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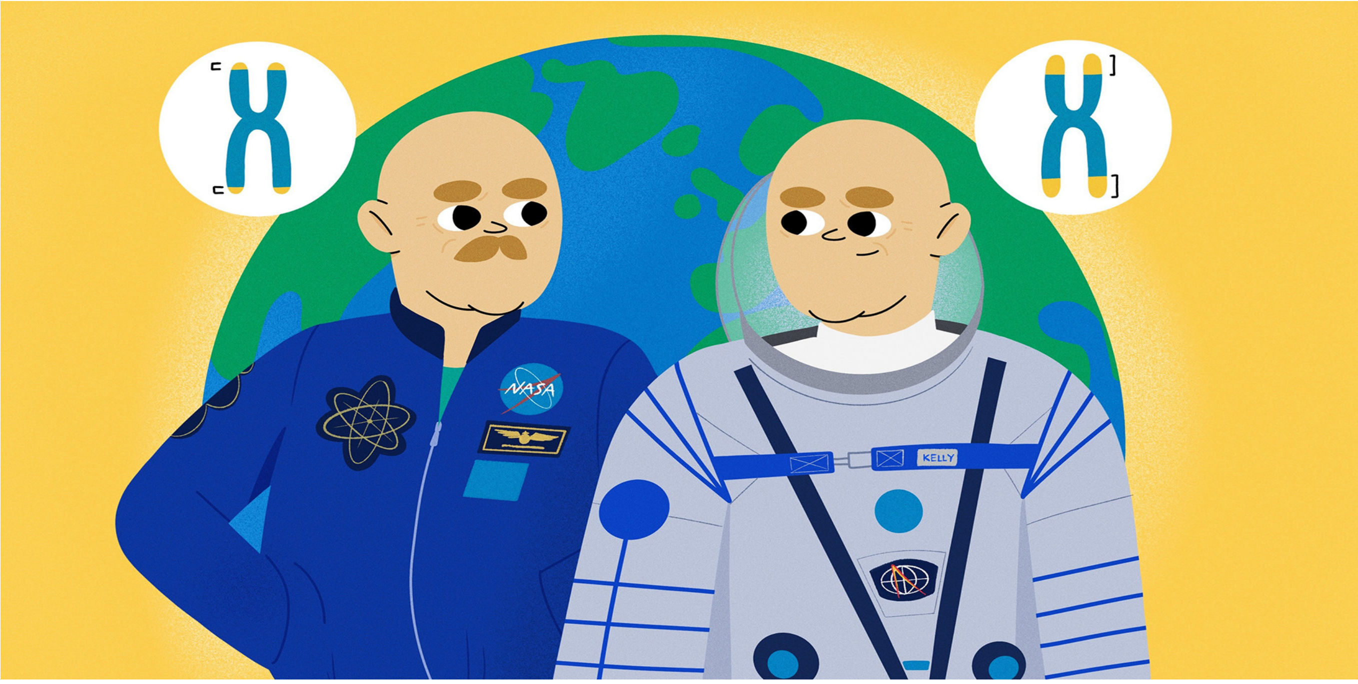

TWINS AND TELOMERES-IN SPACE!

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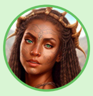
YOUNG REVIEWERS:


BRAYDON
AGE: 13


ELLOUISE
AGE: 12


KAJ
AGE: 10

As part of the NASA Twins Study, our investigations related to telomeres and DNA damage responses (genome stability) during long-duration spaceflight have important implications for the health and performance of astronauts participating in exploration missions, as well as for long-term aging and disease risk outcomes. Together with the other Twins Study investigations, results will guide future studies and development of personalized medicine approaches for evaluating health effects for individual astronauts as we make our way back to the moon and beyond. Particularly as the number and diversity of space travelers and even space tourists increases over the coming years, identifying individual differences in response to the extreme environment, experiences and chronic exposures associated with space travel, exploration, and eventual habitation of other planets, represents a critical next step for ensuring future astronaut performance and health during, and improving disease and aging courses following, such missions. *Ad astra*!

SPACE IS HARD!

