, and along with that reduced tau function. Similarly, phosphorylation of TDP-43 and FUS may induce cytoplasmic aggregation into NCI, and promote sequestration of normal TDP-43 and FUS into the aggregation process through a seeding effect. However, by so doing, loss of nuclear localization will cause loss of normal RNA-binding properties, and reduce transcriptional activity.

There are other issues. For example, how can molecular changes in three distinct proteins lead to three separate pathological cascades, each of which can threaten the viability of

neurons in the same regions of brain, and bring about a similar clinical dysfunction in each? Perhaps, the question is better asked as to how changes in these three proteins trigger or promote the same pathological cascade? Where is the common ground that links these molecular changes? Many believe the molecular and pathological changes of Alzheimer's disease can be linked to formation of soluble and toxic oligomers of beta amyloid protein, which are either overproduced in familial forms of disease, or accumulated in the brain in sporadic disease through deficiencies in amyloid clearance pathways through the extracellular fluid, or failures of enzymatic degradation. Similarly in Parkinson's disease, oligomerisation of phosphorylated forms of alpha-synuclein can lead to Lewy body formation. It is clear that in FTLD, when aggregated, tau, TDP-43, and probably also FUS, are phosphorylated, and although tau may undergo a similar process of oligomerisation in FTLD, as seen in AD, it is not so clear that TDP-43 and FUS in FTLD follow a similar route to aggregation and inclusion body formation.

What other clues are there? Certain inherited forms of FTLD (i.e. those associated with *CHMP2B* [71] or *VCP* [84] mutations) implicate issues in protein trafficking and sorting, and proteasomal failures, or both. Such evidence is supported by genetic associations with variations in *UBAP-1* [65]. In addition, mutations in *UBQLN2* in familial X-linked ALS, and the association of ubiquilin-2 immunoreactivity with inclusions in ALS unrelated to *UBQLN2* mutations, FTLD-TDP, synucleinopathies, multiple system atrophy, polyglutamine disorders, and neuronal intranuclear hyaline inclusion disease [10, 25, 48], suggests that failure of proteasomal degradation of ubiquitinated proteins may play a role in the pathogenesis of diverse degenerative disorders. Cellular stress may cause a redistribution of TDP-43 to the cytoplasm where its intrinsic self-aggregating property leads to inclusion body formation, or results in its trafficking to stress granules. Failure to degrade aggregated proteins is a common theme across many neurodegenerative diseases where inclusion bodies are characteristic. However, this may 'simply' represent a neuroprotective response on the part of the 'diseased' cell—a way of sequestering potentially harmful molecules and packaging them into a relatively innocuous form. Nonetheless, a consequence of this may involve the depletion of normal protein, or even its conversion into a form or structure compatible with the abnormal form, promoting further aggregation. Large aggregates of protein may simply be too large for the proteasomal pathways to handle and degrade, and intracellular accumulation is the price paid. Notwithstanding this, extreme accumulations of protein may ultimately bring about metabolic collapse through a volume effect, crowding out useful membranes and organelles. Failure to degrade protein aggregates may be a downstream consequence of primary physiological or structural changes in proteins which promote or trigger that tendency to self aggregate, far removed from the principal events that drive the neurodegenerative cascade, though loss of efficiency in protein degradation pathways, associated with mutational events, will only exacerbate this process.

In short, we have provided evidence in this paper arguing as to whether the underlying pathogenetic mechanism(s) appertaining to the major pathological proteins of FTLD can be best represented by 'gain' or 'loss' of function effects. In reality, it is likely that each is a single face of either side of the coin, and that both will play separate, though complementary, roles in driving the damage which ultimately leads to the downfall of neurons and clinical expression of disease.

