Nature Reviews Neurology | Published online 14 Oct 2016; doi:10.1038/nrneurol.2016.161

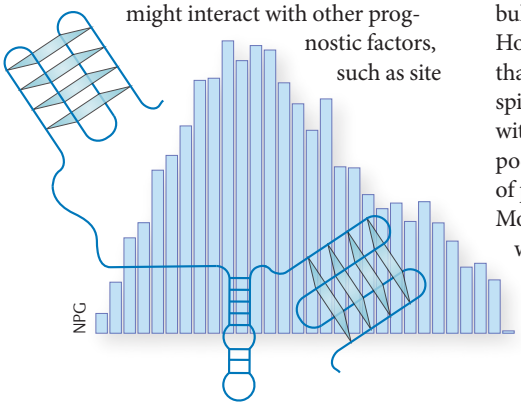
MOTOR NEURON DISEASE

C9orf72 repeat expansion linked to aggressive disease in male patients with spinal-onset ALS

> Our findings demonstrate an … interaction … which appears to drive the overall survival effect

Male patients with spinal-onset amyotrophic lateral sclerosis (ALS) who carry *C9orf72* repeat expansion variants are more likely to have a rapidly progressing disease than are other patients with spinal-onset ALS, according to new research. The findings provide novel insight into the factors contributing to prognostic variability among patients with ALS.

C9orf72 repeats have previously been linked with young age at ALS onset and reduced survival. "We wondered whether the *C9orf72* status might interact with other prognostic factors, such as site of onset," says James Rooney, the lead author of the study.



The investigators compared the *C9orf72* status and demographic and clinical data in 4,925 European patients with ALS. Using Royston-Parmar flexible parametric regression, the researchers produced survival curves for subgroups of patients.

The main predictors of prognosis were age, diagnostic delay, *C9orf72* status and site of onset. In line with earlier studies, Rooney and colleagues found an association between bulbar onset and shortened survival. However, the researchers also found that a subgroup of patients with spinal onset — namely, male patients with *C9orf72* repeats — also had poor prognosis, comparable to that of patients with bulbar-onset disease. Moreover, patients in this subgroup were on average aged 59 years at disease onset — younger than patients with spinal-onset or with bulbar-onset disease.

"Our findings demonstrate an intriguing and previously unrecognized interaction between the expanded variant and male patients with spinal-onset disease, which appears to drive the overall survival effect," Rooney summarizes. The results suggest that the pathophysiological impact of the *C9orf72* expansion in this subgroup could differ from that in female patients and/or patients with bulbar-onset disease.

According to the researchers, limited understanding of disease heterogeneity in ALS has been one of the factors limiting progress towards new treatments. The discovery could help us to understand the distinct pathophysiological mechanisms of ALS in different patient populations.

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ORIGINAL ARTICLE Rooney, J. *et al.* C9orf72 expansion differentially affects males with spinal onset amyotrophic lateral sclerosis. *J. Neurol. Neurosurg. Psychiatry* http://dx.doi.org/10.1136/jnnp-2016-314093 (2016)