Science AMA Series: I'm Ali Torkamani of the Scripps Translational Science Institute and co-leader of the first large scale genomic study of healthy aging. AMA!

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

[1]Affiliation not available

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Abstract

Hi Reddit! I'm Ali Torkamani, Director of Drug Discovery at the Scripps Translational Science Institute in La Jolla, CA. Edit: And Director of Genome Informatics My colleagues and I believe studying the genetics of healthy aging is potentially a powerful means for the identification of genetic mechanisms for resistance to age-associated disease. We recently completed a comprehensive whole genome analysis of healthy aging individuals and found that these individuals have lower overall genetic risk for Alzheimer's and coronary artery disease, and that genetic factors for cognitive performance appear to be important for overall resistance to age-associated disease. Surprisingly, we found no decrease in the genetic risk for other common killers like cancer and diabetes, suggesting there are other hidden protective factors to be discovered. Here's a summary! And a video! I'll be back at 1 pm EST (10 am PST, 6 pm UTC) to answer your questions, ask me anything about genetics, genomics, healthy aging, and individualized medicine!

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SCRIPPSSTSI R/SCIENCE

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My colleagues and I believe studying the genetics of healthy aging is potentially a powerful means for the identification of genetic mechanisms for resistance to age-associated disease. We recently completed a comprehensive whole genome analysis of healthy aging individuals and found that these individuals have lower overall genetic risk for Alzheimer's and coronary artery disease, and that genetic factors for cognitive performance appear to be important for overall resistance to age-associated disease. Surprisingly, we found no decrease in the genetic risk for other common killers like cancer and diabetes, suggesting there are other hidden protective factors to be discovered.
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Hi Dr. Torkamani, and thank you for doing this AMA.

As you might infer from my username, I have always been passionate about the biology of aging. I think the idea of sequencing the genomes of healthy, elderly people (what you call the "Wellderly" in the paper) is an intriguing one. Looking at the design of the study, though, I'm left with some questions:

- You compare the genomes of the 'Wellderly' (people over 80 who don't have any major age-related disease) to the genomes of the ITMI cohort. But this ITMI cohort seems like an odd choice. First, they aren't representative of the general population: they have lower BMIs and higher degrees of educational attainment. Second, they are an average of 33 years old, so you don't know if they are 'normal' or 'likely to be wellderly'. Third, the gender ratios in this group are also significantly different from the normal, aged populations. So I guess the question is, how much does the choice of the ITMI cohort affect your results? Why not choose to sequence the genomes of elderly people who do not meet the 'Wellderly' criteria? Particularly interesting if you are looking for genetic modifiers, would have been to compare the genomes of the Wellderly to aged individuals with similar demographics (BMI, exercise, education) but who did not meet the Wellderly criteria.
- Perhaps the most striking difference to me between the 'Wellderly' group and the normal aging group was the fact that the 'Wellderly' have lower BMIs, exercise more and attain higher levels of schooling. This seems to suggest that there are pretty susbtantial lifestyle differences between the groups. In that light, is it perhaps not surprising that you didn't find too many differences between the groups - suggesting that a healthy lifestyle may be the biggest driver of healthy aging?

- Also, it seems that one-third of the participants in the ITMI cohort were parents of prematurely born babies. Were these parents excluded from the analysis? That seems like it could be a potential confounder.

SirT6

Thanks for your questions.

- Good question - there are a number of different factors that come into play here. In terms of unselected general population control vs 'non-Wellderly', the decision was to attempt to utilize a general population control (sub-selected for European indivduals) so that there is no influence on the signal from any diseases that may be enriched in a 'non-Wellderly' control population. The Wellderly phenotype is rare, so although some of the ITMI individuals may be destined to be Wellderly, any dilution in the statistical signal from those pre-Wellderly individuals is likely to be minor. In regard to whether the ITMI population is actually representative of the general population - you are right to point out that some factors (BMI, educational attainment etc.) are not representative of the average person. However, this is most likely due to socioeconomic rather than genetic factors. Of course, it is possible that there is some genetic underpinning to those factors that confounds the signal slightly. Finally, there is a technical reason - both cohorts were sequenced on the same genome sequencing platform, which is an important factor in studies like this so that any systematic technical biases can be accounted for.
- Yes, "environmental factors" are likely to play a major role in this phenotype. The goal is to identify genetic factors above and beyond these environmental factors.
- Yes, this is a potentially confounder. However, we did not observe any signal from known genetic factors for issues such as pre-eclampsia etc - so any statistical signal from those individuals is not likely to have risen to the top.

