Dr. Svante Paabo, PhD

Nobel Conference 50

Of Neanderthals, Denisovans, and Modern Humans

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So thank you very, very much for that kind introduction. And above all for the invitation to come back to this amazing and unique event. I'm really extremely happy to be here for the second time. It feels little bit like coming home for me, not only because I've been here once before but also because I grew up in Sweden, as it were. And coming here to Gustavus is a bit or little like coming to place that's more Swedish than Sweden itself. It's sort of like [laughter and applause] It's like some ultra-homecoming for me.

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So what I wanted to start out then by doing is to remind you about what you all know and that you've already that our genetic material is stored in the nuclei of all cells in our body in the form of the DNA. And information there is stored in the sequence of these four letters abbreviated A, T, C, and G. And it's stored twice, if you like, once on each strand in a way that whenever there's a C on one strange, there will be a T on the other. And if there's a G on one, there will be C on the other and so on.

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And that is important because when a cell is going to divide, particularly cells then in a [inaudible] line when new individuals might then be created. There are then enzymes that unwind these strands and two new strands are formed with old ones as templates. And that's a very, very exact process but nothing is totally perfect, of course. So sometimes an error is made. Say in this case up there, A is built in instead of a G opposite of a T. Opposite of a C. And if that is not repaired before the cell divides again, that will then result in a mutation, in a new letter at one position in our DNA.

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And you can detect then the effects of these mutations and then you compare DNA sequences between two people in the room, for example. You will find a difference every 1,000 or 1200 such bases or nuclueotides when you compare two individuals. Every baby that is born carries in the order of 50 to 150 new mutations that are there neither in the mother nor in the father. And these mutations then rain down, as we heard in Sean's talk, essentially randomly across the genome and as a function of time. So if you take in the chimpanzee in this case, you will find more differences in the order of one every hundred such letters. And if you're interested in the history of the evolution of the piece of DNA, you then use the best models you have for how these mutations accumulate and try to reconstruct what has happened in the past.

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And in this case, it's very simple. You have an ancestor of the two human sequences quite recently. Quite much further back, the common ancestor also with the chimpanzees. So as you also have heard, our genome is composed of 3 billion base pairs. There are a lot of information there, around 3 million differences between two genomes. And if you study those differences on a global scale, something that you will find is that you find more differences among DNA sequences in Africa than outside Africa.

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So although there are a lot more people of course living outside Africa than inside Africa when more genetic variation in Africa then outside. And not only that, the DNA sequences you find outside Africa most of the time have closely related sequences inside Africa. But there is then the component of the genetic variation inside Africa that had no close relatives outside. So the interpretation of this is that modern humans, our direct ancestors, evolved in Africa, accumulated DNA sequences there. And a component, a part of that variation, a part of that population, went out and colonized the rest of the world. And by different genetic tricks you can even figure out when that exodus out of Africa was. And it was quite recently, between 60,000 and 100,000 years ago, approximately.

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So this is then the sort of data behind the genetic evidence for a recent African origin for modern humans. But there is, if you'd like, a problem with that model. And that is that there were other forms of humans around, since a long time, 100,000 years ago or so. Since about 2 million years ago, there were different forms of humans, not only in Africa but also in Asia and in Africa. So around 100,000 years ago, most famously then are the Neanderthals. In Europe and Western Asia, and other forms of now-extinct humans in Asia. So we are interested in many, many years in my laboratory in studying the relationship then between present-day humans and these extinct forms of humans.

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The problem then, if you want to approach this with genetic means, is that these guys are extinct, so you will have to go into their bones and try to retrieve the DNA. And that is work that goes back approximately exactly almost 30 years when I then started studying the preservation or looking for DNA in ancient Egyptian mummies that are just two to three or four thousand years old. Most such mummies contain no DNA. But this is actually the first mummy of a child that's 2,400 years old where you could see in the upper layers of the skin here, things that look like cell nuclei, and indeed we could also stain them with dyes that [inaudible] that bind to DNA and then fluoresce. So here DNA is indeed preserved.

