NASA and NSBRI's Kelly Twins Study: Progress Implementing The First Integrated Omics Pilot Demonstration Study in Space

American Society for Gravitational and Space Research (ASGSR) Annual Meeting
Cleveland, OH; Saturday October 29, 2016

Graham B.I. Scott, Ph.D.; Chief Scientist, NSBRI

The Twins Study Was Initiated Following A Question Posed By Astronaut Scott Kelly

SCIENCE

30 COMMENTS

NASA will separate twin brothers for a year: one on Earth, one in space

By Carl Franzen on August 5, 2013 09:24 pm Email @carlfranzen

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141

Of all the members of NASA's current crop of distinguished astronauts, only two have the unique distinction of being identical twin brothers. And now NASA is using an idea [illegible] by the brothers, Mark Kelly and Scott Kelly, to perform a study that's been [illegible] to sci-fi up until now. Beginning in March 2015, the space agency will be [illegible] the biological states of both twin brothers over the span of a year, with a twist: Scott will be aboard the International Space Station for the duration of that period, while Mark, who retired from NASA back in 2011, will remain back here on Earth.

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THE VERGE

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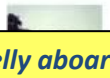
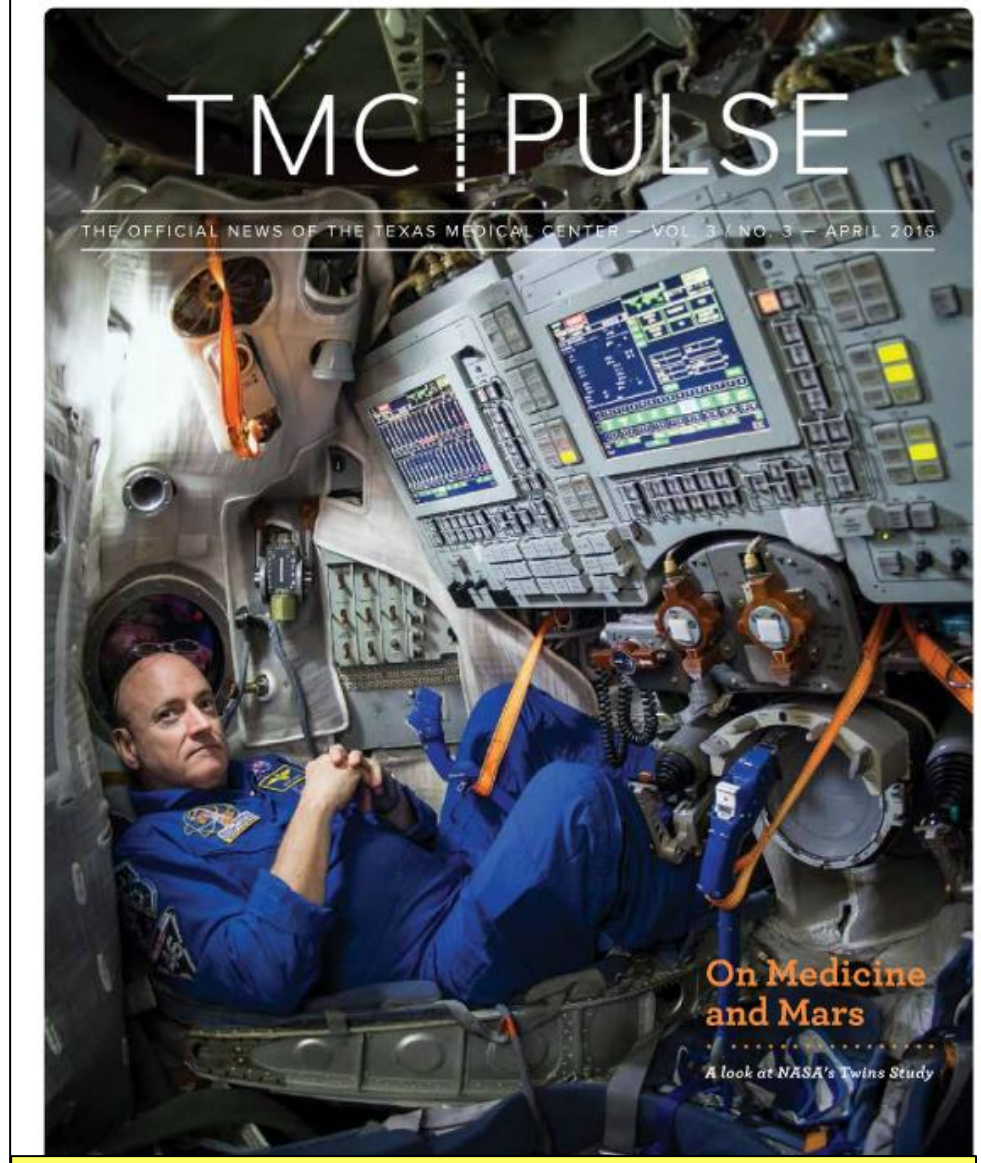


US government considers

"This opportunity has emerged from NASA's decision to fly veteran NASA astronaut Scott Kelly aboard the International Space Station (ISS) for a period of one year commencing in March 2015, while his identical twin brother, retired NASA astronaut Mark Kelly, remains on Earth. Scott Kelly, a veteran of two Space Shuttle flights as well as a six-month ISS mission, will have a cumulative duration of 540 days in low Earth orbit at the conclusion of the one-year flight, while Mark Kelly, a veteran of four Space Shuttle flights, has a cumulative duration of 54 days (2 hours and 4 minutes) in low Earth orbit. This opportunity originated at the initiative of the twin astronauts themselves."

[a] Upon his return to Earth on 3/1/2016 - Scott Kelly has now flown .... ***520 days and 10 hours in space***

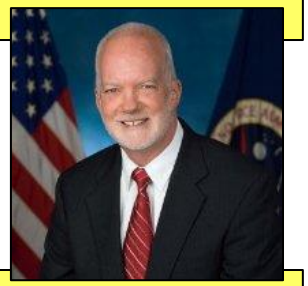
"Studying the Kelly Twins Will Help Shape the Future of Space Exploration and Human Health Here on Earth"



http://www.tmcnews.org/2016/04/on-medicine-and-mars/

"There have been very few integrated omics studies where you look at the genome, transcriptome, proteome, metabolome and microbiome together, and nobody has ever done this kind of study with twins before."

Graham Scott, Ph.D.
VP, Chief Scientist, and Institute Associate Director – NSBRI
Associate Professor – Baylor College of Medicine's Center for Space Medicine and Department of Molecular and Cellular Biology

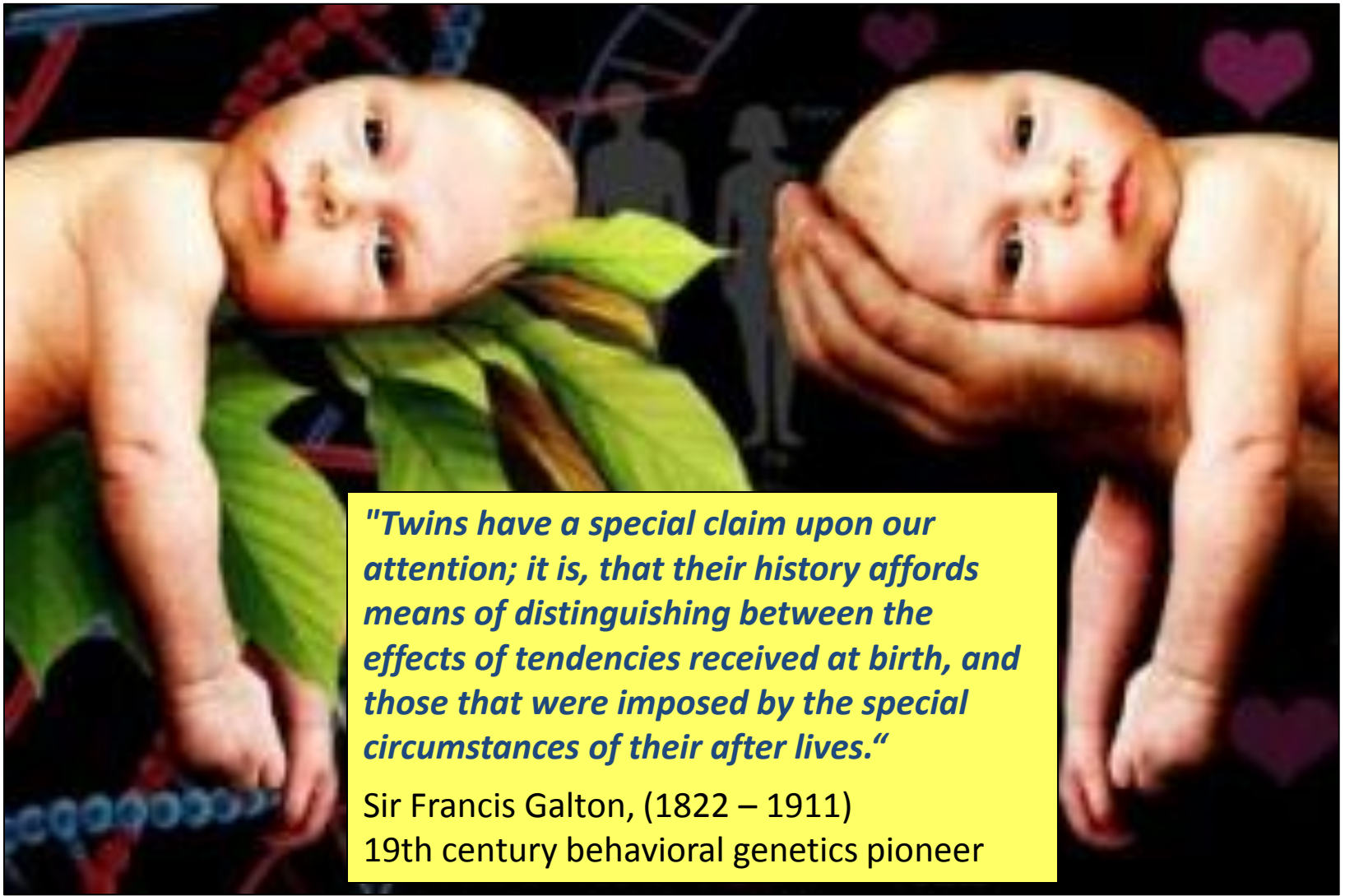


"I don't think it's an exaggeration to say that everything we learn about the human body, whether it's in space or on the ground, benefits all of us here on Earth."

John Charles, Ph.D.
Chief Scientist for NASA's Human Research Program

Twins Studies Help Scientifically Inform The "Nature Versus Nurture" Debate

Are Differences Between People Due to Genetic or Environmental Factors … Or Both?



"Twins have a special claim upon our attention; it is, that their history affords means of distinguishing between the effects of tendencies received at birth, and those that were imposed by the special circumstances of their after lives."

Sir Francis Galton, (1822 – 1911)
19th century behavioral genetics pioneer

Are Identical Twins Really Identical?

THE STATE OF THE UNIVERSE. | SEPT. 12 2014 11:26 AM

Life Is Random

Biologists now realize that "nature vs. nurture" misses the importance of noise.

3.9k

By Cailin O'Connor

Even identical twins brought up in similar environments won't *really* be identical.

"Even identical twins brought up in similar environments won't *really* be identical. They won't have the same fingerprints. They'll have different freckles and moles. Even complex traits such as intelligence and mental illness often vary between identical twins."

http://www.slate.com/articles/health_and_science/science/2014/09/random_noise_in_biology_why_genetically_identical_twins_aren_t_identical.html

The DNA of Identical Twins … Is Nearly Identical

The DNA of identical twins is ***nearly identical*** but environmental conditions influence certain genetic factors.

Environmental factors and external elements affect the switching on and off of genes in twins. This phenomenon is known as ***epigenetic modification.***

A survey conducted on twins of varying age groups revealed that the ***epigenetic differences increase with growing age.***

It also brought out the fact that twins who had spent their lives apart showed greater differences.

Identical Twins Grow More Dissimilar With Age …

Differences result from epigenetic processes that the DNA undergoes.

One of the major epigenetic processes is *methylation.*

It is a process by which the gene expression changes with ascending age.

Due to this process, *identical twins grow more and more dissimilar with growing age.*

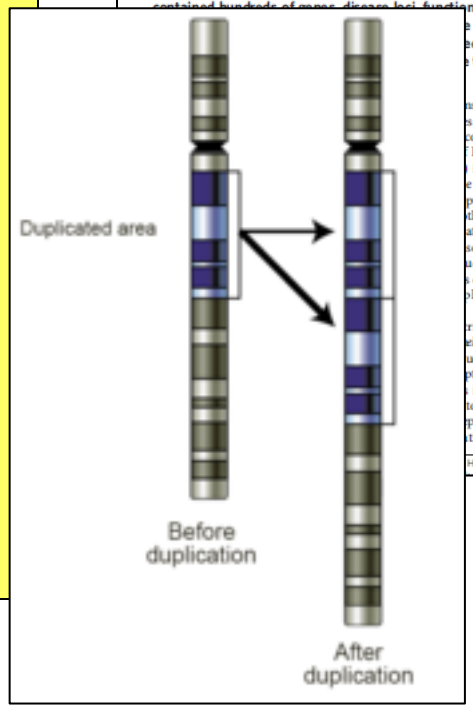
Copy Number Variants, (CNV's)

CNV's Explain The Majority of Human Variation

In certain cases, identical twins have different copy-number-variations (CNVs).

By this we mean that one of the identical twins can have a DNA segment missing, have multiple copies of the segment or may even have a different orientation of the genome.

This explains the reason for dissimilarities between identical twins.



nature Vol 444|23 November 2006|doi:10.1038/nature05329

ARTICLES

Global variation in copy number in the human genome

Richard Redon[1], Shumpei Ishikawa[2,3], Karen R. Fitch[4], Lars Feuk[5,6], George H. Perry[7], T. Daniel Andrews[1], Heike Fiegler[1], Michael H. Shapero[4], Andrew R. Carson[5,6], Wenwei Chen[4], Eun Kyung Cho[7], Stephanie Dallaire[7], Jennifer L. Freeman[7], Juan R. González[8], Mònica Gratacòs[8], Jing Huang[4], Dimitrios Kalaitzopoulos[1], Daisuke Komura[3], Jeffrey R. MacDonald[5], Christian R. Marshall[5,6], Rui Mei[4], Lyndal Montgomery[1], Kunihiro Nishimura[2], Kohji Okamura[5,6], Fan Shen[4], Martin J. Somerville[9], Joelle Tchinda[7], Armand Valsesia[1], Cara Woodwark[1], Fengtang Yang[1], Junjun Zhang[5], Tatiana Zerjal[1], Jane Zhang[4], Lluis Armengol[8], Donald F. Conrad[10], Xavier Estivill[8,11], Chris Tyler-Smith[1], Nigel P. Carter[1], Hiroyuki Aburatani[2,12], Charles Lee[7,13], Keith W. Jones[4], Stephen W. Scherer[5,6] & Matthew E. Hurles[1]

Copy number variation (CNV) of DNA sequences is functionally significant but has yet to be fully ascertained. We have constructed a first-generation CNV map of the human genome through the study of 270 individuals from four populations with ancestry in Europe, Africa or Asia (the HapMap collection). DNA from these individuals was screened for CNV using two complementary technologies: single-nucleotide polymorphism (SNP) genotyping arrays, and clone-based comparative genomic hybridization. A total of 1,447 copy number variable regions (CNVRs), which can encompass overlapping or adjacent gains or losses, covering 360 megabases (12% of the genome) were identified in these populations. These CNVRs contained hundreds of genes, disease loci, functional elements and segmental duplications. Notably, the CNVRs e than SNPs, underscoring the importance of CNV in genetic diversity and equilibrium patterns for many CNVs, and reveal marked variation in copy the utility of this resource for genetic disease studies.

at genes at which other types of mutation are strongly associated with specific diseases: CHARGE syndrome[21] and Parkinson's and Alzheimer's disease[22,23]. Furthermore, CNVs can influence gene expression indirectly through position effects, predispose to deleterious genetic changes, or provide substrates for chromosomal change in evolution[10,11,17,24].

