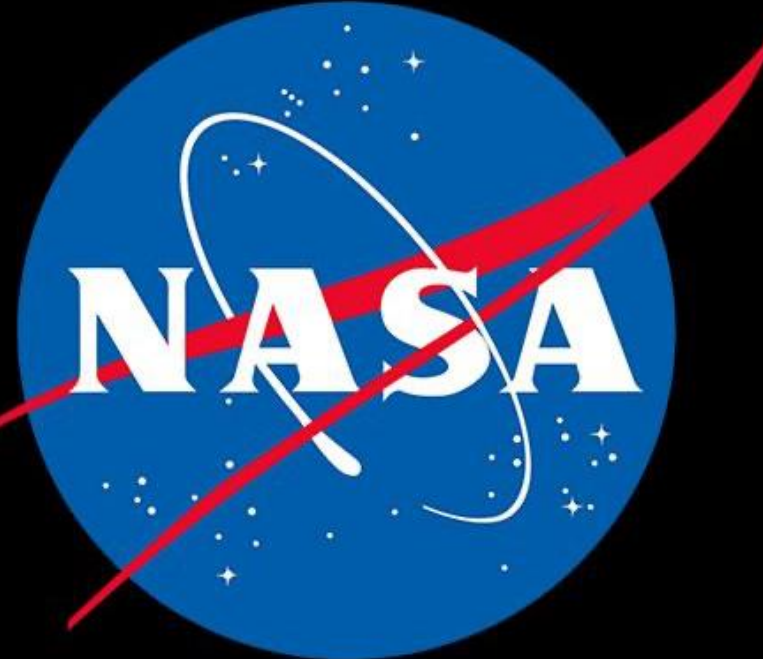




SOMATIC MUTATION ANALYSIS IN SPACEFLIGHT: NASA TWINS GENOME STUDY

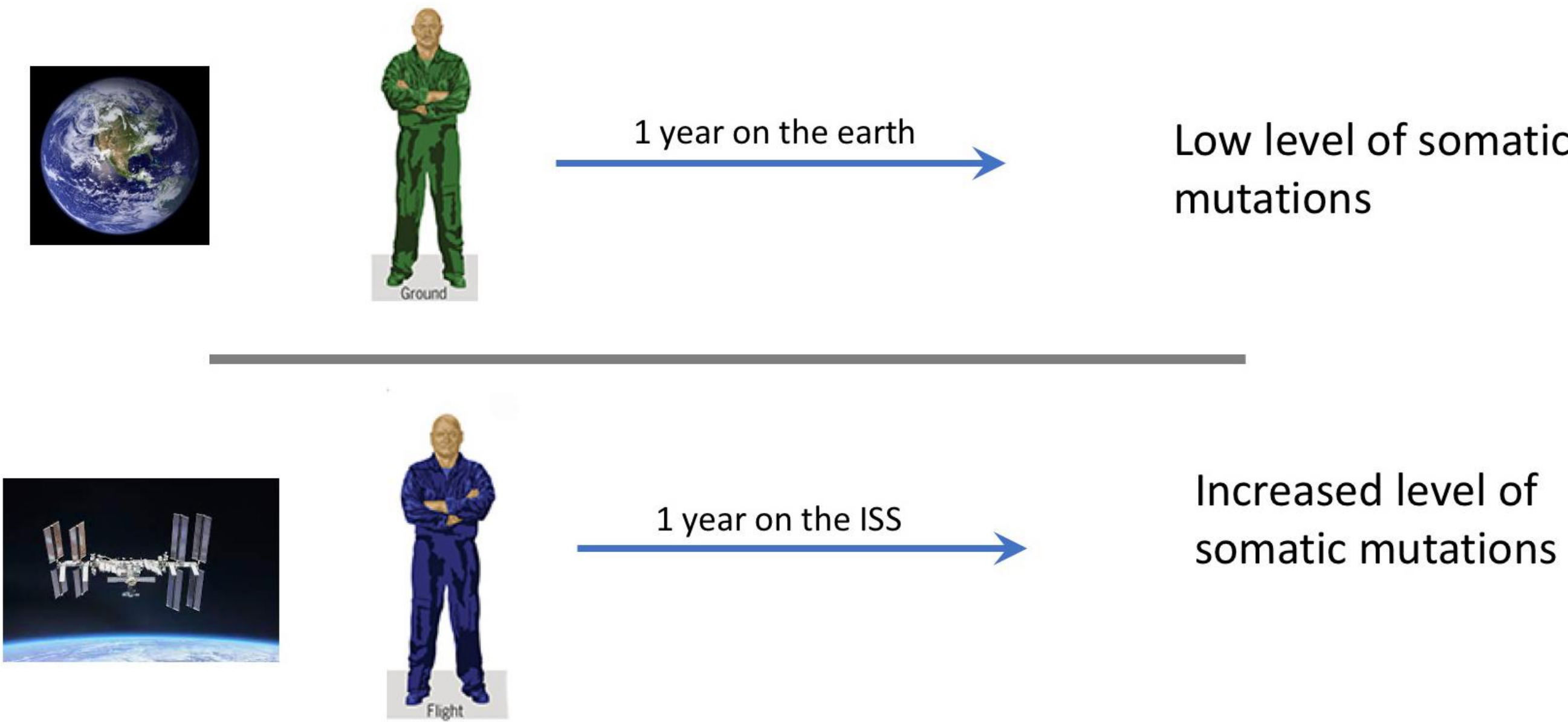
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ABSTRACT