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So that's what then followed were almost 10 years of work where we sort of discovered that it was much, much harder than we initially thought to retrieve the DNA from such old remains. And the reason for that is really that if you extract DNA from fresh tissues, you might get say a microgram of DNA from a gram of tissue. And in old remains of say bones from ancient Egyptian mummies, there's in order of 10,000 or 10 millionfold less DNA preserved. But there's lots of DNA in that, in spite of that, and then that's large amounts of DNA from bacteria and fungi that have grown in the bone since individual died.

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So what this means then is that tiny amounts of present-day human DNA that will sort of not disturb you if you extract DNA from a blood sample today because there are millionfold more of the real DNA you want there. Such small amounts might

totally out-compete the indulginess [sounds like] DNA you extract from an old bone. So this led to sort of a progressing case of paranoia in our lab of contaminating our experiments with DNA from ourselves, or from people [inaudible] to us so that we now work under clean room conditions where the air is filtered. It's UV light in the night to destroy DNA. You dress up in funny clothing and so on, and so on. And it also resulted in that most of the work for the decades in this field was focused not on the DNA that you find in the cell nuclei, where must of our DNA is, but a tiny part of the genome outside the cell nucleus in the mitochondria. That's a small part of the genome that comes from mothers to offspring and that are many, many copies per cell so it's much easier to retrieve.

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And over 10 years of work [inaudible] progress [inaudible] the photo back in time starting with zoological collections that are 100 years old or so to animals that are recently extinct within the last hundred or two hundred thou-, two hundred years, back to animals that disappeared during the last glaciation such as the giant ground sloth in America.

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But what really interested us were them, our closest extinct relatives, particularly the Neanderthals, the left here is a reconstructed Neanderthal skeleton compared to present-day skeleton. So Neanderthals were, as you know, these robust forms of humans. They appear somewhere three, four hundred thousand years ago in Europe and Western Asia, where they then exist until becoming extinct in the order of 30 or 40 thousand years ago. And there are since decades two ideas about, around what happened to Neanderthals when modern humans come out of Africa here and eventually replace Neanderthals in Europe and other forms in Asia. One idea is that there is no contact whatsoever, no contributions of Neanderthals to people today. Another idea is that Neanderthals are replaced by present-day humans but they contribute genetically to Europeans today and at others, extinct [inaudible] may have contributed in Asia.

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So the first chance to test this came in '96, '97 when we then got samples from the Neanderthal's type specimen. So that's the Neanderthal that was found in 1856 in

Neanderthal and gave its name to this group of humans. Got a sample from the upper bone there, worked this mitochondrial genome, a particularly valuable part of it, cumbersome with the technology of the time reconstructing a little part of it and estimating [inaudible] genetic tree of the history of the mitochondrial genome and present-day human mitochondrial genomes which are here, they go back to common ancestor 100, 200 thousand years ago. And much, much further back, in order of half million years or little more, is through common ancestor with the mitochondrial genome of Neanderthals.

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So since then more Neanderthals mitochondrial genomes have been studied and tens of thousands of present-day humans. It is very clear there is no one running around today with a mitochondrial genome of a Neanderthal. So very clearly it is this model that applies for the mitochondrial genome, total replacement. But it's also clear that this is just, was just a history of the mitochondrial genome and that the big story is in the cell nucleus where the vast majority of our genetic information is, and information both from our mothers and from our fathers.

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So I think I'm on the published record somewhere 10, 12 years ago saying we will never see a nuclear genome of the Neanderthals. The DNA is too graded, it's chemically modified, it can't be done, etcetera. And you should, of course, never make negative predictions like that, especially not in science because what often makes what you said obsolete is technical developments. And in this case it was High Throughput DNA Sequencing, new technologies that came around the first years of this millennium, to sequence millions and millions of DNA molecules rapidly and rather inexpensively. So what you can then do is extract the DNA from such a piece of bone [inaudible] sequence all the DNA in there and then compare it to the human genome sequence [inaudible] got to other genomes and try to figure out which molecules of DNA in there might come from a Neanderthal.

