

## Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update

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One year ago, in this journal, we published a recommended nomenclature for the neuropathologic subtypes of frontotemporal lobar degeneration (FTLD) [7]. A major impetus behind this was to resolve the confusion that had arisen around the use of the term “FTLD with ubiquitinated inclusions” (FTLD-U), following the discovery that the molecular pathology of these cases was heterogeneous, with most, but not all, being characterized by pathological TDP-43 [6, 11]. In addition, a system of nosology was introduced that grouped the FTLD subtypes into broad

categories, based on the molecular defect that is most characteristic, according to current evidence. This system provided a concise and consistent terminology that has now been widely adopted in the literature. Another anticipated advantage was the ability to readily accommodate new discoveries. At the time, we did not anticipate how quickly this attribute would be put to use.

Although most FTLDs are characterized by cellular inclusion bodies composed of either tau (FTLD-tau) or TDP-43 (FTLD-TDP), approximately 10–15% of cases

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remain, that include a number of uncommon FTLN subtypes, in which the pathologic protein is unknown. Recently, two studies identified mutations in the gene encoding the *fused in sarcoma* (FUS) protein (also known as *translocated in liposarcoma*, TLS), as the cause of familial amyotrophic lateral sclerosis (ALS) type 6 [5, 14]. The recognized clinical, genetic and pathological overlap between ALS and FTD, and the high degree of functional homology between FUS and TDP-43, prompted a number of subsequent studies that demonstrated that the inclusions of several of the tau/TDP-43-negative FTLNs are immunoreactive (ir) for FUS [8–10]. One such group are those cases with TDP-43-negative FTLN-U pathology, originally referred to as atypical FTLN-U (aFTLN-U) [6, 11]. According to the previous nomenclature recommendations, the neuropathology of these cases was designated as FTLN-UPS because the inclusions were only detectable with immunohistochemistry against proteins of the ubiquitin proteasome system (UPS) [7]. However, based on the discovery that all the ubiquitin-positive pathology in these cases is immunoreactive for FUS, we now recommend that they should be reclassified as FTLN-FUS [9]. In addition, the characteristic neuronal cytoplasmic inclusions of basophilic inclusions body disease (BIBD), previously of unknown biochemical composition, have also been shown to be consistently FUS-ir [8]. Perhaps most surprising has been the identification of abundant FUS-positive pathology in cases of neuronal intermediate filament inclusion disease (NIFID) [10]. The diagnostic criterion for NIFID is the presence of neuronal inclusions that are negative for tau,  $\alpha$ -synuclein and TDP-43 but immunoreactive for class IV intermediate filaments (IF) [1] and therefore the term FTLN-IF was designated in the previous nomenclature recommendations [7]. However, the finding that only a minority of the inclusions in NIFID are IF-ir, the absence of any identifiable genetic or molecular abnormality of IF

in these cases and the recognition that immunohistochemistry for IF is not specific for this condition, is consistent with the possibility that another protein may be more central to the pathogenesis. The recent demonstration that a much larger proportion of the inclusions in NIFID are FUS-ir, that all the cells with IF-ir inclusions also contain pathological FUS, and that there are widespread FUS-ir glial inclusions, suggests that the abnormal accumulation of FUS may be more fundamental in the disease process and that IF pathology probably develops as a secondary process [10].

Taking these studies together, we now recommend that aFTLN-U, BIBD and NIFID should be grouped together under the designation of FTLN-FUS (Table 1). It is important to recognize, however, that this does not imply that a defect in FUS metabolism is known to be causal in any of these conditions. Rather, it simply indicates that they share FUS accumulation as the most prominent molecular pathology. Whether or not this indicates that aFTLN-U, BIBD and NIFID are actually all part of a continuous spectrum of disease must await detailed comparative clinicopathological studies of larger numbers of cases. Nonetheless, the presence of FUS pathology sets these cases apart and should aid in their neuropathological diagnosis and classification.

