NEURODEGENERATIVE DISEASE

Researchers identify the protein in c9FTD/ALS inclusions

Frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) are thought to belong to a spectrum of neurodegenerative disorders with shared clinicopathological and genetic features. Recent studies have identified a class of disorders collectively termed c9FTD/ALS, which are caused by GGGGCC hexanucleotide repeat expansions in the *C9orf72* gene. Research groups led by Leonard Petrucelli of the Mayo Clinic and Dieter Edbauer of Ludwig–Maximilians University have now independently shown that translation of the GGGGCC expansions in *C9orf72* results in the characteristic TDP-43-negative neuronal inclusions of c9FTD/ALS (the protein composition of which was previously unknown), and may be an underlying pathogenetic mechanism in these diseases.

The researchers' analysis of RNA transcripts of *C9orf72* suggested that GGGGCC expansions in this gene undergo repeat-associated non-ATG (RAN) translation. They generated poly-(Gly-Ala), poly-(Gly-Pro) and poly-(Gly-Arg) peptides representing all possible RAN translations of GGGGCC (termed C9RANT by Petrucelli's team), and created polyclonal anti-C9RANT antibodies that targeted these peptides. In brain and CNS tissue from patients

C9RANT immunoreactivity in the thalamus and cerebellum. Image courtesy of L. Petrucelli.

with c9FTD/ALS, but not from patients lacking GGGGCC expansions in *C9orf72*, these antibodies were shown to bind to the neuronal cytoplasmic and intranuclear inclusions—a finding that was corroborated by Edbauer's group.

“Targeting RAN-translated peptides, their aggregation or the RNA structures necessary for their formation may show great promise as treatment strategies in patients with c9FTD/ALS,” comments Petrucelli, noting that anti-C9RANT-immunoreactive aggregates are specific to this disease. “Therapies to target C9RANT aggregates may [also] prove beneficial to *C9orf72* mutation carriers,” he continues. “Detection of C9RANT in cerebrospinal fluid may provide a valuable diagnostic and prognostic tool for identifying patients

carrying the *C9orf72* repeat expansion and then tracking the progression of the disease in at-risk individuals.” Petrucelli also highlights the key role of immunoassays for detection of C9RANT in cerebrospinal fluid. His team plans to conduct further evaluations of their preliminary findings to confirm whether C9RANT peptides are neurotoxic.

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Original articles Ash, P. E. *et al.* Unconventional translation of *C9ORF72* GGGGCC expansion generates insoluble polypeptides specific to c9FTD/ALS. *Neuron* doi:10.1016/j.neuron.2013.02.004 | Mori, K. *et al.* The *C9orf72* GGGGCC repeat is translated into aggregating dipeptide-repeat proteins in FTLD/ALS. *Science* doi:10.1126/science.1232927