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First place where this worked was in this place in Southern Europe, in Croatia, this bone that's 38,000 years old, this fragment of the bone there. And the first thing you will see, if you look at the DNA molecules there that come from the

Neanderthal is that they're indeed very short, 60, 70 nucleotides, whereas the DNA you would extract from the blood sample from me would be 10 or 20,000 base pairs long.

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You will also find that the vast majority, as we said, come from bacteria and fungi in the bone and very little, a few percent at most, actually from the Neanderthals. So last time I was here, we then were in a middle of a project to improve the technology where which would come from the bones to a form of the DNA we could feed into the sequencing machines. And over 5 years we got a lot better on that. And the machines also got more efficient in how many molecules they could sequence. We looked through a lot of Neanderthal sites and a lot of bones to find the best ones, the ones that have proportionally most Neanderthal DNA. We focused in on three bones from this this cave in Croatia from three different Neanderthals and sequenced a little over a billion DNA molecules from them. Most of them then from bacteria, not from the Neanderthals.

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But so we then filtered these molecules and tried to see where they could match to the human genome, taking into account that they also have chemical modifications here of different sorts. And we found that the most common chemical modification was one of the spaces abbreviated C, the Cytosines there that lose its amino in a spontaneous reaction that goes on over time and becomes another chemical form of the base, a non-natural base for DNA that is misread when you sequence it as Ts. So if you look at these molecules we sequenced and compare them to the human genome, you will find that they often contains T's where the human genome has C's, or for the other strands, A's where the human genome is G's.

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So this was the problem, but it was also a chance to recognize which molecules might be old and then identify [sounds like] fossils that have a lot of endogenous old DNA in them and then you could actually remove this unnatural basis by various chemical tricks. So in the end in 2010, we ended up having a first rough overview over the Neanderthal genome. Had a little over half of it and could begin to ask

questions. So one of the first questions we were interested in was this question: What happened when modern humans met Neanderthals in Europe? Did one mix or not?

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So we tried to address that in several different ways since it was a very controversial question in paleontology that people had fought over during their entire careers often. But one of the approaches we took is this very simple one of saying, if there was a contribution from Neanderthals to Europeans, we would expect Europeans to share more genetic variance with Neanderthals than what Africans do since there has never been Neanderthals in Africa so there is no reason to assume Neanderthals would have contributed there.

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So this idea here, if there's no contribution, a Neanderthal genome would be equally far from someone in Africa as from someone in Europe. Whereas in this case, on average the Neanderthal would be slightly more close to the Europeans. So we're then worried about small errors in the sequences. We decided to compare our Neanderthal genome here to five present-day humans' genomes that we sequenced ourselves to be sure that it had the same error frequency or types of errors in all the genomes.

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So we had one individual from Europe. We debated a long time what European we should sequence. It became clear to us that archetypical European for us is a person from France, so this is a French person. We have two African individuals. One person from China and one from Papua, New Guinea. And then we do a very simple analysis. We simply compare two individuals and find places where they differ in their genome. To test this of two Africans and there is no reason to assume a Neanderthal to be closer to one African than the other since Neanderthals have never been in Africa. And then we take in the Neanderthal here and say how often does the Neanderthal match this African or the other African at positions where these two present-day people differ?

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And we find that statistically speaking, this is 50/50, close to 100,000 times each of them. When we now do this with the European individual and an African individual, to my surprise, I must say, because I was biased to think there had been no contribution from Neanderthals. From our mitochondrial work, we found statistically significantly more matching to the European individuals. Even more surprising was that we took a Chinese individual and an African individual, we again saw more matching to the Chinese person although most people would say there have never been Neanderthals in China. And with Papua, New Guinea versus Africa, again, more matching to the non-African individual, although everyone agrees there have never been Neanderthals in Papua, New Guinea.