In this study, we investigated genome-wide characteristics of CNV in four populations with different ancestry, and classified CNVs into different types according to their complexity and whether copies have been gained or lost (Supplementary Fig. 1). To maximize the utility of these data and the potential for integration of CNVs with SNPs for genetic studies, we performed experiments with the International HapMap DNA and cell-line collection[25] derived from apparently healthy individuals. The result is the first comprehensive map of copy number variation in the human genome, which provides an important resource for studies of genome structure and human disease.

Two platforms for assessing genome-wide CNV

The HapMap collection comprises four populations: 30 parent–offspring trios of the Yoruba from Nigeria (YRI), 30 parent–offspring trios of European descent from Utah, USA (CEU), 45 unrelated

Hinxton, Cambridge CB10 1SA, UK. [2]Genome Science, and [3]Dependable and High Performance Computing,

Identical Twins Differ in ~ 300 Locations (Loci) Out of ~ 3 Billion [A,C,G,T] Letters

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Article:

Identical Twins Are Genetically Different, Research Suggests

Tia Ghose, LiveScience Staff Writer
Date: 09 November 2012 Time: 05:33 PM ET

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SAN FRANCISCO – Identical twins may not be so identical after all. Even though identical twins supposedly share all of their DNA, they acquire hundreds of genetic changes early in development that could set them on different paths, according to new research.

The findings, presented Friday (Nov. 9) here at the American Society of Human Genetics meeting, may partly explain why one twin gets cancer while another stays healthy. The study also suggests that these genetic changes are surprisingly common.

"It's not as rare as people previously expected," said study presenter Rui Li, an epidemiologist at McGill University.

Somatic point mutations occurring early in development: a monozygotic twin study

Rui Li,[1,2] Alexandre Montpetit,[3] Marylène Rousseau,[4] Si Yu Margaret Wu,[4] Celia M T Greenwood,[2,5,6] Timothy D Spector,[7] Michael Pollak,[8] Constantin Polychronakos,[4] J Brent Richards[1,2,7]

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ABSTRACT
The identification of somatic driver mutations in cancer has enabled therapeutic advances by identifying drug targets critical to disease causation. However, such genomic discoveries in oncology have not translated into advances for non-cancerous disease since point mutations in a single cell would be unlikely to cause non-malignant disease. An exception to this would occur if the mutation happened early enough in development to be present in a large percentage of a tissue's cellular population. We sought to identify the existence of somatic mutations occurring early in human development by ascertaining base-pair mutations present in one of a pair of monozygotic twins, but absent from the other and assessing evidence for mosaicism. To do so, we genome-wide genotyped 66 apparently healthy monozygotic adult twins at 506 786 high-quality single nucleotide polymorphisms (SNPs) in white blood cells. Discrepant SNPs were verified by Sanger sequencing and a selected subset was tested for mosaicism by targeted high-depth next-generation sequencing (20 000-fold coverage) as a surrogate marker of timing of the mutation. Two de novo somatic mutations were unequivocally confirmed to be present in white blood cells, resulting in a frequency of 1.2×10^{-7} mutations per nucleotide. There was little evidence of mosaicism on high-depth next-generation sequencing, suggesting that these mutations occurred early in embryonic development. These findings provide direct evidence that early somatic point mutations do occur and can lead to differences in genomes between otherwise identical twins, suggesting a considerable burden of somatic mutations among the trillions of mitoses that occur over the human lifespan.

INTRODUCTION
Mutation is an important source of genetic variation in the human genome. It can introduce deleterious nucleotide changes to genes or provide fuel for phenotypic evolution. It is well accepted that such mutations may lead to cancer,[1] but it is unlikely that *all* base-pair mutations would cause malignancy. Rather, such stochastic events could also lead to possible disruption of an organ's function, particularly so if the mutation were present in a large proportion of the cells within a tissue. Such mutations could exist if they were introduced early in embryogenesis and their identification could identify important control points in disease aetiology, such as has happened for malignant disease.

Indeed, somatic mutations have previously been demonstrated to cause non-malignant disease. Rapid advances in molecular genetics have demonstrated the importance of somatic mutation in a great variety of human diseases other than cancer (reviewed elsewhere).[2] For instance, a recent proof-of-concept study has revealed the existence of early embryonic somatic mutations causing Dravet syndrome,[3] as well as another novel finding of mosaic *AKT1* mutation in a Proteus syndrome patient.[4] A more recent publication identified somatic mutations in individuals with clonal haematopoiesis but without haematopoietic malignancies.[5]

In addition, the identification of early somatic mutations would provide preliminary insights into somatic mutation rates, which have been previously estimated in in vitro cell models[6–10] or disease–gene data.[11 12] Recent advances in sequencing technology have provided such rates in tumour samples,[13–16] and genotyping arrays have led to the detection of copy number variation in population studies.[17–19] However, the burden of point mutations in non-malignant tissue is not known, and further we are not aware of previous reports identifying the existence of somatic point mutations in otherwise apparently healthy individuals.

Monozygotic twins provide a natural experiment to address these questions since any differences between monozygotic co-twins would arise due to somatic changes. In the current study, we genome-wide genotyped 66 monozygotic twins (33 pairs) to identify somatic point mutations. In addition, we sought validation of the candidate somatic mutations through Sanger sequencing. Given that mutations occurring later in organ development would lead to somatic mosaicism within a cell line, we assessed the degree of mosaicism of identified mutations using next-generation sequencing. Together, these data provide direct evidence of the existence of somatic mutations occurring early in human development and a preliminary estimate of the rate at which they occur in an otherwise normal population.

RESULTS
Data generation
By genome-wide genotyping with Illumina 610K single nucleotide polymorphism (SNP) arrays, in the same laboratory at the same time, we obtained genotype calls on 506 821 SNPs in 33 pairs of monozygotic twins (66 individuals) after quality

Li R, Montpetit A, Rousseau M, Wu SY, Greenwood CM, Spector TD, Pollak M, Polychronakos C, Richards JB. "Somatic point mutations occurring early in development: a monozygotic twin study."
J Med Genet. 2014 Jan; 51(1): 28-34. Epub 2013 Oct 11.

One Twin Can Be Affected By Multiple Sclerosis – and One Twin May Be Unaffected

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Researchers Probe Genomes of Twins with Multiple Sclerosis for Nature vs. Nurture Clues

For release: Wednesday, April 28, 2010

In a new study, researchers scoured the genomes of several identical twin pairs, in which one twin had developed multiple sclerosis (MS) while the other did not. The researchers were searching for any genetic differences that could explain the twins' different fates.

The study touches on the influence of nature vs. nurture in MS, which occurs when the body's immune system inappropriately attacks the brain and spinal cord. It has long been known that identical twins often have different outcomes when it comes to MS, a phenomenon called discordance. This has been interpreted to mean that environmental factors must play a strong role in the disease.

However, as genetic technology has advanced, researchers have found that there are sometimes subtle genetic differences between identical, or monozygotic, twins. (Monozygotic twins are derived from the fertilization of a single egg in their mother's womb.)

The authors of the new study wondered if those differences might explain the discordance of MS in some monozygotic twins, but they were unable to find a genetic explanation. The study was funded in part by the National Institutes of Health, and was published in Nature*.

"To date, this represents the most thorough genomic analysis of twins with an autoimmune disease. The findings are intriguing not only for MS but for all studies that rely on twins to probe the roles of nature and nurture in complex diseases," said Ursula Utz, Ph.D., a program director at NIH's National Institute of Neurological Disorders and Stroke (NINDS).

"The study demonstrates the extent to which we might expect differences in the genomes of monozygotic twins," said lead author Sergio Baranzini, Ph.D., an associate professor of neurology at the University of California San Francisco (UCSF). The evident lack of differences should not be over-interpreted, Dr. Baranzini said. Limitations of current technology may have caused the team to miss important genetic differences between twins.

Typical symptoms of MS include weakness, loss of vision and numbness or tingling sensations. About 1 in

"Allelic Imbalance" Detected In Identical Twins

Mom's Gene Being Expressed More Than Dad's – or Vice Versa

Vol 464|29 April 2010|doi:10.1038/nature08990 nature

LETTERS

Genome, epigenome and RNA sequences of monozygotic twins discordant for multiple sclerosis

Sergio E. Baranzini[1], Joann Mudge[2], Jennifer C. van Velkinburgh[2], Pouya Khankhanian[1], Irina Khrebtukova[3], Neil A. Miller[2], Lu Zhang[3], Andrew D. Farmer[2], Callum J. Bell[2], Ryan W. Kim[2], Gregory D. May[2], Jimmy E. Woodward[2], Stacy J. Caillier[1], Joseph P. McElroy[1], Refujia Gomez[1], Marcelo J. Pando[4], Leonda E. Clendenen[2], Elena E. Ganusova[2], Faye D. Schilkey[2], Thiruvarangan Ramaraj[2], Omar A. Khan[5], Jim J. Huntley[3], Shujun Luo[3], Pui-yan Kwok[6,7], Thomas D. Wu[8], Gary P. Schroth[3], Jorge R. Oksenberg[1,7], Stephen L. Hauser[1,7] & Stephen F. Kingsmore[2]

Monozygotic or 'identical' twins have been widely studied to dissect the relative contributions of genetics and environment in human diseases. In multiple sclerosis (MS), an autoimmune demyelinating disease and common cause of neurodegeneration and disability in young adults, disease discordance in monozygotic twins has been interpreted to indicate environmental importance in its pathogenesis[1–8]. However, genetic and epigenetic differences between monozygotic twins have been described, challenging the accepted experimental model in disambiguating the effects of nature and nurture[9–12]. Here we report the genome sequences of one MS-discordant monozygotic twin pair, and messenger RNA transcriptome and epigenome sequences of $CD4^+$ lymphocytes from three MS-discordant, monozygotic twin pairs. No reproducible differences were detected between co-twins among ~3.6 million single nucleotide polymorphisms (SNPs) or ~0.2 million insertion-deletion polymorphisms. Nor were any reproducible differences observed between siblings of the three twin pairs in HLA haplotypes, confirmed MS-susceptibility SNPs, copy number variations, mRNA and genomic SNP and insertion-deletion genotypes, or the expression of ~19,000 genes in $CD4^+$ T cells. Only 2 to 176 differences in the methylation of ~2 million CpG dinucleotides were detected between siblings of the three twin pairs, in contrast to ~800 methylation differences between T cells of unrelated individuals and several thousand differences between tissues or between normal and cancerous tissues. In the first systematic effort to estimate sequence variation among monozygotic co-twins, we did not find evidence for genetic, epigenetic or transcriptome differences that explained disease discordance. These are the first, to our knowledge, female, twin and autoimmune disease individual genome sequences reported.

We sought to assess the magnitude of genetic, epigenetic and transcriptomic differences in $CD4^+$ lymphocytes from MS-affected and unaffected monozygotic twin sibships (Supplementary Fig. 1). $CD4^+$ T cells are involved in the pathophysiology of MS (Online Mendelian Inheritance in Man (OMIM) accession 126200)[1]. mRNA, genomic DNA (gDNA) and reduced-representation, bisulphite-treated gDNA were prepared from negatively isolated, $CD4^+$ T lymphocytes from three pairs of adult, monozygotic twins who were discordant for MS (-001, affected; -101, unaffected). Affected individuals fulfilled McDonald criteria for MS diagnosis[13]. A lack of sibling affectation was assessed by clinical evaluation, and, for twin 041896-101, confirmed by magnetic resonance brain imaging and cerebrospinal studies. Monozygotic twin pair 041896 was female, of Ashkenazi Jewish origin and beyond the susceptibility age-range for MS at the time of study (Supplementary Table 1). Twin pair 230178 was female and African-American, whereas twins 041907 were white males. Individual 041896-001 had an onset of MS at age 30 years, and is at present in the secondary progressive phase; individuals 230178-001 and 041907-001 had MS onset at ages 38 and 13 respectively, and have relapsing-remitting disease. Molecular typing of HLA loci showed identical genotypes within the three twin pairs (Supplementary Table 1). Only co-twins 041907 had DRB1*1501, the strongest genetic susceptibility factor for MS[14].

Nucleic acid samples were sequenced by sequencing-by-synthesis with reversible-terminator chemistry[15–18]. mRNA was prepared from blood samples drawn on different days from twin pair 041896 to ascertain sampling variance. A total of 50–68-million, high-quality, 36–44-nucleotide, singleton sequences from each of eight mRNA samples were aligned to the NCBI human genome reference, and read-counts per gene were calculated[18–20] (Supplementary Table 2). Sequencing to this depth (median relative transcript coverage of 5.0-fold and 6.4-fold for 041896-001 and 041896-101, respectively) allowed the determination of the diversity of the polyadenylated transcriptome in $CD4^+$ lymphocytes: ~92% of 20,601 genes with exon annotations were expressed, as assessed by aligned reads and the upper asymptote of the best-fit sigmoid curve (Supplementary Table 2 and Supplementary Fig. 2). The distribution of transcript abundance was a left-skewed, bell-shaped curve with >7 $\log_{10}$ dynamic range (Supplementary Fig. 2), in agreement with a previous study[17]. Digital gene expression values correlated well with exon-resolution array hybridization results (Supplementary Fig. 3), in agreement with another report[21]. Surprisingly, diagnosis or treatment of MS accounted for only 9.4% of variance in transcript abundance in T cells of monozygotic twins, compared with 57.3% being attributable to twin-pair-to-twin-pair differences, 23.6% to day-to-day variation (as assessed in twin pair 041896 alone), and 3.5% to lane-to-lane sequencing variation (Supplementary Figs 4–7). The variance in transcript abundance attributable to MS was within the range of variances obtained by random permutation of MS diagnosis labels (Supplementary Fig. 8 and Supplementary Table 3). Thus, robust gene expression differences were not observed between MS-affected and unaffected twins in $CD4^+$ lymphocytes that were inexplicable by other variables.

One-billion, high-quality, shotgun, whole-genome sequences were generated from twins 041896-001 and -101, corresponding to 21.7- and 22.5-fold aligned coverage, and representing 99.6% and 99.5% of the

Between affected and unaffected twins, there were no reproducible differences in SNPs, other DNA changes, or gene expression levels. Nor did affected twins have distinct signs of viral infection. There were some differences in CpG methylation – a chemical tag at certain sites in DNA – between affected and unaffected twins, but none of those differences were observed in more than one twin pair.

