The Potential of Melanoma Cancer Predisposition Genes in Personalized Healthcare for Pilots, Aircrew, and Astronauts

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Background

- Space ionizing radiation poses significant cancer risks for astronauts, pilots, and aircrew. Recent data from the Armed Forces Health Surveillance Division reveals an 87% increase in melanoma incidence among Department of Defense aircrew.
- Melanoma, the most dangerous and lethal type of skin cancer, is highly invasive and can spread to other organs if left untreated. Major risk factors include exposure to UV and ionizing radiation, as well as genetic predisposition.
- Despite known carcinogenic effects of ionizing radiation, the interaction between genetic predisposition and occupational radiation exposure in melanoma progression remains poorly understood, hindering the development of effective prevention and detection strategies for high-risk groups, especially astronauts, pilots, and aircrew.
- *CDKN2A* is a major tumor suppressor controlling cell cycle progression. *TERT* encodes an essential part of the telomerase enzyme, responsible for telomere elongation, which is crucial for cancer cell replicative immortality. *BRCA1, ATM, CHEK2* are key for cellular DNA damage repair machinery, which is responsible for maintaining genomic integrity. *TP53* is an important tumor suppressor regulating cell proliferation, cell cycle progression, apoptosis, etc.

Methods

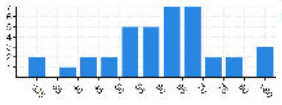
- We analyzed 23 melanoma cancer predisposition genes (CPGs) and identified the frequency of pathologic variants using data from the National Institutes of Health – All of Us database.
- Additionally, we examined The Cancer Genome Atlas (TCGA) data from the National Cancer Institute, encompassing 1,849 melanoma patients across 11 cohorts, to determine the impact of CPGs on melanoma metastasis.
- Melanoma genomic data were then processed and mapped in Integrative Genomics Viewer and other graphic programs to plot mutations of cancer predisposition genes.
- Metastasis site percentage values were calculated based on TCGA data. Chi-squared Tests were applied for statistical analysis.

NIH National Cancer Institute Center for Cancer Genomics

TCGA The Cancer Genome Atlas

(https://www.genome.gov/Funded-Programs-Projects/Cancer-Genome-Atlas)

Diagnosis age



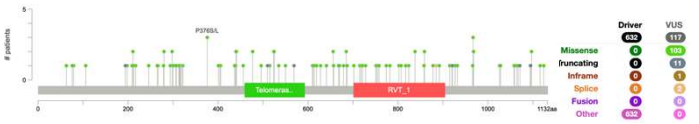


Figure 1: *TERT* gene mutation map in melanoma patients

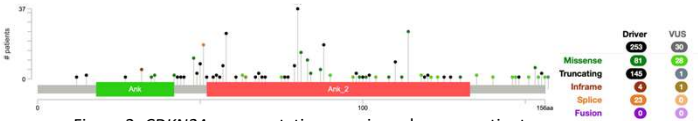


Figure 2: *CDKN2A* gene mutation map in melanoma patients

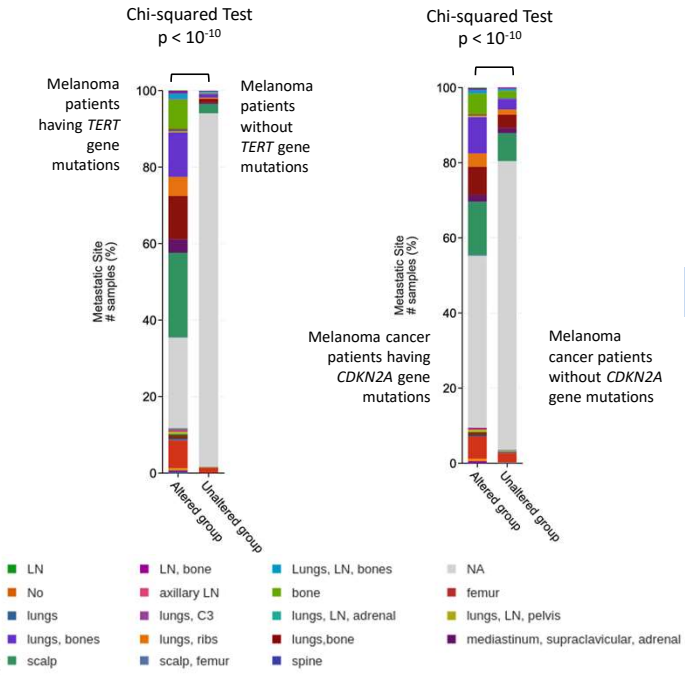


Figure 3: Increase in melanoma metastasis in the presence of *TERT* or *CDKN2A* cancer predisposition gene mutations

Results

- Pathogenic or likely pathogenic gene variants such as *BRCA1, ATM, CDKN2A, ERCC2, CHEK2, TERT*, and *TP53* were found to be most prevalent within the American population.
- More importantly, our study discovered specific melanoma CPG mutations in *TERT, CDKN2A, ATM, MITF, and other genes that are strongly associated with* a remarkable increase in patient metastasis.

Conclusion

- This study highlights the critical role of melanoma CPGs in advancing cancer prevention for high-risk occupational groups.
- Individuals with specific melanoma CPG variants, particularly those associated with increased metastasis risk, may benefit from intensified screening protocols and early interventions for preventing metastatic progression.
- These findings have the potential to transform melanoma cancer prevention for high-risk populations and improve clinical outcomes as the survival rate for melanoma varies significantly based on the stage of diagnosis: over 99% for localized disease, 74% for regional disease, and 35% for distant disease. Further research is needed to evaluate the prevalence of these variants in aircrew and astronaut populations, with the goal of refining melanoma prevention, screening, and treatment strategies for these vulnerable groups.

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