Reactive Oxygen Species in the Brain: The Good, the Bad, and the Ugly

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Symposium on "Short or Long Sleep Duration and its Links with Sleep, Mood, Psychomotor and Immune Disorders"

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Global Metabolic Pandemic: the prevalence of Metabolic Dysfunction (T2DM) has been increasing at an alarming rate despite the use of obesity drugs and diabetic agents.

Incidence and prevalence:

- 285 million in 2010 (annualized Inflation Rate 6.55%),
- 422 million in 2014 (annualized Inflation Rate 10.3%),
- 463 million in 2019,
- 537 million in 2021,
- 568 million projected in 2030

Health care costs in the US total $3.2 trillion per year (75% is chronic metabolic disease).

WHY is it getting worse?

WHAT is the cause of metabolic disease?

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- **Metabolic Syndrome Diseases:**

- Cardiovascular Disease
- Hypertension
- Diabetes
- Lipid abnormalities
- Non-alcoholic fatty liver disease
- Cancer
- Dementia
- **Sleep Disorders**

- No cures, just treatments: **How to stop the pathology?** **Reduce sugar intake.**

Differentiating Between Causes and Symptoms in Metabolic and Brain Health

Clinically recognized *subcellular* pathologies associated with metabolic dysfunction:

1. Oxidative stress (excess reactive oxygen species, ROS),
2. Glycation,
3. Mitochondrial dysfunction,
4. Insulin resistance,
5. Inflammation,
6. Epigenetics (Methylation),
7. **DNA mutation (GWAS)**

What do these cellular dysfunctions have in common? **Excess ROS!**

Fructose-Induced Oxidative Stress: Understanding the Role of Excess Reactive Oxygen Species in *Depletion of Neuronal Energetics*.

1.Effects on the Brain: High fructose intake is linked to changes in brain function, affecting areas governing appetite and reward (and addiction), including the hypothalamus.

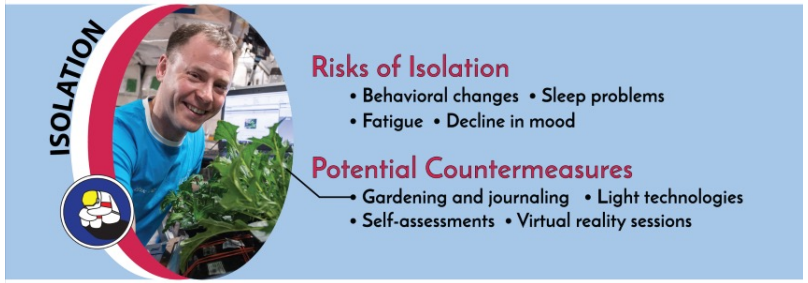
2.Insulin Resistance: Insulin resistance reduces cells' sensitivity to insulin, raising blood sugar levels. Excessive fructose intake might contribute to insulin resistance in the brain.

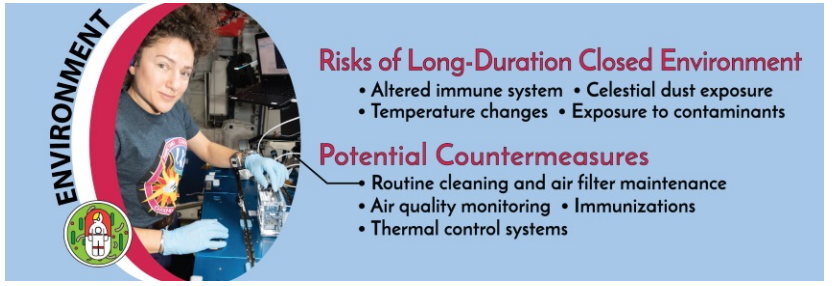
3.Neurological Conditions: Studies connect insulin resistance and metabolic issues to neurological conditions like Alzheimer's disease. Emerging evidence indicates *metabolic dysfunction* in neurodegenerative disease development.

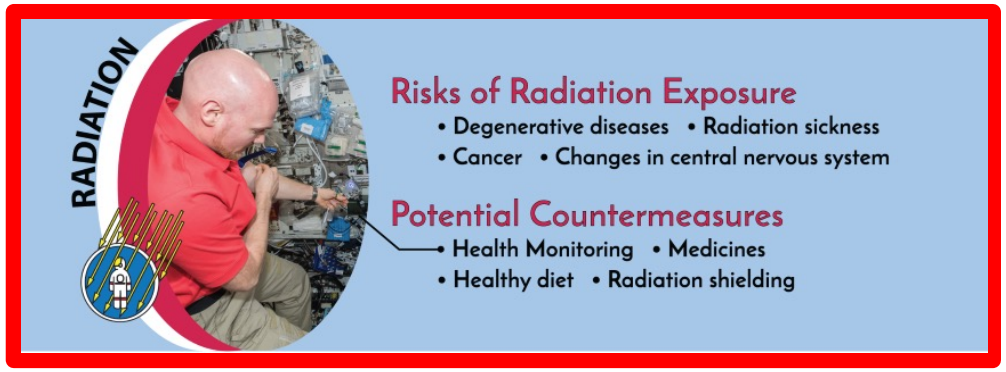
4.Inflammation and Oxidative Stress: Too much fructose intake leads to higher inflammation and oxidative stress, harming tissues, including the brain. Chronic inflammation and oxidative stress contribute to insulin resistance. In animal studies, fructose lowers ATP by inducing mitochondrial dysfunction (by inhibition of AMP kinase).

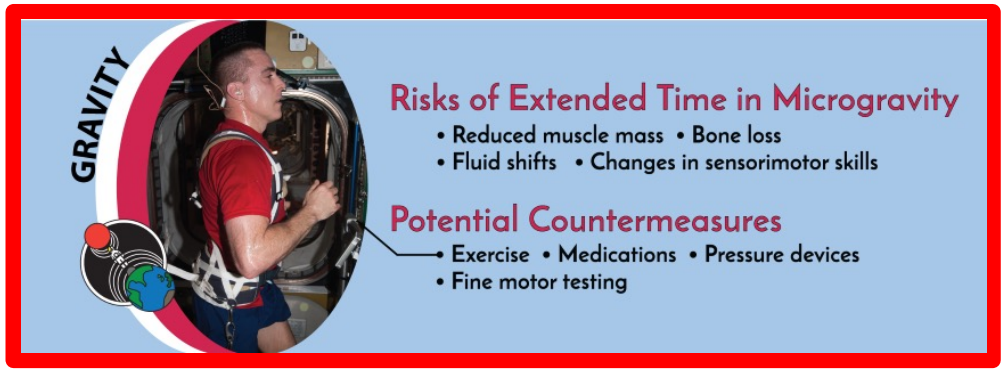
***This is an energy problem*: fructose lowers ATP.**

The Health Risks of Spaceflight









- Time is an essential non-random variable of the information content and processing functions in cellular systems.
  --Keep this in mind for the rest of this talk!