The researchers noticed surprising differences between twins, but no correlation to MS, in a trait called allelic imbalance. Most of our genes exist in two copies, or alleles. Allelic imbalance describes a common situation where one copy of a gene is expressed at higher levels than the other copy.

"We found many instances where an allelic imbalance was larger in one twin than in the other, or where the imbalance was flipped between the two alleles," **said Dr. Baranzini. Those differences were unexpected and are likely to be of interest in future studies of twins, whether the focus is on MS or other diseases, he said.**

In July 2013 - NASA & NSBRI Released The "Twins Study" Solicitation & Received 40 Proposals

National Aeronautics and Space Administration
Johnson Space Center
Human Exploration and Operations Mission Directorate
Human Research Program
Houston, TX 77058

Human Exploration Research Opportunities (HERO)

Appendix D

Differential Effects on Homozygous Twin Astronauts Associated with Differences in Exposure to Spaceflight Factors

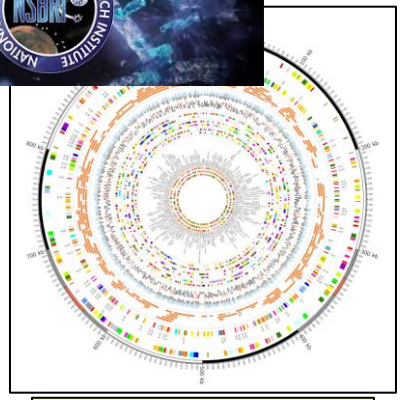
Response Period: July 30, 2013 – September 17, 2013
Proposals Due: September 17, 2013, 5 PM Eastern Time
Estimated Selection Announcement: January 2014

Appendix D - 1

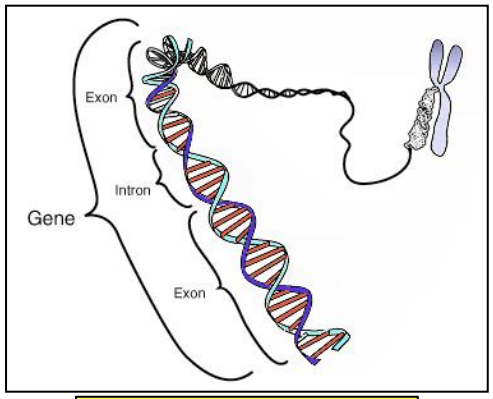
"To capitalize on this unique opportunity, NASA's Human Research Program (HRP) and the National Space Biomedical Research Institute (NSBRI) are initiating a pilot demonstration project focused on the use of integrated human -omic analyses to better understand the biomolecular responses to the physical, physiological, and environmental stressors associated with spaceflight."

http://www.nsbri.org/default/Funding/NNJ13ZSA002N/HERO_Twins.pdf

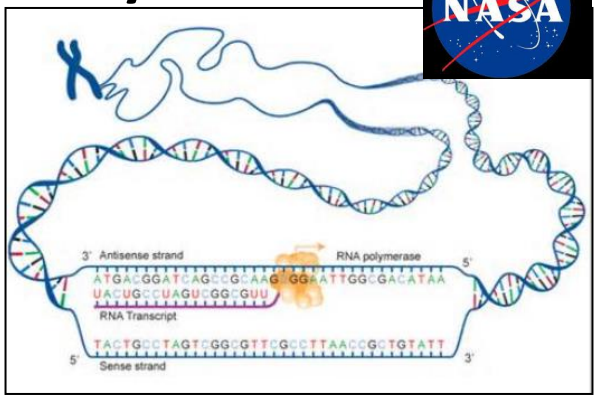
Goal: Perform Integrated Omics On Kelly Twins



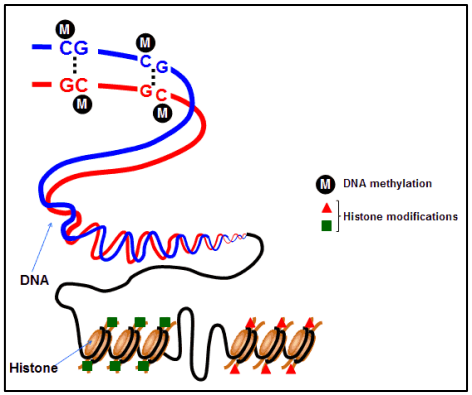
Genomics



Exomics

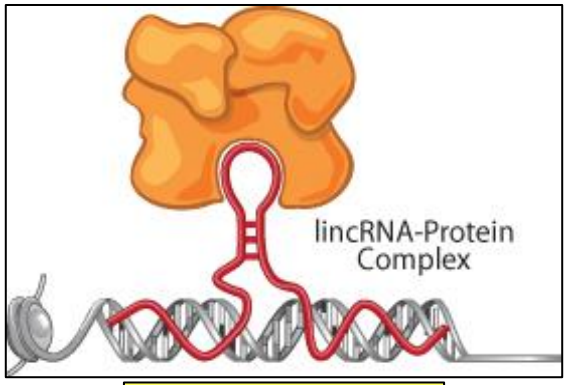


Transcriptomics



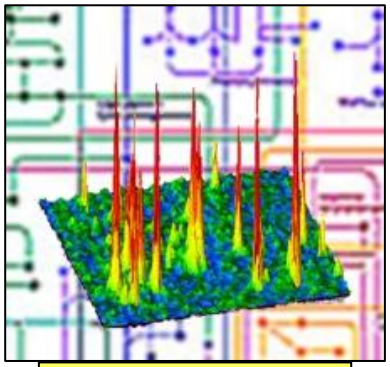
Epigenomics

Genomics ~ 30,000 genes	*What can happen*
Transcriptomics ~ 100,000 transcripts	*What appears to be happening*
Proteomics ~ 1,000,000 proteins	*What makes it happen*
Metabolomics ~ 1,000,000 metabolites	*What has happened and is happening*

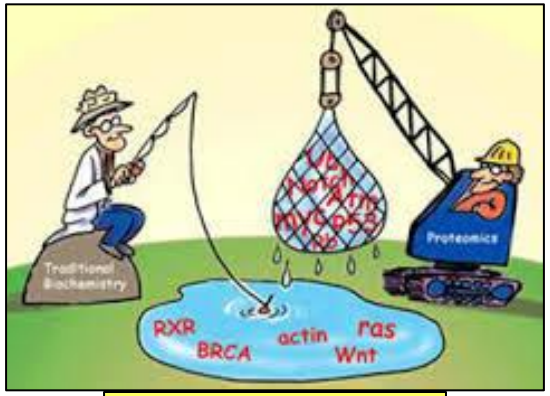


RNAomics

Microbiomics



Metabolomics



Proteomics

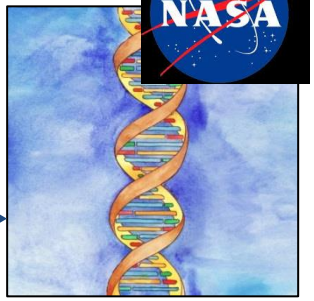
Biofluid Sampling Approach – For Scott and Mark Kelly

Saliva

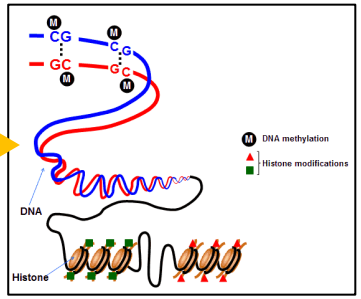
Buccal Cheek Swab

Blood

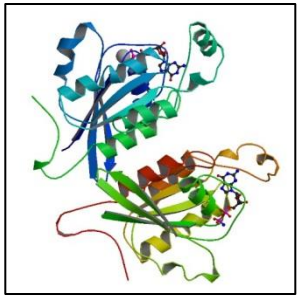
Stool



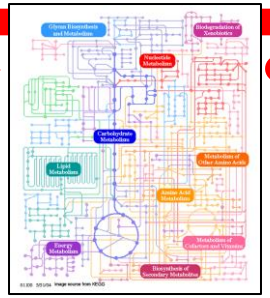
DNA



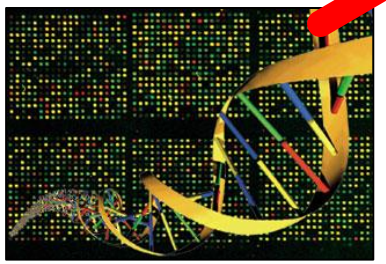
Epigenome



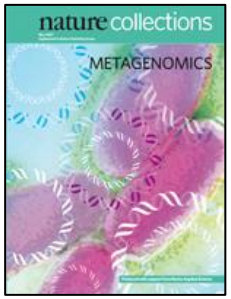
Proteins



Metabolites



RNA



Metagenome

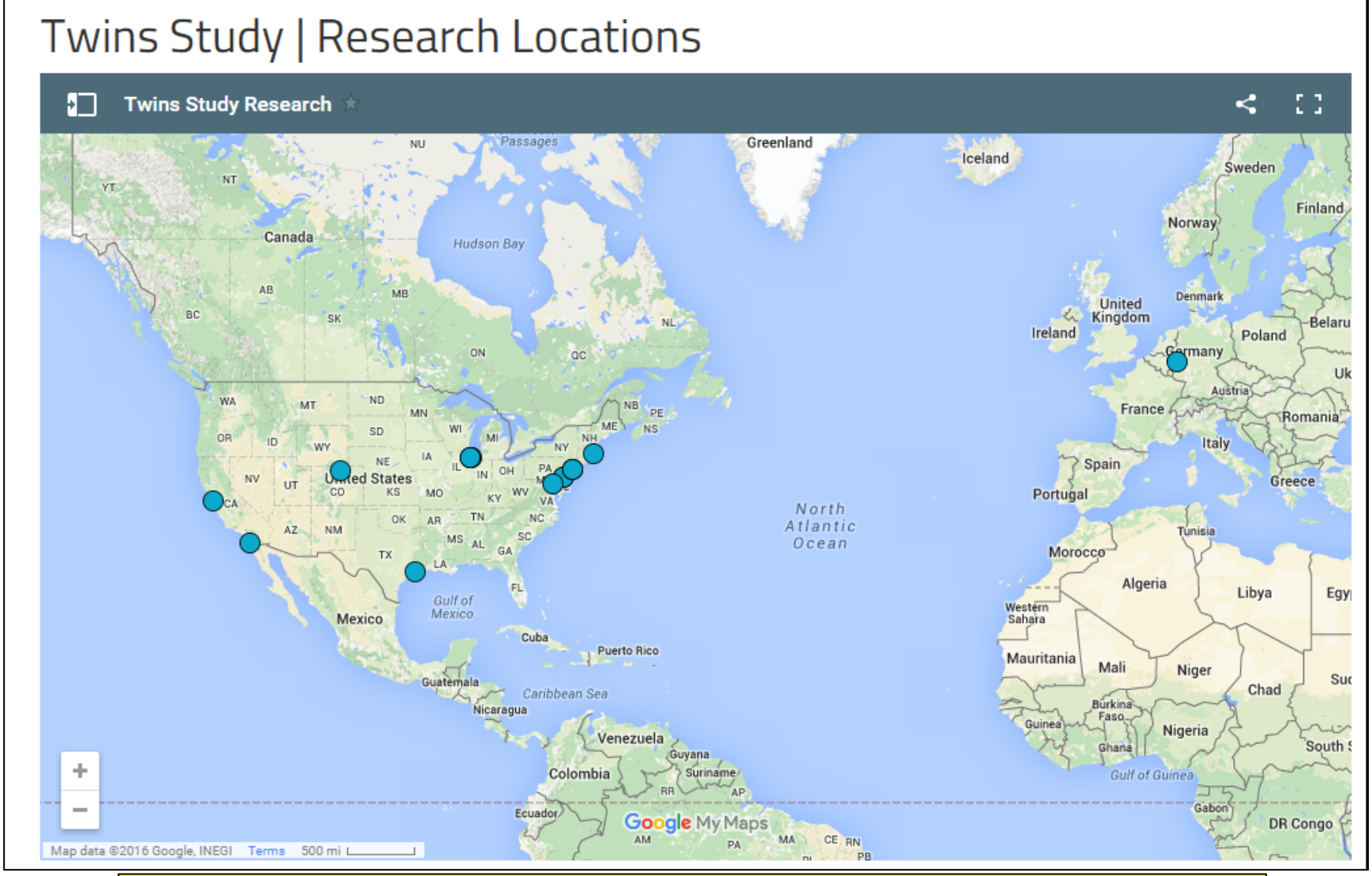
NASA Funded 10 Research Proposals In Response to its "Twins" Solicitation

Scientific and technical experts from academia and government reviewed 40 proposals submitted in response to the research announcement "Human Exploration Research Opportunities - Differential Effects on Homozygous Twin Astronauts Associated with Differences in Exposure to Spaceflight Factors." The following 10 selected proposals, which are from 10 institutions in seven states, will receive a combined $1.5 million during a three-year period:

1. **Emmanuel Mignot,** Stanford University School of Medicine, HERO Twin Astronaut Study Consortium (TASC): Immunome Changes in Space
2. **Michael Snyder,** Stanford University, HERO Twin Astronaut Study Consortium (TASC) Project: Longitudinal integrated multi-omics analysis of the biomolecular effects of space travel
3. **Brinda Rana,** University of California, Proteomic Assessment of Fluid Shifts and Association with Visual Impairment and Intracranial Pressure in Twin Astronauts
4. **Susan Bailey,** Colorado State University, Differential effects on telomeres and telomerase in twin astronauts associated with spaceflight
5. **Fred Turek,** Northwestern University, HERO Twin Astronaut Study Consortium (TASC) Project: Metagenomic Sequencing of the Bacteriome in GI Tract of Twin Astronauts
6. **Andrew Feinberg,** Johns Hopkins University School of Medicine, Comprehensive whole genome analysis of differential epigenetic effects of space travel on monozygotic twins
7. **Christopher Mason,** Weill Medical College of Cornell University, The Landscape of DNA and RNA Methylation Before, During, and After Human Space Travel
8. **Mathias Basner,** University of Pennsylvania School of Medicine, HERO Twin Astronaut Study Consortium (TASC) Project: Cognition on Monozygotic Twin on Earth
9. **Stuart Lee,** Wyle Laboratories, Metabolomic And Genomic Markers Of Atherosclerosis As Related To Oxidative Stress, Inflammation, And Vascular Function In Twin Astronauts
10. **Scott Smith,** NASA Johnson Space Center, Biochemical Profile: Homozygous Twin control for a 12 month Space Flight Exposure

http://www.nasa.gov/content/nasa-selects-10-proposals-to-explore-genetic-aspects-of-spaceflight/

