TDP-43 IN SPORADIC AND FAMILIAL ALS

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For nearly 20 years the neuropathological hallmark of ALS has been polyubiquitinated skein-like and globular inclusions in the perikaryon and proximal axon of motor neurons in the brain stem and spinal cord. These have recently been shown to colocalise with a 25kDa, C-terminal, detergent-resistant fragment of TAR DNA binding protein TDP-43. These inclusions are present in ~90% of ALS cases and a subset of frontotemporal lobar degeneration cases now termed the "TDP-43 proteinopathies" (1–3). TDP-43 is predominantly a nuclear protein but in those neurons with the most striking cytoplasmic inclusions there is a marked reduction in nuclear TDP-43, suggesting that it has been sequestered in the cytoplasm and that miss-localisation may play a role in pathogenesis.

We have recently identified a TARDBP mutation (the gene encoding TDP-43) in a single familial ALS kindred (4). The mutation is predicted to result in a single amino-acid substitution of methionine for valine at residue 337. We also identified two sporadic MND missense mutations (Q331K and G293A) in neighbouring amino acids. The only two mutations studied showed increased tendency to protein cleavage and were toxic to the embryonic chick spinal cord neurons causing apoptosis and developmental delay.

Fourteen missense mutations have now been reported in familial and sporadic MND (3, 5–7). All but one of the mutations, reside in the C-terminal domain.

The finding of rare mutations in TARDBP in familial and sporadic ALS does implicate a mechanistic role for TDP-43 cleavage, mislocalisation and aggregation in ALS and FTD. These pathogenic mutations should provide important biological tools that will enable us to develop more informative cellular and animal models of ALS.

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