PLOS Science Wednesdays: Hi, I'm Stuart Kim here to talk about gene sequencing the world's oldest people to unlock the secrets of human longevity, AMA!

PLOSScienceWednesday [1] and r/Science AMAs[1]

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Abstract

Hi Reddit, My name is Dr. Stuart Kim and I am professor at Stanford University. My research focuses on genes that contribute to extreme longevity, such as supercentenarians that live to be over 110 years. I recently published a study titled "Whole Genome Sequencing of the World's Oldest People" in PLOS ONE. Supercentenarians are the world's oldest people, with just 17 or so alive in the United States at any time. Supercentenarians often show a remarkable delay in aging, such as one that worked as a physician in Georgia until age 103 and another that worked as a stockbroker on Wall Street until age 109. In order to begin to find the genetic basis for extreme longevity, we sequenced the genomes of 17 supercentenarians. The full genome sequences of the supercentenarians are available as supplemental data from the paper, and we hope that our data contributes to future research to unlock the secret for extreme longevity. Thank you everyone for your questions, it was a pleasure to answer your questions. I think trying to understand the biology of aging is really interesting and I hope you find it interesting too. I've signed off for now. Best wishes, Stuart Kim

the WINNOWER

REDDIT

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PLOSSCIENCEWEDNESDAY R/SCIENCE

ABSTRACT

Hi Reddit,
My name is Dr. Stuart Kim and I am professor at Stanford University. My research focuses on genes that contribute to extreme longevity, such as supercentenarians that live to be over 110 years.
I recently published a study titled "Whole Genome Sequencing of the World's Oldest People" in PLOS ONE. Supercentenarians are the world's oldest people, with just 17 or so alive in the United States at any time. Supercentenarians often show a remarkable delay in aging, such as one that worked as a physician in Georgia until age 103 and another that worked as a stockbroker on Wall Street until age 109. In order to begin to find the genetic basis for extreme longevity, we sequenced the genomes of 17 supercentenarians. The full genome sequences of the supercentenarians are available as supplemental data from the paper, and we hope that our data contributes to future research to unlock the secret for extreme longevity.
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Best wishes, Stuart Kim

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You make it sound like longevity is entirely determined by genetics. What proportion of this phenomenon is determined by the environment (such as diet and other behaviors) and gene by environment interactions (how different genetic backgrounds respond to the environment)?

Jobediah

It is believed that about 25% of longevity is due to genetics. Twin studies were used in which they compared the lifespans of identical twins (same genetics) to fraternal twins (50% different genetics). They found that identical twins tend to have lifespans that are more similar than fraternal twins. From this, one can calculate the amount of lifespan that is due to genetics.

The twin studies were performed on people with normal lifespans (~80 years). Our study searched for genetic differences in supercentenarians, who are extremely rare (1 in 10 million). We were hoping that these rare people might harbor genetic variation that has a strong effect on lifespan.

There are many environmental factors known to play a role in lifespan, such as diet, exercise and healthy habits. Our study does not change what we know about these environmental factors.

It seems like sequencing individuals in the extreme tail of the longevity distribution makes a lot of sense, but that 17 individuals is too few to find significant differences in the frequency of rare alleles that you're looking for. Is it possible to prospectively seek out future supercentenarians by finding people 100-109 years old that are still working or driving or free

of major age-related diseases?

arboyko
Your idea is very very good. If I can expand on it, you propose to find a proxy for lifespan (driving over age 100) that could be used to find longevity genes when people are still alive. In effect, the ability to drive/walk over age 100 can be thought of as a biomarker for aging. If we could identify a really good biomarker for aging, we could design experiments to search for genetic variation that slowed down this biomarker. Studying a biomarker for aging would be much better than using lifespan data because it would be so much faster and cheaper. You could be expand your idea to include any type of biomarker for aging, such as skin youthfulness, staying disease-free in late life, physical strength in late life etc.

Besides the biomarker idea, other ideas we are thinking of:

1. more supercentenarians. There are ~10 new supercentenarians each year in the US, and ~35 each year in the world. If you sequence these each year, you would increase the number by a great deal.

2. centenarians. For every supercentenarian, there is about 10,000 centenarians. Several groups have been studying centenarians for quite some time. At least five groups have done DNA analysis of a large number of centenarians using DNA chips that detect ~1 million DNA variants.

3. Families. For certain supercentenarians, we think there might be some longevity gene that is segregating in the family. There is one family in New York in which all four children lived to > 100 yo. There is another family in LA with anecdotal evidence in which each generation seems younger. The 90 yo daughter of the supercentenarian appears ~70, the 62 yo granddaughter appears ~40 yo! I would love to do a study on youthfulness in different generations for families that seem to be segregating a longevity trait.

There's been a push to treat aging related issues as diseases to be treated. What do you think of this line of thought with respect to the potential for vastly increasing the life span of people, as well as the moral question of whether humans should live 'forever'?

