PFN1 in Amyotrophic Lateral Sclerosis – *In silico* Analysis, Computational Structural Modeling and Molecular Dynamics

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INTRODUCTION: Non-synonymous single nucleotide polymorphisms (nsSNPs) in the profilin 1 gene (*PFN1*) have been reported to be involved in the development of familial amyotrophic lateral sclerosis (fALS), a fatal adult-onset motor neuron disorder with no effective treatment that leads to rapid death. In the present study, we used bioinformatics tools to model mutated PFN1 sequences and study the mechanisms through which the mutations affect protein structure and functionality. **OBJECTIVE:** Evaluate the mutational effects on protein structure and function of the SNPs of human PFN1 using predictive computational methods and modeling. **MATERIAL AND METHODS:** We performed a predictive functional analysis of all of the described PFN1 nsSNPs associated with fALS development using 10 different algorithms. The Rosetta server was used to create theoretical models that were evaluated using TM-align for each mutation. These structures were energetically optimized by GROMACS package 4.5.5 using the AMBER 99S force field. During energy minimization, both native and mutant structures were solvated in an octahedral box with simple point charge (SPC) water molecules. Initially, the solvent molecules were relaxed, and all solute atoms were harmonically restrained to their original positions. Then, the whole molecular system was subjected to energy minimization. **RESULTS AND DISCUSSION:** The predictive functional analysis corroborated the link between PFN1 SNPs and the functional abnormalities that may be linked to fALS. A theoretical model was created for each sequence (native and mutant) and according to TM-Align results, the wild type model was topologically similar to the PFN1 experimental structure, but the mutated sequences resulted in significant structural changes that may contribute to functional disturbances related to fALS development. **CONCLUSION:** Our findings suggest that PFN1 polymorphisms may affect protein structure and function, and thus can be a factor in fALS development.

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