LOWER CIRCULATING GAS6 LEVELS ARE ASSOCIATED WITH BULBAR PHENOTYPE AND FASTER DISEASE PROGRESSION IN AMYOTHROPIC LATERAL SCLEROSIS PATIENTS.

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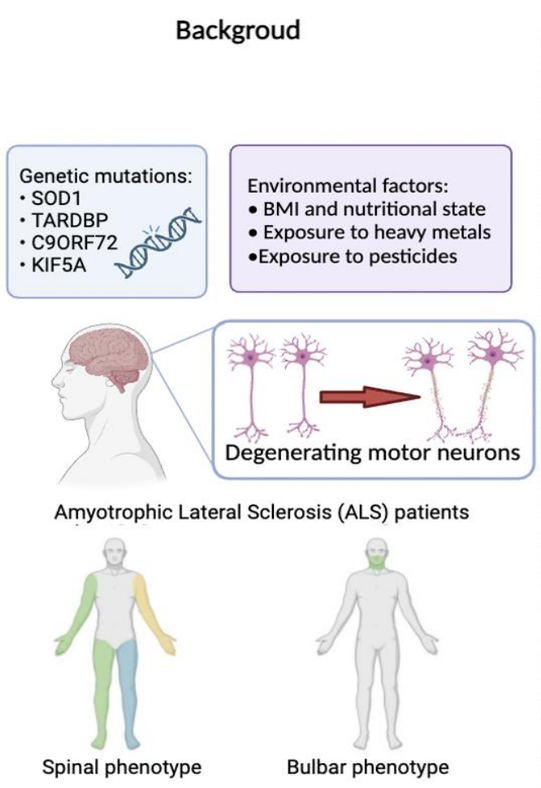

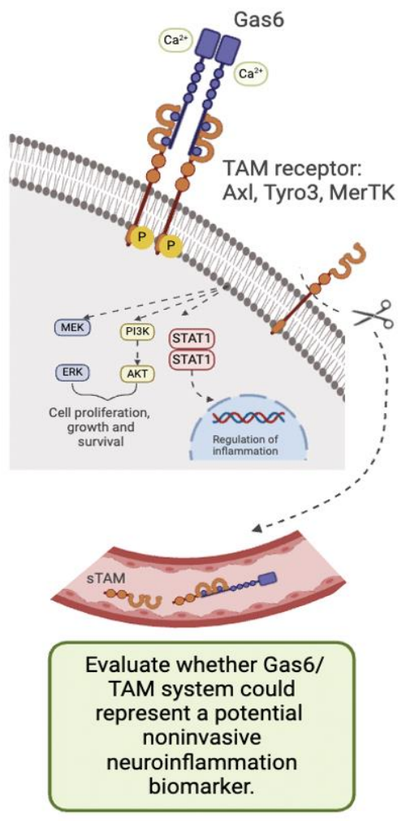

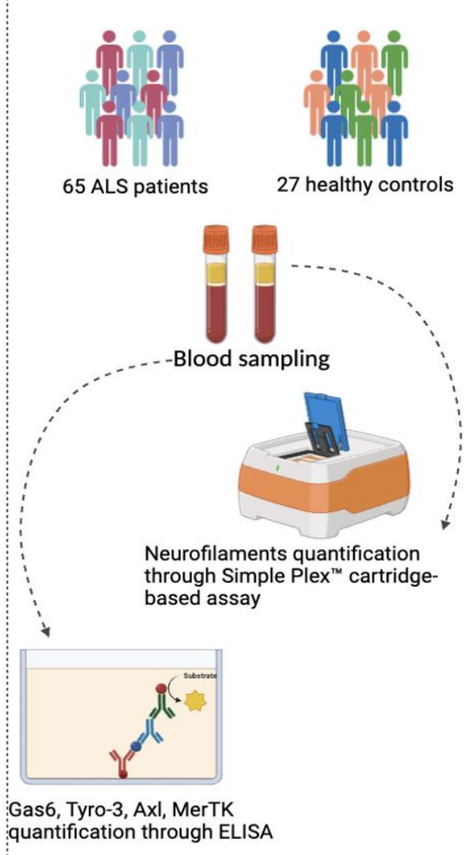

Introduction and aim: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder that primarily affects the motor neurons in the brain and spinal cord. While the exact cause of ALS is not fully understood, a combination of genetic and environmental factors is believed to contribute to its development. Growth Arrest-Specific 6 (Gas6), a vitamin K-dependent protein, has been recognized to enhance survival of oligodendrocytes and neurons and it has been associated with different kinds of (neuro)inflammatory conditions [1]. Therefore, our aim was to determine a possible implication of Gas6 in ALS by evaluating the prognostic value of circulating Gas6 and its soluble receptors (sAxl, sMer, sTyro-3) in ALS patients.

Methods: We conducted a prospective observational study including 65 ALS patients and measured the circulating serum levels of Gas6, sAxl, sMer, sTyro-3 and neurofilaments (NfLs). Serum levels of Gas6, sAxl, sMer and sTyro-3 were determined in duplicate by enzyme-linked immunosorbent assay (ELISA) using a commercial kit. Serum neurofilaments concentration was measured in duplicate using the Simple Plex™ cartridge-based assay on the Ella™ platform. As controls, 27 subjects were included, matched for age and sex and without clinical evidence of any neurological disease.

Results: In our ALS cohort, lower serum levels of Gas6, and concomitantly higher levels of NfLs, were associated with a more aggressive disease, expressed with bulbar phenotype (*p*-value for Gas6=0.03) and faster progression (*p*-value for Gas6=0.03). Also, serum Gas6 was able to distinguish (area under the curve, cut-off 13.70 ng/mL, sensitivity 69.57%, specificity 72.72%) between fast and slow progressors.