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So you can actually then if you go into the genome sequences, sort of see these chunks of DNA that look like they could come from Neanderthals. This is a picture of variation on one chromosome in Europeans, valuable positions are indicated in yellow and below is the Neanderthal genome. And you will see a group of Europeans, four or five Europeans, that have a piece in this chromosome that is almost identical to the Neanderthals and quite different from other Europeans. So the shanks [sounds like] are 20, 30, 40 thousand base pairs that are quite close to the Neanderthal.

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So the model that then came from this, or the dilemma for us was really to explain why do we find this contribution, not only in Europe where Neanderthals had lived but also in China, also in Papua, New Guinea, where Neanderthals had not been. And the models we proposed that have since then borne out by much other work both by us and others is to say that when these modern humans came out of Africa, they presumably passed by the Middle East. And we know there were Neanderthals in the Middle East. So these early humans mixed with the Neanderthals and then went onto become the ancestors of everybody outside Africa, they could sort of carry a Neanderthal contribution with them in their genome out to other parts of the world also where there have not been Neanderthals to the extent of something like 1 to 2 percent of the genomes of people outside Africa come from Neanderthals.

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This is the simplistic model. It's already clear that it's more complicated than this. For example, people in East Asia have slightly more Neanderthal contribution than people in Western Europe. There seems to be at least one more contribution, maybe in Central Asia or something like that, to the ancestors of present-day East Asians. So there was then a lot of follow-up work in the scientific community where people have used and are using the genomes for different things. That's very satisfying. Can never stop myself from sort of pointing out that there are a lot of people in the public that are also interested in what we do. And a lot of them started writing us e-mails and letters after our paper came out. And from lots of people wrote that self-identified as Neanderthals and wanted to send us blood samples for us to analyze. [laughter]

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And after a while I started noticing this pattern in this correspondence that's almost exclusively men that write to us and very few woman have self-identified as Neanderthals. [laughter] So we thought, we discussed this a lot in a lab and one idea was that while man are more interested in [inaudible] genetics so they would write to us and women are less interested. But that's actually not the case because if you went back to the correspondence, we found quite a lot of women who did write to us and say they were married to Neanderthals. [laughter] Where so far there's not a single man who has claimed that he's married to Neanderthal woman. So this is of course extremely interesting from a genetic perspective and something you have to sort of go after.

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But we're doing other things than just counting e-mails, too. One other thing was not to, of course to apply these new techniques now to other parts of the world. And we are very, very lucky to work together with archeologists in [inaudible] cities [sounds like], particularly Professor Derevianko and Professor Shunkov, who excavated many sites in Siberia, but particularly [inaudible] this cave in Southern Siberia, then this sort of cave on the border to Mongolia and China. It's a beautiful area. This cave, where in 2008 they found in an excavation in this cave a tiny little bone that they were very skilled to realize that it might come from a human. It's a part of the last phalanx of the pinky. So we got to sample this bone and fortunately we had then developed even more sensitive techniques, particularly a way to make

DNA libraries from tiny amounts of DNA where we start by separating the two DNA strands and make libraries from both strands. So each double-stranded molecule will have two chances to end up in the libraries.

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So with that we are then able to retrieve many, many DNA fragments, much, much more than we could before. To have hardly any holes in our sequences abytnmore and sequence the genome 20, 30 times over. And we were very surprised then with this tiny little bone to find that, yes, this individual had a common origin with Neanderthals but far, far back. Much further back than any divergence between people who live today. And Neanderthals since had a long independent history. It became clear to us that we had sort of a new form of extinct human. We debated a long time what we would call them. And ended up calling them then Denisovans, after Denisova Cave where they were first found. Just as Neanderthals are called Neanderthals after the Neanderthal sites.

