

Investigating the Pathogenic Mechanisms of ALS and FTD Caused by C9orf72 Repeat Expansions

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Frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) are adult-onset neurodegenerative diseases that impose a significant socioeconomic burden. FTD is the most common form of dementia in individuals under the age of 60 and is marked by progressive neurodegeneration primarily affecting the frontal and temporal lobes of the brain. ALS, the most prevalent motor neuron disease, selectively targets motor neurons, leading to paralysis and death typically within 2–5 years of diagnosis. Hexanucleotide (GGGGCC) repeat expansions in a non-coding region of the C9orf72 gene represent the most common genetic cause of both ALS and FTD, collectively referred to as C9ALS/FTD. Proposed disease mechanisms include both loss-of-C9ORF72-function and gain-of-repeat-toxicity resulting from the expression of mutant repeat RNAs and the accumulation of dipeptide repeat proteins. To investigate these mechanisms, we have developed a range of animal models that separately or jointly assess the contributions of loss-of-C9ORF72-function and gain-of-repeat-toxicity. Our findings demonstrate that both mechanisms contribute to disease onset and progression in an age-dependent manner. These results highlight the urgent need for therapeutic strategies that can concurrently address these complex and intertwined disease pathways in C9ALS/FTD.

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