Published in final edited form as:
Acta Neuropathol. 2011 July ; 122(1): 111–113. doi:10.1007/s00401-011-0845-8.

A harmonized classification system for FTLD-TDP pathology

Ian R. A. Mackenzie,
Department of Pathology, University of British Columbia and Vancouver General Hospital, 855 West 12th Avenue, Vancouver, British Columbia V5Z 1M9, Canada

Manuela Neumann,
Institute of Neuropathology, University Hospital Zurich, Zurich, Switzerland

Atik Baborie,
Department of Neuropathology, Walton Center for Neurology and Neurosurgery, Liverpool, UK

Deepak M. Sampathu,
Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Pennsylvania, PA, USA

Daniel Du Plessis,
Department of Pathology, Hope Hospital, Salford, UK

Evelyn Jaros,
Department of Neuropathology, Newcastle General Hospital, Newcastle-Upon-Tyne, UK

Robert H. Perry,
Department of Neuropathology, Newcastle General Hospital, Newcastle-Upon-Tyne, UK

John Q. Trojanowski,
Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Pennsylvania, PA, USA

David M. A. Mann, and
Greater Manchester Neurosciences Centre, University of Manchester, Manchester, UK

Virginia M. Y. Lee
Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Pennsylvania, PA, USA

Ian R. A. Mackenzie: ian.mackenzie@vch.ca

In 2006, two papers were published, each describing pathological heterogeneity in cases of frontotemporal lobar degeneration (FTLD) with ubiquitin-positive, tau-negative inclusions (FTLD-U) [7, 11]. In both studies, large series of cases were evaluated and the investigators felt that they could recognize three distinct histological patterns, based on the morphology and anatomical distribution of ubiquitin immunoreactive neuronal inclusions. The findings of Sampathu et al. were further supported by differential labelling of the pathology, using a panel of novel monoclonal antibodies; whereas, Mackenzie et al. found relatively specific clinicopathological correlations. Most importantly, the pathological features that defined the subtypes in these two studies were almost identical, providing powerful validation of the results. However, because the studies were conducted simultaneously and independently, the numbering of the subtypes, used in the respective papers, did not match (Table 1).

Correspondence to: Ian R. A. Mackenzie, ian.mackenzie@vch.ca.

Shortly thereafter, further work by one of the two groups led to the identification of the transactive response DNA-binding protein with M_r 43 kD (TDP-43) as the ubiquitinated pathological protein in most cases of FTLD-U as well as the majority of sporadic amyotrophic lateral sclerosis (ALS) and some familial ALS [10]. It was subsequently confirmed that most FTLD-U cases had TDP-43 pathology and that the same pathological patterns could be recognized based on the results of TDP-43 immunohistochemistry (IHC) [1, 2]. By this time, a fourth FTLD-U subtype had been described, specifically associated with the familial syndrome of inclusion body myopathy with Paget's disease of bone and frontotemporal dementia (IBMPFD) caused by mutations in the valosin-containing protein (*VCP*) gene [4], and this was also shown to have TDP-43 pathology [9]. As a result, cases of FTLD with TDP-43 pathology are now designated as FTLD-TDP and the term FTLD-U is no longer recommended [8].

The two classification systems for FTLD-U/FTLD-TDP have now gained wide acceptance and have repeatedly been validated by the discovery of additional clinical, genetic and pathological correlations. However, the continued use of two discordant numbering systems proves to be an ongoing source of confusion within the field. Previous attempts, by other groups of authors, to promote one classification over the other have not been successful.

To resolve this issue, the principal authors of the original two papers are now proposing a new classification for FTLD-TDP pathology, the sole purpose of which is to provide a single harmonized system that replaces the two currently in use. In developing this new classification, the following principles were adhered to: (1) different pathological subtypes are designated by letters to help distinguish this from the pre-existing number-based systems, (2) the order of subtypes should not exactly match either of the previous systems to avoid any apparent bias, and (3) the order of the subtypes should be based on their relative frequency, with "A" being the most common.

The result is summarized in Table 1. Type A is equivalent to type 1 of Mackenzie et al. and type 3 of Sampathu et al., being characterized by numerous short dystrophic neurites (DN) and crescentic or oval neuronal cytoplasmic inclusions (NCI), concentrated primarily in neocortical layer 2. Moderate numbers of lentiform neuronal intranuclear inclusions (NII) are also a common but inconsistent feature of this subtype. Type B matches Mackenzie et al. type 3 and Sampathu et al. type 2, with moderate numbers of NCI, throughout all cortical layers, but very few DN. Type C is the same as Mackenzie et al. type 2 and Sampathu et al. type 1, having a predominance of elongated DN in upper cortical layers, with very few NCI. Finally, Type D refers to the pathology associated with IBMPFD caused by *VCP* mutations, characterized by numerous short DN and frequent lentiform NII.

