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00:06 Sarah Crespi: Welcome to the Science Podcast for September 11th, 2020. I'm Sarah Crespi. First up this week, senior correspondent, Dan Clery talks about a boost in the search for extraterrestrial intelligence. And as part of a special issue on how gene expression makes people different, Brandon Pierce joins us to discuss his work on variation in telomeres. These are the tips of our chromosomes that wear away as we get older, and they're not the same in all people.

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00:38 SC: Now we have senior correspondent, Daniel Clery. He wrote this week about a big boost in the search for extraterrestrial intelligence. Hi, Dan.

00:45 Daniel Clery: Hi.

00:46 SC: The big money that we're talking about now for SETI research, this is the search for extraterrestrial intelligence, is not from NASA or other space agencies in this case. Where is this funding coming from?

00:58 DC: Well, it's coming from a very rich individual called Yuri Milner, who, five years ago, decided that with some of his accumulated wealth, he wanted to support science. And he supports things like the Breakthrough Prizes for one thing, which people may have heard of, but also Breakthrough Listen, which is a project to listen out for messages from other civilizations. And he put $100 million into it over a 10-year span, and we're halfway through that now.

01:30 SC: How has having this much money enter this research space change things? Has it changed who's doing the work, what kinds of work they're doing?

01:39 DC: It has allowed them to do a much more thorough search. Prior to that, they had money from other private sources, and it only allowed them to have a few dozen hours of observing time a year on big radio telescopes, but now they can afford thousands of hours. So it just means the volume of data and the volume of space that they can search through is huge compared to what it was before, and it is allowing them to try other techniques too.

02:10 SC: Right. This change, though, in telescope time, how much is being dedicated to SETI research, is it strange to have a privately funded project get a bigger share or sometimes a large share of telescope time at some of these installations?

02:24 DC: It does make some people uncomfortable because it's not something that goes through the usual academic vetting process that projects have to go through. But for some of the telescopes, it's a valuable source of income. These telescopes are sometimes hard up, but having a private foundation come along and say, "We'd like to buy 20% of your observing time," that's useful to

them. And that was the case for the Green Bank Telescope in West Virginia, which the National Science Foundation wanted to cut down their support, Breakthrough Listen was a useful source of income for them.

03:01 SC: I really like this point that you make in the story that we humans look for signs of alien life based on our own technology, really our own biases, like looking for canals on Mars when canals are a big thing here, and then radio became the focus. What does modern life and technology suggests that we look for? What are the signatures or signals that today's technology suggest?

03:26 DC: Yeah, well, lasers is this one thing. When SETI started lasers, I don't think it'd even been discovered yet. And now Breakthrough Listen, certainly, and other people are looking with optical telescopes, and what you need to look for is a very, very short flash. It's the sort of thing that nature couldn't produce because it's so short, but it could be produced by a laser beam, say, just happening to scan over Earth, and we would see a little bunch of photons in a very, very short space of time, and that's what they look for to distinguish it from other sources of light. But it takes a lot of telescope time because, essentially, you're just looking at it and not seeing anything in the hope that one day you'll see a very, very short flash.

04:14 SC: That's looking for an intentional signal, someone trying to get attention. What about this newish area of research where we look for a signature of life but not necessarily something that's a message?

04:30 DC: This is referred to as technosignatures, and it's sort of analogous to biosignatures, which researchers are very active in looking for at the moment, where you're looking for the fingerprint that life might leave when we look at an exoplanet. So it might be something in the atmosphere that suggests life such as methane or oxygen, and technosignatures is the same. So you're looking at things that might give away the fact that there is a technological society there without them deliberately trying to send a message to us. So it might be something in their atmosphere, like chlorofluorocarbons, which is something that we've polluted our atmosphere with, or it could be the lights of cities. Our planet is aglow with lights, if you look at it in the dark, and other planets might be the same.

05:25 SC: We should mention that NASA is also funding new research and study, and this isn't something that they have really expanded much in the past. What are they looking at now?

05:36 DC: I think they've realized that technosignatures and biosignatures are pretty closely aligned, that if you're looking for biosignatures, why not look for technological signatures at the same time? And so they had a workshop to look at what might be possible a couple of years ago and have opened up their funding streams to people that wanna do that sort of research. So the first grant was awarded a couple of months ago, and technosignature researchers are optimistic that they might get more federal funding.

06:11 SC: What's the difference, I guess, in the thinking about the value of searching for biosignatures versus technosignatures? Why is technosignatures something that had to come later?

06:23 DC: I think it's because people think that while life may have arisen on many planets, the chances that it evolved to technological life would be much less likely. So while there might be a lot of planets around us with algae or plants or even creatures on it, the ones that evolved to a civilization that might be able to communicate must be much rarer.