Twins Study – Research Locations Distributed Across the U.S. (and Europe)



https://www.nasa.gov/twins-study/research-locations

Overview of the "Twins" Study – By Dr. Craig Kundrot

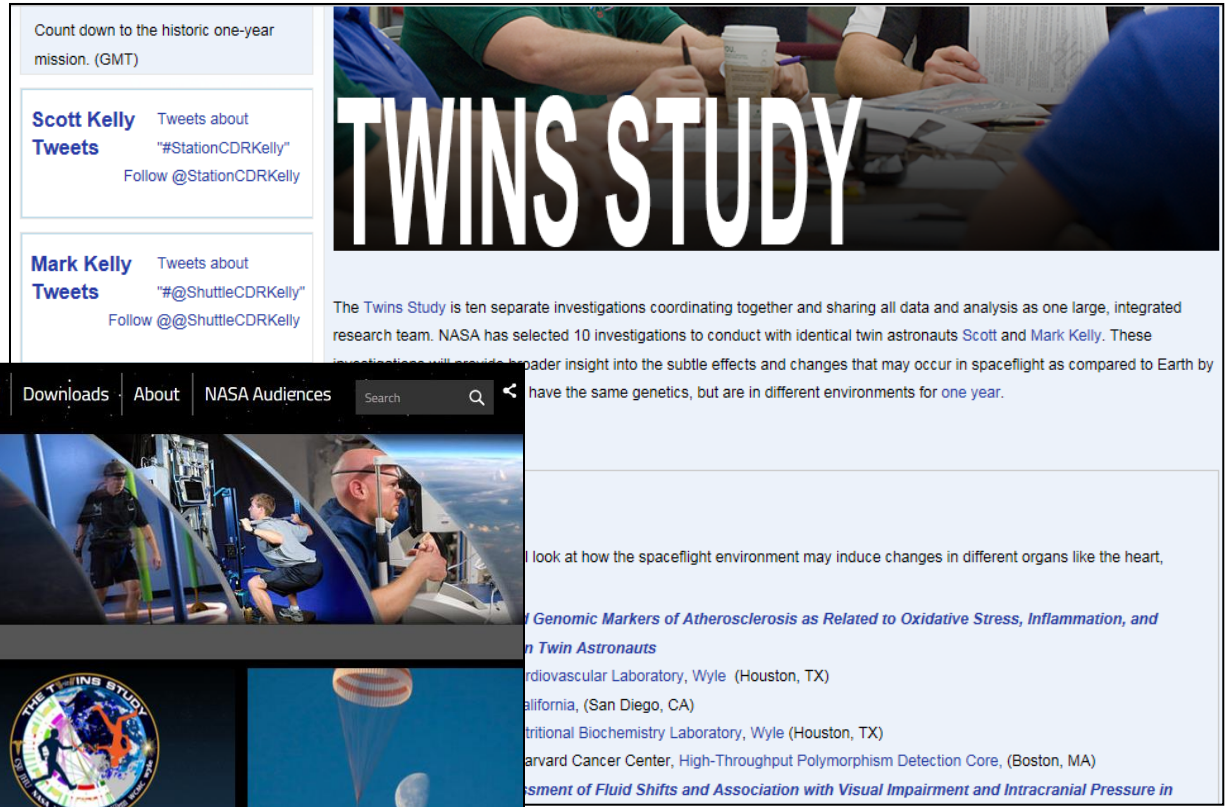
NASA to conduct the first-ever twin study in space

Comments 3 Email Share 1K Tweet 121 Like 1.3k g+1 7

Identical twins Mark and Scott Kelly have signed up to be part of the first-ever study of twins that takes

http://www.youtube.com/watch?feature=player_embedded&v=cnM_ZVvZA_o

Content - Including “One Pagers” for the 10 Twins Projects Is Posted Online



http://www.nasa.gov/content/twins-study/

Scott Kelly Has Now Been Back On Earth For Well Over 230 Days

http://www.nasa.gov/content/twins-study/

Differential Effects on Telomeres and Telomerase in Twin Astronauts Associated With Spaceflight

Susan Bailey, Ph.D.
Colorado State University

Kerry George
Wyle Labs/JSC

Specific Aims

The rate at which telomeres shorten provides an informative biomarker of aging and age-related pathologies (e.g., cardiovascular disease and cancer) that captures the interplay between genetics and lifestyle factors.

We propose that for the astronauts telomere maintenance is particularly relevant, as it reflects the combined exposures (e.g., radiation) and experiences (nutritional, psychological and physical stressors) encountered during space travel.

The Twins study provides the extraordinary opportunity to control variables of individual genetic differences, susceptibilities and lifestyle factors, making differential effects observed between the twins space-flight specific.

Comparisons with unrelated astronauts (separate study), will allow evaluating role of genetics/individual susceptibilities.

Implications of Research for Space & Earth

Space: This twins study will identify space-flight specific factors that influence telomere length and telomerase activity, informative biological indicators of aging and age-related degenerative diseases (e.g., cardiovascular disease and cancer). Our mechanistic investigations will begin to establish relevant relationships and suggest potential mitigation strategies for future study and to improve astronaut overall health.

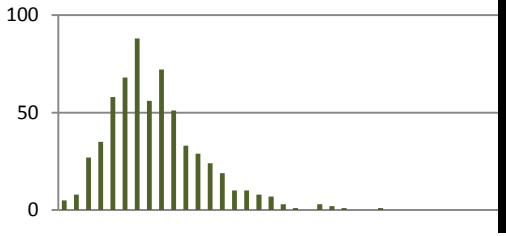
Earth: Aging and age-related diseases like cardiovascular disease and cancer are an everyday concern on earth as well, therefore this study also seeks to make comparisons with unrelated astronauts (and controls) that will serve to identify individual susceptibility factors that influence telomere length and telomerase activity. Taken together with our mechanistic studies, mitigation strategies will be improved and applicable to all.

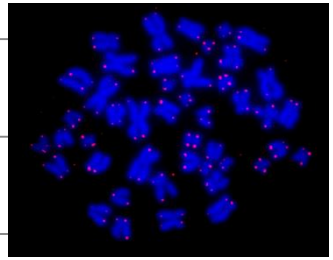
***Our goal* is to assess changes in telomere length and telomerase activity associated with the upcoming yearlong ISS mission in the space- and earth-bound twin astronauts.**

***We hypothesize* that accelerated telomere shortening and elevated telomerase activity will be associated with space flight** as compared to ground based control, in a duration and severity dependent manner.

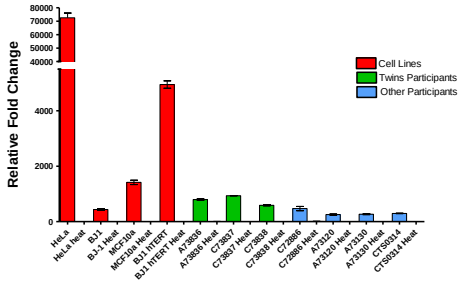
- Blood samples will be taken ***pre-flight*** (to establish baseline), ***in-flight*** (to evaluate short-term/temporary changes) and ***post-flight*** (to evaluate long-term/permanent changes)
- Data sharing for other endpoints will also inform this effort
- *In vitro* studies will investigate potential mechanisms (e.g., oxidative stress) and mitigation strategies (e.g., antioxidants)

Telomere length will be assessed using TELO-FISH
Florescence *in situ* Hybridization (FISH) with telomere probe on chromosomes (and interphase nuclei) is evaluated as Relative Fluorescence Intensity (RFI) distributions.

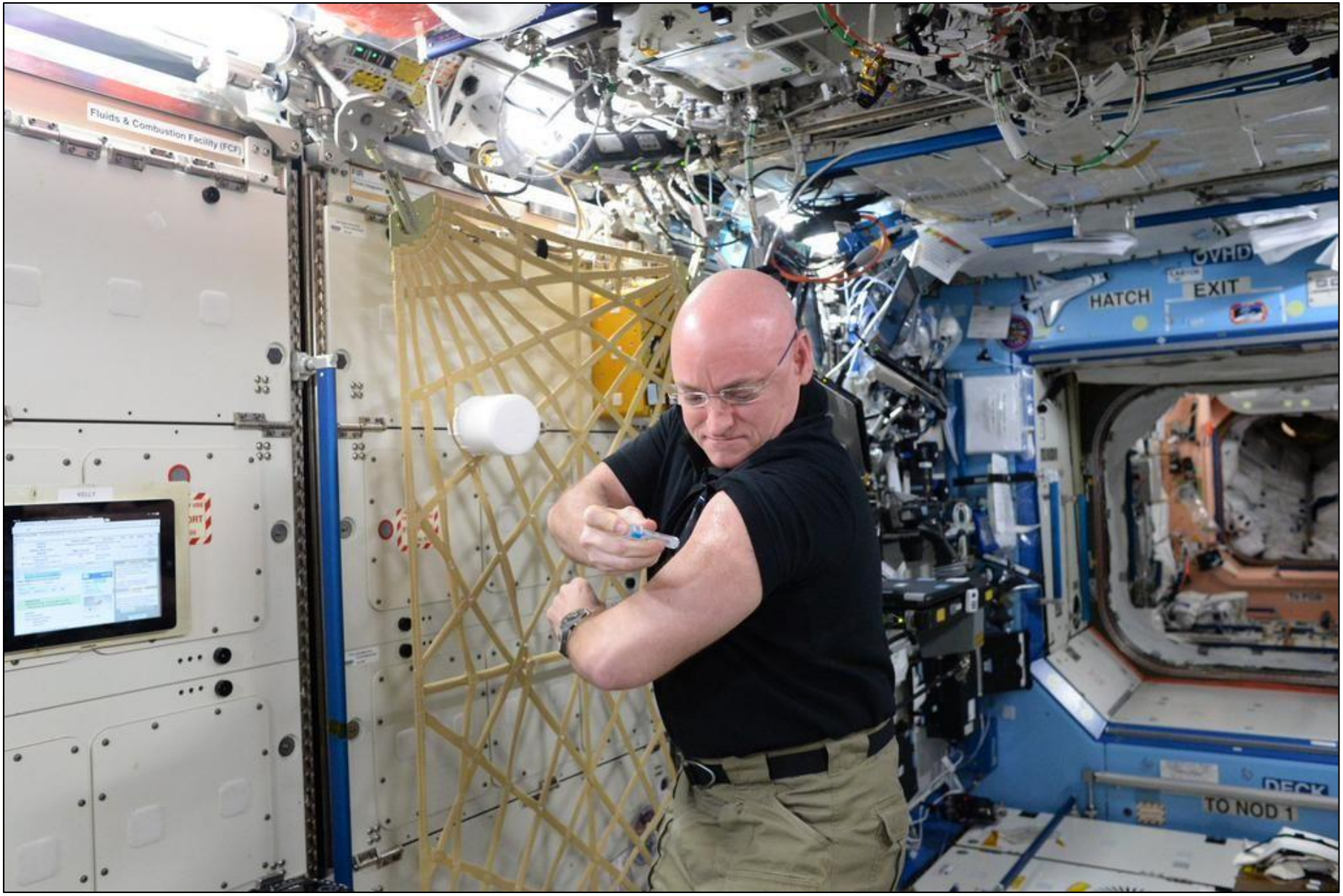


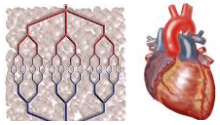


Telomerase activity will be assessed using qRT-PCR TRAP
quantitative Real Time-PCR Telomere Repeat Amplification Protocol