Based on the results of more recent studies, there are a number of other modifications that we could have considered incorporating into this new system. Additional pathological subtypes could be added; for instance, to describe the TDP-43 pathology that is found in the mesial temporal lobe in a high proportion of cases of Alzheimer's disease and most other common neurodegenerative conditions [3]. The pathological criteria for each of the subtypes could be expanded to include characteristic findings in subcortical regions [5, 6]. The description of the pathological features could be modified to take into account the greater sensitivity and specificity of TDP-43 IHC, which may demonstrate additional findings, not recognized with the ubiquitin immunostaining techniques upon which the original classifications were based (such as neuronal "pre-inclusions") [2]. Although these and other recent findings represent important advances in our understanding of FTLD-TDP, most have not yet been broadly replicated or completely defined. Therefore, in order to make the transition to a new classification as simple and widely acceptable as possible and, most

importantly, to allow for direct translation with the currently existing systems, we are not proposing any other significant changes, beyond the coding of the subtypes.

In summary, we believed that adoption of a single harmonized system for the classification of FTLD-TDP neuropathology would greatly improve communication within the rapidly advancing field of FTLD diagnosis and research. Future attempts to resolve any outstanding issues related to the practical implementation and interpretation of FTLD pathological classification should also benefit. As indicated by their inclusion as co-authors on this paper, this proposal has received the unanimous support of all of the neuropathologists involved in the original two studies [7, 11].

Acknowledgments

The authors wish to thank their clinical colleagues, in particular Dr. William Seeley (University of California San Francisco), for their support and encouragement in moving this endeavour forward. Studies reviewed here from the Center for Neurodegenerative Disease Research were supported by AG-10124 and AG-17586.

References

1. Cairns NJ, Neumann M, Bigio EH, et al. TDP-43 in familial and sporadic frontotemporal lobar degeneration with ubiquitin inclusions. Am J Pathol. 2007; 171:227–240. [PubMed: 17591968]
2. Davidson Y, Kelley T, Mackenzie IRA, et al. Ubiquitinated pathological lesions in frontotemporal lobar degeneration contain the TAR DNA-binding protein, TDP-43. Acta Neuropathol. 2007; 113:521–533. [PubMed: 17219193]
3. Dickson DW. TDP-43 immunoreactivity in neurodegenerative disorders: disease versus mechanism specificity. Acta Neuropathol. 2008; 115:147–149. [PubMed: 18034349]
4. Forman MS, Mackenzie IR, Cairns NJ, et al. Novel ubiquitin neuropathology in frontotemporal dementia with *valosin-containing protein* gene mutations. J Neuropathol Exp Neurol. 2006; 65:571–581. [PubMed: 16783167]
5. Geser F, Martinez-Lage M, Robinson J, et al. Clinical and pathological continuum of multisystem TDP-43 proteinopathies. Arch Neurol. 2009; 66:180–189. [PubMed: 19204154]
6. Josephs KA, Stroh A, Dugger B, Dickson DW. Evaluation of subcortical pathology and clinical correlations in FTLD-U. Acta Neuropathol. 2009; 118:349–358. [PubMed: 19455346]
7. Mackenzie IRA, Baborie A, Pickering-Brown S, et al. Heterogeneity of ubiquitin pathology in frontotemporal lobar degeneration: classification and relation to clinical phenotype. Acta Neuropathol. 2006; 112:539–549. [PubMed: 17021754]
8. Mackenzie IR, Neumann M, Bigio EH, et al. Nomenclature for neuropathologic subtypes of frontotemporal lobar degeneration: consensus recommendations. Acta Neuropathol. 2009; 117:15–18. [PubMed: 19015862]
9. Neumann M, Mackenzie IR, Cairns NJ, et al. TDP-43 in the ubiquitin pathology of frontotemporal dementia with VCP gene mutations. J Neuropathol Exp Neurol. 2007; 66:152–157. [PubMed: 17279000]
10. Neumann M, Sampathu DM, Kwong LK, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science. 2006; 314:130–133. [PubMed: 17023659]
11. Sampathu DM, Neumann M, Kwong LK, et al. Pathological heterogeneity of frontotemporal lobar degeneration with ubiquitin-positive inclusions delineated by ubiquitin immunohistochemistry and novel monoclonal antibodies. Am J Pathol. 2006; 169:1343–1352. [PubMed: 17003490]

Table 1

Proposed new classification system for FTLD-TDP pathology, compared with existing systems

New system	Mackenzie et al. [7]	Sampathu et al. [11]	Cortical pathology	Common phenotype	Associated genetic defects
Type A	Type 1	Type 3	Many NCI Many short DN Predominantly layer 2	bvFTD PNFA	*GRN* mutations
Type B	Type 3	Type 2	Moderate NCI Few DN All layers	bvFTD MND with FTD	Linkage to chromosome 9p
Type C	Type 2	Type 1	Many long DN Few NCI Predominantly layer 2	SD bvFTD	
Type D	Type 4[a]	Type 4[a]	Many short DN Many lentiform NII Few NCI All layers	Familial IBMPFD	*VCP* mutations

bvFTD behavioural variant frontotemporal dementia, *DN* dystrophic neurites, *GRN* progranulin gene, *IBMPFD* inclusion body myopathy with Paget's disease of bone and frontotemporal dementia, *MND* motor neuron disease, *NCI* neuronal cytoplasmic inclusions, *NII* neuronal intra-nuclear inclusions, *PNFA* progressive non-fluent aphasia, *SD* semantic dementia, *VCP* valosin-containing protein gene

[a]Described subsequently by Forman et al. [4]