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The Impact of Missense Mutation in Phosphatidylinositol Glycan Class A Associated to Paroxysmal Nocturnal Hemoglobinuria and Multiple Congenital Anomalies-Hypotonia-Seizures Syndrome 2: A Computational Study

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Abstract : Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal blood disorder that manifests with hemolytic anemia, thrombosis, and peripheral blood cytopenias. The disease is caused by the deficiency of two glycosylphosphatidylinositols (GPI)-anchored proteins (CD55 and CD59) in the hemopoietic stem cells. The deficiency of GPI-anchored proteins has been associated with the somatic mutations in phosphatidylinositol glycan class A (PIGA). However, the mutations that do not cause PNH is associated with the multiple congenital anomalies-hypotonia-seizures syndrome 2 (MCAHS2). To best of our knowledge, no computational study has been performed to explore the atomistic level impact of PIGA mutations on the structure and dynamics of the protein. In the current work, we are mainly interested to get insights into the molecular mechanism of PIGA mutations. In the initial step, we screened the most pathogenic mutations from the pool of publicly available mutations. Further, to get a better understanding, pathogenic mutations were mapped to the modeled structure and subjected to 50ns molecular dynamics simulation. Our computational study suggests that four mutations are highly vulnerable to altering the structural conformation and stability of the PIGA protein, which illustrates its association with PNH and MCAHS2 phenotype.

Keywords : homology modeling, molecular dynamics simulation, missense mutations PNH, MCAHS2, PIGA
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