Confirmation that the C9orf72 expansion is associated with accelerated respiratory function decline in Amyotrophic Lateral Sclerosis.

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Introduction: The C9orf72 hexanucleotide repeat expansion is causal in ALS and has a negative effect on prognosis. Recently the C9orf72 repeat expansion was associated with an accelerated deterioration of respiratory function and survival in a cohort of 372 Portuguese patients [1].

Methods: Cases presenting to the Irish ALS MDT with both longitudinal Sniff Nasal Inspiratory Pressure (SNIP) and C9orf72 testing were including in the present study. Clinical variables and survival characteristics of these patients were collected. Joint longitudinal and time to event models were constructed to explore the longitudinal characteristics of the cohort by C9orf72 status.
Results: Six hundred and thirty cases were included and 58 (9.2%) carried the C9orf72 repeat expansion. In a Cox survival model age of onset, diagnostic delay, bulbar onset and C9orf72 status were all prognostic. Plots of the longitudinal trend after joint modelling revealed that those carrying the expansion had a worse respiratory function throughout the course of their disease than those without. Furthermore, modelling by site of onset and sex sub-groups revealed that this difference was maximal in male spinal onset cases.

Discussion: Our results confirm findings in the Portuguese cohort that the C9orf72 repeat expansion is associated with accelerated respiratory function decline. Furthermore, our finding that male spinal onset patients with the C9orf72 repeat expansion suffer faster respiratory decline than others is congruent with previous findings form 5 European cohorts that male spinal onset C9orf72 expansion carrying patients suffer a worse prognosis than others[2].

References:1.Miltenberger-Miltenyi G, Conceição VA, Gromicho M, Pronto-Laborinho AC, Pinto S, Andersen PM, et al. C9orf72 expansion is associated with accelerated decline of respiratory function and decreased survival in amyotrophic lateral sclerosis. Journal of Neurology, Neurosurgery & Psychiatry. 2019;90:118–20./ 2. Rooney J, Fogh I, Westeneng H-JH, Vajda A, McLaughlin R, Heverin M, et al. C9orf72 expansion differentially affects males with spinal onset amyotrophic lateral sclerosis. Journal of neurology, neurosurgery, and psychiatry. 2017;88:281.