

QnAs with David Reich

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Harvard Medical School geneticist David Reich feels lucky to have found paleogenetics, a field that combines his love of history with his love of science. Reich plumbs data, collected by transcribing ancient DNA, to learn about human history, including migration patterns, social structures, health, and disease. Paleogenetics has exploded in the last few years, with massive increases in the world's dataset of ancient DNA. For his work in this field, Reich won the 2019 National Academy of Sciences Award in Molecular Biology. PNAS recently spoke with Reich about his role in invigorating the field.

PNAS: How did you become interested in analyzing ancient DNA as a means to understand human history?

Reich: I've always been interested in human history. I began college majoring in sociology and history. I switched to physics in my third year and then did a fifth undergraduate year in biochemistry at Oxford. I found work in a [laboratory] with David Goldstein (now at Columbia University) who was studying human history with genetic data. It was immediately interesting. I ended up staying for what became a PhD. But I entered the field before its time had come. We were trapped by the small amount of data, and we were trapped by the fact that our samples were from the present. I left the field and went to medical school at Harvard where I did two years of coursework and then moved to a postdoc in Eric Lander's genomics laboratory at the Whitehead Institute/MIT Center for Genome Research.

PNAS: What would you say has allowed the field to take off so rapidly?

Reich: In 2006, when I reentered the field, the technology was finally catching up. This reflected a million-fold drop in [DNA] sequencing costs, and a thousand-fold improvement in efficiency of ancient DNA extraction through a variety of technical molecular improvements. It was clear to me that this would revolutionize our understanding of the past.



David Reich. Image courtesy of Howard Hughes Medical Institute/Bizuayehu Tesfaye.

PNAS: Which of your findings have been the most surprising?

Reich: I'll list three.

In 2006 I joined a consortium organized by Svante Pääbo to study archaic humans. We compared Neanderthal genomes to modern humans and tested if interbreeding had occurred. Based on previous work, I was skeptical. So when I became the person who found the evidence of interbreeding I was more resistant than almost anyone to what the data were saying. I tried to make the results "go away," but the evidence just kept getting stronger. Because of our skepticism we ended up building a stronger case for interbreeding than we would otherwise have done: it took three independent lines of evidence all pointing in the same direction to convince us. The data forced us to say something we were initially heavily biased against.

Then, in 2010, my colleagues got DNA out of another archaic human from Denisova cave in Siberia (1). We showed that the Denisovans also interbred with the ancestors of modern humans, and left a substantial legacy in some humans today, for example New Guineans. This was a huge surprise, as there was no well-described fossil or archeological record for these archaic humans. It was the genetics that drove the observation and genetics that is now playing a key role in forcing us to rethink our understanding of the human landscape of Eastern and Southern Asia.

The third surprise is what happened in Europe after 5,000 years ago. In 2012 we found that modern northern Europeans have ancestry from a group that's related deeply to Native Americans. In 2015 we showed that this ancestry swept into Europe after about 5,000 years ago from people from the Steppe north of the Black and Caspian Seas. It displaced about 70% of the ancestry of the German, 90% of the British, and 40% of the Spanish gene pool within a few hundred years (2–4). Before this, the orthodoxy in the archeological community had been that when changes occur in the way people made pots or tools, it should be assumed to be due to the spread of ideas but not large-scale movements of people. We now know that such changes are often accompanied by large-scale turnovers of people.

PNAS: What are the modern-day implications of the work in this field?

Reich: The genetic data repeatedly show we [humans] are all profoundly mixed. The idea of purity is almost always wrong. Take the example of "white people."

When we used the time machine of ancient DNA to go back 10,000 years in western Eurasia, we found that there were at least four populations, each as different from each other as Europeans and East Asians are today. None of these groups disappeared; instead they mixed to form a 10-times more homogeneous group.

PNAS: What are you most excited about moving forward?

Reich: I'd like to help midwife this explosive new field into something that is mature and fully integrated into archeology. One goal is to help generate a lot more data from understudied places in the world, especially outside of Europe, and to build an ancient DNA-based atlas of human migrations all around the world. I would also like to help realize the potential of ancient DNA to provide insights into biology. To understand biological change over time, it is critical to understand how the frequencies of genetic variations change. To do that, large sample sizes of ancient people are needed. In the last two years, due to efforts by our lab and others to scale-up data production, the needed sample sizes are finally becoming available.

PNAS: What does the National Academy of Sciences Award in Molecular Biology mean to you?

Reich: It is an extraordinary honor, not just for me but for the field as a whole. I see it as a mark of the coming-of-age of this field and recognition of work that people around the world, as well as in my group, have done and that I'm representing.

1 D. Reich et al., Genetic history of an archaic hominin group from Denisova Cave in Siberia. *Nature* **468**, 1053–1060 (2010).

2 W. Haak et al., Massive migration from the steppe was a source for Indo-European languages in Europe. *Nature* **522**, 207–211 (2015).

3 I. Olalde et al., The Beaker phenomenon and the genomic transformation of northwest Europe. *Nature* **555**, 190–196 (2018).

4 I. Olalde et al., The genomic history of the Iberian Peninsula over the past 8000 years. *Science* **363**, 1230–1234 (2019).