In Silico Analysis of HnRNPA1 in Amyotrophic Lateral Sclerosis

Krebs, B.B.; Oliveira, C.C.S.; De Mesquita, J.F.

Bioinformatics and Computational Biology Laboratory, UNIRIO, RJ, Brazil

Introduction: Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease that affects the upper and lower motor neurons. 5-10% of cases are genetically inherited, including ALS type 20, which is caused by mutations in the hnRNPA1 gene. **Objectives:** The goals of this study are to analyze the effects of non-synonymous single nucleotide polymorphisms (nsSNPs) on hnRNPA1 protein function, to model the complete tridimensional structure of the protein using computational methods and to compare the stability difference between the wild type and its variants through molecular dynamics simulations. **Material and Methods:** nsSNP, PhD-SNP, Polyphen2, SIFT, SNAP, SNPs&GO, SNPeffect, I-MUTANT, MutPred and PROVEAN were used to predict the functional effects of nsSNPs. *Ab initio* modeling of hnRNPA1 was made using Rosetta and refined using KoBaMIN. The structure was validated by PROCHECK, Rampage, ERRAT, Verify3D, ProSA and Qmean. TM-align was used for the structural alignment. FoldIndex, DICHOT, ELM, D2P2, Disopred and DisEMBL were used to predict disordered regions within the protein. Amino acid conservation analysis was assessed by Consurf, and the molecular dynamics simulations were performed using GROMACS. **Results and Discussion**: All mutations were predicted to decrease protein stability. Mutations D314V and D314N were predicted to increase amyloid propensity, and predicted as deleterious by at least three algorithms, while mutation N73S was predicted as neutral by all the algorithms. D314N and D314V occur in a highly conserved amino acid. The tridimensional model created using Rosetta showed an RMSD of 0.60Å when compared to the crystallographically solved fragment 1L3K. The structure was further optimized through molecular dynamics simulations. High scores on all validation algorithms confirmed the good quality of the modeled structure. **Conclusions:** Our findings show that the *in silico* modeled structure is reliable. They also suggest that the mutations affect hnRNPA1 structure, function, stability, and may play a major role in ALS20 development.

Keywords: Amyotrophic Lateral Sclerosis; *In Silico*; Molecular Dynamics

Sponsored by: FAPERJ, CNPq, CAPES-DAAD, UNIRIO