06:54 SC: Your chances are better for finding biosignature than technosignature. And I think that leads us back to this question is, how do you make the case for this much money, this much resources, this many people spending time on something that is a risky endeavor. We might not see a result from this any time soon or possibly ever.

07:17 DC: It's true. That's why the federal agencies like National Science Foundation and NASA have generally left it to private investors to fund this sort of thing because it is risky and it makes a lot of assumptions about what an alien civilization might be like. We assume that they might use radio or lasers, but they could use something entirely different. It is a high-risk strategy.

07:43 SC: And people are writing the cotels of this research as well. They're using the same data that's pulled out of the sky that might help the search for biosignatures, technosignatures, the lasers and radio and looking for other astronomical phenomena [chuckle] in that pile of data.

08:00 DC: Yeah, definitely. And Breakthrough Listen is collecting so much radio data just of many, many nearby stars and galaxies that's useful to other people. So others have started coming through that data for things like fast radio bursts, which is a current obsession because they're so mysterious. These are very powerful and very short bursts of radio waves.

08:25 SC: But definitely not alien.

08:27 DC: No. They think they are an actual phenomenon, but they are coming from a very distant source and we don't know what it is. Though, they think they might be magnetized neutron stars, but we don't really know yet. People don't have enough data, so that's one thing. And there's another search for a sort of hypothesized particle that could explain dark matter, which is called an axion. And people are thinking they might be able to find the signature of these axions using Breakthrough Listen data.

09:00 SC: As we look at all these new fields, bands, buckets, whatever you wanna call them, as we search in different areas of space, it shrinks the amount of work that we've done in proportion to how much more is out there. There's a really nice graphic in your story that outlines this. Can you talk a little bit about that?

09:20 DC: Yeah, certainly. Some people say, they've been looking for aliens for so long, and how come they haven't found anything yet. For an alien civilization to contact us deliberately, they would have to use a vast amount of energy to send a strong enough signal. So the search is so far have focused on nearby stars, nearby galaxies that we might get a signal from. But the universe is a big place, and researchers have estimated that if you think of all the possible types of communication and places and distances and represent that as all the world's oceans, what we've searched so far is about the equivalent of a hot tub for a water. So we've got a lot to do.

10:03 SC: Yeah. Alright, Dan, speaking of putting things in perspective, we've made it seem like this is a lot of money, a lot of people and a lot of time. But is this field really that big at this point?

10:13 DC: It's not. It's because there has been no money, most researchers have done it as a sort of the hobby alongside their day jobs, but Breakthrough Listen has changed that. It's allowed some people to specialize and to focus all their energies on this, but it's still a small field compared to Astrobiology in general and other types of astronomical searches. So it's niche, but it's burly.

10:41 SC: Thank you so much, Dan.

10:42 DC: Thank you.

10:42 SC: Daniel Clery is a senior correspondent for science. You can find a link to his story at sciencemag.org/podcast. Stay tuned for an interview with Brandon Pierce on how telomeres, the protective caps on the end of our chromosomes, change in different people and different tissues.

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11:06 SC: This week, we have a special issue on the latest results from a decades-long enterprise called GTex or Genotype-Tissue Expression Consortium. The project's aim is to catalog how gene expression changes from person to person and tissue to tissue. The current special issue really, it covers so many topics. One article looks at sex differences in gene expression, another looks at the pancreas cell by cell to see variation and how a gene linked to diabetes is expressed in this key organ. And we have an article by Brandon Pierce and colleagues on how telomeres, these are repetitive sequences of DNA that with the help of proteins, protect the ends of chromosomes. Their team looks at how these protective caps vary tissue by tissue. Hi, Brandon.

11:54 Brandon Pierce: Hi, Sarah.

11:55 SC: Alright, I did a quick pass on what telomeres are, that they're these caps on the end of our chromosomes, and some people might even know that they tend to get shorter as we age. Can you talk a little bit more about what it means to have long or short telomeres?

12:12 BP: Sure, every cell in our body has a copy of our genome, and this genome is organized into 23 chromosomes, we have two copies of each, so each chromosome contains a long strand of DNA, a very long strand of DNA. And each end of the strand, so there's two ends to each strand, and each of these ends contains a protective cap called the telomere. These protective caps are very important just to maintain stability of the genome, and they shorten as we age. In this study, we found they shorten in many different issues, that age-related shortening, which is caused by cell division, so when cells divide they're unable to essentially make a copy of that chromosome to the very end, so you lose a little bit of telomere length each time cells divide. And this is believed to be one of the underlying causes of why we age. So as our telomeres get shorter, they get to a critical length as to where the cells stop dividing. They recognize that the telomeres are getting short, that's sort of a warning signal to them that they're losing that protective cap at the end of the chromosome, so the

cells stop dividing, what we call senesce. Cell senescence due to telomere shortening is believed to be one of the underlying causes of why we age.