The NASA Twins Genome Study investigates the effects of spaceflight on somatic mutation accumulation by comparing genome-wide sequence data from a spaceflight astronaut and his Earth-bound twin. Utilizing advanced computational software on high performance computers, this study identifies and maps somatic mutations, with implications for understanding spaceflight-associated health risks, including cancer, neurodegeneration, and cardiovascular disease. The findings aim to bridge rodent and human space research, offering insights into tissue-specific pathophysiology, risk models, and potential therapeutic interventions.

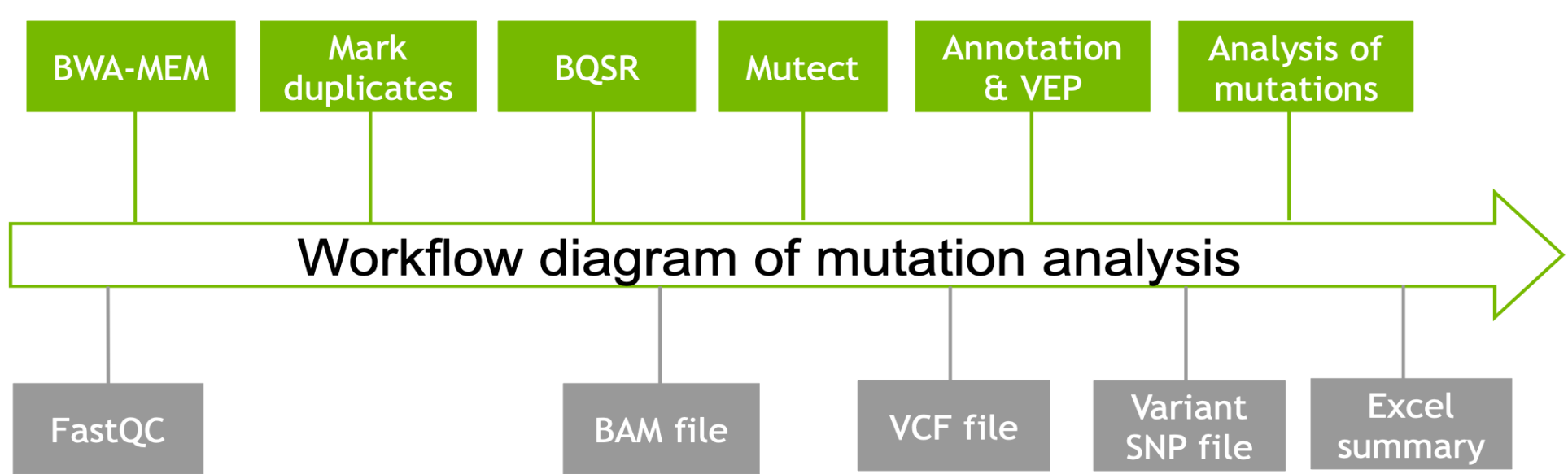
BACKGROUND

Somatic Mutations are acquired genetic alterations in somatic cells, distinct from heritable germline mutations. They are known to drive cancer and are implicated in degenerative and inflammatory diseases. **Benefits** of studying somatic mutations include better understanding of spaceflight-induced disease risk, and potential development of biomarkers for disease diagnosis and disease monitoring (“personalized medicine”).