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So there are many, many things you can now do when you have high-quality genomes that are old. One thing I just want to point out is that you can start seeing what you would expect to see. Namely that this individual lived in the past. So it hasn't had as much time as people that live now to accumulate mutations. So there are, if you like then, missing mutations here. It's, if you go back to the common ancestor with the chimp in order of one to one point three percent of mutations you see in present-day humans are missing in this individual, so you can catch evolution red-handed, if you like, and sort of see that there are mutations that haven't taken place.

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If you assume that this is 6.5 million years to the common ancestor here, this then means that this bone is 60 to 80 thousand years old. That's very rough. We have problems with the quality in present-day genomes, for example, to estimate this. But is anyway fascinating to me that you now have a bone that's so tiny that you cannot even carbon date it. But when we can get a good genome, we can start estimating its age from the missing mutations. And I think that's something that will come much more in the future.

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You can, of course, with this genome do as you do for the Neanderthals, have the Denisovans contributed to present-day humans and you find particularly contribution then in the Pacific. So people in Papua, New Guinea, Aboriginal Australians, and that was quite surprising to us because we of course find this bone in Siberia and we don't think the ancestors of people in the Pacific has been in Siberia. But so rather it suggests that these Denisovans have been more widespread than the past and maybe was in Southeast Asia somewhere within that ancestors of present-day people in the Pacific.

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So I think this is something that we will see more in the future and from tiny little bones, this is a copy of the bone that we used for this, you can reconstruct a lot of the population history, the genetic history of a group. But we frustratingly don't know how these individuals looked, stone tools they made, etcetera.

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We also now have a good Neanderthal genome, again from the same Denisova Cave, deeper down in the cave where in 2010 one found a toe bone that allowed us to reconstruct a good genome of a Neanderthal. So we have one good Neanderthal genome, two low-quality Neanderthal genomes and the Denisovan genome. So we can now begin to sort of look at genetic contributions, not only to present-day humans but also among these extinct groups.

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So we can see now when we compare the Neanderthals in the middle to modern humans to the left and Denisovans to the right, what we already know, the Neanderthal contribution to non-Africans today of 1 or 2 percent, Denisovan contributions to people in the Pacific of up to 5 percent. Can also see a tiny contribution from Denisovans on Mainland Asia. People in China, for example, carry in order of 0.2, 0.3 percent Denisovan DNA. We see a contribution from Neanderthals to Denisovans of less than 1 percent. And quite interesting, an old component in the Denisovan genome from something else, that’s not there in the Neanderthals but that diverged earlier from human lineage, 1 to 4 million years ago or so.

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This is very tempting to say that this is homo erectus or something like that that in Asian mixes with Denisovans. So conclusion from this is then that human groups have always mixed at least a little bit, so to say. We don't find large, large contributions of 30, 40 percent, but small contributions.

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So the last quarter of the talk then I wanted to take up this theme where do we go from here? What's next? And there are three things I wanted to bring up. One is of course to go further back in time, to apply now these super-sensitive techniques, the single-stranded approach, for example, to even older fossils. And over the past year we have been very lucky to work at a site in Spain, Atapuerca, where one finds human remains that are around 400,000 years old, so five to ten times older than the Neanderthals we study.

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It's a deep site, around 30 meters down in the ground where they find many, many bones. And from this femur here, we were able to reconstruct the mitochondrial genome so that, so far not the nuclear genome just to give you a feeling from this. Starting from half a billion DNA molecules in the bone, we trim it down to 10 or 15 thousand that actually come from the mitochondrial genome from this individual. And then reconstruct the mitochondrial genome and estimate its relationship to the mitochondrial genomes of Denisovans, Neanderthals, and present-day humans. And quite surprisingly, this individual, the mitochondrial genome has a common origin, but far, far back with Denisovans, rather than with Neanderthals, that we would have expected perhaps to be the case.

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So it's still very, very unclear what this means. Perhaps it's simply so far back in history here that we have an ancestral population both of Denisovans and Neanderthals that we study. It's really the nuclear genome that will tell that story. But exciting thing that we will see more of the next few years is that so far I sort of believe that around 100,000 years ago was the limit we could go back in time. And now it seems we can go further back, perhaps even approaching a million years ago or so.