13:21 SC: What makes this study that we're talking about today so special, is this broad range of tissues and people included in the data set. Can you talk about how many people and tissues were involved in the study?

13:32 BP: In this study, which is the Genotype-Tissue Expression Project, for our telomere measurements, we were able to generate data on over 950 donors. And from each of these donors, we were able to obtain anywhere between one, up to maybe 20 different tissue types from these donors. So the total number of tissue samples for which we'd measure telomere length is over 6,300 tissues.

14:00 SC: I know there are some disorders associated with telomere problems. Did you pick up on any of that in your survey, did you see any variety in telomere length linked with health or disease?

14:12 BP: This is a good point to sort of mention the overall motivation for this study. It is linked to understanding telomere length in this relationship with disease. I'm an epidemiologist and we study health in human populations. And when you're working with human populations, free-range humans, you can't experiment on them, we're using observational research and we're usually quite limited into the types of bio-specimens that we can get. Say, "Sarah, can you give a saliva sample or a blood sample for this study?" And you say, "Sure." But I can't exactly ask you to donate a brain sample or a liver sample.

14:47 SC: Yeah, no liver... No liver biopsy for you.

14:50 BP: Or a sample of your colon or pancreas, we can't get those in the vast, vast majority of human observational research. We're always working with blood or saliva, and we have all these biomarkers that we're interested in. In addition to telomere length, there's tons of biomarkers people measure whether it's hormones, whether it's aspects of the immune system. And the hope is that, that blood sample reflects other things going on in the body, but for most of those, it's really hard to know for the biomarkers is how well they reflect what's going on in the rest of the body. So when we learn more about the GTEx study we're like, "This is a great opportunity, they have tissues for a thousand people, they have all these different issues." So we were like the key question we wanted to answer that really motivated our research is, "Does telomere length in blood, reflect telomere length in all these other tissues?" 'Cause every epidemiological study that looks at telomere length is measuring it in blood and relating it to health. So this study, lets us essentially make a fairly strong claim that telomere length in blood, at least to some extent, reflects variation in telomere length in lots of other tissues. I study cancer, so what we really wanna know is, "What do the telomere lengths look like in those cancer-prone organs?" 'Cause we see blood telomere length is associated with couple of different types of cancer.

16:02 SC: Is telomere length in the blood, longer or shorter when cancer is going on in the body?

16:10 BP: That was sort of a counter question.

16:11 SC: Yeah, yeah, yeah. [chuckle]

16:14 BP: Are we talking about telomere length as a risk factor for future cancer, how it responds to a cancer that is present?

16:20 SC: Right, so if you have active cancer, are your blood cells going to have longer telomeres 'cause there's something going on, or is it... Yeah, that's a good point. It could be both, is probably what you're gonna answer.

16:33 BP: Right. So, you know the question I'm more interested in is, "Does variation in telomere length impact your future risk of subsequent cancer?" The other question is, "How do blood telomeres respond to cancer?" The few studies I've seen on this topic suggest there is shortening, meaning once you have a cancer, your either the treatment related to that cancer might shorten blood telomeres or your body's immune system responds to that cancer might increase proliferation and shorten telomeres through cell division. So there is some story of shortening in the presence of cancer.

17:05 SC: How would it play into being a risk for cancer?

17:08 BP: If we go back, let's say, 10 years on this topic, when people were looking at variation in telomere length and studies of cancer, the general story initially was, "Short telomeres are bad." That was sort of the underlying idea of the aging phenomenon to these diseases of aging may be related to short telomeres or short telomeres are bad 'cause they shorten as we age. Now, the view has changed a bit, my sense is that a lot of those early studies are flawed because a lot of them were collecting data after cancer diagnoses occured, so the shortening in that case is probably due to cancer or its treatment. But if you look back, if you do prospective studies meaning you collect blood for healthy people and then observe them over time, some of those studies started to suggest that long telomeres were bad, they were a risk factor for some types of cancer.

17:55 BP: More recently, we've done genetic studies where we take inherited genetic variation that predicts telomere length, so these are snips that influence an individuals telomere length from birth, and we take those snips and say, "Okay, we can predict someone's telomere length with this genetic variation." Now we see for a set of cancers there's a pretty clear relationship between longer telomeres and increased risk for cancer, and the reason we think that is, is that because you have longer telomeres, you're able to go through more rounds of cell division, and every round of cell division a cell goes through is an opportunity for mutations to occur, mutations that naturally occur as a part of the DNA replication process. So that additional capacity to replicate that longer telomeres gives itself may be an opportunity for more mutations to occur and an increased risk for cancer in that organ or in that tissue.