I have seen a lot of people show interest in 'paleo' eating styles with very high fat and meat intake. I was always suspicious of this eating style as there seems to be nowhere on earth where you have a large group of people who are eating this way and can be followed long term (compared to something like a Mediterranean style of eating). Have you guys ever come across anything related to healthy aging with regard to these high fat low carb style diets?

PQbutterfat

I can't comment n the 'paleo' diet specifically - as far as I know there haven't been any long term studies to evaluate it's effects. However, the Atkins diet is similar and there have been a couple long term studies showing benefit on body weight. It's not known what the long term influence on healthy aging would be, but given the dramatic influence of body weight on many diseases, it's not a stretch to conclude there is probably a short term benefit.

What advice would you give to an 18-year-old just about to start college looking to pursue a career in genetics? Thanks!

patienceandthyme

Learn some scripting/programming in addition to your genetics education. The future of genetics (and many other fields) is in analysis and understanding of large datasets.

I've been told quite often that a large portion of aging healthily comes down to healthy diets and habits. How great would you think the role of genetics is in longevity compared to lifestyle?

Furthermore, what's the most counterintuitive or puzzling association you've found between certain genes and longevity?

Thanks for doing this AMA!

Piconeeks

The heritability of many (perhaps most) of the most common causes of death are below 50% - meaning that non-genetic factors play a larger role in their incidence. We were not able to measure the heritability of healthy aging, but it's most likely also below 50%. So non-genetic factors are most likely the major contributor to the trait.

In retrospect it's probably not counterintuitive, but I would say I was surprised to learn that decreased reproductive success is associated with longevity.

You are welcome!

What is your most controversial opinion?

coneballs15

There are measurable genetic differences between sub-groups of humans.

Hi Dr. Torkamani,

Many thanks for doing this AMA.

Did the study also analyze the intestinal microbiota which consists of a vast bacterial community that resides in the lower gut and lives in a symbiotic relationship with the person.

Do you think there might be anything different between the wellderly's microbiota and the rest of us.

Clivebw

No, we have not studied the microbiome of the Wellderly individuals. This would definitely be an interesting study. I am constantly being surprised by the associations made between gut microbiome and disease. It wouldn't be a stretch to hypothesize that the Wellderly have at the very least maintained a "healthy" microbiome over time. I would be more hesitant to hypothesize that the microbiome would have a more causal role in healthy aging.

If you could only give one tip, what would it be?

bravetravels

Pursue a passion that plays to your strengths.

Hello professor. In your paper:"Whole-Genome Sequencing of a Healthy Aging Cohort", you make the following observation:

However, we also observed no difference in genetic risk for more heritable cancer types (breast and

prostate especially), neither via common variant risk nor rare pathogenic variant burden.

and yet towards the end of that sentence you attribute the cause of this to:"

could be indicative of disease resistance via behavioral or other genetic characteristics."

I wonder if you could explain this point a bit more as it sounds a bit like circular logic (heritable cancers that are being resisted by behavioral activities.) Thanks for doing this AMA Cheers

jerkgasm

In basic terms, there are two ways to avoid genetic disease: 1) a reduction in the presence of genetic factors that increase your risk for disease, or 2) the presence of genetic factors that decrease your risk for disease. The Wellderly did not meet the first criteria (there was no evidence for a lack of genetic risk factors for cancer in this cohort), which could indicate the second criteria is operative.

Somewhat of an over simplification of the problem - but hopefully that sheds some more light on the reasoning.

How likely is it that risk for cancer/some cancers is genetic? Women with family members diagnosed with breast cancer are told to be diligent with their self-checks and imaging, are they not?

rustytimbone

Different types of cancer are more or less genetic than others. A good rule of thumb is that if you have family members with cancer at an early age (before 50 yrs) - the likelihood of the genetic risk for cancer in that person (and relatives of that person) is elevated.

Forget age and cancer related genetics, where are we on solving balding genetics?

ardothewan

Embrace it :)

What do you think is the next big step in your research ? and what are any obstacles towards it?

lulzmort

Validation of our COL25A1 finding would be a big step forward. Appropriate models for validation will be challenging.

What is and are the best thing(s) for a person to do who is disabled to help live longer and happier?

stallister

I really don't have any expertise here, but I would say that most of my sources of happiness do not come from any physical abilities - family, friends, hobbies, etc are all major source of happiness for me.

hello, what is your opinion of the small geographical areas around the world known as "blue zones" where people routinely live long healthy lives?

https://en.wikipedia.org/wiki/Blue_Zone

Bluest_waters

Yes, these are very interesting groups of individuals. I think the characteristics in your wikipedia link have probably got it right. They are probably due to a confluence of healthy behaviors, diets, family relations etc coupled with a beneficial genetic profile.

