Genetic and functional analysis of TIA1 in a large cohort of FALS and patients with early onset ALS.

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Progress in genetics accelerated the discovery of causative genes in Amyotrophic Lateral Sclerosis (ALS) and about 25 genes have now been incriminated in the disease. Mutations in TIA1 have recently been identified in patients with familial or sporadic forms of the disease. This gene is also known as a cause of Welander Distal myopathy (WD), mostly affecting the upper distal muscles and characterized in some cases by the presence of rimmed vacuoles in muscular biopsy. Mutations identified in ALS or WD patients were all located in the C-terminal prion-like domain of the protein. Other genetic studies performed on cohorts of Abstracts ENCALS meeting 2019 15-17 May Tours

ALS patients did not find any TIA1 mutation and additional analyses are needed before considering TIA1 as a genetic cause of the disease. TIA1 encodes a protein involved in the formation of stress granules, small and transient compartments allowing the protection of mRNA in cells exposed to stress conditions. To confirm the contribution of TIA1 to ALS disease, we performed exome analyses of 150 FALS (devoid of mutation in any major ALS genes) and 80 ALS patients with early onset of the disease (including 20 trios) as genetic causes could be preponderant in these patients. We identified a c.653G>A, p.Cys218Tyr (C218Y) variant, located in a RNA-recognition motif of the protein, in a female patient who started ALS at 30 years. The analysis of the trio showed that this variant was transmitted by her healthy father. This variant was absent from gnomAD control database, affected a residue that is conserved among species (including Zebrafish) and was predicted to be deleterious by in silico analyses (SIFT, MutationTaster, Polyphen-2 and Panther) and by a pathogenic CADD phred score at 29. Analysis of fibroblasts from this patient showed round TIA1-positive inclusions, some of which were also positive for p62, one of the neuropathological hallmarks of ALS disease detected in post-mortem motor neurons. Similar inclusions were also positive for TDP-43 but remained negative for FUS. Our future directions will evaluate the dynamics of stress granules after exposing the fibroblasts to stress conditions and CRISPR/Cas9 gene editing technology will be used to determine whether these phenotypes can be rescued by suppressing the expression of this TIA1 mutation. Overall these results will help to conclude about the pathogenicity of this novel TIA1 mutation.