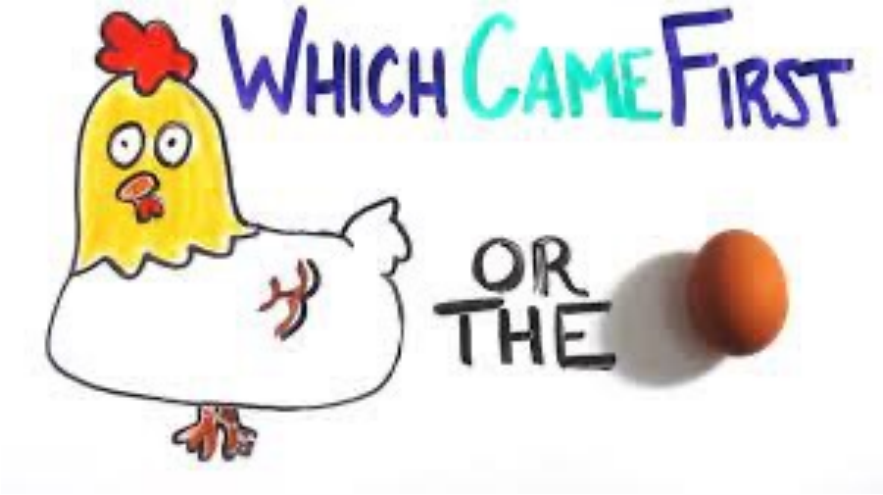
Sleep in space

- Sleep is critical for human health and is required by all mammals.
- Timing and duration of sleep are controlled by the circadian system, which keeps a 24-h internal rhythm that synchronizes to environmental stimuli. All organisms, from mammals to prokaryotes, have an internal clock adapted to the Earth's rotational schedule of 24 h.
- By contrast, the ISS orbits within 93 min, creating a 93 min day-night cycle with different environmental stimuli.

What time is it (for sleep) in space?

The Link Between Metabolism and Circadian Timekeeping

Question: If circadian timekeeping results in cyclical metabolism, might some of the products of metabolism serve to reinforce or influence circadian timekeeping?

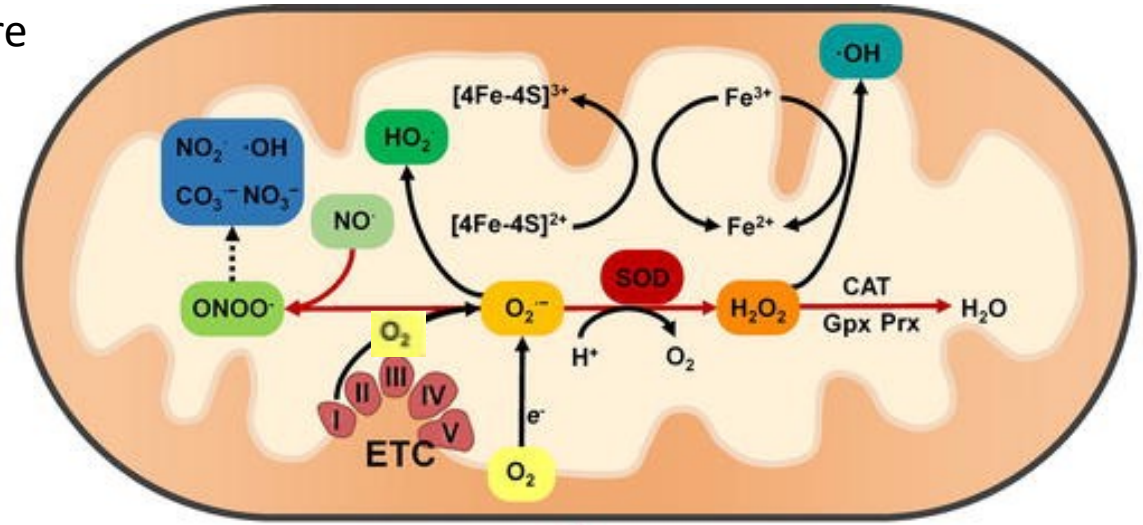


Metabolic basis of timekeeping with redox switches

Reactive Oxygen Species serve a "time-keeping" function as switches of various cellular processes and physiological rhythms.

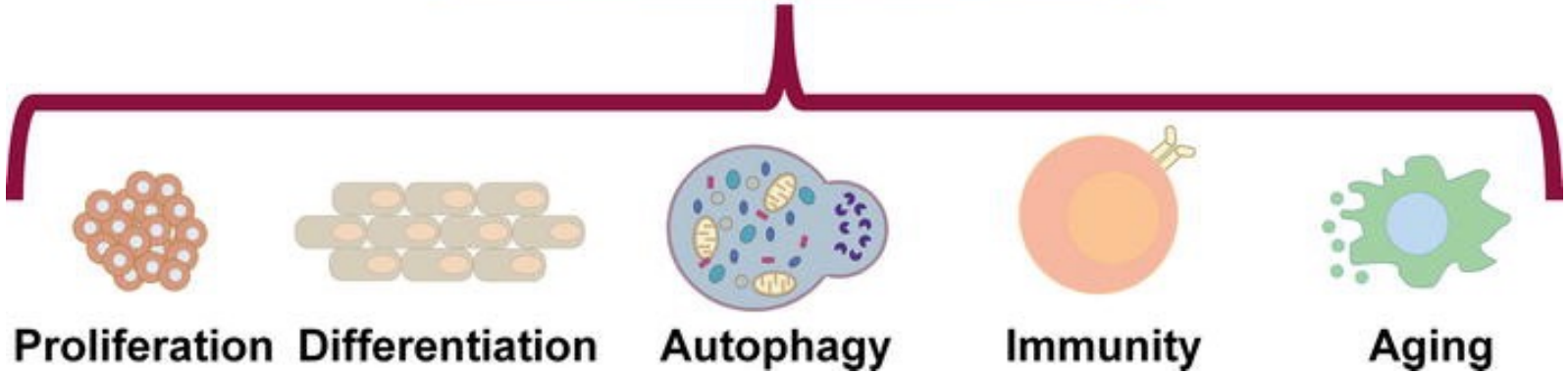
ROS (*e.g.*, hydroxyl radicals) are **produced** as byproducts of bioenergetic metabolism.

