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Digging into Ancient DNA
David Reich unravels prehistoric genetic code to explore human history

David Reich
Interviewers: Stephanie Dutchen, David Cameron

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STEPHANIE DUTCHEN: Hello, and welcome April 2015 Harvard Medical Labcast. This podcast is brought to you by Harvard Medical School's Office of Communications in Boston. I'm Stephanie Dutchen.

DAVID CAMERON: And I'm David Cameron.

DUTCHEN: In this episode, David tells us about recent gene therapy studies that may one day help treat inherited blindness.

CAMERON: And Stephanie speaks with David Reich, a geneticist here at the Medical School, about some of the work that he is doing with ancient DNA. Now, Stephanie, we know that David is -- the work that he does is not the typical sort of genetics that you would expect from a person here at the Medical School. So maybe you could give us a quick overview of what he does.

DUTCHEN: Yeah, he's doing really cool work. He studies the way human populations have split and mixed over time. Sometimes that means ancient history. Like, he and his collaborators have shown that Neanderthals interbred with the ancestors of non-Africans. And, now they're investigating what the biological significance of the inherited genes might be.

CAMERON: OK, so there's a little Neanderthal in all of us.

DUTCHEN: In everyone who is not from Africa.

CAMERON: OK.

DUTCHEN: Another fascinating study that just came out showed evidence of a migration thousands of years ago from what's now Turkey into Germany that could help linguists understand the origins of Indo-European languages. He's also helped reconstruct the deep population history of Europeans, Indians and Native Americans. And, he's done a lot of work to understand the genetics of what he calls recently mixed populations, like African Americans and Latinos. So, for example, he's uncovered seven genetic risk factors that help explain why African Americans have higher rates of prostate cancer. And the hope there is to improve people's health.

CAMERON: Interesting. So it's like -- it's where natural history and genetics come together.

DUTCHEN: Exactly.

CAMERON: Well, very good. Let's jump right in.

[MUSIC PLAYS]

DUTCHEN: So, thanks for joining us for this podcast, David. It's great to be here with you this morning.

DAVID REICH: Nice to see you, Stephanie.

DUTCHEN: So, you are a professor of genetics at Harvard Medical School, in addition to many other things. And, you focus on population genetics and medical genetics, which to me, sounds like studying what our DNA can tell us about, not only health and disease,

but also about our past, our identities as people, as families, as cultures, as humans. So, what is fun about doing that kind of work?

REICH: Well, I think it's a real -- we're at a very exciting time when there's a science that wasn't possible before that's now suddenly possible. It's a kind of new science of looking at the human past. There have been many times in the past when new technologies became available, and they opened up new areas of science. For example, the invention of the microscope made it possible to study microbiology, or the invention of the telescope made it possible to study deep space. In the same way, the invention of the ability to look at ancient DNA from people long gone and the ability to sequence whole genomes makes it possible to look at very high, kaleidoscopic resolution at the past.

DUTCHEN: And, what interests you about all of those things?

REICH: I'm very interested in where people come from and how things got to be the way they are today, and the genetic data seems to be able to tell us something about that we didn't know about before.

DUTCHEN: So, over the last -- what 10, 15, 20 years -- all of these amazing technologies have come along where -- I mean, previously, when you think about studying human history, the first thing that comes to mind is archeology, linguistics, things like that, and now you can bring genetics to bear on understanding where we have all come from. So, what are the kinds of things that we have learned that we didn't know before?

REICH: I think that archeology and linguistics are incredibly powerful ways of looking at the past, but they are not very powerful for looking at how people are related to each other, how the past peoples are related to each other. And that's always been something that archaeologists and linguists have always been extremely curious about, whether the

changes that they see occurring from the evidence that they study are mediated by movements of people or whether they're mediated by cultural communication.

And people have attempted to look at that by comparing morphology, by comparing the skeletons of people that are in graves that are archaeologically well defined. And, in general, that's not been very successful; the skeletons can look similar to each other just by chance, or they can look similar to each other because they live in similar environments, not because they have a shared history. So what genetics brings to bear on these areas is the ability to document migrations and when they occurred and when they didn't occur.

What's happening in the last five years, since genome-scaled ancient DNA work became practical as a technology, is that people have started using ancient DNA technology -- we've been involved in this work -- to study a number of past populations and ask how do they relate to the populations living in the same place today?

And, time and again, it's been observed that the populations that have lived in a place in the past are very different from the populations that live there now, implying that there's been massive population turnovers, mixtures, migrations, something that a lot of archaeologists had become skeptical about over the last 50 years.

