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# A systematic approach to investigate the predicted effect of nonsynonymous SNPs in the human prion protein gene: A molecular modeling and molecular dynamics study

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## Abstract

Human prion diseases are caused by misfolding or aggregation of the Human Prion Protein (HuPrP). Missense mutations in the HuPrP gene, contribute to conversion of $HuPr^{PC}$ to $HuPrP^{Sc}$ and amyloid formation. In order to better understand and predict the role of HuPrP mutations, we developed the following procedure: first, the Human Genome Variation database and dbSNP databases were consulted, and literature were reviewed for the retrieval of aggregation-related nsSNPs of the HuPrP gene. Next, we used three different methods – Polymorphism Phenotyping (PolyPhen), PANTHER, and Auto-Mute – to predict the effect of nsSNPs on the phenotype. The predictions against experimentally reported effects of these nsSNPs were compared to evaluate the accuracy of the three methods. Also, structural analyses of the native protein against mutated models were investigated using molecular modeling and molecular dynamics (MD) simulation methods. From these results, three missense mutations, from different functional groups, including V210I, Q212P, and E219K were selected and extensive molecular dynamics simulations of these three mutations performed to compare their dynamics and conformations to those of the wild type HuPrP in both monomeric and dimeric forms. In conclusion, our results show the applicability of our procedure for the prediction of damaging nsSNPs. Our study also elucidates the obvious relationship between predicted values of aggregation-related nsSNPs in HuPrP gene and molecular modeling and MD simulations results.

## Biography

Dr. Jahandideh received his Ph.D. in Biophysics from Tarbiat Modares University, Tehran, Iran in 2010. He then took his postdoctoral training in computational biology at the University of Alabama at Birmingham and Sanford-Burnham Medical Research Institute, La Jolla, California. Before moving to USA, he has worked as an assistant professor and Vice-Chancellor for Research in the Department of Medical Physics at Shiraz University of Medical Sciences, Shiraz, Iran. He has published more than 25 papers in reputed journals and reviews research manuscripts at number of journals, including Bioinformatics, BMC Bioinformatics, and BMC Genomics.