In the summer of 1969, Apollo 11 rocketed American astronauts to the Moon, and on July 20th the world stood still and watched as Neil Armstrong took those first small steps on the surface. Fast forward almost 50 years and NASA astronauts Scott Kelly and Christina Koch each spend nearly a year in space aboard the International Space Station (ISS). In 2020, and marking a new era of human space exploration, the first commercial rocket SpaceX Falcon 9, launched NASA astronauts from U.S. soil in the Crew Dragon spacecraft Endeavor to the ISS. NASA and its commercial partners are rapidly advancing innovative space technologies, and with the Artemis (twin sister of Apollo) program and astronauts, plans are to send the first woman and next man back to the moon before the end of the decade. Humankind will then be poised to take the next giant leap—pioneering human exploration of Mars.

For more than 20 years now, the ISS has supported continuous human presence in low Earth orbit (LEO). While living onboard the ISS is exciting and gives astronauts an "out-of-this-world" view and a life-changing perspective of our own home planet that few of us ever personally experience (see video: Down to Earth: The Astronaut's Perspective), life on the ISS is also extraordinarily challenging and stressful. Their "home" in space travels at a speed of over 17,000 mph, approximately 250 miles (~400 km) above the Earth, and astronauts experience microgravity, **space radiation** exposure, and 16 light/dark cycles every 24 h—all while isolated from family and friends and floating around in a confined spacecraft the size of a football field, with a handful of folks they depend on for everyday survival. If this sounds hard, it is! With NASA's first one-year mission on the ISS (2015–2016), they have been interested in better understanding how long-duration space travel can affect human health and the way that people age in space.

SPACE RADIATION

Once outside of the Earth's protective atmosphere, astronauts are exposed to higher levels of more harmful radiations, energetic particles from the sun and cosmos that damage DNA.

NASA TWINS STUDY—A FIRST FOR ASTRONAUTS

Simply by chance and good fortune, the astronaut selected for NASA's first 1-year mission, Scott Kelly, had an identical twin brother, Mark Kelly, who was also an astronaut and former Navy test pilot. This remarkable coincidence set the stage for the perfect experiment—identical twin sons of similar nature and nurture, one spending a year in space ("space twin"), while the other remained on Earth ("Earth twin"). This launched the most in-depth study of the human body's response to spaceflight ever conducted. Ten investigations from around the country were selected for what became known as the NASA Twins Study (Figure 1). The Twins Study represented many firsts for the space program, including an assortment of "genomics-based" studies [e.g., genomics (**DNA**), transcriptomics (RNA), proteomics (proteins), metabolomics

DNA

Deoxyribonucleic acid, is the hereditary material that carries genetic information or the code for life – it is what makes you, you.

(metabolites)], the first test of a vaccine (a flu vaccine) in space, as well as the first assessments of the space microbiome and a biological marker of aging—**telomeres**.

TELOMERES

Protective "caps" on the ends of chromosomes, much like the plastic aglet on the end of a shoestring, that shorten with cell division and provide an indicator of aging.

Figure 1

Figure 1

The NASA Twins Study patch showing the space- and Earth-twins holding on to a DNA molecule, which represents the genomic focus of the study—a first for astronauts.

The Twins Study sparked a great deal of global attention and renewed interest in space. One of the questions often asked of Scott was whether he would return from space younger than his brother Mark, usually in the context of the movie "Interstellar" or Einstein's "Twin Paradox" thought experiment. Although a year onboard the orbiting space station would produce an age difference of only ∼ millisecond (one thousandth of a second), the question of aging associated with long-duration spaceflight, and possible increased risk of developing age-related diseases like frailty, dementias, heart disease and cancer—is an important one, and one we aimed to address as our part of the Twins Study. Here, I highlight findings from our investigations and propose potential mechanistic roles for chronic space radiation exposure underlying changes in telomere length dynamics (changes over time) and persistent **DNA damage responses (DDRs)** associated with long-duration spaceflight.

DNA DAMAGE RESPONSE (DDR)

Complex signaling pathways in cells that detect and repair damaged DNA in order to preserve DNA integrity and maintain genome stability.

Telomeres are protective "caps" at the physical ends of our **chromosomes** that serve to shield them from damage and keep them from "fraying"—much like an aglet at the end of a shoestring (Figure 2). Functional telomeres are therefore important for maintaining genome integrity and stability. However, telomeres shorten as we age (due to normal cell division), as well as with a variety of lifestyle factors (nutritional, physical, psychological stresses) and environmental exposures (air pollution, ultraviolet, and space radiations).