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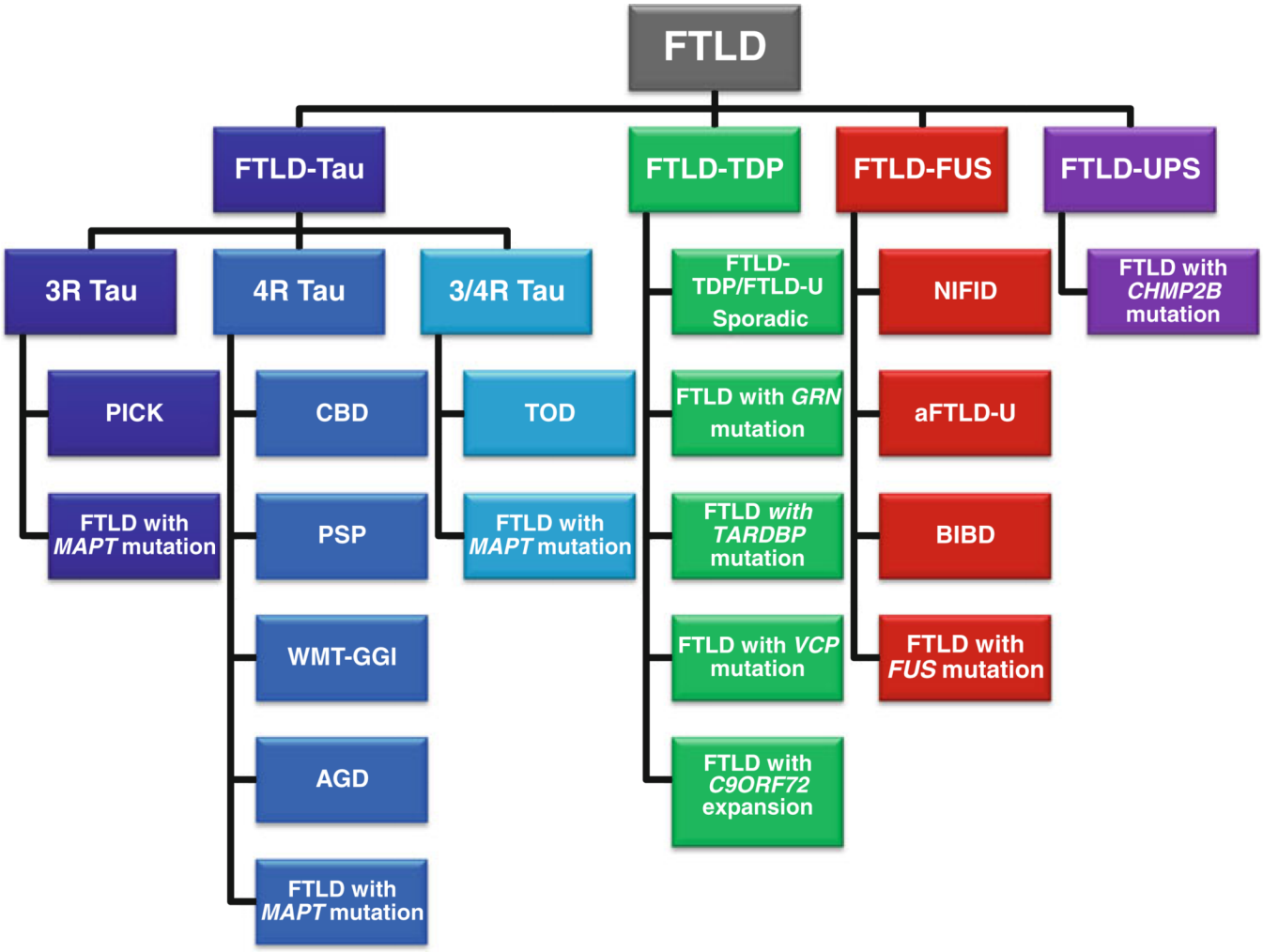


**Fig. 1.**

The molecular and genetic classification of FTLD. Three distinct neuropathologic categories may be identified based on the molecular pathology of the misfolded protein within the inclusion: FTLD-Tau, FTLD-TDP, and FTLD-FUS; the molecular pathology of a fourth category, FTLD with epitopes of the ubiquitin–proteasome system (FTLD-UPS), remains indeterminate. 3R, 4R, 3R/4R the predominant tau isoform within the inclusion; PICK, Pick's disease; FTLD with microtubule-associated protein tau (*MAPT*) mutation with inclusions of 3R, 4R, or 3R and 4R tau protein; CBD, corticobasal degeneration; PSP, progressive supranuclear palsy; AGD, argyrophilic grain disease; TOD, tangle only dementia; WMT-GGI, white matter tauopathy with globular glial inclusions; FTLD-U, FTLD with ubiquitin inclusions, now called FTLD-TDP; FTLD with progranulin (*GRN*) mutation; FTLD with TAR DNA-binding protein 43 (*TARDBP*) gene mutation; FTLD with valosin-containing protein (*VCP*) mutation; FTLD with *C9ORF72* expansion, chromosome 9-linked FTLD with *C9ORF72* hexanucleotide repeat expansion; NIFID neuronal intermediate filament inclusion disease; aFTLD-U atypical FTLD with ubiquitin inclusions; BIBD basophilic inclusion body disease; FTLD with fused in sarcoma (*FUS*) mutation; FTLD with charged multivesicular body protein 2B (*CHMP2B*) mutation. There may still be unclassified entities within each molecular pathology grouping (modified from [12])