

Structural Characterization of missense mutation identified in BRCA2 using Comparative Biophysical and Dynamics Studies

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Breast cancer type 2 susceptibility (BRCA2) protein plays an essential role in the repair of DNA double-strand breaks and interstrand cross-links by Homologous recombination [1]. Germ-line mutations in *BRCA2* confer an increased risk of hereditary breast and ovarian cancer [2]. A large number of missense mutations have been identified in the DNA binding carboxy-terminal domain of BRCA2 which is also known to interact with FANCD2 [3]. However, majority of these missense mutations are classified as variants of 'Uncertain Significance' due to lack of structural, functional, and clinical studies. Accurate and reliable methods to predict the pathogenicity of variants are utmost required for better clinical management of the disease. Here we present a multi-disciplinary approach to characterize a missense mutation identified in the C-terminal domain of BRCA2. Different functional domains of the wild-type and mutant BRCA2 protein were cloned and the proteins were expressed and purified in bacterial system. Circular - dichroism and Fluorescence spectroscopic techniques were employed to evaluate the differences between secondary and tertiary structures of wild-type and mutant protein. Molecular Dynamics Simulation was further utilized to measure the effect of mutations on the structural conformation of the protein.

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