METHODS

Integration of Mutation Workflow Analysis



Accelerated mutation analysis workflow. This diagram illustrates the integration of NVIDIA **Parabricks** (a GPU-accelerated genomics toolkit) and **GATK4** (Genome Analysis Toolkit version 4) with open-source workflow frameworks like **Nextflow** (a data-driven workflow management system), **WDL** (Workflow Description Language), and **Toil** (a scalable workflow engine) for high-performance, customizable genomic analysis pipeline. Supporting tools include **Samtools** (Sequence Alignment/Map tools), **BCFtools** (Binary Alignment/Map and Variant Call Format tools), and **FastQC** (a quality control tool for high-throughput sequence data). Leveraging **GPUs** (Graphics Processing Units) and containerization enhances scalability and reproducibility.

METHODS

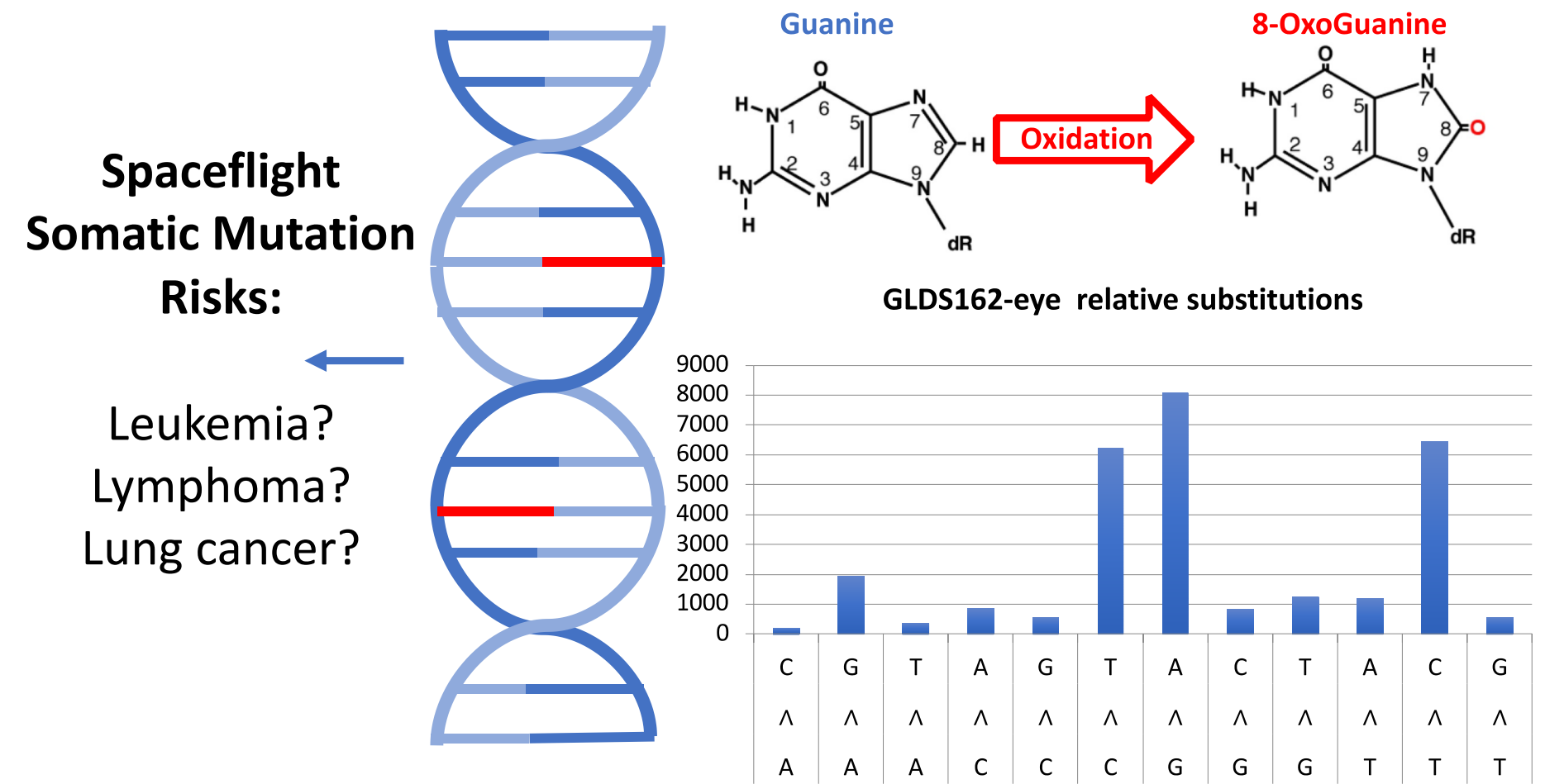
Mutation Calling Pipeline (Software):