Timekeeping mechanism is based on the redox cycle, which generates **circadian rhythms conserved from bacteria to animals**.



To **counteract ROS**, cells contain antioxidant systems, including **peroxiredoxin** enzymes, to protect against **oxidative stress.**

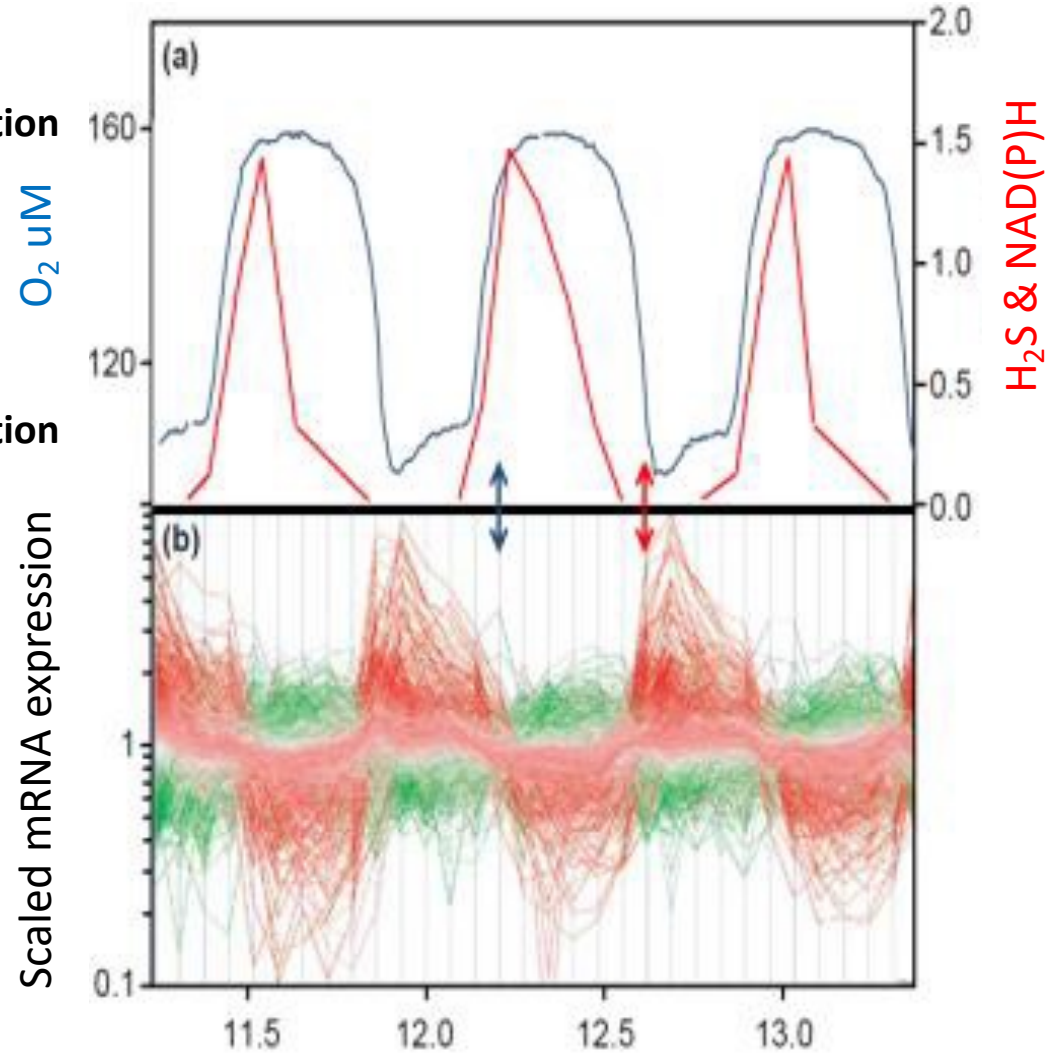
Mutants with defective peroxiredoxin enzymes exhibit increased somatic mutations caused by ROS.

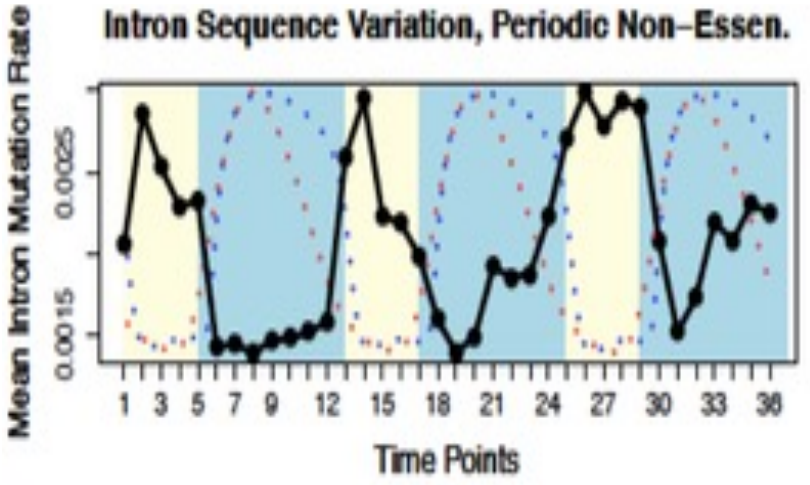


Choi, T. G. , & Kim, S. S. (2019), Free Radical Medicine and Biology.

Edgar, R., *et al.* (2012) *Nature* **485**, 459–464.

Temporal coordination of metabolic cycle is maintained by the oscillating reduction-oxidation reactions.