Although it now appears that most, if not all, cases of sporadic FTLN-UPS (i.e. aFTLN-U) have FUS-immunoreactive pathology [9], the designation FTLN-UPS remains appropriate for at least one condition: familial FTD linked to chromosome 3 (FTD-3), caused by mutations in the *CHMP2B* gene. In addition to being negative for tau and TDP-43 [2], a recent study has shown that the ubiquitin/p62-immunoreactive neuronal inclusions in these cases do not label with antibodies against FUS [3]. Although these inclusions may eventually be discovered to contain a single major pathologic protein, it is also possible they have more heterogeneous composition that results from a primary defect of endosomal function [13]. Until this is determined, FTLN-UPS remains an appropriate designation for the neuropathology of FTD-3 and possibly for some FUS-negative sporadic cases.

With these recent advances, virtually all cases of FTLN can now be assigned to one of the three major molecular subgroups (FTLN-tau, FTLN-TDP or FTLN-FUS). This classification does not presuppose a primary role of the signature protein in pathogenesis (although in FTLN-tau and FTLN-TDP there is growing evidence to support this), but provides a logical way of grouping neuropathologic subtypes that is likely to have relevance regarding common disease mechanisms, diagnostic tests and possibly treatments. The specific role of the pathologic proteins and their relationship to causal gene defects is crucial information

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**Table 1** Updated nomenclature for neuropathologic subtypes of frontotemporal lobar degeneration

2009 recommendation		2010 recommendation		Associated genes
Major molecular class	Recognized subtypes <sup>a</sup>	Major molecular class	Recognized subtypes <sup>a</sup>	
FTLD-tau	PiD	FTLD-tau	PiD	<i>MAPT</i>
	CBD		CBD	
	PSP		PSP	
	AGD		AGD	
	MSTD		MSTD	
	NFT-dementia		NFT-dementia	
	WMT-GGI		WMT-GGI	
FTLD-TDP	Unclassifiable	FTLD-TDP	Unclassifiable	<i>GRN</i> <i>VCP</i> 9p ( <i>TARDBP</i> ) <sup>b</sup>
	Types 1–4		Types 1–4	
	Unclassifiable		Unclassifiable	
<b>FTLD-UPS</b>	<b>FTD-3</b> <b>aFTLD-U</b>	<b>FTLD-UPS</b>	<b>FTD-3</b>	<i>CHMP2B</i>
<b>FTLD-IF</b> <b>BIBD</b>	<b>NIFID</b>	<b>FTLD-FUS</b>	<b>aFTLD-U</b> <b>NIFID</b> <b>BIBD</b>	( <i>FUS</i> ) <sup>c</sup>
FTLD-ni		FTLD-ni		

Entries in bold indicate major revisions

aFTLD-U, atypical frontotemporal lobar degeneration with ubiquitinated inclusions; AGD, argyrophilic grain disease; BIBD, basophilic inclusion body disease; CBD, corticobasal degeneration; CHMP2B, charged multivesicular body protein 2B; FTD-3, frontotemporal dementia linked to chromosome 3; FTLD, frontotemporal lobar degeneration; FUS, fused in sarcoma; *GRN*, progranulin gene; IF, intermediate filaments; MAPT, microtubule associated protein tau; MSTD, multiple system tauopathy with dementia; NFT-dementia, neurofibrillary tangle predominant dementia; ni, no inclusions; NIFID, neuronal intermediate filament inclusion disease; PiD, Pick's disease; PSP, progressive supranuclear palsy; TARDBP, transactive response DNA binding protein; TDP, TDP-43; UPS, ubiquitin proteasome system; VCP, valosin containing protein; WMT-GGI, white matter tauopathy with globular glial inclusions; 9p, genetic locus on chromosome 9p linked to familial amyotrophic lateral sclerosis and frontotemporal dementia

<sup>a</sup> Indicates the characteristic pattern of pathology, not the clinical syndrome. Note that FTDP-17 is not listed as a pathological subtype because cases with different *MAPT* mutations do not have a consistent pattern of pathology. These cases would all be FTLD-tau, but further subtyping would vary

<sup>b</sup> Rare case reports of patients with clinical FTD and TDP-43 pathology associated with *TARDBP* genetic variants [4]

<sup>c</sup> One patient reported with a *FUS* mutation and FTD/ALS clinical phenotype but no description of pathology [12]

that requires further neuropathological and experimental investigations.