With exciting advances in CRISPR technology/techniques, what do you feel the most promising targets are?

lzawwlgood
I am a basic scientist drawn to aging because of the scientific mystery. One thing that fascinates me is that I see no reason why human lifespan needs to be limited to ~80-100 years. Other animals such as whales, turtles and clams live hundreds of years.

Beyond understanding the process of aging for pure knowledge, I think there are very serious moral, ethical and legal issues about using that knowledge to radically change lifespan in society.

I don't know of any targets to slow down aging that could be used for CRISPR at the moment.

Good morning, and thanks for doing this AMA! I'm a chemist, not a biologist, and my understanding of aging is necessarily immature. I apologize for asking such a basic question, but I look forward to reading your answers!

I heard in one of my classes (~5 years ago) that many features of aging have to do with telomerase enzymes DNA replication slowly degrading the telomeres, and then accidentally snipping off genetic information. It would stand to reason that a reverse telomerase Telomerase might partially defeat the causes of aging. Is this true, or a gross simplification that doesn't have any bearing on reality? Could we defeat some aspects of aging with an artificial telomerase or something similar?

atchemey
There is a good deal of evidence that telomere shortening is part of aging, especially in cells that divide such as stem cells. Besides telomerase, there are literally hundreds of other targets known to affect lifespan in model organisms. In the roundworm, there are about 330 mutants that show longer lifespan. In mice, there are about 62 genes that can extend lifespan. Telomerase is one of the targets, but it is not the only one.

Dr. Kim, I've developed a program that allows for high speed intersection of large populations of entire genomes and the software finds commonalities of SNP's, CNV's, etc. I'm having difficulty syncing up with researchers so I can further investigate how effective my software is. I'm trying to find enough genomic sequences within a common cohort to see if my software is as viable as my initial mock testing has shown. So far emails and phone calls have gone unanswered. I'm not from academia, but have done this on my own. Can you offer any advice or pointers as to who I could talk to? Thanks!

meikeric
Meikeric, You can download the entire supercentenarian DNA sequences from the PLOS ONE paper. Then you can test your software on the DNA sequence directly.

From the paper: Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. The data are available from supercentenarians.stanford.edu and from Google Genomics dataset 18254571932956699773. Apply for data access at http://goo.gl/MGcYJ5.

Good morning for Prof Kim,

Under the assumption that you'd think that extreme age is the result of common variants, likely individually responsibly for relatively small amounts of observed variance, and given that your samples should be quite heterogenous, has power analysis been performed? What sort of sample size do you think you'll require to start finding results.

Thank you very much for you time,

/u/Surf_science - McGill University Department of Human Genetics.

Surf_Science
A power calculation is a way to predict whether there are enough people in the experiment to see a genetic effect. If the genetic effect is small, then the power calculation might reveal that you need 10,000 cases for a result to be statistically significant. If the genetic effect is large, you might need only a small number to find the longevity gene.

We did the power calculations. But the main issue is that we had no idea about the size of the genetic effect in the supercentenarians. Some genetic traits like Miller's syndrome, have a large effect and can be found by sequencing a small number of people. This was done by my co-author Lee Hood.

Other genetic traits are complex, like height, and you need tens of thousands of people in order to start finding the many genetic loci that make small contributions.

We had no idea whether the genetic effect in supercentenarians was going to be large or small at the start of the experiment. Our paper would have found a gene if it was always the same gene in different people and it had a large effect, so we can rule out this most simple model.

As global life expectancies slowly creep higher and higher, what do we know about where this trend must end? Is there a cap on the length of a human being's life?

kink_hoes
This is a great question. It has been debated in the field for a long time like this: someone in the world today will live to be 200 years old ($1,000,000 bet).

No: There are many reasons to seriously doubt that human lifespan can be extended to 200 years. Russianpotato makes a good point.

Yes: Human lifespan has been steadily increasing over history. In 1900, median lifespan was 46 years. Lifespan has been increasing about 0.3 years/year every year for the last 100 years; i.e. if median lifespan was 78 in 2000, it was 78.3 in 2001. The increase in lifespan does not show signs of slowing down. Over the last hundred years, human lifespan has doubled. One of the visionaries in the field, Steve Austad, has bet $1,000,000 that the 200 yo has already been born. Of course, it will take about ~100 more years to find this person, ~$1,000,000 will not be worth that much by then, and it will be Steve's great granddaughter that has to pay up.

Hi Dr. Kim,

Have you thought about studying longevity from the other side of the genetic spectrum as well? It seems that combining both sets of information would yeild more than the sum of its parts.

Thank you so much for visiting today.

CompMolNeuro
Progeria is a diease in which people age faster than normal. Werner's progeria is caused by a mutation in RecQ helicase. Hutchison-Guilford progeria is caused by a mutation in lamin A. We looked at RecQ helicase and lamin A in the supercentenarians, to see if they harbored anti-aging changes, but did not find anything.