DUTCHEN: And, is that exciting to work on? I mean, has that--

REICH: I think it's really exciting. I mean, for example, we just published a series of two papers on European population history. We documented that the present-day people of Europe are not the same as the people who were there 40,000, 30,000, 20,000 years ago. That -- part of that was known already, but what we can see evidence of in the data is that there's multiple layers of mixture and migration of very different people in Europe today.

And the present-day people in Europe are the result of these three major, highly differentiated populations that come in at different times, the first being the indigenous original population of Europe, which is only a small fraction of European ancestry today. And after that, a major migration around 8,000 years ago, and then another major recreation about 4,500 years ago.

DUTCHEN: It's still kind of mind-blowing that you can take this tiny bone from an ancient person and sequence the DNA that's left and learn all of these incredible things.

REICH: Yeah, that's an incredible thing. It's sort of an amazing thing that it's possible to do. It's a very lucky thing.

DUTCHEN: So, when you were a kid, did you ever imagine that you would be like this Indiana Jones geneticist-archaeologist-researcher who could, like, get invited to go out to Siberia and hang out in a cave?

REICH: I think all kids imagine that they're going to be explorers, but I actually am not an Indiana Jones. I think the first generation of ancient DNA researchers are Indiana Joneses, I think Svante Pääbo, and Ellen Cooper, and Eske Willerslev. They go out to remote places and do things that are a bit wild. But, really, I'm not an explorer myself. We're really trying to interact with people who sample.

DUTCHEN: So, what was it like then to go out of your usual comfort zone and go to that cave that one time?

REICH: It's an amazing place. I mean, in the Siberian landscape in the mountains of the Altai is like nothing I had ever seen before; vast, impressive landscape. And the caves are very ancient caves, and I had a very strong personal feeling for what had happened based on all the work that I had been involved in studying these caves and the humans who had lived there. So, it's very moving to visit these places.

DUTCHEN: What do you mean, strong personal feeling?

REICH: I think I have a strong visceral sense of -- I'm trying -- I have perhaps an imagination of some of the people we're studying in the past. And if you work on an ancient person's DNA for a year or two, I think you've spent a lot of time thinking about these people and they have more meaning to you than you would if you met them -- only if you just learned about them in a class or something like that.

DUTCHEN: I'd love to hear more about this story of how you arrived at being a geneticist. You studied all kinds of different, perhaps unusual things to get here.

REICH: Yeah, well, my story is funny, because I was really interested in a lot of things, even from high school. I used to read history all the time in my spare time. And when I went to college, I was kind of split between the humanities and science, and I was a social studies major, which is a combination of history, and economics, and sociology, for the first two years.

And then I didn't finish that major and I switched to physics, which I had already been taking classes for. And I graduated in physics. And I wasn't sure whether I wanted to get a PhD in physics, although I had applied to graduate schools. And so, at the same time, I applied for these fellowships that can take you to England to do -- to Oxford, for example. And, I didn't get the fellowship, but my parents gave me a fellowship.

And I started a second BA in biochemistry at Oxford, and I did that for two quarters and then I switched into a research program, because I didn't feel like taking classes anymore. And that was what was called a Master's By Research, and I ended up stumbling into this area. I thought, "Oh, this is interesting, it's biology, I want some experience in biology research, and it touches on history, and I'm interested in history, why don't I work on this for a while."

DUTCHEN: "This" being genetics?

REICH: "This" being genetic studies of history. So, exactly what I do right now. And then I kept going, working on this and applying to positions in the United States. I got into medical school here at Harvard. And so, I left a year and a half later, and when I left they said, "Well, you can get a PhD with just a little more work." So I came back the following summer. So I had like the world's fastest PhD. But, it was sort of a successful PhD, because it was very productive and [I] had done a lot of things that were publishable.

And then I started medical school here, which I did for two years, and then I kind of dropped out because part of that program involved a research requirement and the research requirement was to -- I used to do work in the same area, and I got too distracted, and I dropped out and ended up doing a postdoc. And then, I got this job that I have now.

DUTCHEN: What did you want to be when you were a kid?

REICH: I think -- my parents are writers, so there was a high value on writing. And I think there's an extremely high value in my family on creativity. And I wanted to be, I think -- I think that whether that was science or whether that was art did not matter very much. I think I wished somehow to be both.

DUTCHEN: So, where does creativity come into play in what you do?

REICH: I think the creativity is mostly in the science not in the writing, and the data that we're faced with. It's a very exciting time -- the data on human history -- nobody -- this is like, um -- it's like virgin territory that what we're working on. So, we're not the only people working on it, but there's not many people working on it, and the people have not been working on it for very long. So, as a result, there's many undiscovered things all over the place. And so, we're walking around virgin territory trying to look for seams of information.