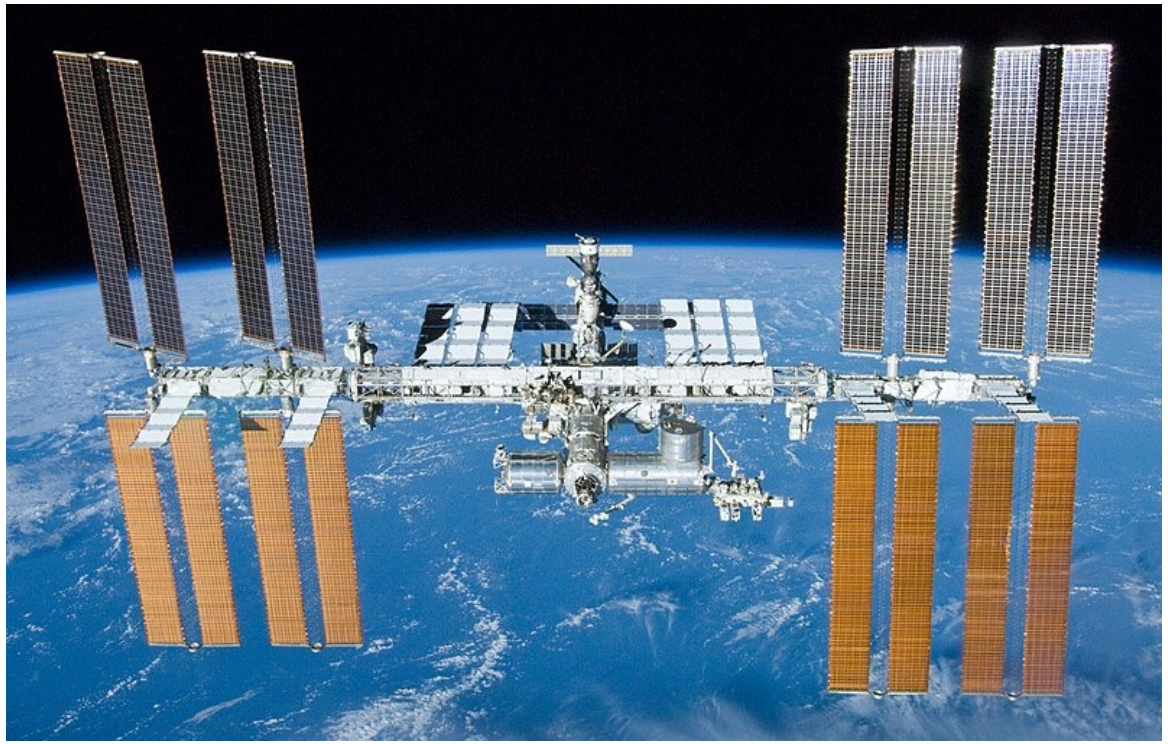


- ROS induced mutation is a fundamental genetic process that affects all species.
- ROS induced mutations may have clinical relevance for astronauts subjected to metabolic stress in spaceflight.

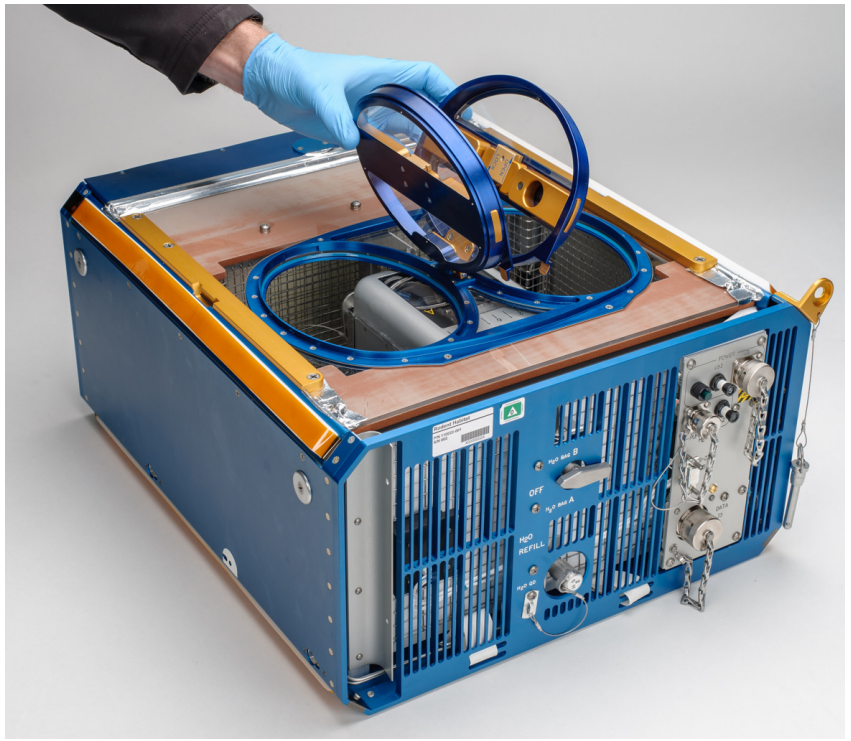
Murray D.B., *et al*. (2011) Redox regulation in respiring *S. cerevisiae*. *Biochim Biophys Acta*. 1810:945-958.

Stolc V, *et al*. (2011) PLOS ONE 6(9): e25270.

Long-duration experiments with rodents on the International Space Station



The ISS consists of pressurized habitation modules



The Rodent Research Hardware System Platform (designed at Ames)

What time is it (for sleep) in space?

