ABSTRACT

Breast cancer is globally the second most common invasive cancer. Mutations in *BRCA1* contribute to largest proportion of breast cancer cases. BRCA1 belongs to the tumor suppressor gene family, known for the ability to protect cells becoming cancerous. It plays a crucial role in genomic stability and controlled cell division through its involvement in DNA repair mechanism. RING (Really Interesting New Gene) finger domain is present at N-terminal of BRCA1 and aids in mediating protein-protein interactions. Cancer-linked mutations within the RING finger domain greatly impair the stability of BRCA1, predicted to have functional consequences and binding with other proteins. Functional effects of three previously reported mutations; C39R, C44R and P62S were analyzed in this study through bioinformatics analysis by Polyphen-2, ConSurf, MutPred and SWISS Model and cloning of RING finger domain and full BRCA1 gene for the evaluation of BRCA1 localization and function. cDNA was used to amplify the RING finger and BRCA1 using cloning PCR and ligated vector and inserts were transformed into DH5α cells to grow colonies. Cloned DNA was sequenced and matched with original gene sequences. All three mutations were damaging and residues were highly conserved with high scores as predicted in bioinformatics analysis. Homology based 3-D models of RING finger domain indicated the location of each variant. It is evident that mutation in these hydrophobic and conserved amino acids hinders the interaction of RING finger domain with several other proteins. In conclusion, it was found that selected variants of RING finger domain can be pathogenic and can damage the interactions of BRCA1 with its binding partners, hence leading cell towards instability. However functional assays are needed to further investigate and confirm these predictions.