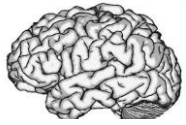


Scott Kelly: Vaccination In Space On September 24, 2015



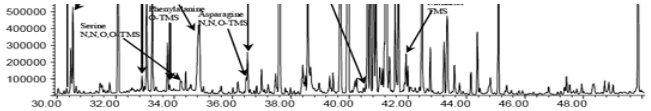


Vasculature
Lee

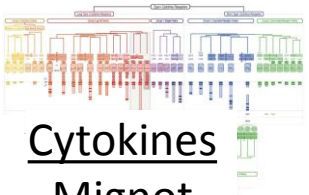


Cognition
Basner

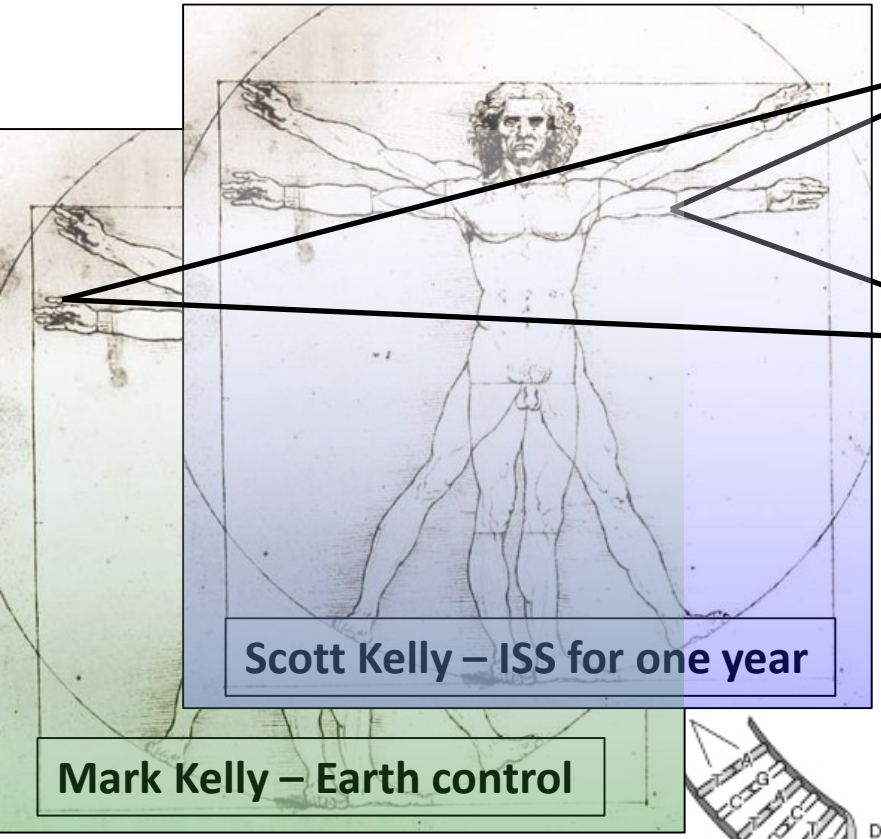
Microbiome
Turek



Targeted and Global Metabolomics
Lee/Rana, Mignot/Snyder & Smith

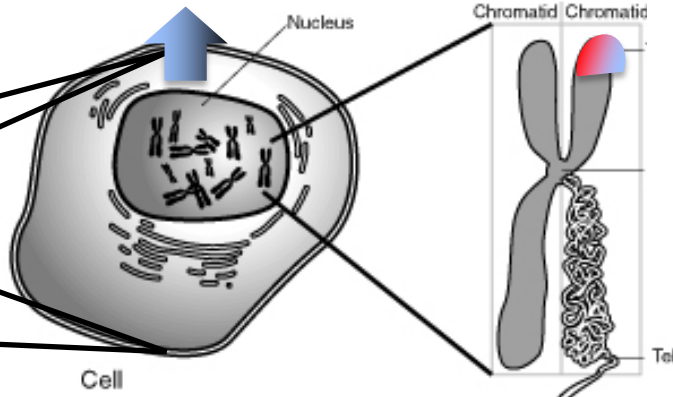


Cytokines
Mignot



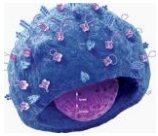
Scott Kelly – ISS for one year

Mark Kelly – Earth control

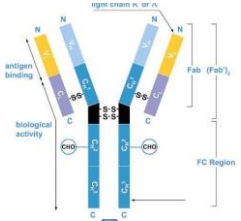


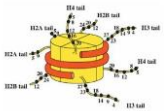
Telomere Length
Bailey

B-cells / T-cells
Mignot

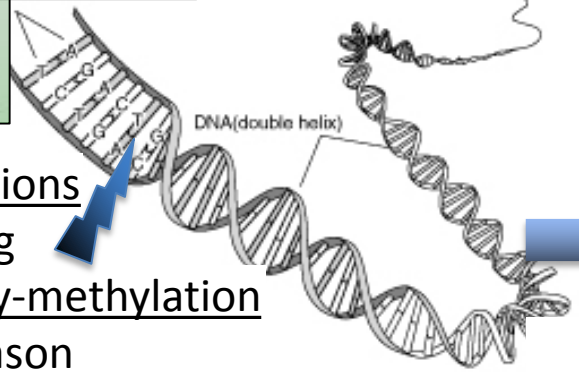


Antibodies
Mignot/Snyder



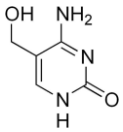


Chromatin
Feinberg

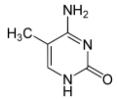


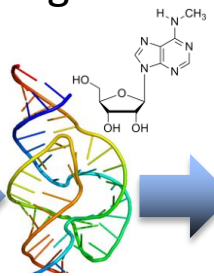
DNA Mutations
Feinberg

DNA Hydroxy-methylation
Mason

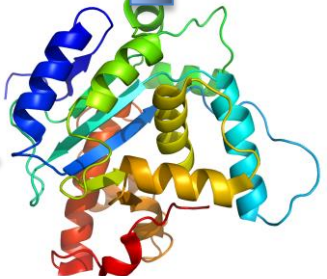


DNA Methylation
Feinberg & Mason





large/small RNA
& RNA Methylation
Mason



Proteomics
Lee/Rana

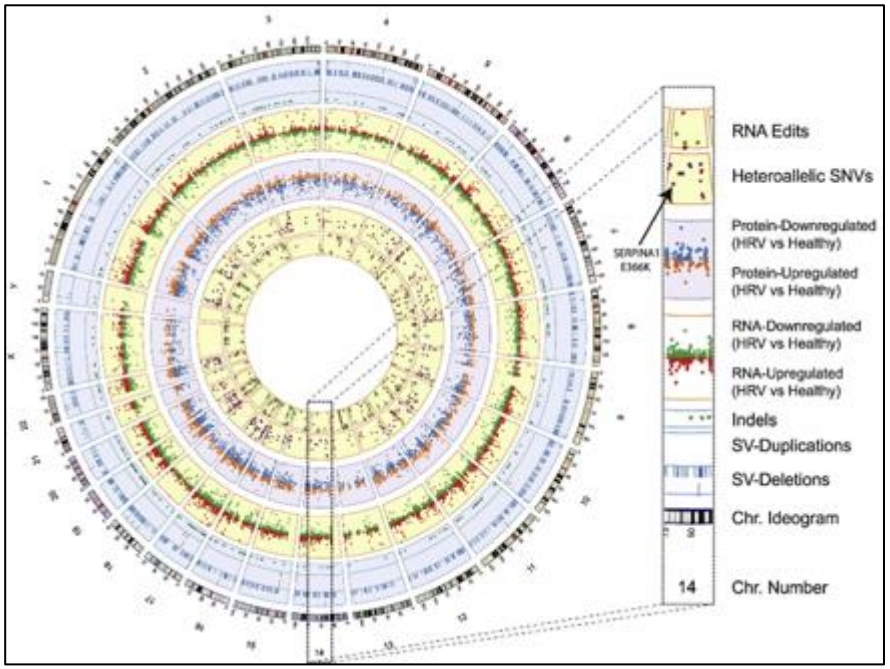
Integrated Omics

Michael Snyder, Ph.D.

Juliane Winkelmann, M.D.

Specific Aims

Our main objective in the twin study is to perform a complete analysis of all biomedical and molecular data collected during the mission to produce the singular most comprehensive portrait of the human biophysical response to the rigors of spaceflight. We are at an unprecedented era in genomic medicine, allowing for the sensitive and precise measurement of billions of biochemical molecules, which will allow us to detect the subtlest of changes in Scott and Mark's physiology over time. By integrating these data, we can follow alterations in their cellular systems to both better understand the effects of space travel on human health, and how an astronaut's genome may contribute to his/her own unique physiologic response to microgravity.

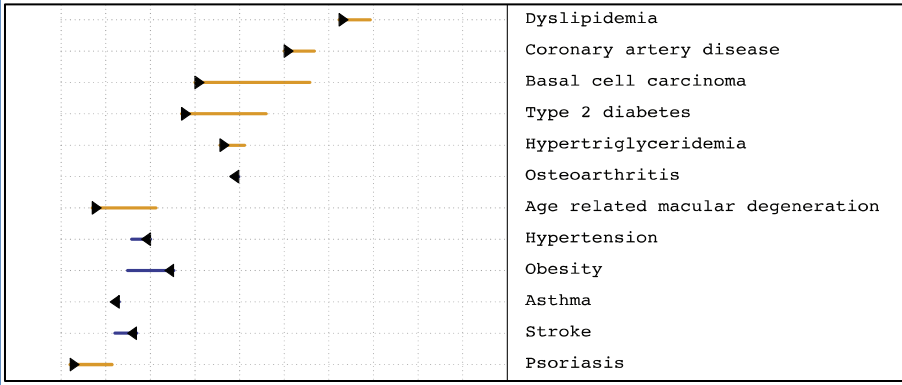


Integrative multi-omic model

Implications of the Research for Space & Earth

Space: We will generate a detailed benchmark for how human physiology changes in space in great molecular detail. This wealth of data will be essential for any future planning of long duration space exploration missions, and provide a proof-of-principle for better monitoring and managing astronaut health.

Earth: With this study, Scott and Mark Kelly will be the most thoroughly profiled twins in history, and the resultant data will offer new insights into how two siblings with nearly-identical genomes respond to different conditions.



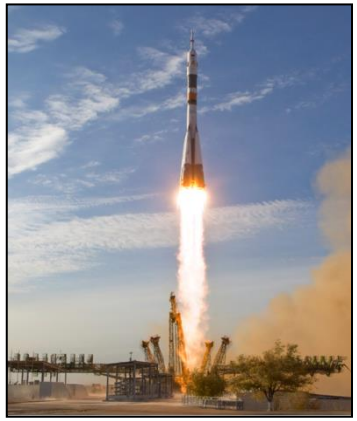
Risk-o-gram

Scott Kelly: 11 In-flight Blood Collections

Total Available for Twins Study In-Flight Blood for Science Requirements = 362.5 ml

FD- Flight Day
R- Return to Earth
NET- No earlier than
nmS- Soyuz flight number

4/10/2015	6/9/2015	7/27/2015	9/24/2015	10/5/2015	11/19/2015	1/21/2016	2/24/2016			
45.5 ml Frozen	45.5 ml Frozen	45.5 ml Frozen	45.5 ml Frozen	4 ml Frozen (post- vacc)	45.5 ml Frozen	45.5 ml Frozen	45.5 ml Frozen			
FD14	FD 74	FD122	FD181	FD192	FD237	FD300	R-14/FD334			
March 27, 2015				October 2015			March 3, 2016			
	FD76 41S↓ 24 ml (ambient)				FD259 43S↓ 8 ml (ambient)		R-1 44S↓ 8 ml (ambient)			
		6/11/2015				12/11/2015		3/1/2016		



Launch

Scott Kelly

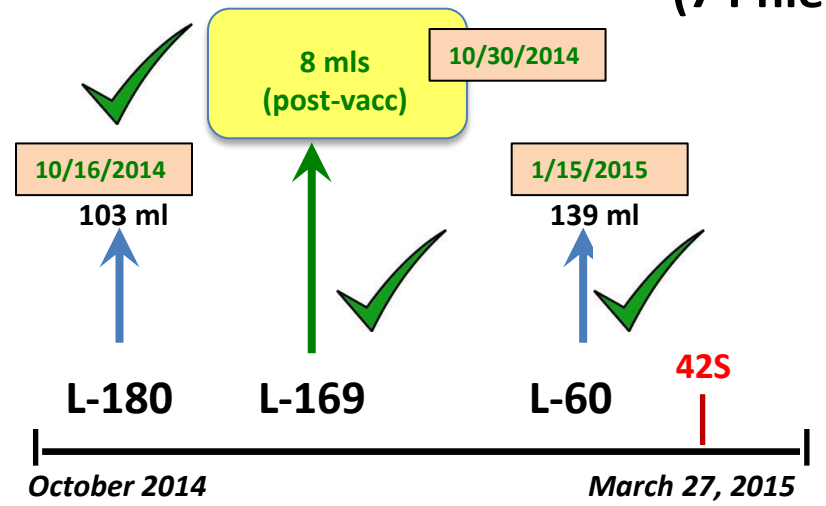
1 Year ISS Mission

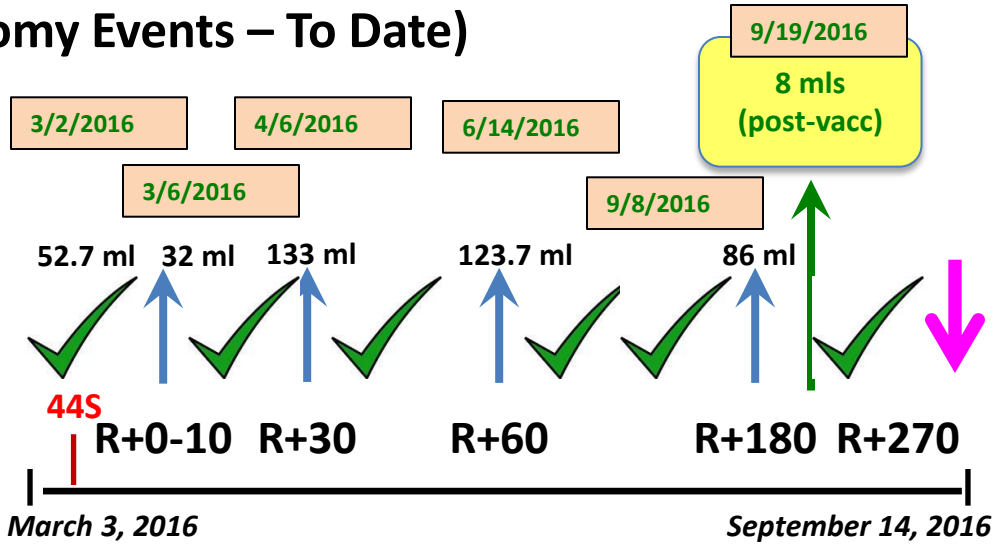
Landing

Scott Kelly: Pre- and Post-Flight Blood Collections

3 Collections Pre-Flight; 6 Collections Planned Post-Flight

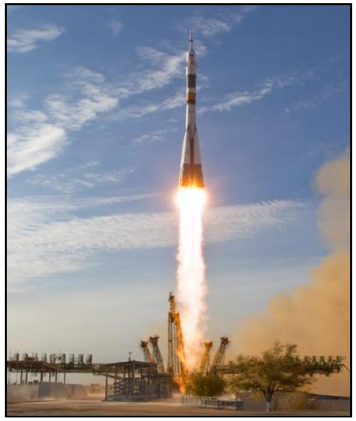
(7 Phlebotomy Events – To Date)





L- Launch
R- Return to Earth
nmS- Soyuz flight number

Scott Kelly



Launch

Landing

Tahiti

Scott Kelly

Mark Kelly: Blood Collections

12 Planned Phlebotomy Events
(9 Phlebotomy Events - To Date)

Mark Kelly

12/13/2014

Pre- vacc

8 mls (post-vacc)

12/3/2014

103 ml

1/20/2015

103 ml

Dec 2014

Jan 2015

42S

March 28, 2015

9/10/2016

8 mls (post-vacc)

3/4/2016

107 ml

5/6/2016

96 ml

7/17/2016

86.2 ml

85.9 ml

44S

Mar 2016

April 2016

July 2016

Sept 2016

March 7, 2016

8/30/2016

FD- Flight Day
R- Return to Earth
nmS- Soyuz flight number

7/30/2015

94 ml

July 2015

10/1-2/2015

Pre- vacc

10/17/2015

8 ml Frozen (post- vacc)

103 ml

Oct 2015

1/19/2016

103 ml

Jan 2016

March 2015

March 2016

FD45
41S

FD233
43S

R-1
44S

The Twins Study Will Generate Two Longitudinal Omics Analyses - Like the "Synderome"

Resource

Cell

Personal Omics Profiling Reveals Dynamic Molecular and Medical Phenotypes

Rui Chen,[1,11] George I. Mias,[1,11] Jennifer Li-Pook-Than,[1,11] Lihua Jiang,[1,11] Hugo Y.K. Lam,[1,12] Rong Chen,[2,12] Elana Miriami,[1] Konrad J. Karczewski,[1] Manoj Hariharan,[1] Frederick E. Dewey,[2] Yong Cheng,[1] Michael J. Clark,[1] Hogune Im,[1] Lukas Habegger,[6,7] Suganthi Balasubramanian,[6,7] Maeve O'Huallachain,[1] Joel T. Dudley,[2] Sara Hillenmeyer,[1] Rajini Haraksingh,[1] Donald Sharon,[1] Ghia Euskirchen,[1] Phil Lacroute,[1] Keith Bettinger,[1] Alan P. Boyle,[1] Maya Kasowski,[1] Fabian Grubert,[1] Scott Seid,[2] Marco Garcia,[2] Michelle Whirl-Carrillo,[1] Mercedes Gallardo,[9,10] Maria A. Blasco,[9] Peter L. Greenberg,[4] Phyllis Snyder,[1] Teri E. Klein,[1] Russ B. Altman,[1,5] Atul J. Butte,[2] Euan A. Ashley,[2] Mark Gerstein,[6,7,8] Kari C. Nadeau,[3] Hua Tang,[1] and Michael Snyder[1,*]

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[2]Division of Systems Medicine and Division of Immunology and Allergy, Department of Pediatrics
[3]Center for Inherited Cardiovascular Disease, Division of Cardiovascular Medicine
[4]Division of Hematology, Department of Medicine
[5]Department of Bioengineering
Stanford University, Stanford, CA 94305, USA
[6]Program in Computational Biology and Bioinformatics
[7]Department of Molecular Biophysics and Biochemistry
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[9]Telomeres and Telomerase Group, Molecular Oncology Program, Spanish National Cancer Centre (CNIO), Madrid E-28029, Spain
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*Correspondence: mpsnyder@stanford.edu
DOI 10.1016/j.cell.2012.02.009

SUMMARY

Personalized medicine is expected to benefit from combining genomic information with regular monitoring of physiological states by multiple high-throughput methods. Here, we present an integrative personal omics profile (iPOP), an analysis that combines genomic, transcriptomic, proteomic, metabolomic, and autoantibody profiles from a single individual over a 14 month period. Our iPOP analysis revealed various medical risks, including type 2 diabetes. It also uncovered extensive, dynamic changes in diverse molecular components and biological pathways across healthy and diseased conditions. Extremely high-coverage genomic and transcriptomic data, which provide the basis of our iPOP, revealed extensive heteroallelic changes during healthy and diseased states and an unexpected RNA editing mechanism. This study demonstrates that longitudinal iPOP can be used to interpret healthy and diseased states by connecting genomic information with additional dynamic omics activity.