When analyzing blood do you scan for chemicals as well like fire retardant ,biphenyl (derivatives), lead or mercury levels Etc?

Gallionella

No, we have largely been addressing this question from a genetics rather than environmental angle.

Hi Dr Torkamani. Thank you for doing this AMA and for the helpful and succinct summary.

I noticed in your summary, the gene COL25A1 was specified in particular. I know it's likely very early days to make any definitive conclusions, but I was wondering if you might be able to provide some quick thoughts on the biochemical mechanisms that may underlie this and methods we could potentially use to harness this?

Furthermore, during your research did you identify any further notable sites of interest/variants between or across the Wellderly and ITMI? For example, those genes associated with antioxidant defence and susceptibility (e.g. the Nrf1/2-ARE pathway)?

ash356

I am totally speculating here, but my guess would be that the mutations in COL25A1 influence the aggregation of amyloid plaques through direct interaction with A-beta. Not sure how you would actually use this though - hard to imagine injecting COL25A1 with the appropriate changes in someones brain to influence progression of Alzheimer's disease.

The one site of interest we don't comment on extensively in the published manuscript is the signal at the carnitine transporter (SLC22A4). There has been a long standing interest in treating elderly individuals with carnitine supplements for a variety of purposes. Not sure what this signal in our study represents, but it is an intriguing one.

What is your opinion on the SENS approach to anti ageing? Do you think it could deliver promising results or should other avenues be the focus point?

demostravius

The SENS approach is quite broad - but I think the central point of their thesis revolves around treating/removal senescent cells. There is some good preliminary evidence that removal of senescent cells in mice is an effective means to lengthen healthy lifespan.

Coming from a place of complete ignorance: Is there any indication that epigenetics are important for healthy aging? Are telemeres subject to epigenetic changes?

BaitJunkieMonks

I'm not aware of any studies on epigenetics and healthy aging. There are certainly studies linking the environment of a pregnant woman to epigenetic changes in a fetus that could have long term health consequences. Epigenetics likely plays a role in healthy aging in this regard.

The association between telomeres and lifespan has to do with the length of the telomeres.

Hi Ali Torkamani, thanks for doing this. I have had a longtime interest in oncology and aging and what distinguishes them at a genetic regulatory level. I was hoping you can comment on what is known, and anything you have found regarding disruption of normal aging and how it contributes to progression of disease (e.g. cancer)?

Juneyeah

I think of aging and cancer as opposite sides of the same coin. In oversimplified terms: aging is the gradual decline of your bodies ability to maintain and repair itself, cancer is in some ways the bodies repair mechanisms gone haywire.

With so much research and awareness about Alzheimer's, it's something that terrifies me even as a young adult. How much can I count on my genetics to determine if I am likely to develop some form of dementia?

Also, what is the MOST exciting discovery we've made in Alzheimer's research so far?

mudra311

Family history is a great way to estimate your genetic risk for Alzheimer's disease. There is a particular risk marker APOE4 (http://snpedia.com/index.php/APOE-%CE%B54) that plays a significant role in the genetics of Alzheimer's disease.

There are a couple drugs in trials for Alzheimer's disease that are showing efficacy that has not been previously achieved by many other failed efforts.

What role could advances in CRISPR and human genome synthesis play in helping us understand and control aging?

ChromeGhost

CRISPR (and other genome engineering techniques) are a great way to build models to study the role of particular genetic factors. Statistical findings (such as those described in our Wellderly manuscript) could be engineered to create paired lines of cells where the only genetic differences between them are those that are thought to influence aging. You could use this model to study the downstream influence of these genetic factors. This approach is being taken for many genetic conditions and will certainly be applied to factors controlling aging.

Thank you very much Dr. Torkamani

What are your thoughts on the TAME trial and it's potential to open up a new field of drug discovery, attempting to combat "aging" as a whole as opposed individual diseases one by one?

Breesfan09

I'm not sure the trial is combating aging as a whole as it claims, but your metabolic profile does have a broad influence on many different diseases - it makes sense that interveing there could have a broad influence on health.

What are your thoughts on the concept of the *Longevity Escape Velocity?*

Is indefinite life extension a real possibility over the next few decades?

