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Computational Investigation on Structural and Functional Impact of Oncogenes and Tumor Suppressor Genes on Cancer

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Abstract : Within the sequence of the whole genome, it is known that 99.9% of the human genome is similar, whilst our difference lies in just 0.1%. Among these minor dissimilarities, the most common type of genetic variations that occurs in a population is SNP, which arises due to nucleotide substitution in a protein sequence that leads to protein destabilization, alteration in dynamics, and other physio-chemical properties' distortions. While causing variations, they are equally responsible for our difference in the way we respond to a treatment or a disease, including various cancer types. There are two types of SNPs; synonymous single nucleotide polymorphism (sSNP) and non-synonymous single nucleotide polymorphism (nsSNP). sSNP occur in the gene coding region without causing a change in the encoded amino acid, while nsSNP is deleterious due to its replacement of a nucleotide residue in the gene sequence that results in a change in the encoded amino acid. Predicting the effects of cancer related nsSNPs on protein stability, function, and dynamics is important due to the significance of phenotype-genotype association of cancer. In this thesis, Data of 5 oncogenes (ONGs) (AKT1, ALK, ERBB2, KRAS, BRAF) and 5 tumor suppressor genes (TSGs) (ESR1, CASP8, TET2, PALB2, PTEN) were retrieved from ClinVar. Five common in silico tools; Polyphen, Provean, Mutation Assessor, Suspect, and FATHMM, were used to predict and categorize nsSNPs as deleterious, benign, or neutral. To understand the impact of each variation on the phenotype, Maestro, PremPS, Cupsat, and mCSM-NA in silico structural prediction tools were used. This study comprises of in-depth analysis of 10 cancer gene variants downloaded from Clinvar. Various analysis of the genes was conducted to derive a meaningful conclusion from the data. Research done indicated that pathogenic variants are more common among ONGs. Our research also shows that pathogenic and destabilizing variants are more common among ONGs than TSGs. Moreover, our data indicated that ALK(409) and BRAF(86) has higher benign count among ONGs; whilst among TSGs, PALB2(1308) and PTEN(318) genes have higher benign counts. Looking at the individual cancer genes predisposition or frequencies of causing cancer according to our research data, KRAS(76%), BRAF(55%), and ERBB2(36%) among ONGs; and PTEN(29%) and ESR1(17%) among TSGs have higher tendencies of causing cancer. Obtained results can shed light to the future research in order to pave new frontiers in cancer therapies.

Keywords : tumor suppressor genes (TSGs), oncogenes (ONGs), non synonymous single nucleotide polymorphism (nsSNP), single nucleotide polymorphism (SNP)
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