Quality Control: Tools like FastQC assess raw sequencing data; low-quality bases and adapters are trimmed.
Alignment: High-quality reads aligned to the reference genome using BWA-MEM, generating BAM files for spaceflight and ground-control samples.
Recalibration: GATK tools correct systematic sequencing errors to enhance variant calling accuracy.
Somatic Mutation Detection: GATK Mutect2 identifies mutations exclusive to the spaceflight sample, refined using FilterMutectCalls for high-confidence somatic variants.
Annotation: Functional insights provided by ANNOVAR, detailing impacts, pathogenicity, and gene associations.

Computational Resources:
NASA Ames Supercomputer:
Pleiades Architecture: 11,207 nodes, 241,324 cores, 7.09 petaflops peak performance.
Advanced GPU-enhanced nodes for high-throughput, parallel processing.

Proven capability in studying complex biological systems, including human genome analysis.

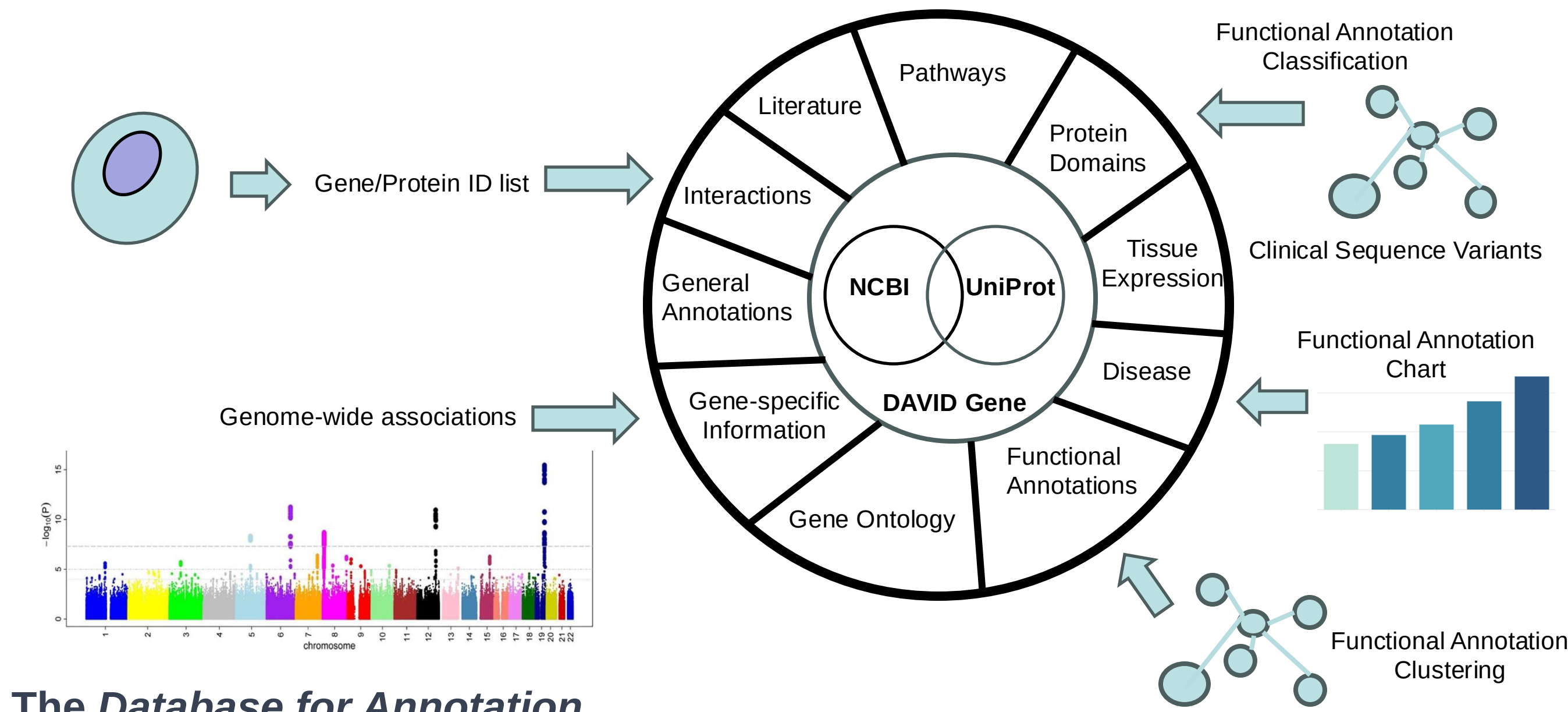
Oxidative DNA Damage: Guanine Substitutions Link to Cancer Risk



Guanine was the most frequently substituted base, most often involving conversion to adenine. This suggests that guanine oxidation may be playing a significant role in the process of somatic mutation on board the ISS. Of all the nucleotide bases, guanine is the most readily oxidized because of endogenous production of reactive oxygen species (ROS) inside cells.

RESULTS

Implications for Astronaut Health Deriving biological meaning from somatic mutations