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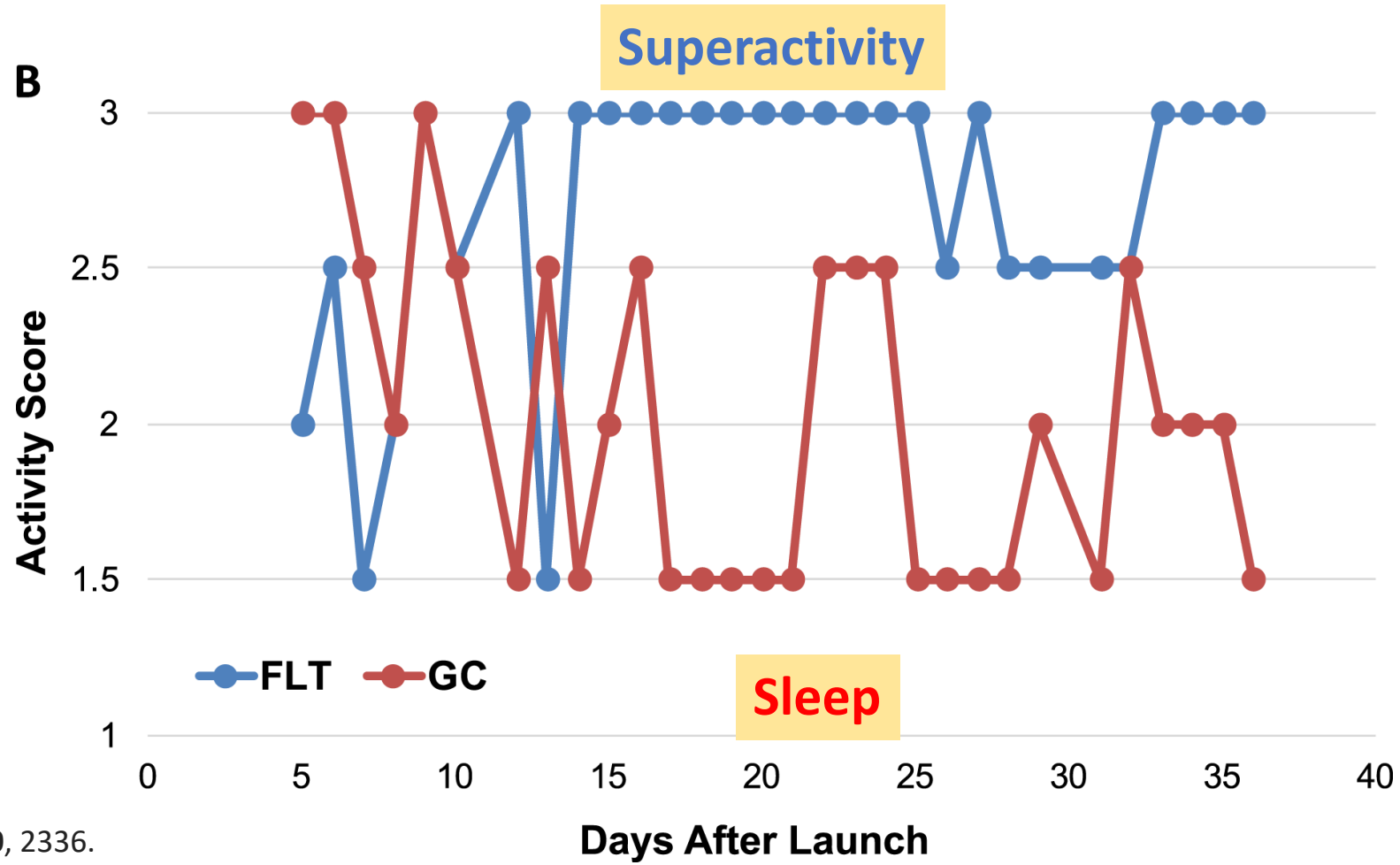
A

	Score	Activity/Behavior
Low	1	Sleeping, sitting, standing, periodic grooming
Moderate	2	Eating, drinking, slow ambulation, sustained grooming of others and self
High	3	Running laps, climbing, exploring, playing, fast ambulation, jumping

Quantitative Behavior (Activity) Assay revealed that mice became sleepless in about 14 days on the ISS.

B



Choi, S.Y., (2020) *Sci Rep* **10**, 2336.

Experiment to Evaluate Somatic Mutation Rate in Space

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Method:

16 wk. old, female, C57BL/6J,
18 wk. old, female, BALB/c

Rodent Research 1, 2014

37-42d, Rodent Habitat, **ISS** → Euthasol, CD, -80° C → Thaw, Dissection → Kidney, Skeletal muscle, Eye, Liver (n = 72 each)

37-42d, Rodent Habitat, **Ground** → Euthasol, CD, -80° C → Thaw, Dissection → Kidney, Skeletal muscle, Eye, Liver (n = 72, each)

RNA sequencing library construction done at UC Davis.

Illumina HiSeq 4000

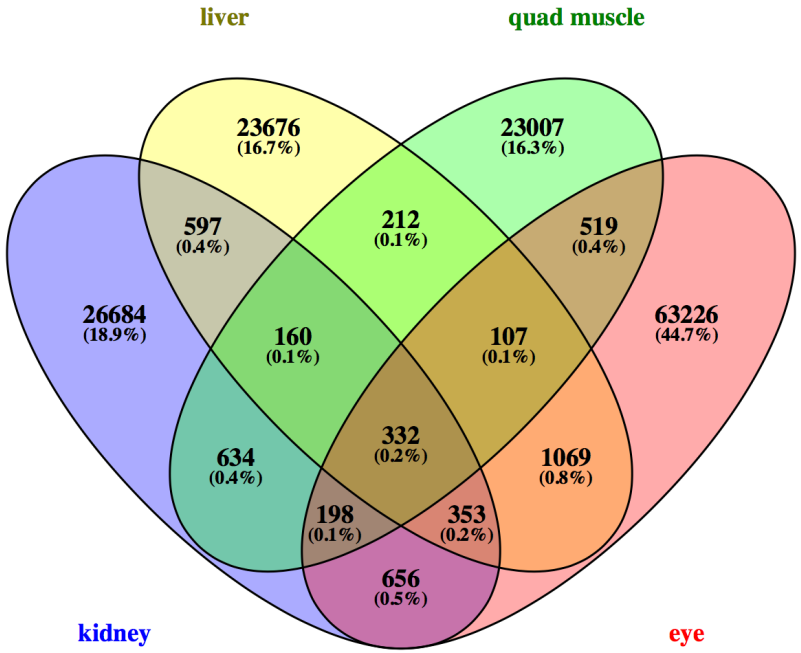
Sequence variants determined by a novel analytical pipeline developed at NASA Ames Research Center.

