Characterization of the p.L145F and p.S135N mutations in SOD1: impact on the metabolism of fibroblasts derived from Amyotrophic Lateral Sclerosis Patients

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Abstract: ALS is a fatal neurodegenerative disease characterized by the loss of the upper and lower motor neurons (MNs). About 10% of patients have a family history (familial, fALS); however, most patients seem to develop the sporadic form of the disease (sALS). *SOD1* (Cu/Zn superoxide dismutase-1) is the first studied gene among the ones related to ALS. Mutant SOD1 can adopt multiple misfolded conformation, lose the correct coordination of metal binding, decrease structural stability, and form aggregates. For all these reasons, it is complicated to characterize the conformational alterations of the ALS-associated mutant SOD1, and how they relate to toxicity. In this work, we performed a multilayered study on fibroblasts derived from two ALS patients, namely $SOD1^{L145F}$ and $SOD1^{S135N}$, carrying the p.L145F and the p.S135N missense variants, respectively. The patients showed diverse symptoms and disease progression in accordance with our bioinformatic analysis, which predicted the different effects of the two mutations in terms of protein structure. Interestingly, both mutations had an effect on the fibroblast energy metabolisms. However, while the $SOD1^{L145F}$ fibroblasts still relied more on oxidative phosphorylation, the $SOD1^{S135N}$ fibroblasts showed a metabolic shift toward glycolysis. Our study suggests that SOD1 mutations might lead to alterations in the energy metabolism.