Exploring the correlation between bioenergetic profile and ALS pathogenesis in fibroblasts of TARDBP p.G376D mutation carriers

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Amyotrophic Lateral Sclerosis is an incurable neurodegenerative disease in which the death of motor neurons causes weakness and wasting of muscles until death [1]. About 5-10% of cases are due to genetic mutations inherited from a family member (fALS). ALS patients display heterogeneous phenotypes, and the differences can also be seen among individuals bearing the same mutation.

TDP-43, a versatile RNA/DNA binding protein involved in RNA metabolism, is associated with a risk of the disease [2,3], but the mechanisms by which it exerts the pathogenetic effects are still not well known.

For these reasons, in this work we studied fibroblasts derived from an Italian family bearing the p.G376D mutation in the glycine-rich domain, a critical component of the protein [4]. We performed a metabolic analysis of cells derived from symptomatic and asymptomatic carriers and our data suggest that the G376D mutation causes an imbalance in the oxidative stress/antioxidant defence system which leads (or may be caused) to metabolic alterations. Generally, ALS cells display mitochondria impairments that possibly cause a deregulation of the oxidative phosphorylation/glycolysis balance inducing a switch toward a predominantly glycolytic metabolic profile at late disease stage. Of note, our data suggest that the mitochondria impairments represent an underlying family trait compensated in different ways depending on individual background.

References

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