You get a data set, which is in the end, a genome sequence, or some kind of partial genome sequence, from one, or dozens, or sometimes hundreds or thousands of people, and basically, it's a bunch of ones and zeros and we have to figure out what to look at in that data that was going to be informative about the history of the population. So that's a -- sort of, there's creativity there.

DUTCHEN: What are the most exciting open questions in the field these days?

REICH: I think the important questions are trying to understand how present-day people got to where they are today. Another question is, trying to understand how ancient peoples moved around the landscape. There's other questions that I'm not directly working on, but about the nature of domestication of plants and animals and how that happened. And, I think there are very critical questions about the biological impact of these many ancient mixtures on populations; how it affects the phenotypes people have, the natural selection that brought us to phenotypes we have right now, and the disease risks we have. Those are things that are all possible, potentially, to address with this data.

DUTCHEN: Do you get frustrated by the limitations of what can be known in the kind of work that you do?

REICH: I mean, of course we always get frustrated by limitations and the sort of mysteries and things that we can't see through the data or the approaches that we're using. But, I think that that's a frustration of all science and all sort of scholarship. We're lucky, in this field, in that there are so many big stories close to the surface, that somehow just working on this work it's often possible to find really important things.

DUTCHEN: And, what do you do for fun?

REICH: Well, I mean, apart from family, which we spend a lot of time together, I just work all the time.

DUTCHEN: That can't possibly be true. I know sometimes you ride your bike, you run.

REICH: I run, but that's just for -- I'm addicted to running. And I would feel ill if I didn't run. But, I don't -- I don't sort of, like, have -- I basically work all the time. I'm sorry, I'm very boring.

DUTCHEN: Surely you've read a book, watched something, listened to something lately?

REICH: I did used to read books all the time until we had kids. But now, I just, the -- my wife and I take care of the children and we, uh, I work all the time.

DUTCHEN: What do you hope to achieve when you're one day winding down?

REICH: Oh, I don't think that way. I just want to learn as much as possible. So, it'll be very sad to have to retire.

I don't think in terms of achievement, so I guess I don't want to accomplish a certain thing. I guess you could say, oh, one wants to achieve figuring out how everybody's related to each other or get some kind of award or something. But, that's not right now how I'm thinking; I'd like to just enjoy finding out things as much as possible and find out important things and solve mysteries; that's what I want to do as much as possible for as long as possible.

DUTCHEN: Seems like a good career to be doing those kinds of things in.

REICH: Yeah.

DUTCHEN: We really appreciate you taking the time to talk with us this morning. It's somehow still snowing outside.

REICH: Yeah, but it's going to get better in the next month.

DUTCHEN: We've been talking this morning with Dr. David Reich, who's a professor of genetics here at Harvard Medical School. Thank you.

REICH: Thank you. Thank you.

[DINGING]

DUTCHEN: And now, for this month's abstract.

[SOUND OF CROWD]

CAMERON: Gene therapy is dead! Long live gene therapy!

[CROWD FADES]

CAMERON: That pretty much sums up the identity crisis that gene therapy has been dealing with over the last 25 years. With this approach, researchers used viruses to insert a healthy version of a damaged gene into people suffering from certain genetic conditions. But in 1999, a clinical trial went terribly wrong and gene therapy, at least in humans, came to a grinding halt.

But over the years, researchers have been fine-tuning the science, and now gene therapy is entering a renaissance. Researchers in the lab of Harvard Medical School geneticist Connie Cepko have developed an antioxidant gene therapy that prolongs vision in mice going blind from the slow death of photoreceptor cells in their eyes. This is an inherited condition that many people suffer from as well.

Scientists know that oxidative damage is a major cause of this, but they haven't been able to combat it. Here, the researchers aim to boost antioxidant activity by providing extra copies of genes that fight oxidative damage. In fact, they delivered those genes directly into the mice's eyes. With one particular gene, the researchers slowed vision deterioration in the mice. None of these treatments cured blindness, but this work opens the door for possibly using antioxidant gene therapy for human patients one day.

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DUTCHEN: To learn more about the research discussed in this episode, or to let us know when you think, visit hms.harvard.edu/podcasts. You can also follow us on Twitter, where our handle is @harvardmed, or like us on Facebook.

Now, we'd like to leave you with a thought by Louis Pasteur: "Science knows no country because knowledge belongs to humanity and is the torch which illuminates the world."

END OF INTERVIEW