Why focus so closely on protein altering mutations when promoter/enhancer mutations could lead to drastic changes as well? Can you talk about other loci or SNPs that were found to be mutated in the supercentenarians that were not located within the encoding region of a gene?

ardreeves
Protein altering mutations are easier to interpret and occur in the protein-coding part of the genome which is just 2%.

Promoter/enhancer mutations are hard to recognize, and are splayed out over a very large area.

We did a naive search of the entire genome for common genetic changes in the intergenic region but did not find any.

Are there any cases of two supercentenarians having a child together, *a la* Lazarus Long and the Howard Foundation?

readonly_reddit
I don't know of any case in which the mother and father both lived to be supercentenarians.

In studying and looking at super-centenarians is their anything in common with lifestyle that the rest of us should adopt that might not have these genes you're identifying? I've always heard that having kids helps with longevity as it gives you motivation to live to see your next generation of family and was wondering if you have seen that it makes an impact. Another example would be having a dog, brings the owner joy (for the most part) and they would get

more exercise.

kofclubs
Nir Barzilai and Tom Perls have looked into the lifestyles of centenarians. What is really interesting, is that they do NOT have healthier lifestyles than normal people on the average. Their eating habits were not especially healthy, they were not overly active in exercise and they often smoked.

Do you also probe for epigenetic markers?

How great a role do you think epigenetic modifications play in longevity?

Thankyou

electronseer
We did not do any epigenetic experiments in this study. We have blood sample, so could do some simple experiments on blood cells. But this was beyond the scope of our first experiment.

In your paper, you state that there is no single Mendelian gene that can be associated with longevity.

Also you state that it was surprising to find the existence of a pathogenic allele in one of the subjects (yet he did not die from this).

Is there a chance that these subjects might have a trait which makes these pathogenic genes / allele's dormant or protect them from being disrupted?

leon_reynauld
One possibility is that the supercentenarians carry protective DNA variation that minimizes the negative effect of pathogenic alleles that would affect normal people.

Another possibility is that the pathogenic allele we found is only pathogenic part of the time. It was known that the pathogenic allele was present in some people with the disease. What is not known is how many people have the pathogenic allele and do not have the disease.

Hello Dr. Kim. In layman's terms (or ELI5), did you find any interesting commonalities in the sequences of the supercentenarians?

If you did, what? And what do you think that means?

If you did not, do you think this means that the presence of genetic anti-aging components are very subtle, or that environment, behaviour, and luck play more important roles? Why or why not?

Thank you for sharing the full sequence data for future studies, that's awesome. If you could lead the 'next study' right away, what would it be and what would you do/try to find?

Bagoole
In layman's terms, our paper did not identify any strong genetic signals for longevity. We did make our supercentenarian genome sequences available to the research community so that they could be included in future studies to find longevity genes.

There are many reasons why we missed finding genes. It could be that the anti-aging components are subtle, as you said. It could be that we were not smart enough and we need to think some more about how to find the longevity genes.

When I was a kid my mom worked with Senior Citizens and I saw a few of them who made it to over 100 years of age. What I noticed about them was they were always women, and they were active until they got sick which seems to set of a chain of events leading to their eventual death.

1. **Are women biologically set up to live longer?**
2. **Did a change in their diet or physical activity degrade their immune system affecting their homeostasis dramatically?**

fozzit
About 95% of supercentenarians are women. Only 1 of the 17 supercentenarians that we sequenced was a man. No one knows why women have a higher chance of reaching 110 than men.

Has any (genetic) link been found between longevity and resistance to Alzheimer's/dementia? Do supercentenarians develop dementia at rates significantly lower than the general 85+ population?

bazoid
There is a genetic link between living to be 100 yo and NOT having the Alzheimer's disease allele APOE4. APOE4 is a mutation in the APOE gene that greatly increases your risk for Alzheimer's disease. When people looked in centenarians, the strongest signal found was that less centenarians had the APOE4 mutation than the normal population.

I assume your study must include some historical/archival research to verify that the supercentenarians are as old as they claim to be. Have you come across any instances of people exaggerating their age? And have you run into any difficulties with age verification? I imagine that records from circa 1900 might, in some instances, be difficult to track down.

maclure
We did this study with Steve Coles, who was the foremost expert in supercentenarian research. Steve was meticulous at verifying the true age of the supercentenarians using at least two valid sources. Steve found many examples that he did not believe because there were no written records, such as 130 yo in Russia and a 150 yo in Tibet. It is difficult to validate the ages of these people without written records. Unfortunately, Steve passed away three weeks after the paper was published and the world lost a true leader in gerontology.

What masters program did you participate in?

PleasePullMeOut
I got my PhD from CalTech and did post-doctoral work at MIT.