OMICS Group Conferences
Accelerating Scientific Discovery

3rd International Conference on
Clinical Microbiology & Microbial Genomics
September 24-26, 2014 Valencia Convention Centre, Spain

Investigation of S315R and S315T through structural analysis coupled with docking studies of isoniazid prodrug to wild type & mutant KatG of MDR-MTB

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Tuberculosis (TB) is one of the well spread and alarming disease worldwide, responsible for millions of deaths every year. With respect to TB cases, Pakistan ranks 8th among the 22 high burden countries of the world with 15% multiple drug resistance. Isoniazid resistant strains of Mycobacterium tuberculosis is increasingly becoming a global threat especially in the developing countries. Isoniazid resistance is considered to be directly associated with mutations in katG gene, encoding the catalase-peroxidase enzyme. KatG mutations (S315R and S315T) responsible for MDR-MTB, were considered in the present study to better understand their impact through structure based systematic computations and evaluations. It was observed that these mutations affect the protein structure and its interactions in the network. Our result showed important conformational changes in the structure of mutated KatG enzyme, which lead to changes in INH binding residues at the active site of KatG enzyme. Significant changes were observed in total ligand-receptor energy, interaction energy, electrostatic energy, salvation free energy and ligand-receptor conformational entropy. It can be inferred that, S315R and S315T mutations minimized the stability and flexibility of protein at INH binding residues that can lead to impaired enzyme function. We hoped that our analysis will help to explore the consequences of these mutations in a better way and will provide a detailed insight of some previously unexplored features.

Keywords: KatG; isoniazid; resistance; mutation; docking.

Biography

Muhammad Mumtaz Khan has completed his undergraduate degree in Microbiology from Hazara University, Manshera, Pakistan in 2005 at the age of 23. Dr. Khan completed his PhD degree from University of Karachi, Karachi, Pakistan in 2014. He is currently working as Assistant Professor in Department of Microbiology University of Haripur, Haripur, Pakistan. He worked in doctoral research on rifampicin and isoniazid associated multiple drug resistance in Mycobacterium tuberculosis in Pakistan. He has published 9 articles in international reputed journal and also made 14 NCBI/GenBank submissions.

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