Spinal and bulbar phenotypes

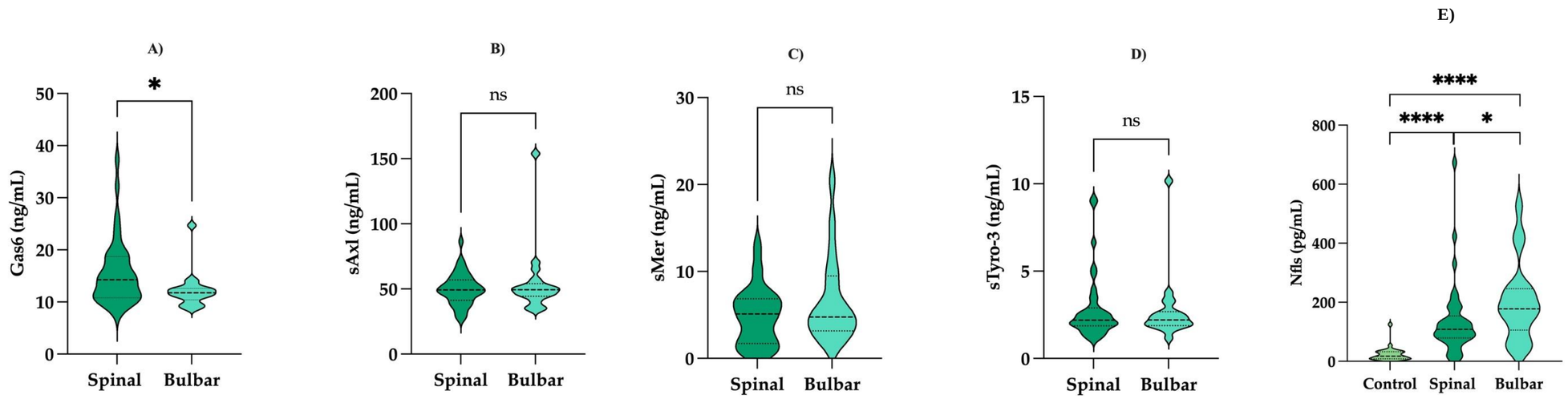

Figure 1 Comparison between median serum levels of Gas6 (A), sAxl (B), sMer (C), sTyro-3 (D) and NfLs (E) in patients with spinal and bulbar disease phenotypes.

Fast and slow disease progression

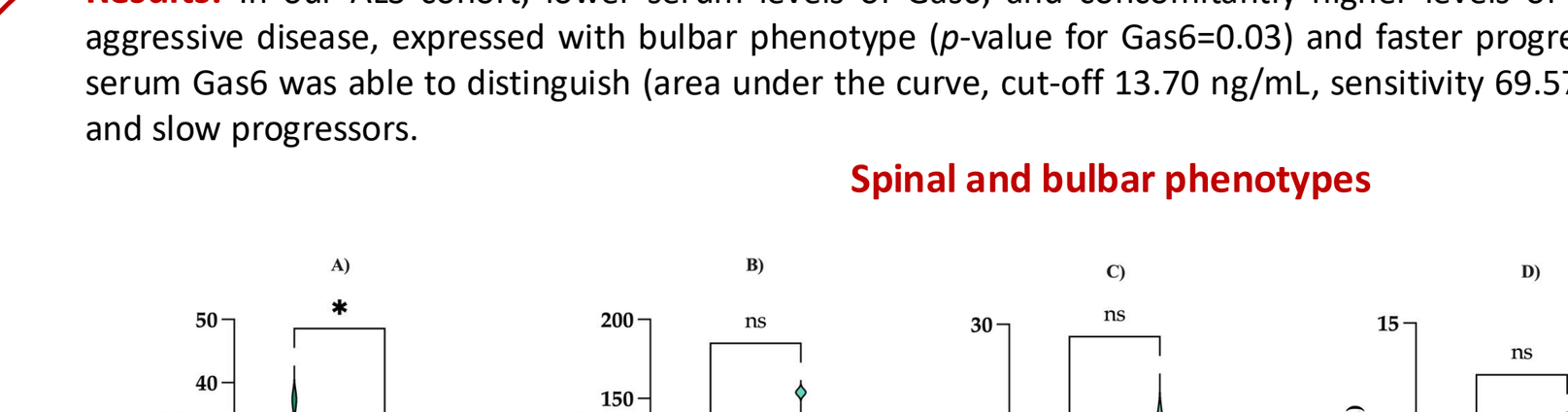

Figure 2 Comparison between median serum levels of Gas6 (A), sAxl (B), sMer (C), sTyro-3 (D) in patients with fast and slow disease progression.

Figure 3 Comparison between median serum levels of NfLs (E) and Gas6 (F) in patients with fast and slow disease progression and healthy controls. Results are shown as medians [IQR]. ROC curve for serum Gas6 levels (G) predicting a faster disease progression.

Conclusion: Our data uncover Gas6 as a new player in ALS. Higher Gas6 levels are associated with the spinal phenotype and with a slower disease progression, suggesting a possible role of this protein as a protective molecule in ALS patients. Lastly, although this was not the main outcome of the study, the clear difference between NfL levels in ALS patients compared to healthy controls, and in patients with faster disease progression, supports the fundamental role of this molecule in detecting an active neurodegenerative process.

Bibliography:
1. Shankar SL, O'Guin K, Cammer M, et al (2003) The growth arrest-specific gene product Gas6 promotes the survival of human oligodendrocytes via a phosphatidylinositol 3-kinase-dependent pathway. Journal of Neuroscience 23:4208–4218. https://doi.org/10.1523/jneurosci.23-10-04208.2003