https://www.nasa.gov/ames/research/space-biosciences/nbisc

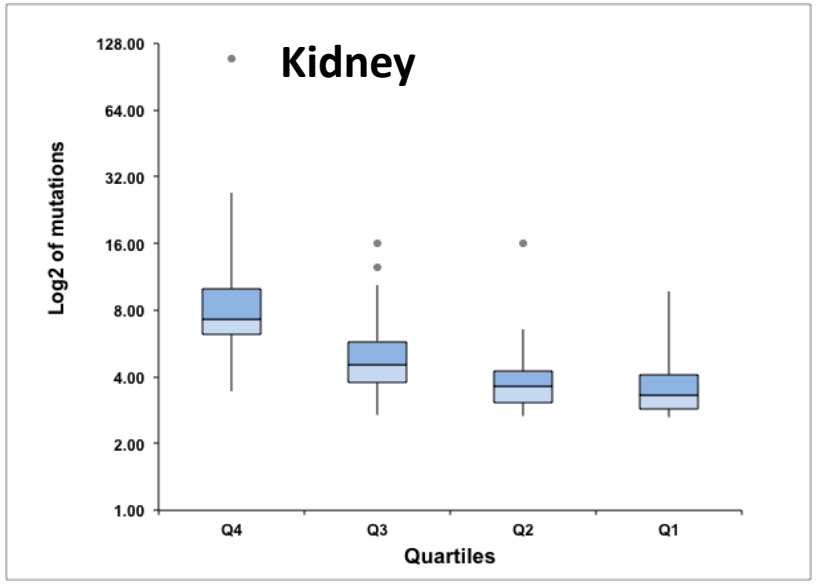
https://genelab.nasa.gov/

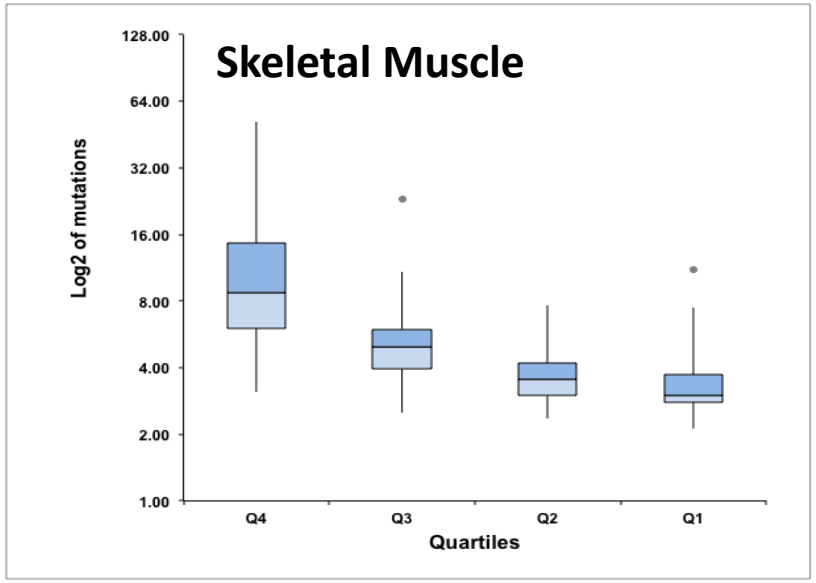
Hypermutation Results

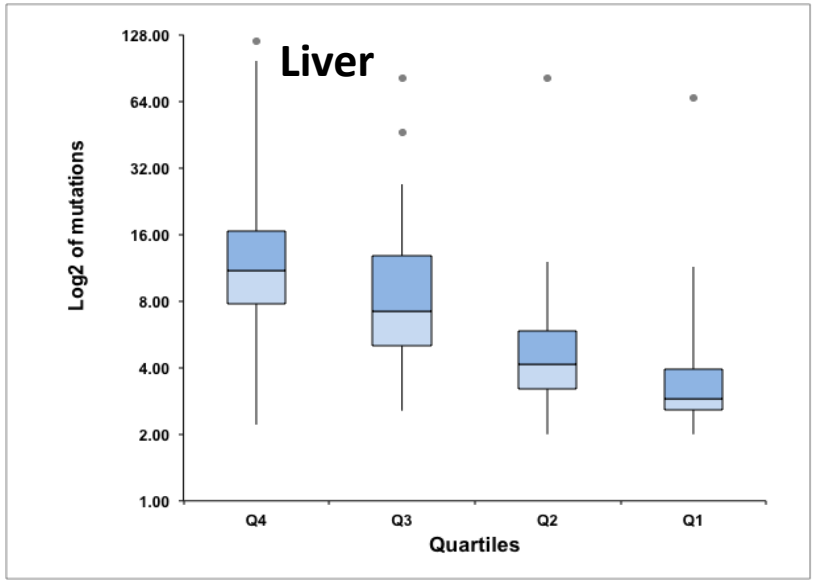
Tissue	Variants	unique SNVs	unique NSMs	unique(NSMs/SNVs)
GLDS-162 (eye)	94755	63226	22865	36%
GLDS-137 (liver)	50701	23676	6516	28%
GLDS-102 (kidney)	48577	26684	9780	37%
GLDS-103 (quad muscle)	43883	23007	7722	34%

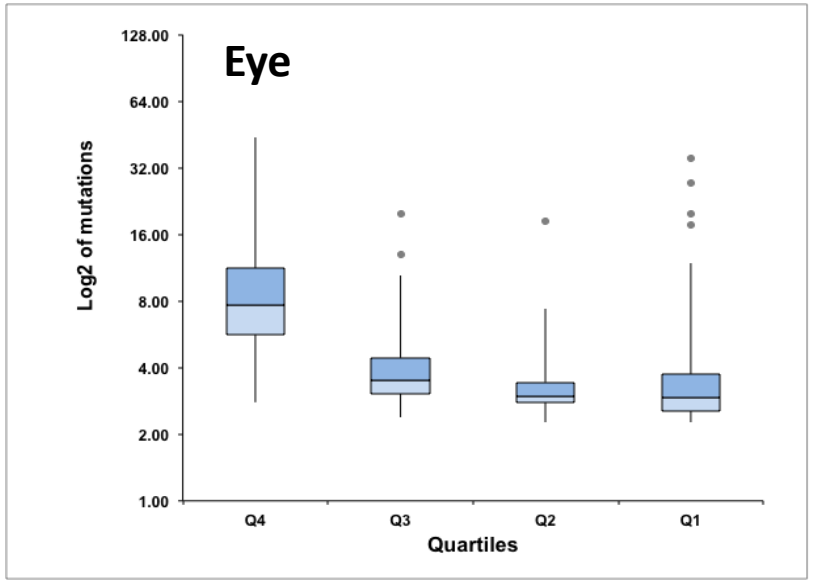


Mutation increased by induced RNA transcription during spaceflight on the ISS relative to ground controls