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Another thing that's interesting is if there's any functional contribution from the Neanderthals and from Denisovans to present-day people. What does it mean that many of us carry parts from the Neanderthal genome in us? Does that mean anything for how we function physiologically. And there is beginning to come information about that. There were two papers that came out in January that looked across hundreds of present-day people, looking for contributions from Neanderthals in Europe and in Asia and finding some parts of the genome were actually 60, 70 percent of people, for example, in Europe carry a contribution or here in Asia.

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So you can then ask what genes are particularly in those parts that have reached high frequency. There's just one thing that stands out there statistically and these are structure proteins and skin and hair keratins. So probably we will learn with time that there is some feature in the more [inaudible] function of skin and hair that actually come from Neanderthals to people today. There are more important variants, too, that come from these things. All righty in 2011, Peter Parham's group at Stanford discovered that transplantation antigen genes, so genes at percent antigens to the immune system variants of such genes, come both from Neanderthals and from Denisovans to present-day humans. And have sometimes reached high frequency, presumably because they are of advantage to fight certain infectious diseases. There is also a group in China that has shown that genes involved in lipid catabolism, so how we break down lipids, come in Europe from Neanderthals, more than you would expect statistically. What that exactly means we don't know.

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We know a little bit more of a gene that was discovered and published in January by a big consortium headed from a group in Boston that found a risk variant of a gene that confers risk for Type 2 Diabetes, the type of Diabetes you get in old age. This gene encodes a lipid transporter that transports lipid into your cells. This protein has four amino acid differences in this risk variant. And this risk variant is quite common in East Asia [inaudible] 25 percent, up to 25 percent of people can carry it.

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And when you estimate such a phylogenetic tree between the red risk [inaudible], and the blue non-risk [inaudible] here and put in the Neanderthal version, you find that this comes from Neanderthals. So it's surprising that something comes from the Neanderthals that give you disease. But it's likely that this is something to do, for example, with surviving in starvation. And that this variant actually helped you during starvation and today when we have ample nutrition all the time, it results in Diabetes. So this might be a Neanderthal adaptation to starvation.

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In Tibet, people, of course, live at very high altitudes. And [inaudible] already knew that there were adaptations for that in certain genes, particularly this gene here, EPAS1, sort of confirm the ability to survive at high altitudes and avoid problems, for example, during pregnancy and birth. So a group at Berkeley recently published when they compared this variant with the Denisovans genome, they found that this variant that's very common in Tibet comes from Denisovans.

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So ancestors of Tibet [inaudible] seemed to have picked this up sometime in the past. This is fascinating that perhaps people [inaudible] Tibet [inaudible] high plateau was made possible only through the interaction with Denisovans. So this fits into parenting that you see also in other groups of organisms of adaptive introgression. Where you can imagine that Neanderthals and Denisovans have lived for hundreds of thousands of years in an environment, accumulated genetic variants that gave an advantage there. And then came these newcomers from Africa, mixed with these a little bit and picked up variants ethendrols [sounds like] to high frequency because they were of an advantage to survive in different places in Eurasia.

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Finally then, the third area I think we will see a lot of things done in the future is what functions that are truly unique to modern humans relative to Neanderthals. So things then that are accumulated in our genome in modern humans since we separated from Neanderthals. Why are such interests particularly interesting? Well, I think they're particularly interesting because of certain things that start

happening with fully modern humans. Technology, for example. The stone tools of Neanderthals when they first appear around three, four hundred thousand years ago, and when they disappear around 30, 40 thousand years ago, are pretty much the same. And I think that when modern humans appear, hundred, hundred and fifty thousand years ago, compared to today, we all agree that our technology has changed pretty dramatically in that time.

