MOLECULAR MODELING OF HUMAN VAPB VARIANTS IN FAMILIAL AMYOTROPHIC LATERAL SCLEROSIS TYPE 8

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Introduction and objectives: Human single nucleotide polymorphisms (SNPs) are the most frequent type of genetic variation in the human population and can be associated with pathological conditions, such as Familial Amyotrophic Lateral Sclerosis (FALS). Over 20 genes have been implicated in the etiology of ALS, particularly the human vesicle-associated membrane-protein-associated protein B (VAPB) gene, which is widely related to ALS type 8. The objective of this study is to investigate, using a molecular modeling approach, the conformational changes in the VAPB mutant protein structures with respect to its native conformation.

Materials and methods: Through *in silico* analysis, 3D structural models were produced for VAPB wild type and mutants. Comparative modeling was performed by the Modeller, RosettaCM, SWISS MODEL, M4T, Hhpred and Phyre2 algorithms. *Ab initio* modeling was performed by the I-Tasser and Rosetta algorithms. The model evaluations were inferred using TM-align algorithms and were compared to the VAPB X-ray structure in the Protein Data Bank (PDB ID: 3IKK).

Results and conclusions: This analysis has generated models, topologically similar to the VAPB X-ray structure, as shown by the TM-align RMSD values. Structural changes were observed and may contribute to functional disorders, suggesting pathogenicity for most of the mutations. Therefore, the results suggest that the mutations in the VAPB protein (T46I, P56S, A145V, A160del, and V234I) can cause pathological protein variations associated with ALS8 development. The results were gathered, and a curated, actualized and free database is available at http://bioinfogroup.com/database/. Acknowledgments: CAPES-DAAD, CNPq, FAPERJ, UNIRIO. Key words: ALS 8, Molecular modeling, VAPB.