Acta Neuropathol (2009) 118:629–631
DOI 10.1007/s00401-009-0602-4

COMMENTARY

# Frontotemporal lobar degeneration: toward the end of conFUSion

**Stephan Frank · Markus Tolnay**

Published online: 21 October 2009


Frontotemporal dementia (FTD) comprises all behavioral and language variants of a clinical syndrome that can be attributed to molecularly heterogeneous alterations. In contrast, taking a neuropathologist's perspective, the term frontotemporal lobar degeneration (FTLD) is reserved to describe the associated histopathological findings. Following this approach, the currently most widely accepted FTLD classification relies on the assumption that the predominant protein pathology (i.e., the formation of abnormal neuronal and glial aggregates of certain proteins) more or less appropriately reflects the underlying pathogenic process or at least represents the most characteristic histopathological signature of the disease, and has thus consequently led to the definition of major FTLD subtypes [17]. The two most common forms characterized by pathological accumulation of the microtubule-associated protein tau or TDP-43 (transactive response DNA-binding protein with $M_r$ 43 kDa) account for the vast majority of FTLD cases. However, there have remained so far several distinct smaller subgroups within the FTLD spectrum, typified by either intraneuronal accumulation of otherwise not specified ubiquitinated protein inclusions, termed atypical FTLD-U (a-FTLD-U), accumulation of intermediate filaments (known as neuronal intermediate filament inclusion disease, NIFID) or basophilic inclusion bodies (known as basophilic inclusion body disease, BIBD) [reviewed in 21]. Latest reports [18–20], including two original papers in this issue of *Acta Neuropathologica* [18, 20], now provide insight into the so far mysterious molecular pathogenesis of a-FTLD-U, NIFID and BIBD.

S. Frank · M. Tolnay (✉)
Department of Neuropathology, Institute of Pathology, Schönbeinstrasse 40, 4031 Basel, Switzerland
e-mail: mtolnay@uhbs.ch

Without getting into a discussion of the appropriate terminology of FTLD subtypes [17, 21], the most recent identification of fused in sarcoma (FUS)-immunoreactive pathology in the smaller, pathogenically ill-defined FTD subsets comprising a-FTLD-U [19], NIFID [20] and BIBD [18] patients not only represents a significant step toward the completion of a molecularly based FTLD classification but also provides initial insights into the underlying pathogenic mechanisms of these neurodegenerative disorders. The FUS story took off when two papers published earlier this year described FUS mutations as the cause of familial amyotrophic lateral sclerosis (FALS) type 6 [14, 15, 24]. In vitro studies from both groups pointed to an increased cytoplasmic localization of FUS in cells expressing a mutant version of this protein, and the study by Kwiatkowski et al. [14] even demonstrated increased levels of insoluble FUS.

Prompted by the clinical, genetic and pathological overlap between FTD and ALS, Neumann et al. [19] subsequently identified by immunohistochemistry pathological FUS accumulations in neurons as well as in glial cells in a-FTLD-U, where by immunoblotting increased levels of insoluble FUS are found in postmortem brain extracts. Of note, at least all of the so far identified cases of a-FTLD-U are sporadic, and no mutations have been identified [16, 19, 22].

Following up on NIFID, another form of FTLD characterized by pathological accumulation of intermediate filaments and α-internexin, Neumann et al. [20] now demonstrate in the present issue that, in addition to a-FTLD-U, abundant FUS-immunoreactive inclusion pathology in neurons as well as in glial cells is a consistent histopathological finding in NIFID. In addition, as Munoz et al. [18] report in this *Acta Neuropathologica* issue, FUS pathology preferentially presents as neuronal cytoplasmic

and abundant glial cytoplasmic inclusions as a characteristic feature in BIBD.

Taken together, these three papers have identified intracellular FUS accumulations in neurons and glial cells as a unifying histopathological signature of three previously separate entities of the FTLD spectrum, which can now collectively be referred to as FUS proteinopathies [FTLD-FUS (instead of the previous term a-FTLD-U) and the two FUS subforms FTLD-FUS (NIFID) and FTLD-FUS (BIDB)]. However, not all forms of the former a-FTLD-U cases belong to the FUS proteinopathy family. As further reported in this issue by Holm et al. [13], FUS-immunoreactive inclusion pathology is absent in a hereditary form of FTD linked to chromosome 3 (FTD-3 [9, 25], caused by mutations in the *CHMP2B* gene [23, 25]). Thus, at present, FTD-3 seems to remain the only unknown within FTLD-U (i.e., yet unidentified ubiquitinated protein).