The Database for Annotation, Visualization, and Integrated Discovery (“DAVID”) encompasses a suite of functional annotation tools tailored to elucidate the biological relevance of somatic mutations. Built upon the comprehensive DAVID Knowledgebase and the DAVID Gene concept, which integrates diverse functional annotations from multiple sources, DAVID’s tools excel in establishing connections between gene sequence variants (somatic mutations) and diseases. DAVID’s tools can unravel crucial associations between specific gene sequence variants and diseases, thereby gaining deeper insights into their biological implications.

INSIGHTS FROM MICE

- **Rapid accumulation of somatic mutation occurs in mice flown aboard the ISS.**
- **Genome instability in space occurs to a much higher degree than expected and may contribute to some of the known effects of spaceflight.**
- **Guanine oxidation pathways of somatic mutation are strongly associated with cancer risk.**

PROJECT STATUS

The next step will be to perform an analysis of somatic mutations in humans flown aboard the ISS, using already-obtained data from the **NASA Twin Study**. We have completed LSAH approval, NASA IRB approval, and we have finalized the documents for subject consent. *Consent pending.*

REFERENCE

Stolc, V., Karhanek, M., Freund, F., Griko, Y., Loftus, D. J., & Ohayon, M. M. (2024). Metabolic stress in space: ROS-induced mutations in mice hint at a new path to cancer. *Redox biology*, 78, 103398.

FUNDING

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