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Mutation induced conformational fluctuations in glucokinase: A molecular dynamics study

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Glucokinase (GK) is the predominant hexokinase that controls hepatic glucose disposal and acts as a glucose sensor for insulin secretion in pancreatic β-cells. Inactivating and activating mutations in GK gene can influence the affinity for glucose that can leads to altered glucose levels in the blood and are responsible for Type 2 diabetes (MODY2). Molecular Dynamics is a powerful computational simulation technique that can produce numerical estimations of physical properties of a molecule by making use of a variety of molecular mechanics force fields. In this study the impact of a total of 42 MODY2 mutations on the confirmation of GK was studied. The list of MODY2 mutations were retrieved from SWISS PROT data base and the X-ray crystallographic structure of pancreatic Glucokinase with resolution of 1.5 A^{o} was obtained from PDB data base. The intact structure was optimized with Polak-Ribiere conjugate gradient algorithm at an RMS gradient of 0.1 and dynamics simulations were carried out in AMBER force field for a period of 0.6 ps and a simulation temperature of 300 K. The same procedure was carried out by introducing the MODY2 mutations in the intact GK structure sequentially and the energy values were compared to the intact structure. All the 42 mutated structures were submitted to PDBSum to analyze the variations in the secondary confirmations that are aroused due to each mutation. The results showed there is variation in the Kinetic and Potential energies of mutated structures with respect to intact GK structure. The PDBSum results clearly showed that the induced mutations affected the intact conformation and these conformational changes were seen in Substrate and ATP binding regions also. The results allowed following the influence of mutations on conformational variations of GK structure, especially in the substrate and ATP binding regions. This can help to elucidate the variations in binding affinity of Glucose to the substrate binding region in the MODY2 condition.

Biography

Nanda kumar has completed his post graduation in Bioinformatics from Sri Venkateswara institute of medical science, Tirupati and worked as Lecturer and research fellow in Thapar University, Punjab. Presently pursuing his doctoral studies in Bioinformatics in department of Zoology, Sri Venkateswara University, Tirupati. He is hard working and quick grasping with good communication skills. He stood first and received best student award for his post graduation from Sri Venkateswara institute of medical sciences. He is one of the DST INSPIRE Award winners of the year 2010 and is the first person to receive this fellow ship in Sri Venkateswara University.