CHROMOSOME

Long, tightly coiled DNA molecules in the nucleus of most living cells that carry genetic information in the form of genes.

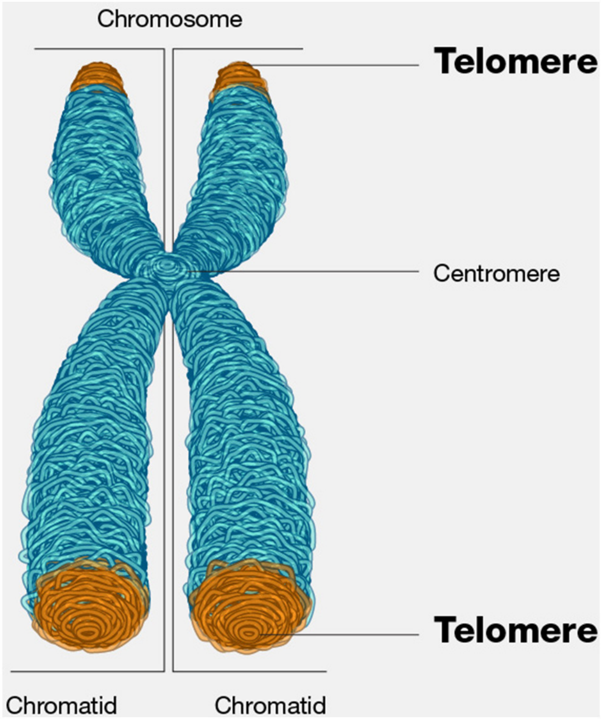


Figure 2

Figure 2

Telomeres are the "end-parts" of linear chromosomes that protect them from damage and loss, as well as from fusing to other telomeres or actual broken DNA ends. Available online at: https://www.genome.gov/genetics-glossary/Telomere.

We hypothesized that the unique stresses and chronic exposures experienced by astronauts living in space would speed up telomere shortening during spaceflight (they would shorten more quickly in space). That is, an astronaut's genetics, exposure to the extreme conditions of space (e.g., microgravity, space radiations, altered atmospheres), as well as a many other stressors (e.g., confinement and isolation, biologically hostile and closed environment) [1], are all captured as changes in telomere length over time. To test this, we evaluated telomere length in blood samples collected from both Scott and Mark Kelly before, during, and after the one-year mission onboard the ISS [2] (Figure 3).

UNEXPECTED RESULTS!

While Earth twin's telomere lengths remained relatively stable during the study, much to our surprise space twin's telomeres were *longer* at every time point tested during spaceflight—exactly the opposite of what we thought we would see! Similar results were also observed in a separate study involving 10 unrelated astronauts on other, shorter ISS missions (~6 months), compared to healthy age- and sex-matched subjects on Earth [3, 4]. Another unexpected result was that astronaut telomere length shortened very quickly upon return to earth, and astronauts in general had many more short telomeres *after* spaceflight than they had before. Consistent with chronic (every day, every hour) exposure to space radiation, we also observed DNA damage in the