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## References

- Cairns NJ, Uryu K, Bigio E et al (2004)  $\alpha$ -Internexin in neuronal intermediate filament inclusion disease and other neurodegenerative diseases. *Acta Neuropathol* 108:213–223. doi:10.1007/s00401-004-0882-7
- Holm IE, Englund E, Mackenzie IRA, Johannsen P, Isaacs A (2007) A reassessment of the neuropathology of frontotemporal dementia linked to chromosome 3 (FTD-3). *J Neuropathol Exp Neurol* 66:884–891. doi:10.1097/nen.0b013e3181567f02
- Holm IE, Isaacs A, Mackenzie IRA (2009) Absence of FUS-immunoreactive pathology in frontotemporal dementia linked to chromosome 3 (FTD-3) caused by mutation in the *CHMP2B* gene. *Acta Neuropathol* 118:719–720. doi:10.1007/s00401-009-0593-1
- Kovacs GG, Murrell JR, Horvath S et al (2009) TARDBP variation associated with frontotemporal dementia, supranuclear gaze palsy and chorea. *Mov Disord* 24:1843–1847. doi:10.1002/mds.22697
- Kwiatkowski TJ, Bosco DA, LeClerc AL et al (2009) Mutations in the FUS/TLS gene on chromosome 16 cause familial amyotrophic lateral sclerosis. *Science* 323:1205–1208. doi:10.1126/science.1166066
- Mackenzie IRA, Foti D, Woulfe J, Hurwitz TA (2008) Atypical frontotemporal lobar degeneration with ubiquitin-positive, TDP-43-negative neuronal inclusions. *Brain* 131:1282–1293. doi:10.1093/brain/awn061
- Mackenzie IR, Neumann M, Bigio EH et al (2009) Nomenclature for neuropathologic subtypes of frontotemporal lobar degeneration: consensus recommendations. *Acta Neuropathol* 117:15–18. doi:10.1007/s00401-008-0460-5

8. Munoz DG, Neumann M, Kusaka H et al (2009) FUS pathology in basophilic inclusion body disease. *Acta Neuropathol* 118:617–627. doi:[10.1007/s00401-009-0598-9](https://doi.org/10.1007/s00401-009-0598-9)
9. Neumann M, Rademakers R, Roeber S, Baker M, Kretzschmar HA, Mackenzie IRA (2009) Frontotemporal lobar degeneration with FUS pathology. *Brain* 132:2922–2931. doi:[10.1093/brain/awp214](https://doi.org/10.1093/brain/awp214)
10. Neumann M, Roeber S, Kretzschmar HA, Rademakers R, Baker M, Mackenzie IRA (2009) Abundant FUS pathology in neuronal intermediate filament inclusion disease. *Acta Neuropathol* 118:605–616. doi:[10.1007/s00401-009-0581-5](https://doi.org/10.1007/s00401-009-0581-5)
11. Roeber S, Mackenzie IR, Kretzschmar HA, Neumann M (2008) TDP-43-negative FTL-D-U is a significant new clinico-pathological subtype of FTL-D. *Acta Neuropathol* 116:147–157. doi:[10.1007/s00401-008-0395-x](https://doi.org/10.1007/s00401-008-0395-x)
12. Ticozzi N, Silani V, LeClerc AL et al (2009) Analysis of *FUS* gene mutation in familial amyotrophic lateral sclerosis within an Italian cohort. *Neurology* 73:1180–1185. doi:[10.1212/WNL.0b013e3181b8ff05](https://doi.org/10.1212/WNL.0b013e3181b8ff05)
13. Urwin H, Ghazi-Noori S, Collinge J, Isaacs A (2009) The role of CHMP2B in frontotemporal dementia. *Biochem Soc Trans* 37:208–212. doi:[10.1042/BST0370208](https://doi.org/10.1042/BST0370208)
14. Vance C, Rogelj B, Hortobagyi T et al (2009) Mutations in *FUS*, an RNA processing protein, cause familial amyotrophic lateral sclerosis type 6. *Science* 323:1208–1211. doi:[10.1126/science.1165942](https://doi.org/10.1126/science.1165942)