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In Silico Analysis of Structural Impact of Single Nucleotide Polymorphisms in the Human KRAS Gene-Implications in Lung Cancer

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ABSTRACT

The protein product of the normal KRAS gene performs an essential function in normal tissue signaling, and the mutation of a KRAS gene is an essential step in the development of many cancers. Lung cancer is one of the most common cancers in the world. It is a leading cause of cancer death in men and women in the United States. Cigarette smoking causes most lung cancers. The more number of cigarettes a person smokes per day the more is the risk of lung cancer. High levels of pollution, radiation and asbestos exposure may also increase risk. Despite the reported association of KRAS gene mutations with human disease susceptibility, the comprehensive computational analysis of coding, non coding and regulatory SNPs, and their functional impacts on protein level, still remains unknown. In this study, we performed a insilico analysis of the structural impact of SNP that are deleterious to KRAS structure and function. An in silico prediction was performed usindg db SNP. Moreover, to understand how mutations can affect the strength of the interactions that bind proteins together we submitted data to I-TASSER server and structural data was obtained from the web server. The PDB structure of KRAS protein was obtained from RCSB Protein Data Bank (PDB ID:4DSO) and Structural theoretical models of KRAS were created using db SNP and I-TASSER servers. Our results demonstrate that 12 SNPs in the KRAS gene may be deleterious to KRAS structure and function. 12 deleterious and high-risk SNPs were identified in KRAS gene. 9 of these are located at highly conserved amino acid sites in the protein domain (RAS). Additionally, we detected 2 SNPs in the core residues of the protein and 8 SNPS at interface. Finally, we classified six SNPs as top high-risk (M72L,F156L,D153G,K147E,K5E and Q61H)) which may alter the putative structure of KRAS's domain, particularly in G1, G2, G3, G4 and G5 motif regions. These same regions are critical to the protein's structure and function. This study adopted an extensive in silico analysis of the highly polymorphic KRAS gene and will be a valuable resource for future targeted mechanistic and population-based studies.

Keywords: KRAS gene;lung cancer;Insilico analysis;PDB; db SNP;I-TASSER.