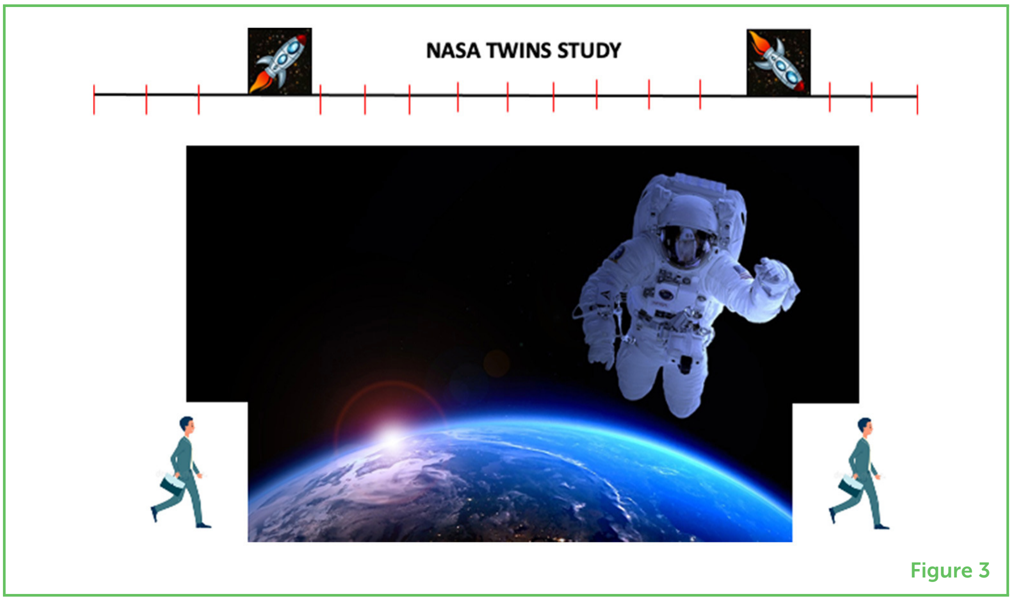


Figure 3

For the NASA Twins Study, blood samples were collected from "space-twin" and "Earth-twin" at various timepoints (red bars on the timeline) before, during and after the 1-year mission onboard the ISS.

form of chromosome rearrangements. Together with other findings from the Twins Study, we have important clues that will guide future studies, as well as evidence of differences in individual responses to investigate further [5].

TO THE STARS!

It is an exciting time for the space program, with NASA and its commercial partners developing and advancing innovative space technologies at a faster pace than ever before. The decade began with the dawn of a new era of human space exploration, as the first commercial rocket, SpaceX Falcon 9 launched NASA astronauts Robert Behnken and Douglas Hurley from U.S. soil in the Crew Dragon spacecraft to the ISS. We have also witnessed the first all-civilian crew to orbit Earth (for ∼3 days) as part of the SpaceX Inspiration4 mission. That crew included the youngest astronaut—a childhood cancer survivor in her early 20s. We saw William Shatner blasting off on a Blue Origin Rocket—the 90-year-old "Captain Kirk" from *Star Trek* setting a record as the oldest person to fly in space (for ∼3 min). The successful uncrewed Artemis 1 mission (late 2022) represented the first step in returning to the moon, and a crewed Artemis 2 mission that will circle the moon is scheduled for late 2024. Plans are to send humans back to the moon to stay before the end of the decade—maybe you will be going!

As the number and diversity of space travelers—and even space tourists—increases in the coming years, we will gain a better understanding of how long-duration spaceflight affects human health. It is certain that people will respond to spaceflight differently, and such knowledge is essential for informing personalized medicine strategies and ensuring future astronaut performance and health during, and improving disease and aging courses following, future exploration missions.

ACKNOWLEDGMENTS

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ORIGINAL SOURCE ARTICLE

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CONFLICT OF INTEREST: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWERS

BRAYDON, AGE: 13
Braydon is an honor middle school student and his favorite subject is math. Braydon enjoys spending time with his family and friends, serving in his church, and participating in athletics. Braydon plays soccer and basketball and runs cross country for his school's junior varsity teams.

ELLOUISE, AGE: 12
Ellouise plays volleyball, chess, and is an avid reader & writer. Conversations are also very important to her. She loves music a lot and appreciates different genres. She particularly enjoys lasagna, despite being lactose intolerant.

KAJ, AGE: 10
A playful boy who plays chess and football. He loves video games and his favorite actor is Kevin Hart. He also enjoys food quite a lot and cooks.

AUTHORS

SUSAN M. BAILEY
Susan M. Bailey, Ph.D., is a Professor of Radiation and Cancer Biology in the Department of Environmental & Radiological Health Sciences at Colorado State University in Fort Collins, Colorado. Dr. Bailey is a Fellow and Past President of the Radiation Research Society, and she serves on numerous National and International committees. As one of the investigators selected for NASA's Twins Study, her research program seeks to better understand the influence of long-duration spaceflight on human health and aging, and ultimately how such information can serve to improve healthspan for astronauts and those on Earth as well. For example, see https://www.allure.com/story/astronaut-health-problems-space-body-skin-effects. *Susan.Bailey@ColoState.EDU