18:45 SC: It's really cool, this idea of can the blood tell us what's going on with telomeres body-wide is very interesting. Did you see anything else related to health in your work?

18:55 BP: The sample size is somewhat limited. There's not a ton of cases for any given disease in

this group. It's only 1000 individuals, so you have maybe a 5% or 10% of them may have common diseases like diabetes, hypertension, things like that, so it's a bit limited into what you can do. That being said, we did see something interesting that actually relates back to one of your earlier questions that I forgot to mention, is that the tissues that are most prone to telomere biology disorders, the sort of rare diseases that are caused by rare mutations in telomere maintenance genes. So there's a set of genes that are involved in telomere maintenance, and if you have mutations in those genes that essentially destroy the function of those genes, like they change the sequence, the protein-coding sequence of that gene, then you lack a key component to maintain your telomeres in your body. And so these mutations are known to lead to these telomere biology disorders. Dyskeratosis congenita, pulmonary fibrosis, and others. The organs where those happen... Many of them occur in the blood and the lung. Those two tissues tend to have shorter telomeres than most of the other tissues that we looked at. So those tissues that are on the shorter end, our data suggests that one reason those tissues may be the target of these types of disorders, 'cause those tissues tend to have shorter telomeres in general.

20:16 SC: So they need to do more maintenance to stay healthy.

20:18 BP: Right. We did look at the instances of diabetes, heart disease, and a few other common diseases in our paper, and we did see some evidence of association with short telomeres, suggesting those short telomeres reflect some of those disease processes in the body. But we didn't highlight that heavily in our paper, mainly because the sample size for this study was only about a 1000. We couldn't draw whole lot of strong inferences from that sample size.

20:41 SC: Does it feel weird to say "Only about 1000"?

20:44 BP: In my world, in sort of the genetic epidemiology world, a 1000 is now small. Large studies are studies like UK Biobank, which have 500,000 participants in that study. So yes, it does seem strange to say that, but that's where genetic epidemiology is headed. Just mega cohorts. Huge numbers of people.

21:05 SC: What was the hard part of this study? What did you find to be the most challenging when doing this work?

21:10 BP: I think the most challenging part of this, of doing this study, was deciding what directions to take the analysis of this data, 'cause as you can see from all the other GTEx papers, this is a vast resource. A treasure trove of data. Inherited genetic information, RNA sequencing, or gene expression data, and all these other types of data that are being generated in this data set. So it's, okay, what are the most important questions we can ask in the course of one paper? And we ended up asking quite a lot of questions, but getting there and deciding what path to take when you have so much data sitting in front of you that you can link you can link this data on telomeres to all these other data types.

21:50 SC: As I said at the beginning, there's so much in this package and there is so much in this paper. This is definitely going to launch a lot of research. What do you see as being some of the main directions for this type of research looking at tissue variation in telomere length?

22:06 BP: Telomere length isn't the only feature of the human genome that changes with age, so we're really interested in looking at some of these other features of the genome that change with age, including DNA methylation. That's a feature of the epigenome or how the genome is packaged. So we know that epigenetic DNA methylation features, they change with age as well, and in blood, this has been studied extensively, so we know pretty well how DNA methylation varies across the genome as people age. There have been epigenetic clocks developed that are really good at predicting people's age with just a DNA sample. But this sort of epigenetic clock has not been extensively studied across lots of different tissues. In addition to epigenetics and DNA methylation, there's somatic mutations occur with aging. Losses of big pieces of chromosomes. I think that's the main next direction for us is to understand additional aspects of how the genome changes with age, understand how those are related to telomere length, and how all of these dynamic features of the genome work together to produce differences in health and disease in human populations.

23:18 SC: Thank you so much, Brandon.

23:19 BP: No problem at all. Happy to join you today, Sarah.

23:22 SC: Brandon Pierce is a professor in the departments of public health sciences and human genetics at the University of Chicago. You can find a link to his article and the whole GTEx special issue at sciencemag.org/podcast. And that concludes this edition of the Science Podcast. If you have any comments or suggestions for the show, write to us at sciencepodcast@aaas.org. You can listen to the show on the Science website at sciencemag.org/podcast. On the site, you'll find the links to the research and news discussed in the episode. And of course, you can subscribe anywhere you get your podcasts. This show was edited and produced by Sarah Crespi with production help from Podigy, Meagan Cantwell, and Joel Goldberg. Jeffrey Cook composed the music. On behalf of Science Magazine and its publisher, AAAS, thanks for joining us.