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A novel carcinogenic PI3Kα mutation suggesting the role of helical domain in transmitting nSH2 regulatory signals to kinase domain

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Mutations in PIK3CA, which encodes p110α subunit of PI3K class IA enzymes are highly frequent (~40%) in breast cancer. Most of the hotspot gain-of-function PIK3CA mutations are clustered in exon 9 and 20 of this gene. In this study, we aimed to probe mutations in exon 9 of PIK3CA and computationally simulate their function since MD simulation is a powerful tool for predicting conformational dynamics of mutant protein kinases. Firstly PCR/HRM and PCR/sequencing were used for mutation detection in 40 breast cancer specimens. The identified mutations were queried via in-silico algorithms to check the pathogenicity. Then, the Molecular Dynamics (MD) simulations were utilized to assess the function of mutant proteins as a result, three samples were found to harbour at least one of the E542K, E545K and L551Q mutations of which L551Q has not been reported previously. All mutations were confirmed to be pathogenic and MD simulations revealed their impact on protein function and regulation. The novel L551Q mutant dynamics was similar to that of previously found carcinogenic mutants, E542K and E545K. A functional role for the helical domain was also suggested by which the inhibitory signal of p85α is conducted to kinase domain via helical domain. Helical domain mutations lead to impairment of kinase domain allosteric regulation. Interestingly, our results show that p110α substrate binding pocket of kinase domain in mutants may have differential affinity for enzyme substrates, including anit-p110α drugs. In conclusion, the novel p110α L551Q mutation could have carcinogenic feature similar to previously known helical domain mutations.

Keywords: Breast cancer, PIK3CA, Novel mutation, Molecular dynamics simulation.

Biography

I am Safoura Ghalamkari second-year PhD student from Department of laboratory of medicine, Medical School, University of Debrecen, Debrecen, Hungary. My research interests are functional and computational genetic study to figure out the effect of mutations on the protein structure and function. Now I am doing functional studies on rare genetic disorders under supervision of prof. Istvan Balogh, head of human genetics department. My previous research has been published in two international journals.

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