

2nd International Summit on **Integrative Biology**

August 04-05, 2014 Hilton-Chicago/Northbrook, Chicago, USA

Molecular dynamics study of the dominant-negative E219K polymorphism in human prion protein

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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 HuPrPC to HuPrPSc and amyloid formation. Based on our previous comprehensive study (Jahandideh and Zhi, 2013), three missense mutations, from two different functional groups, i.e. disease-related mutations, and protective mutations, were selected and extensive molecular dynamics simulations of these three mutants performed to compare their dynamics and conformations to those of the wildtype HuPrP. In addition to simulations of monomeric forms of mutants, in order to study the dominant-negative effect of protective mutation (E219K), 30-ns simulations were performed on E219K-wildtype and wildtype-wildtype dimeric forms. Our results indicate that, although after 30-ns simulations the global three-dimensional structure of models remain fairly intact, disease-related mutations (V210I and Q212P) introduce local structural changes, i.e. close contact changes and secondary structure changes, as well as global flexibility changes. Our results support the loss of hydrophobic interaction in result of mutations in hydrophobic core that has been reported by previous NMR and computational studies. On the other hand, protective mutation (E219K) results in a growth of helix, and significant increases of overall flexibility of protective mutation during 30-ns simulation. In conclusion, the simulations of dimeric forms suggest that the dominant-negative effect of protective mutation (E219K) is due to the incompatible structures and dynamics of allelic variants during conversion process.

Biography

Samad Jahandideh received his PhD 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.

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