INTRODUCTION

Personalized medicine aims to assess medical risks, monitor, diagnose and treat patients according to their specific genetic composition and molecular phenotype. The advent of genome sequencing and the analysis of physiological states has proven to be powerful (Cancer Genome Atlas Research Network, 2011). However, its implementation for the analysis of otherwise healthy individuals for estimation of disease risk and medical interpretation is less clear. Much of the genome is difficult to interpret and many complex diseases, such as diabetes, neurological disorders and cancer, likely involve a large number of different genes and biological pathways (Ashley et al., 2010; Gnyawon et al., 2011; Li et al., 2011), as well as environmental contributors that can be difficult to assess. As such, the combination of genomic information along with a detailed molecular analysis of samples will be important for predicting, diagnosing and treating diseases as well as for understanding the onset, progression, and prevalence of disease states (Snyder et al., 2009).

Presently, healthy and diseased states are typically followed using a limited number of assays that analyze a small number of markers of distinct types. With the advancement of many new technologies, it is now possible to analyze upward of 10^9 molecular constituents. For example, DNA microarrays have allowed the subcategorization of lymphomas and gliomas

Mike Snyder

Cell

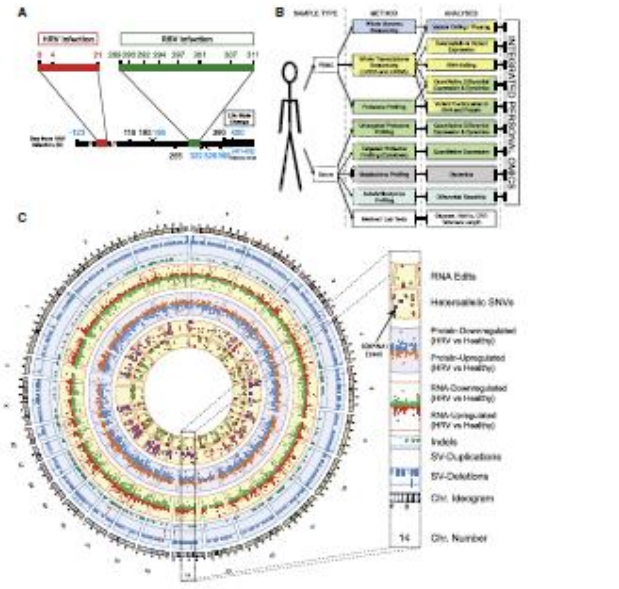


Figure 1. Summary of Study

(A) Time course summary. The subjects are monitored for a total of 720 days, during which there were two infections (red bar, HRV; green bar, RSV). The black bar indicates the period when the subject: (1) increased exercise, (2) ingested 81 mg of acetylsalicylic acid and ibuprofen tablets each day (the latter only during the first 6 weeks of this period), and (3) substantially reduced sugar intake. Blue numbers indicate fasted time points.

(B) iPOP experimental design indicating the tissues and analyses involved in this study.

(C) Circos (Krzywinski et al., 2009) plot summarizing iPOP. From outer to inner rings: chromosome ideogram; genomic data (pale blue ring), structural variants (>50 bp) (deletions [blue tiles], duplications [red tiles]), indels (green triangles); transcriptomic data (yellow ring), expression ratio of HRV infection to healthy states; proteomic data (light purple ring), ratio of protein levels during HRV infection to healthy states; transcriptomic data (yellow ring), differential heteroallelic expression ratio of alternative allele to reference allele for missense and synonymous variants (purple dots) and candidate RNA missense and synonymous edits (red triangles, purple dots, orange triangles and green dots, respectively).

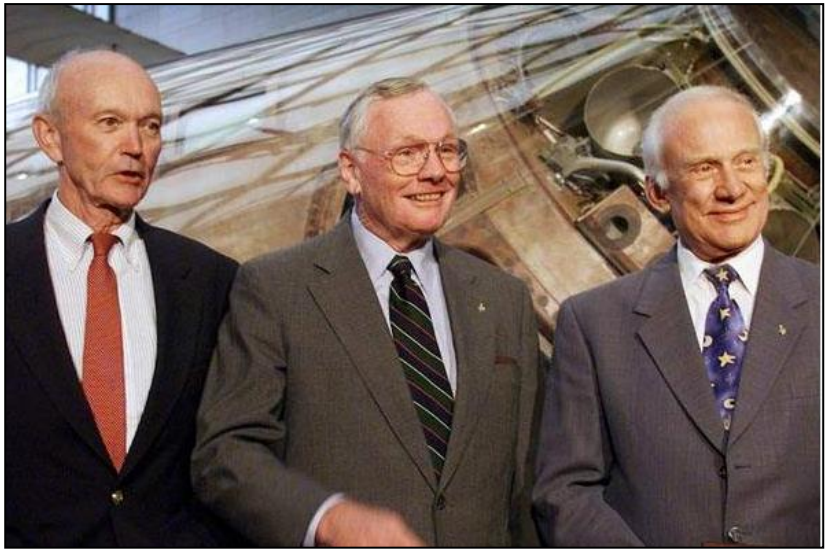
See also Figure S1.

WGS-Based Disease Risk Evaluation

We identified variants likely to be associated with increased susceptibility to disease (Dewey et al., 2011). The list of high confidence SNVs and indels was analyzed for rare alleles (<5% of the major allele frequency in Europeans) and for changes in genes with known Mendelian disease phenotypes (data summarized in Table 2), revealing that 51 and 4 of the rare coding SNV and indels, respectively, in genes present in OMIM are predicted to lead to loss-of-function (Table S2A). This list of genes was further examined for medical relevance (Table S2A; example alleles are summarized in Figure 2A), and 11 were validated by Sanger sequencing. High interest genes include: (1) a mutation (E366K) in the *SERPINA1* gene previously known in the subject, (2) a damaging mutation in *TERT*, associated with acquired aplastic anemia (Yamaguchi et al., 2005), and (3) variants associated with hypertriglyceridemia and diabetes, such as *GCKR*

The Twins Study Is Acting as a Pathfinder For NASA in Tackling Ethical Considerations

Astronauts are Concerned about "Being Grounded"



Astronauts are in the Public Eye and are "Stalked"

Astronauts are Concerned about Their Families

Astronauts are Employees

Both Twins Have Been (And Will Continue To Be) Provided With Genetic Counseling

The Twins Study Investigators & Scientific Leadership

NSBRI providing genetic medical counseling, to support the Twins Study. Genetic medical counseling has been performed, to date, by both John W. Belmont, M.D., Ph.D. (left) and Sharon Plon, M.D., Ph.D. (right).

NSBRI also providing, Scientific (Omics) Expertise and Omics Lab Capabilities to Support the Twins Study.

The Twins Study Has Captured the Imagination of "The Next Generation"

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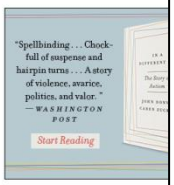
Nature versus Nurture versus NASA

The space agency sends an identical twin into orbit to study the effect of zero gravity on human health

By Amy Nordrum on March 1, 2015 1

Celestial Influence: How living in zero gravity changes the human body
COURTESY OF ROBERT MARKOWITZ NASA



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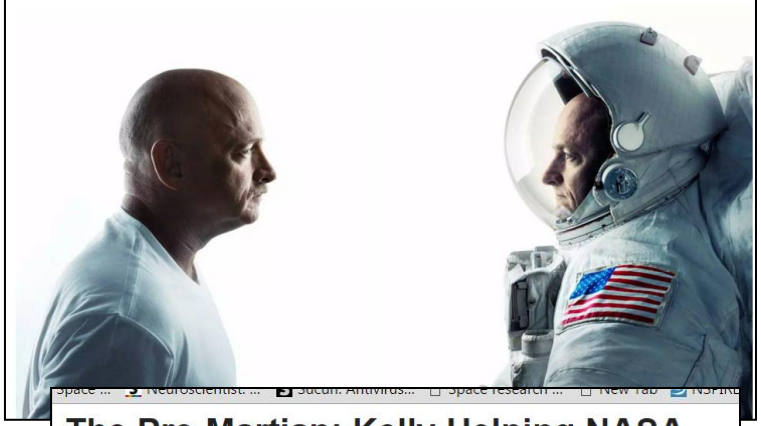
A Year in Space: Latest News

SCIENCE A YEAR IN SPACE

The Great Space Twins Study Begins

Jeffrey Kluger @jeffreykluger | May 1, 2015



The Pre-Martian: Kelly Helping NASA Prep for Future Mission

Scott Kelly and twin brother Mark talk Mars and the future of NASA.

NASA astronaut Scott Kelly floats aboard the International Space Station after the hatch opening of the Soyuz spacecraft Mar. 28, 2015.

Scott Kelly Driven Public Outreach: USA Photographed From Space

As of 10/18/2016 Scott Kelly Has:

- ***2.01 M Twitter Followers***
- ***2539 Tweets***

http://www.usatoday.com/story/news/nation-now/2016/02/27/awe-inspiring-photos-from-scott-kellys-year-in-space/80979296/

Following His Year In Space …..
Scott Kelly Continues To Tweet Prolifically

TWEETS 2,539 | FOLLOWING 153 | FOLLOWERS 2M | LIKES 15

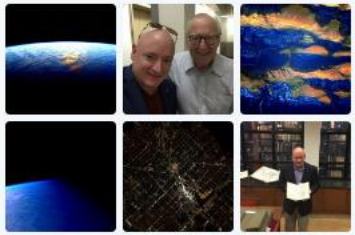
Scott Kelly ✓
@StationCDRKelly

scottkelly.com

Houston, TX

Joined August 2009

1,543 Photos and videos

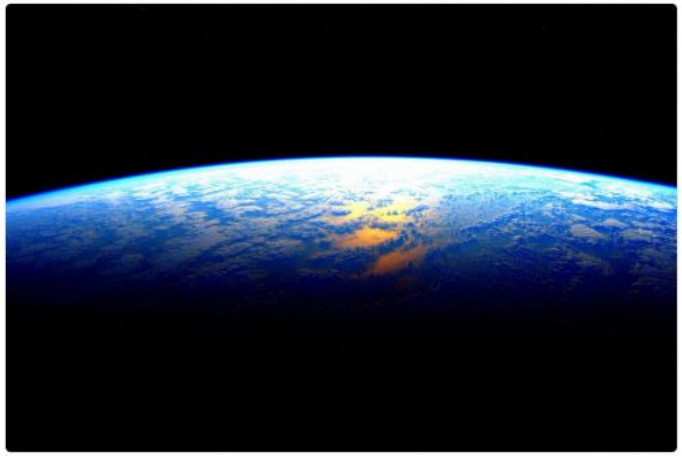


Tweets | Tweets & replies | Media

Scott Kelly @StationCDRKelly · 19m

Good day, blue planet! Excited to share about my #YearInSpace at #PRSAICON 10/23! @PRSA members register here: bit.ly/2cJGXYq

PRSA



85 270 •••

TWEETS 2,539 | FOLLOWING 153 | FOLLOWERS 2.01M | LIKES 15

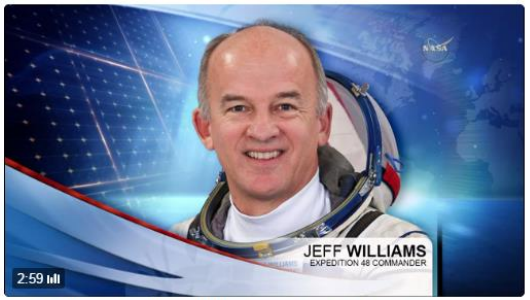
297 1.4K •••

Scott Kelly Retweeted

Intl. Space Station @Space_Station · Aug 24

.@StationCDRKelly congratulates @Astro_Jeff on breaking his record of 520 total days in space by a U.S. astronaut!

NASA



Scott Kelly Congratulates Jeff Williams on Breaking Record

Jeff Williams broke the record for total number of days in space by a U.S. astronaut at 520 days. - Clip from NASA TV

482 1.4K •••

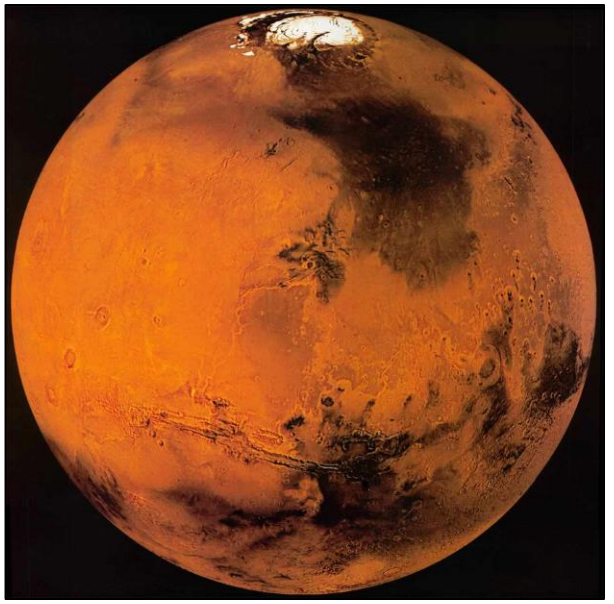
Scott Kelly @StationCDRKelly · Jul 12

Trading spaces. Great talk w my brother @ShuttleCDRKelly and @drsanjaygupta at #ISSRDC today!

https://twitter.com/StationCDRKelly?ref_src=twsrc%5Etfw

To Explore DEEP Space and Return Safely to Earth We Need Omics In Space as a Precursor to Personalized Countermeasures for Astronauts

Different people respond differently to the same therapy: while one treatment brings about the desired success in one group of patients with e.g. colon cancer, it does not change the condition of other groups at all, or even leads to adverse effects (left). The reason: the genetic makeup and metabolic profile of each individual patient influences the effect of a drug. Personalized medicine takes these individual patterns of cellular and metabolic products into account in the diagnostic phase: biomarker diagnostics separates patients into groups with similar characteristics, and provides information on the best individual treatment. This should enable all patients to benefit from their own, "personal" therapy.



Acknowledgements / Key Contributors

Jeffrey P. Sutton, M.D., Ph.D.

Julie Do, M.B.A.

Robert A. Pietrzyk, M.S.

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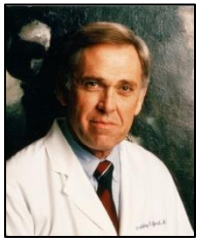
Dorit B. Donoviel, Ph.D.

