Identification of new HSPB8 variants linked to familial Amyotrophic Lateral Sclerosis

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The Heat Shock Protein B8 (HSPB8) is a small heat shock protein involved in the proteostasis network. HSPB8, with its obligatory partner BAG3, promotes the removal of misfolded proteins and protein aggregates, via autophagy. We have demonstrated that the overexpression of HSPB8 enhances the clearance of soluble and insoluble form of mutated SOD1, the C-terminal TDP-43 fragments and RAN translated dipeptide of the C9ORF72 repeats, causative of Amyotrophic Lateral Sclerosis (ALS). Interestingly, mutations in HSPB8 (K141E/N/T) are found in diseases that affect neurons and muscle cells, like distal hereditary motor neuropathy type II and Charcot Marie Tooth (CMT) disease type2L.
Using exome sequencing (NGS) on a large cohort of fALS patients, available at the Istituto Auxologico Italiano, novel HSPB8 gene variants predicted to be pathogenic in fALS have been identified.
We performed preliminary studies aimed to characterize the behaviour of these new variants compared to the wild type form.
We found that one of the ALS-associated HSPB8 variants:
i) affects the capability of endogenous HSPB8 to bind to its partner BAG3 (required for HSPB8 stabilization and functions);
ii) correlates with a reduced stability, although no changes of HSPB8 solubility was found;
ii) presents an altered mobility in native Gel Electrophoresis,
iv) reduces the pro-degradative power of HSPB8 on TDP-43 and mutant SOD1.
These data strongly indicate that the novel HSPB8 variant may be involved in fALS pathogenesis.~~These data strongly indicate that the novel HSPB8 variant may be involved in, or causative of, fALS.~~