Chispy

My opinion is that indefinite life extension is feasible, but I don't believe it will be achieved within our lifetimes. Maintaining the health of the brain and retaining the memories that essentially define you will be a major hurdle.

Also, it seems that one-third of the normal operation of the ITMI cohort were parents of prematurely born babies..

ericw75

Please see my answer above.

I am more curious about the founding of the origination itself, and how the Scripps name was incorporated? I am a Scripps from the UK and had no idea that such an institution existed. Sorry for the off topic question

Scrippsy

Read about Ellen Browning Scripps - she started it all:

https://en.wikipedia.org/wiki/Ellen_Browning_Scripps

I like the idea of studying those who are well in order to see what works. Not that studying what breaks isn't also important. But too often I think we ignore the healthy/happy/successful piece so we have a skewed perspective. And it seems to me that it would be quicker to find solutions if we work on existing pathways of success and how to develop that on a broader scale. Rather than going down potential blind alleys.

My question is whether you think this is an important perspective to take *beyond just genetic mechanisms?* In other words, there is a bit of a stereotype that science focuses on what is broken and self help books focus on what works. While that isn't entirely fair, do you think we ignore potential solutions staring us in the face? Should other fields - even public health, sociology, criminology, etc. - consider more emphasis on studies looking at when things go right and how to tease out causal mechanisms that could be replicated/scaled?

firedrops

Definitely. Being a genetics focused group - we are obviously biased towards studying the genetics of this phenotype. Environment and behavior certainly play a major role in healthy aging - but a lot of those factors are already well known - diet, exercise etc. Genetics provide us with potential novel mechanisms to intervene.

Do you think it's possible that you could identify the "genetic mechanisms for resistance to age-associated disease" within your lifetime? Do you predict that your work will help you, or only future generations?

BrendanTheONeill

The genetic mechanisms for resistance to disease are already starting to trickle into drug development. We will definitely benefit from these discoveries.

I'm sure lots of people have already asked something along these lines, but what is the average person's understanding of ageing like, compared to the cutting edge?

Charles_Karmicheal

The average persons understanding of biology (or science in general) is not great - which is a terrible shame. I'd say the biology of aging is no exception to this.

I once heard there is no such thing as normal memory loss associated with aging. Even the normal forgetfulness is actually pathological. To what extent do you think this is true?

LateNightFright

I suppose it depends on your definition of "normal". Memory loss could be considered "normal" because we all normally age and bodily functions deteriorate. That normal process is negative/pathological.

So ill be greedy and ask another, if I may. Are there any promising possibilities out there to decrease the rate of telomere shortening, or possibly reverse it? Also is the process of telomere shortening with age influenced more by genetics or lifestyle?

PQbutterfat

Telomeres can be lengthened in cells in a dish - but I haven't seen any credible claims for approaches that would work in humans. There is evidence for both environmental and genetic factors that influence the rate of telomere shortening (or their initial length etc.). Overall, the rate of telomere shortening would be directly related to the number of cellular divisions - which could probably be more directly influenced by avoiding wounds/cellular insults of various sorts.

Hello Dr. Ali- Were there any twins in the study groups and any epigenetic differences to explain differeces due to lifestyle?

bpath65

There are certainly siblings (not sure about twins). We have not looked into epigenetic factors.

Is there a hypothetical ideal environment that a human could live in without aging?

threenager

Suspended animation? Living and aging go hand in hand.

I'm nobody special (not a doctor, or anything), but very interested in healthy aging, so thank you for hosting this AMA. At risk of being slightly off-topic, here is my (somewhat relevant) question: within the last year I have have heard much hullabaloo about "nanotechnology leading to disease-free immortality within the next couple of decades" (not to be confused with death related to fatal accidents or tragedies). How much credence do you feel this claim has, and if it is possible, how likely would it be reasonably available or affordable for (currently) middle-aged, middle-class residents of first world countries? If it is on the horizon, how can people contribute to this research if they don't have a background in STEM disciplines? Thanks in advance.

RedditUser46754

I think those claims are totally overblown. Replacing / repairing every organ in your body via nanotechnology or advanced cellular therapies will probably be possible, but our life expentancy has already hit the point where the brain begins to deteriorate. Any true measure of "immortality" would require maintaining the health of the brain and the memories contained within it. That seems like quiet a steep task for the next couple of decades.

Isn't healthy aging an oxymoron? Either there is negligible senescences or there is significant and that's aging, a breakdown of the normal operation of the body.

chilltrek97

Maybe "healthy chronological aging" would be more appropriate