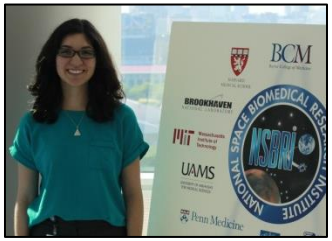
Tracy Johnson, M.S.

Marisa Covington, Ph.D.

William H. Paloski, Ph.D.

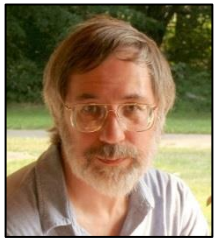


Bobby R. Alford, M.D.



Catherine Moreno, B.A.

The Twins Study Investigator TEAM



Mark Shelhamer, Sc.D.

John W. Belmont, M.D., Ph.D.

Virginia Wotring, Ph.D.

Craig E. Kundrot, Ph.D.

Questions?

Appendices

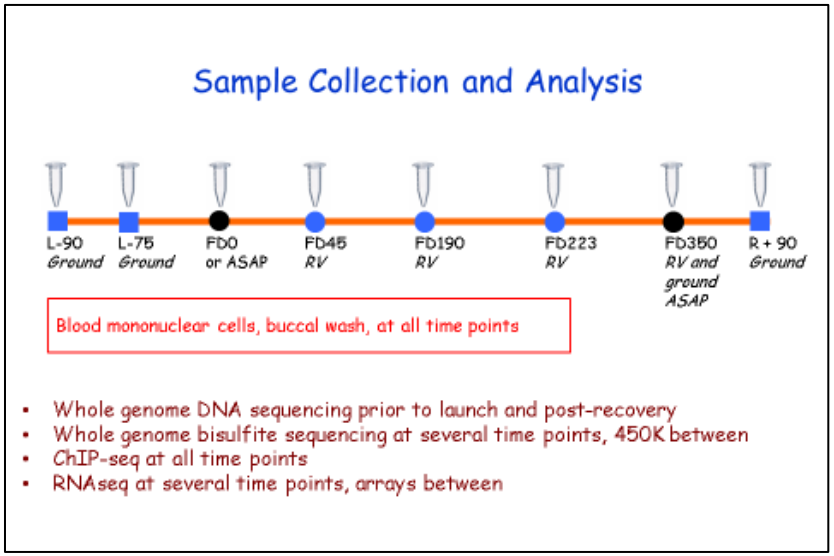
Epigenomics

Andrew Feinberg, M.D., M.P.H., and Jason Feinberg

Specific Aims

Aim 1. We will measure DNA methylation and chromatin at a genome-wide level in biological samples obtained from the space traveler at quarterly intervals, pre- and post-flight, and at times of unexpected exposures such as radiation events, or spacecraft environmental contamination. We also obtain measurements of the ground-based twin.

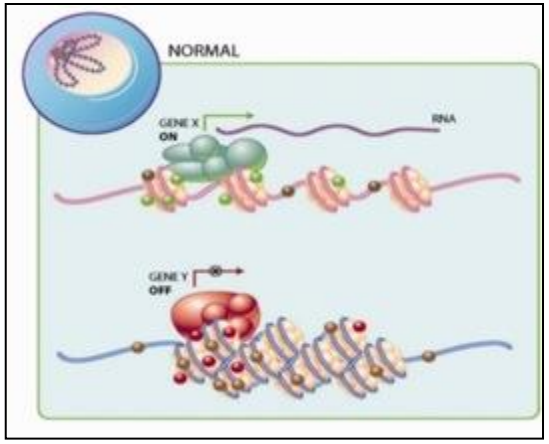
Aim 2. We will integrate epigenomic data with exposure to spaceflight conditions, looking for exposure-linked changes, and by comparison to the ground-based twin, determine whether these are transient or long-lived effects. We will also determine whether DNA mutations arise secondarily to these epigenetic changes.



Implications of the Research for Space & Earth

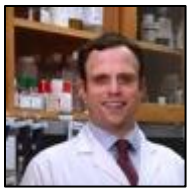
Space: Identify reversible causes of genomic damage in space, e.g. radiation or toxin induced epigenomics change; quantify aging and genomic exposure.

Earth: First human study of the epigenome over time in a defined/controlled environment.



- DNA methylation
- Histone modifications (>200 known)
- Chromatin factor complexes
- Chromatin structure

Landscape of DNA and RNA Methylation



Christopher Mason, Ph.D.

Francine Garrett-Bakelman, M.D. Ph.D.

Specific Aims: DNA to RNA

Epigenome → Epitranscriptome → Epiproteome

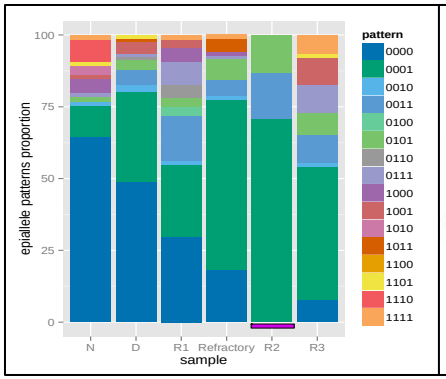
DNA —transcription→ RNA —translation→ Protein

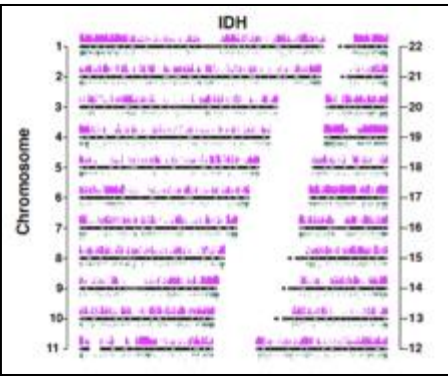
#1 – Genome-wide epigenetic profiles of DNA methylation changes

#2 – A comprehensive catalog of coding and noncoding, small and large RNA

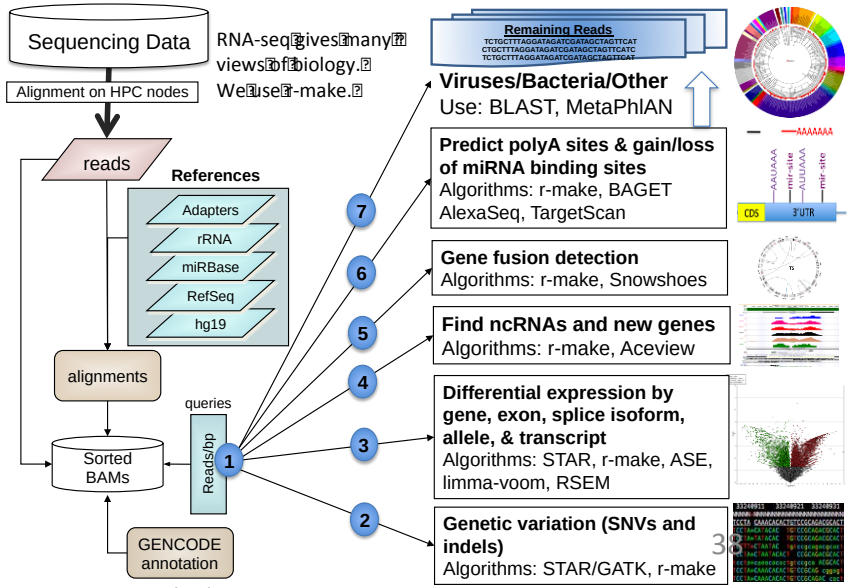
#3 – Transcriptome-wide maps of RNA methylation sites

Δ in Epigenetics : Loci, regions, and clones





Δ in Transcriptome : Genes, Isoform, Edits, Allele, SNVs, ncRNAs, Fusions, & Methylation



Li S, *Nature Biotechnology*, 2014.

Implications of the Research for Space & Earth

Space: (1) Establish the genetic networks and expression patterns activated by space travel, (2) trace clonality of epigenetic changes, (3) examine the methylation of RNA

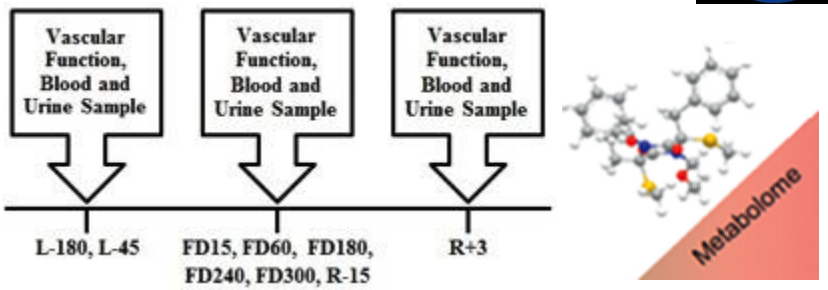
Earth: Aid research on aging, cancer, RNA biology, and circadian rhythm, all of which show differences at the (epi)genome & (epi)transcriptome

Metabolomic and Genomic Markers of Atherosclerosis in Twin Astronauts

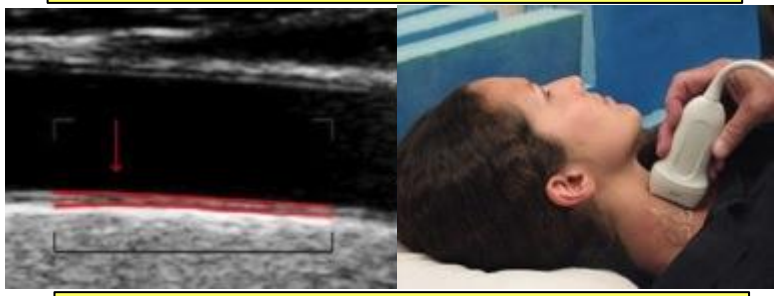
Stuart Lee

Specific Aims

- To study the effects of long-duration spaceflight on the cardiovascular system independent of genotype
- To investigate relationships between gene expression, metabolomic profiles, biomarkers in blood and urine, and arterial structure and function using the space-flown and the ground-based identical twin



Pre- and Post-flight Testing



Inflight Operations

Implications of the Research for Space & Earth

Space: Determine if the spaceflight environment perturbs genomic and metabolomic profiles and accelerates development of atherosclerosis (occupational health)

Earth: Develop novel insights of how longitudinal changes in genomic and metabolomic profiles are related to risk factors for atherosclerosis

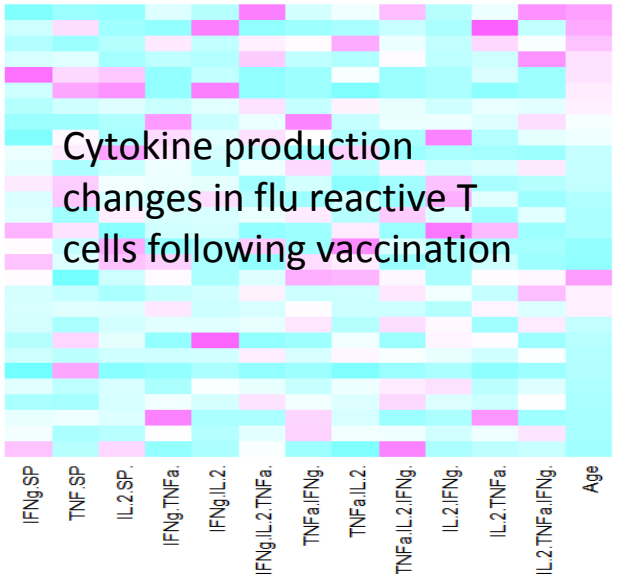
Immunome Studies in Space

Emmanuel Mignot, M.D., Ph.D.

Stanford University

Specific Aims

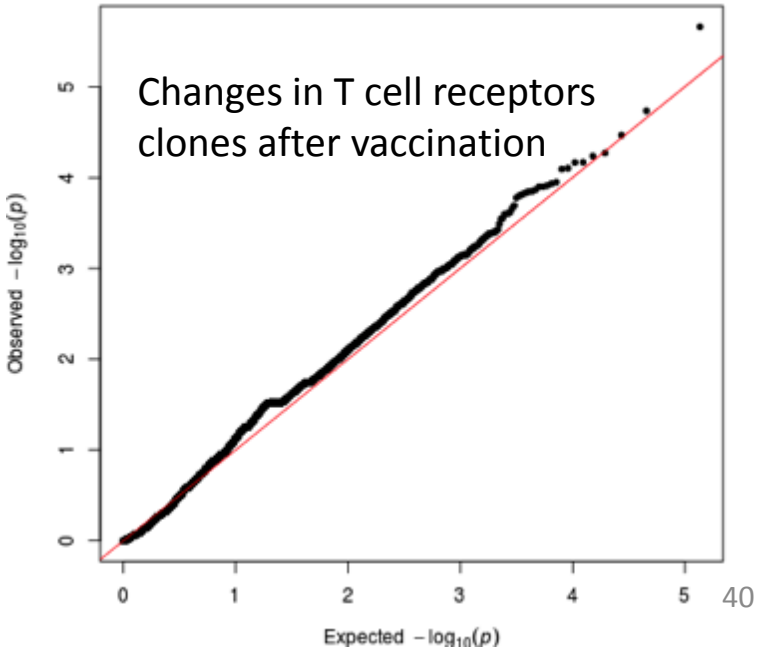
- Study how long term space travel affects the immune system
- We will study how parameters of the immune system change at baseline and after a seasonal flu vaccination
- To do so, we study baseline and post flu parameters before, during and after a one year space flight



Implications of the Research for Space & Earth

Space:
Will ensure that astronauts keep a healthy immune system during long duration flight, and stay protected against infections from earth when visitors are coming.

Earth:
Understand how immune response to vaccination differs in twins



The Bacteriome in the Gastrointestinal Tract

Fred Turek, Ph.D.

Specific Aims

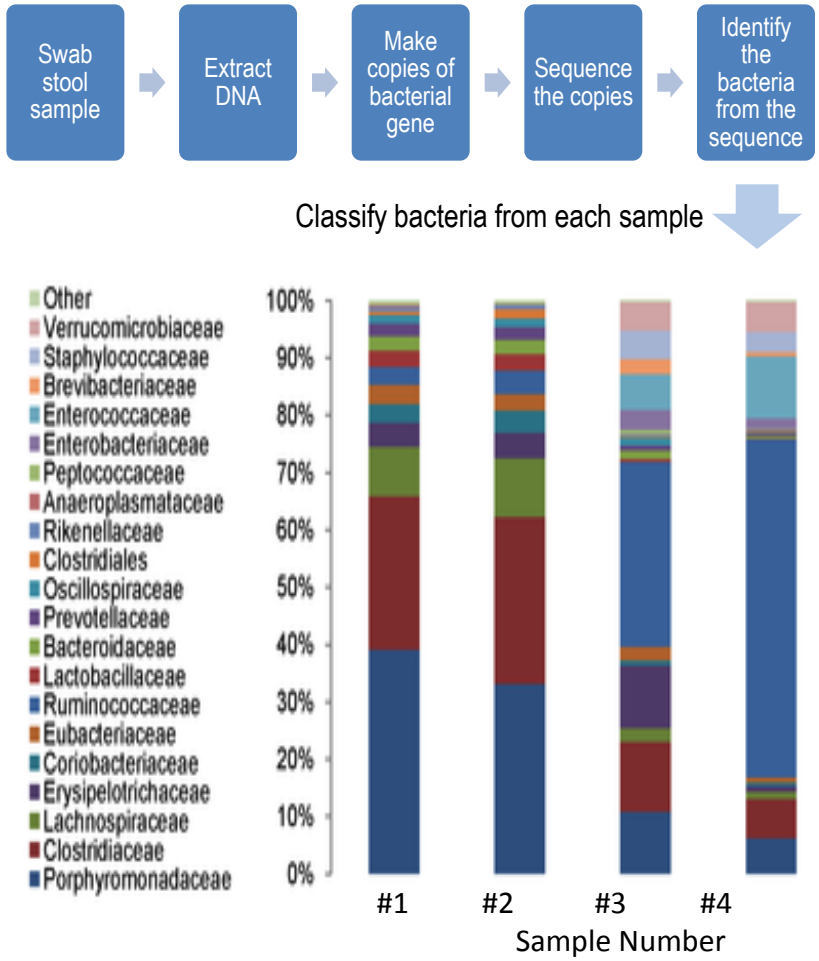
The GI tract of humans is populated by a diverse "ecosystem" of micro organisms, mostly bacteria: the bacteriome. The bacteriome can help-- contributing to digestion and immune system function-- or harm-- overgrowth of some types accompanies illness or stress.

