Mutations in C19orf12 have been identified in patients affected by Neurodegeneration with Brain Iron Accumulation (NBIA), a clinical entity characterized by iron accumulation in the basal ganglia. By using western blot analysis with specific antibody and confocal studies, we showed that wild-type C19orf12 protein was not exclusively present in mitochondria, but also in the Endoplasmic Reticulum (ER) and MAM (Mitochondria Associated Membrane), while mutant C19orf12 variants presented a different localization. Moreover, after induction of oxidative stress, a GFP-tagged C19orf12 wild-type protein was able to relocate to the cytosol. On the contrary, mutant isoforms were not able to respond to oxidative stress. High mitochondrial calcium concentration and increased H2O2 induced apoptosis were found in fibroblasts derived from one patient as compared to controls. C19orf12 protein is a 17 kDa mitochondrial membrane-associated protein whose function is still unknown. Our in silico investigation suggests that, the glycine zipper motifs of C19orf12 form helical regions spanning the membrane. The N- and C-terminal regions with respect to the transmembrane portion, on the contrary, are predicted to rearrange in a structural domain, which is homologs to the N-terminal regulatory
domain of the magnesium transporter MgtE, suggesting that C19orf12 may act as a regulatory protein for human MgtE transporters. The mutations here described affect respectively one glycine residue of the glycine zipper motifs, which are involved in dimerization of transmembrane helices and predicted to impair the correct localization of the protein into the membranes, and one residue present in the regulatory domain, which is important for protein-protein interaction.