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Association of DNA repair genes with Tumor mutational burden and microsatellite instability

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Abstract

DNA repair is a critical process to maintain DNA integrity. It is conducted by distinct pathways of genes, many of whose alterations are thought to result in genomic instability and hypermutability, ultimately contributing to tumorigenesis. Tumor Mutation Burden (TMB) and Microsatellite Instability (MSI) are considered as immunotherapy efficacy biomarkers. However, there has been little characterization of the association between DNA repair genes and TMB/MSI in cancer.

We systematically analyzed 282 DNA repair genes involved in 20 DNA repair pathways. These genes were evaluated for mutations based on 274 sequenced tumor samples from the TCGA database. The functional impacts of these mutations were analyzed, and only damaging mutations were used for the subsequent analysis. The most frequently mutated genes were identified. The association between the damaging mutations and TMB/MSI status was calculated for each gene, and the significant genes were subject to further pathway enrichment analysis. We also compared the gene expression between TMB high and low as well as between MSI-H and MSI-L/MSS for each gene based on their RNAseq data. The potential associations with TMB/MSI high phenotypes were evaluated. 10 genes, including POLE, were identified that are significantly mutated in TMB high samples as compared to MSI-H samples. Loss of function of these genes may result in an ultra-mutated phenotype. Contradicting the notion that POLE mutation is predominantly associated with MSS tumors and are mutually exclusive with the complete loss of MMR, we found about half of POLE-mutant samples (8/16) were MSI high, five of which had MMR mutations.

Biography:

Jason Ding is currently a senior student at Mountain Lakes High School and a student intern at Admera Health, working on genomics data analysis and DNA repair pathway research. Prior to an intern at Admera, Jason had worked as an intern at Mount Sinai Hopital and Memorial Sloan Kettering Cancer Center as intern student. His projects includes genomics CNV analysis and checkpoint protein functional analysis.

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