This project will examine what changes occur to the bacterial populations over a year in space, that are different from the changes over time on Earth. Are particular types of bacteria susceptible to the space environment, and if so, which types?

Implications of the Research for Space & Earth

Space: Knowing how the bacteriome changes over time in space can help us make plans to protect astronauts' health for longer-term space flights. For example, adjustments to diet could help maintain beneficial bacterial types.

Earth: Observing how the bacteriome changes in relation to health and environmental changes, (such as those studied in other Twin Projects) can provide insights into how the bacteriome may respond to challenges and contribute to the human host's health.



Relative abundance of different families of bacteria. Will there be systematic changes in the twin in space not seen in the twin on Earth?

Biochemical Profile: Homozygous Twin Control For A 12 Month Space Flight Exposure

Scott M. Smith, Ph.D.

Specific Aims

To provide a database of biochemical analyses from blood and urine samples. The analyses reflect a broad set of nutritional and physiological variables that may be altered as a result of the space flight environment (including diet, stress, weightlessness). Collecting data on the Ground twin will allow for a more direct comparison of the effects of space flight on human biochemistry and physiology.

Blood and urine collections

Preflight:

L-180, L-45, L-10

In-flight:

FD15, 30, 60, 120, 180, 240, 300, 360

Post flight:

R+0, R+30

Implications of the Research for Space & Earth

Space:

Improve understanding and time course of biochemical changes during flight and how the changes relate to diet during flight.

Earth:

Improve understanding of how diet can impact different biological systems.

Proteomic Assessment of Fluid Shifts and Association with Visual Impairments and Intracranial Pressure in Twin Astronauts

Brinda Rana, PhD
Mike Stenger, PhD
Vivian Hook, PhD

Specific Aims

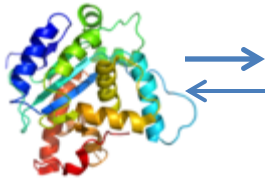
To explore proteomic and genomic biomarkers underlying space flight-induced fluid shifts and visual impairment & intracranial pressure (VIIP) symptoms.

The proteome is the set of proteins produced by the genome at a given time. Proteomics captures the state of molecular and cellular processes at a specific time point.

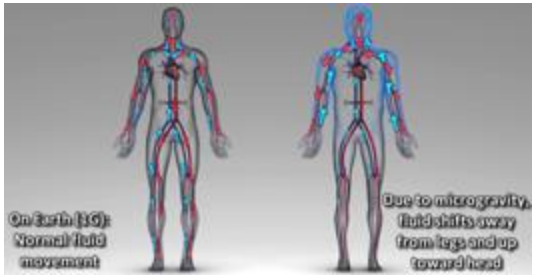
Implications of the Research for Space & Earth

Space: Discovery of molecular pathways involved in the evolution of spaceflight adaptations related to fluid redistribution in-flight and the etiology of visual acuity and ocular changes in-fight and post-flight.

Earth: This project has broader impact on Earth-based clinical areas such as traumatic brain injury-induced elevations of intracranial pressure, hydrocephalus, and glaucoma



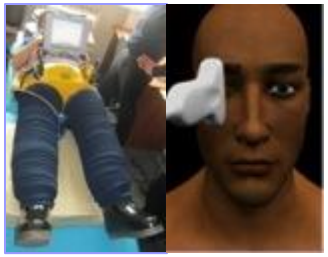
Blood Plasma proteins



In-flight Operations

Blood Plasma collection
Ultrasound measures of fluid shifts
Intracranial Pressure
Intraocular Pressure
Ocular Structure
Blood Pressure
Heart Rate
Vascular Resistance

Pre- and Post-flight Testing



All in-flight operations and:
Tissue hydration
MRI

Cognitive Performance in Spaceflight

Specific Aims

Mathias Basner, M.D., Ph.D.

Ruben C. Gur, Ph.D.

There are a number of environmental stressors unique to the spaceflight environment that may affect cognitive performance, which is crucial for mission success. Our main objective in the TWINS study is to investigate whether cognitive performance is affected by initial and prolonged exposure to the spaceflight environment and after return to Earth. We will use the *Cognition* test battery, which consists of 10 brief neuropsychological tests that were specifically designed for high performing astronauts. We will compare data within subjects, between twins, relative to astronauts flying 6-month missions, and relative to normative data gathered in astronauts on the ground. The cognitive data will be correlated with markers derived from biological samples taken before, during, and after the 12-month mission.

Implications of the Research for Space & Earth

Space: Exploration-type missions will require humans to spend unprecedented durations in space, yet our knowledge on the effects of prolonged exposure to the spaceflight environment is very limited. After the study, we will have an initial understanding of whether and to what extend prolonged ISS missions are associated with changes in cognitive performance, and how these relate to biologic markers.

Earth: The results have direct implication for other high performing populations exposed to stressful environments for prolonged periods of time on Earth.

	Test	Cognitive Domain	Brain Regions (from fMRI studies)	Avg. Time (Min)
	Motor Praxis (MPT)	Sensory-motor ability	Sensorimotor Cortex	0.51
	Visual Object Learning (VOLT)	Visual object learning and memory	Medial Temporal Cortex - Hippocampus	1.69
	Fractal 2-Back (F2B)	Attention and working memory	Dorsolateral prefrontal Cortex, Cingulate, Hippocampus	1.93
	Abstract Matching Task (AMT)	Abstraction and mental flexibility	Prefrontal Cortex	2.33
	Line Orientation (LOT)	Spatial orientation	Right Temporo-Parietal Cortex, Visual Cortex	2.07
	Emotion Recognition (ERT)	Emotion recognition	Cingulate Cortex, Amygdala, Hippocampus, Fusiform Face Area	2.03
	Matrix Reasoning (MRT)	Abstract reasoning	Prefrontal Cortex, Parietal Cortex, Temporal Cortex	2.09
	Digit Symbol Substitution (DSST)	Complex scanning, visual tracking, attention	Temporal Cortex, Prefrontal Cortex, Motor Cortex	1.60
	Balloon Analog Risk (BART)	Risk decision making	Orbital frontal Cortex, Amygdala, Hippocampus, Anterior Cingulate Cortex	2.39
	Psychomotor Vigilance (PVT)	Vigilant attention and psychomotor speed	Prefrontal Cortex, Motor Cortex, Visual Cortex	3.17

The Cognition Test Battery

Cognition was specifically designed for astronauts and is currently used during 6-month ISS missions and in multiple space analog environments (including Antarctica, HI-SEAS, and HERA).

The "Twins" Study Will Enable Phenotype – Genotype Associations

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Researchers to study astronaut twins' physiology

The study will examine the effects of microgravity on a person's functioning

By ALEX GETSOS · **March 17, 2014, 10:13 pm** · **Updated March 18, 2014, 1:59 am**

Penn researchers will work with NASA to examine the biological and cognitive differences in twins while one is on Earth and one launches into space.

The researchers' study, a collaboration among Penn professors Mathias Basner , Ruben Gur and David Dinges , will follow astronaut Scott Kelly as he accompanies Russian cosmonaut Mikhail Kornienko into space for a year, while simultaneously studying his brother, retired astronaut Mark Kelly, who will remain on Earth. The year-long expedition is unprecedented for the International Space Station, where Scott Kelly will live during the study.

"We can detect more subtle changes caused by spaceflight when we compare the genetically identical Kelly brothers," said Basner, the study's lead researcher. "Using identical twins potentially allows scientists to separate

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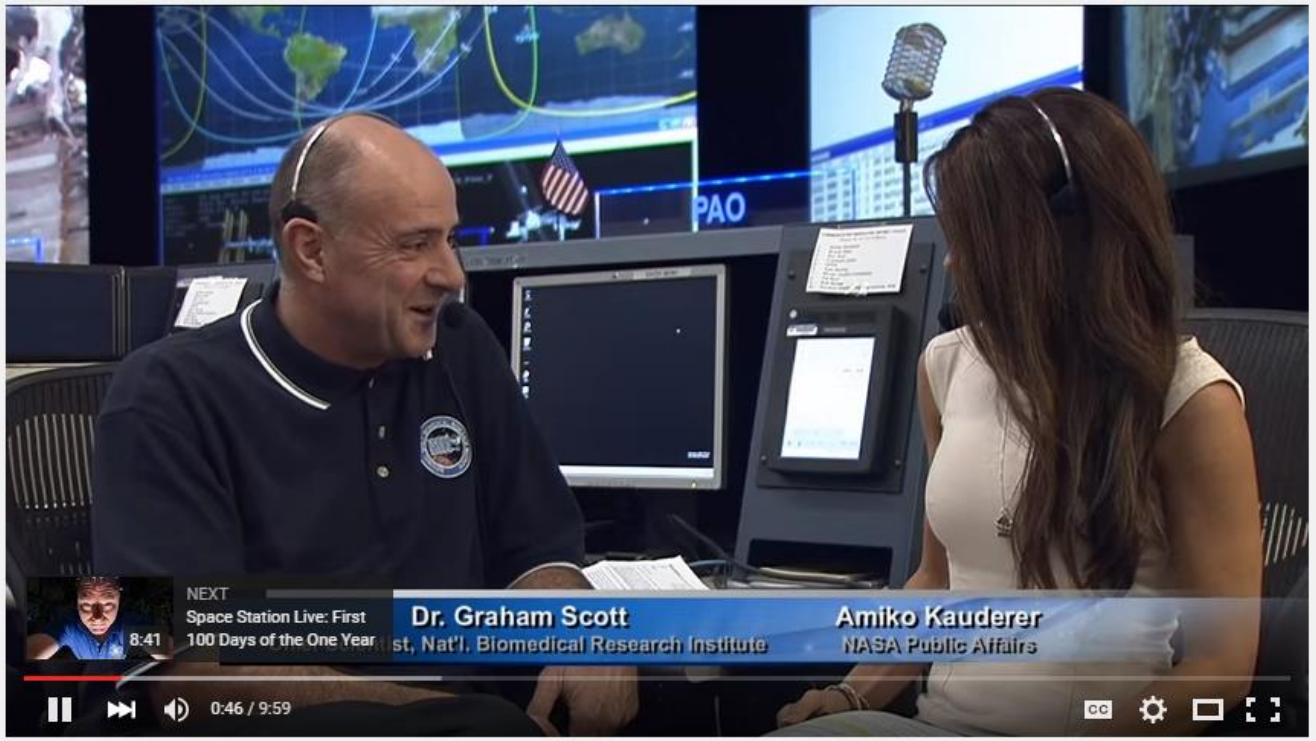
http://www.thedp.com/article/2014/03/researchers-and-nasa-study-kelly-astronaut-twins

Additional Resources – NASA TV



Space Station Live: Astro-omics in Space

NASA Johnson

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Published on Sep 24, 2015

NASA Commentator Amiko Kauderer talks with Dr. Graham Scott, the chief scientist at the National Space Biomedical Research Institute, about how genetics research and the Twins study now underway on the International Space Station could contribute to keeping future space explorers safer on trips to Mars or other destinations in deep space. The investigation using Commander Scott Kelly and his twin brother as

SHOW MORE

https://www.youtube.com/watch?v=bc13InB3hmc

Additional Resources:
NASA's A Lab Aloft – Blog Published Entitled

"Twins Double the Data for Space Station Research – Parts One and Two"

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Twins Double the Data for Space Station Research – Part One

Posted on September 10, 2015 at 8:10 am by rhobson.

Leave a reply

In today's A Lab Aloft, Graham Scott, Ph.D., kicks off a two-part series looking at the National Space Biomedical Research Institute's (NSBRI's) and NASA's Twins Study that is conducting biomedical research on a pair of identical twin brothers, who are both astronauts.

Medical care and biomedical research are rapidly becoming personal—as underscored by President Obama's recently announced Precision Medicine Initiative that considers patient's

In part two of this blog posting, I will share with you the ethics and impacts of personalized medicine in space and on the ground.

Graham B.I. Scott, Ph.D. (NSBRI)

Graham Scott, Ph.D., is the Chief Scientist and Institute Associate Director at the National Space Biomedical Research Institute (NSBRI), NASA's biomedical research institute that was established in 1997 to work in partnership with the agency's Human Research Program. A New Zealander by birth, Scott served as a Royal New Zealand Air Force pilot before obtaining a Ph.D. in astrochemistry. He came to the U.S. in 1997 where he worked for Nobel Laureate Robert F. Curl, Jr, Ph.D., at Rice University. Scott then went on to work on the Human Genome Project at Baylor College of Medicine, followed by a decade of leading R&D and marketing teams in corporate America, before being recruited back to Baylor to undertake his current leadership role with NSBRI.

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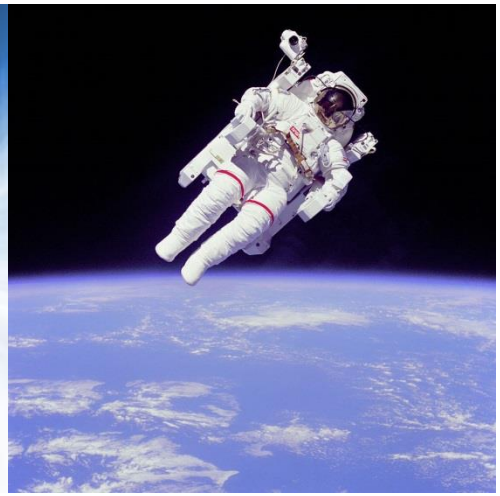
A New Omics for Space: "Astro-Omics"



The term "Astro-Omics" describes experimental and computational activities focused on the detailed characterization and quantification of biomolecules such as DNA, RNA, proteins, metabolites (etc.), that are extracted from biofluids or tissues derived from organisms before, during, and after spaceflight.

When fully integrated, these omic datasets can powerfully inform the understanding of unique phenotypic or personal responses to the space environment at a fundamental biomolecular level.