

ALS with frontotemporal deficits and FTD - a spectrum or separate entities

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Despite significant clinical overlapping, frontotemporal dementia with motor neuron disease and amyotrophic lateral sclerosis (ALS) have been historically considered as separate entities. In 2006, TAR DNA-binding protein 43 (TDP-43), encoded by the TARDBP gene, has been identified as the major pathological protein the so-called frontotemporal lobar degeneration (FTLD) with ubiquitin-immunoreactive (up-in) inclusions (FTLD-U) with or without motor neuron disease and amyotrophic lateral sclerosis (ALS). This finding created the basis for unifying the majority of FTLD-U and ALS as a spectrum of TDP-43 pathies. Interestingly, though, groups focusing on ALS and FTD are yet to integrate fully, either by structural reasons as these groups were historically allocated to different clinics or because it was unclear why some patients showing TDP-43 type B proteinopathy would not manifest motor neuron disease. The discovery of the C9orf72 mutation in 2011 shed light on this questions.

Affected members of families with C9orf72 mutation, an autosomal dominant disease, express a broad range of clinical phenotypes from pure ALS to pure FTD, AD-type symptoms, and parkinsonism. Studies in C9orf72 families unravel that certain genetic variations including in the gene TMEM10b and ATAX2 may contribute to the phenotype variation. In summary, TDP-43 type B proteinopathy underlies the majority of ALS with frontotemporal deficits and FTD cases. Genetic variations may impact the clinical presentation and explain the broad spectrum of presentations seen in these patients sharing similar neuropathological features.