The FUS gene, located on chromosome 16, codes for a ubiquitously expressed 526 amino acid ribonuclear protein capable of binding to RNA and DNA [1, 2] which is involved in a multitude of cellular processes ranging from proliferation [4], DNA repair [3] to transcription regulation as well as splicing [26] and transport of RNA between intracellular compartments [27]. Thus, FUS shares with TDP-43 a number of functional (and to some degree also structural) similarities [reviewed in 15]. Significantly, FUS knock-out mice show perinatal mortality [10]. The fact that FUS has been implicated with neuronal plasticity and maintenance of dendritic integrity [7, 8] does not come as a surprise given its function in RNA transport; indeed, protein synthesis in neurons apparently proceeds in a more compartmentalized manner than previously anticipated [6, 11], and consequently, as one may expect, FUS-deficient neurons exhibit decreased spine arborization and aberrant morphology [7]. On the other hand, if so, what is the molecular mechanism leading to the proportionally higher or even exclusive FUS expression in nuclei of neurons and glial cells, respectively [2], in comparison to most other cell types?

While the studies commented here are significant by themselves in that they close an important gap in FTLD classification, they—probably even more important—have huge potential not only to advance our general understanding of neurodegenerative processes but also to take respective research efforts into new directions. For example, as alluded to earlier, the possibility that spatial organization of protein synthesis in neurons (due to compromised RNA transport) is compromised as a result of FUS deficiency should be rigorously tested.

So, when should we expect FUS pathology in FTD? At present, one should screen for neuronal and glial FUS accumulations in all FTLD cases lacking tau or TDP-43 pathology. At present, due to the rarity of these diseases, it remains unclear whether all a-FTLD-U, NIFID and BIBD cases can indeed be attributed to FUS protein aggregation, requiring the study of additional cases to confidently generalize the reported findings. Also, although no FUS mutations were identified in the a-FTLD-U, NIFID and BIBD cases studied so far, FUS mutations need to be considered in any (sporadic and familial) case of FTLD-FUS. However, even if mutations in the FUS gene would be identified in a subset of these cases, the question arises as to the nature of the mechanisms leading to FUS aggregation. Does, in analogy to other neurodegenerative conditions, cellular stress trigger (or enhance) FUS pathology? Are there FTLD-FUS cases with predominance of neuronal (cytoplasmic, neuritic or intranuclear) over glial FUS pathology (or vice versa), and if so, to what extent do these forms differ clinically? Last but not least, the question of FUS pathology specificity needs to be addressed. Is it indeed specific for a-FTLD-U, NIFID and BIBD (as suggested in the studies for a-FTLD-U and NIFID by Neumann et al. [19, 20] in which no or no concomitant FUS-immunoreactive pathology was found in various TDP-43 proteinopathies, tauopathies and α-synucleinopathies) or does it—in parlance to TDP-43—occur in other conditions including non-neurodegenerative ones as well? In this respect, it is notable that the characteristic small round neuronal intranuclear inclusions in Huntington's disease are strongly stained with antibodies against FUS [5].

In summary, the most recent and present studies in this issue of *Acta Neuropathologica* on FUS pathology significantly close the gap in the classification of FTLD cases. Besides FTLD-tau and FTLD-TDP, FTLD-FUS now emerges as the third most common cause among FTLD proteinopathies. Considering the structural and functional similarities shared by TDP-43 and FUS, the remarkably close relationship between FTD and ALS syndromes with their significant clinical overlap in particular between FTLD-TDP and FTLD-FUS cases does not come as a surprise. This notion is meticulously exemplified by BIBD, where in addition to supratentorial structures anterior horn motor neurons are consistently affected [18]. Of course, in analogy to TDP-43, it still has to be proven beyond doubt that FUS indeed represents the pathogenically underlying biochemical defect and not merely occurs as a secondary phenomenon. Finally, at least for now, two more questions remain open: (1) which proteinopathy (if there is one) is hidden behind FTD-3 [12] and (2) does the enigmatic entity of dementia lacking distinctive pathology (FTLD-ni, no inclusions) still exist? Having these questions answered, conFUSion in FTLD will be history.

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