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There are other things such as art that depict things that come only with modern humans. And this increase in population size and spreading to all habitable part of the world comes only with modern humans. The dream, of course, would be to understand some of the putatively biological background of that. And that that would be hidden in the changes we can now detect and compare present-day humans to our closest extinct relatives and to the apes. So if we take a very strict definition and ask for everything that's present in all humans today, no matter where we live on the planet, but where the Neanderthals and Denisovans look like the apes, that's not a very long list of genetic changes. It's around 31,000 changes in our genome. Not a large number. You can look through them in an afternoon on a computer.

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If you just focus in here, for example, there's just 96 amino acids and proteins encoded by genes that fulfill this criteria. They incur in just 87 proteins. So just focus on that to give us a feeling for this. We're of course biased to think that what might be particularly interesting are those proteins expressed in the brain, so if you think that something with human cognition is rather unique.

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So if you just look during the develop of the brain, we can actually find, when we do statistical controls here comparing these changes that don't change proteins, protein structure, that in one part of the brain, developing pain, the epithelium, where stem cells divide and make neurals, there is an excess of some of these proteins. And these are small numbers, total just 87 proteins, as I said. There are six proteins expressed there. And surprisingly three of them turns out to be involved in cell division, so how the chromosomes are pulled apart during cell

division. This was very surprising to me and I'm not a neurobiologist. But I have learned by talking to colleagues that when the stem cells divide in this epithelium that form nerve cells in our cerebral cortex, the plane of cleavage is very important for how many neurals it will form and what types of neurals it will form. So it may well be, for example, that these three proteins may be particularly interesting. This is just speculation, of course.

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So I want to end on the note of saying, how will we take the step away from just speculation? How will we actually functionally test these things that are human-specific or Neanderthal-specific? And I've gone around for over 10 years joking, saying that what we would like to do is, of course, to put Neanderthal genetic variance into transgenic humans and human genetic variants into transgenic chimps and test their abilities. And there are of course many, many reasons, ethical reasons and technical reasons why that will never happen. But this is not so much of a joke because there are now even professors of, at Harvard even who go around and say we should think about cloning Neanderthals. That is going much, much further, of course. It's putting out in all these 31,000 changes to go back to the ancestor and see what that would be like. And there are the same reasons there, technical and ethical reasons that this should never be done.

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However, what can we do to not just speculate? I think one thing that will happen is that we will find backmutations in humans. As I said, something like 50 to 100, 150 new mutations occur in ever new baby that's born. We have 7 billion humans on the planet and the genome is just 3 billion base pairs so every mutation compatible with human life exists there in the population. They are just at very low frequency. And in the future when millions and millions of people will have their whole genome sequence as soon as they go to their doctor will we be able to find them and study then.

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Something else that you can do is of course to put these changes now into stem cells and study those cells in tissue culture in the laboratory and we and others are doing that. And finally, I think what you can also do is to put some of these changes

into model animals, such as mice. I know some promising experiments that sort of go in that direction, to study some of these changes in an animal model.

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So with that I want to end on the note that I think what will be almost most exciting for the next 5 or 10 years is to study several of these genes then in tissue culture and in cell culture and in animal models and try to understand some of these functional changes that happened early in ordinary modern humans since we separated from Neanderthals that may have been responsible for setting us on this unique path then, which caused us to develop this technology and this culture that allowed us to be so numerous, and eventually then to counter-influence a large part of the biosphere as we've heard that we do today.

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So I hope I convinced you then that if you're interested in recent human evolution, it's very valuable to have the genomes of our closest evolutionary relatives, since you can see what's unique to humans, and eventually what's unique to Neanderthals and then more Neanderthal genomes. And we have now then the tool to start studying these things in tissue culture and also by humanizing, for example, mice. So there are many, many people involved in this. Many more people than I can mention in producing the genomes and analyzing the genomes. I want to point out one person here who developed this ultrasensitive way of doing single-stranded libraries, Matthias Meyer, that really made it possible for us to make these high-quality genomes over the last 1 or 2 years here. So I thank you very much for your attention.