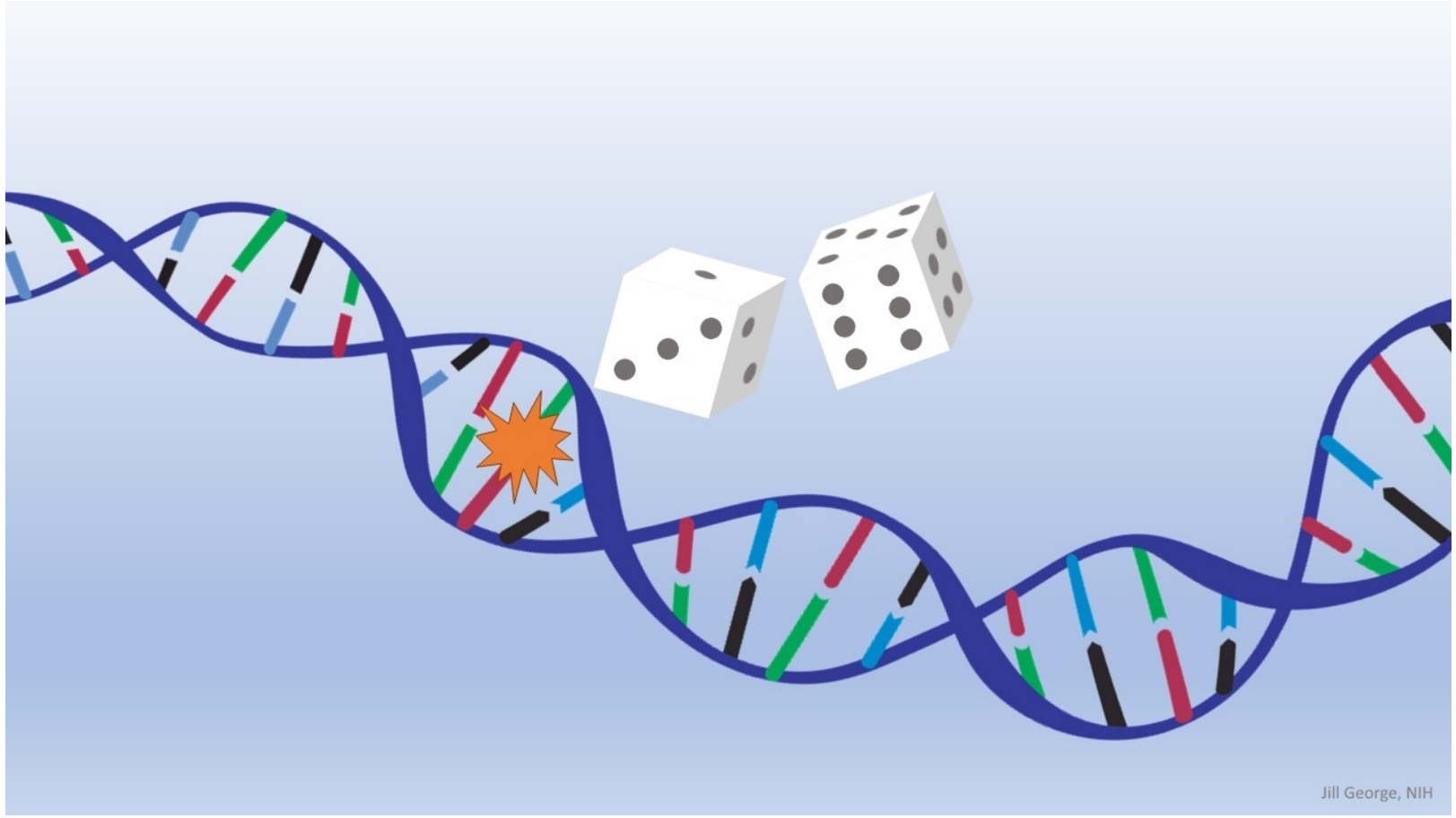


- Average mutation frequency **4.0 x 10^{-4}** per base pair (bp) for all differentially expressed genes (in total 18,140 genes) **on the ISS**,

vs

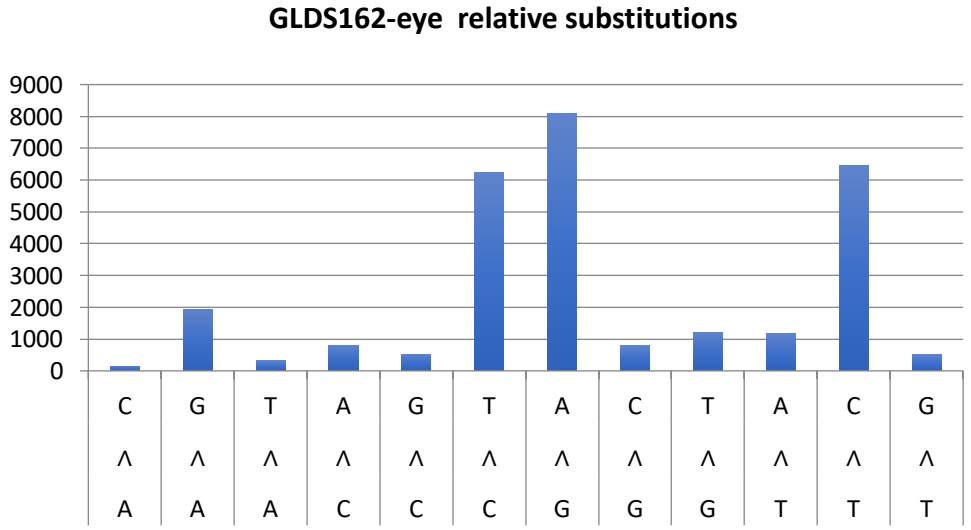
- Average mutation frequency **5.3 × 10^{-9}** mutations per bp (1.7 mutations per genome per generation) **on Earth**.

