Prognostic factors in C9orf72 amyotrophic lateral sclerosis

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Spinal-onset disease in male patients drives the poor survival in a large population of European ALS patients

The discovery of the C9orf72 hexanucleotide repeat expansion heralded significant advancement in the understanding of amyotrophic lateral sclerosis (ALS). Critical, the C9orf72 mutation represents the most common genetic cause of ALS (up to 50% of familial and 20% of sporadic ALS), responsible for the majority of motor and cognitive manifestations across the ALS–frontotemporal dementia (FTD) continuum. Pathologically, the C9orf72 mutation is associated with TDP-43 protein aggregation, the hallmark of ALS cases and is also present in 50% of FTD. The exact function of the normal C9orf72 protein remains undefined; however, it seems to play a major role in cellular trafficking, specifically in neurons. The loss of function of C9orf72, generation of toxic RNAs species and sequestration of RNA-binding proteins, and accumulation of dipeptide-repeate proteins have been proposed as possible pathogenic mechanisms.

The C9orf72-related ALS cases seem to manifest several distinct clinical features, including earlier age of onset, reduced survival and higher prevalence of dementia. Separately, C9orf72 mutation is infrequent in Asian population. Given the significant clinical variability and heterogeneity of prognosis across C9orf72 populations, understanding downstream mechanisms will be critical for the future improvement of ALS/FTD management, the development of biomarkers and disease-modifying therapies, as well as the identification of new prognostic factors.

In the current issue of JNPR Rooney and colleagues delineate a significant advancement in understanding prognostic factors for patients with C9orf72 mutations. Specifically, C9orf72 status and clinical data obtained from a large cohort of 4925 ALS patients were analysed using flexible parametric survival models. Subsequent analysis determined that male patients with spinal-onset disease were driving the reduced survival outcomes, consistent with a gender-mediated effect. This study, representing the largest combined analysis of prognostic features linked to C9orf72 expansion, will inevitably influence future targeted therapeutic strategies and the design of clinical trials.

The suggestion of a gender effect on survival mediated by C9orf72 warrants further consideration. It was proposed that the incidence and prevalence of ALS in general were higher in males, with a male preponderance for early disease onset. Men have a greater likelihood of spinal-onset disease, while in women, the bulbar region appears the more common onset region. Additionally, it has been reported in the SOD1 mouse model that male transgenic mice have a reduced survival in comparison with their female littermates, suggesting differential motor neuron vulnerability driven by gender. Even though the exact mechanics of this difference are not well understood, a recent study suggested that mitochondrial dysfunction may become evident earlier in male mouse models of ALS, possibly attributed to differences in oestrogen levels.

Despite these recent biological and genetic discoveries surrounding the C9orf72 mutation, there remain many questions for ALS patients. Most genetic mutations in ALS have been linked to RNA-mediated mechanisms, suggesting therapeutic strategies against RNA toxicity, including targeting RNA with antisense oligonucleotides (ASOs). Encouragingly, a recent trial of a single-dose injection of ASOs produced a reduction in RNA foci and dipeptide-repeat proteins in a novel C9orf72 transgenic model. It remains to be seen whether these results can be translated into the human disease. In the interim, the contribution of dissecting prognostic factors associated with C9orf72 remains essential, highly relevant for the design of future therapeutic strategies.

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