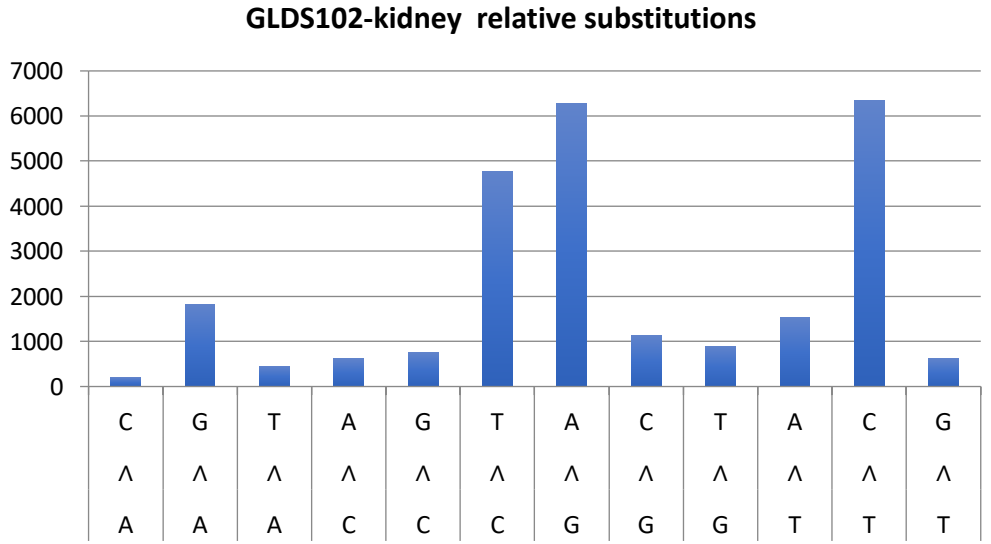
Are Somatic Mutations Completely Random?

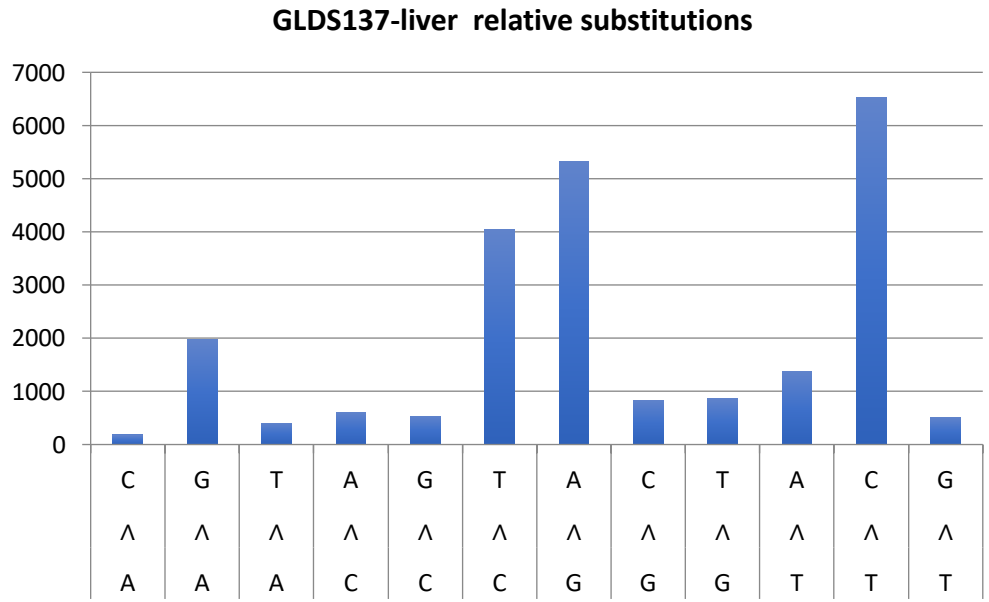


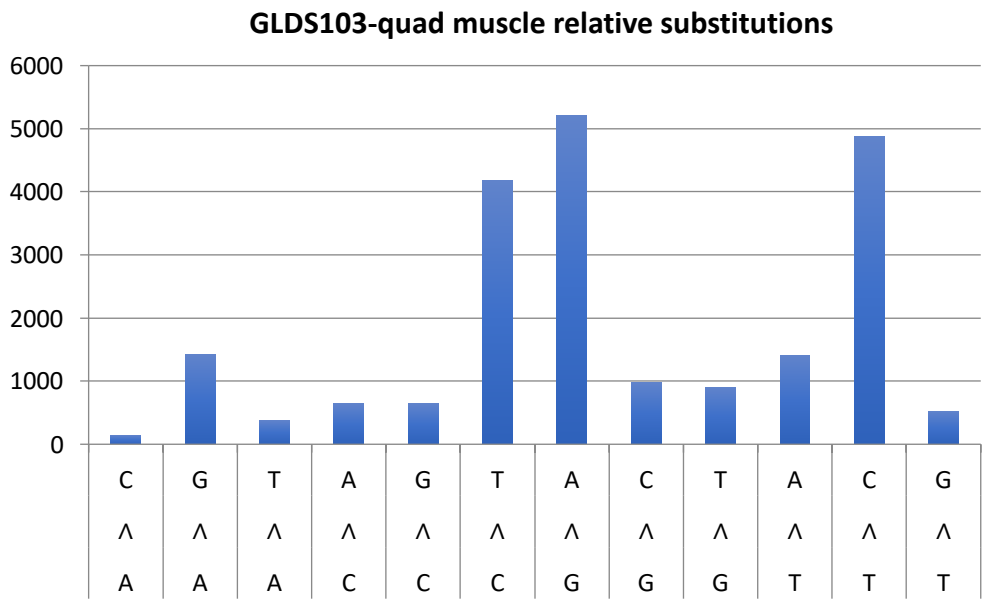
Are As, Ts, Cs and Gs being altered with the same frequency?

Base substitutions, for each of the four tissue types









Guanine is the most easily oxidized of the nucleotide bases, a process that can occur because of endogenous production of reactive oxygen species (ROS).

Summary

- The negative impact of disordered saccharide metabolism, leading to ***increased oxidative stress and depletion of neuronal energetics***, poses a concerning risk factor in various human diseases, including cardiovascular disease, hypertension, diabetes, lipid abnormalities, non-alcoholic fatty liver disease, cancer, dementia, and sleep disorders.

- This heightened oxidative stress may contribute to mutations and cellular damage, potentially exacerbating the progression and development of these health conditions.