OLLI 497: Ancient DNA

Session 2: September 28th Summary and Observations

Chapter 1: How the Genome Explains Who We Are

In this chapter, Reich puts front and center his concept that in order to understand "**WHO WE ARE**", we must look at the "**WHOLE GENOME**." I wanted to emphasize this, as you can probably tell. He is clearly not an advocate for the "single gene" explanation for human traits or behaviors. He also thinks that linking human behavioral traits to variations in the genome is an incredibly complex undertaking, still in its infancy, but an undertaking worth pursuing. But what he thinks we can know about "Who We Are" from an examination of current and ancient genomes is where we came from, what our past was like.

The Master Chronicle of Human Variation

And where we came from can be ascertained through an analysis of variations, mutations, in stretches of DNA. "Although the great majority of scientists are focused on the biological information that is contained within the genes, there are also occasional differences between DNA sequences. These differences are due to random errors in copying of genomes (known as mutations) that occurred at some point in the past. It is these differences, occurring about one every thousand letters or so in both genes and in "junk," that geneticists study to learn about the past. Over the approximately three billion letters, there are typically around three million differences between unrelated genomes. **The higher the density of differences separating two genomes on any segment, the longer it has been since the segments shared a common ancestor** as the mutations accumulate at a more or less constant rate over time. So the density of differences provides a biological stopwatch, a record of how long it has been since key events occurred in the past."

Reich notes that the first application of this sort of analysis was made on "… mitochondrial DNA. This is a tiny portion of the genome…" and is passed down the maternal line of inheritance. The mitochondria in the egg are the starting point for all the mitochondria in a human body.

Reich describes this analysis: "In 1987, Allan Wilson and his colleagues sequenced a few hundred letters of mitochondrial DNA from diverse people around the world. By comparing the mutations that were different among these sequences, he and his colleagues were able to reconstruct a family tree of maternal relationships. What they found is that the deepest branch of the tree—the branch that left the main trunk earliest—is found today only in people of sub-Saharan African ancestry, suggesting that the ancestors of modern humans lived in Africa. In contrast, all non-Africans today descend from a later branch of the tree." This finding supported "… the theory that modern humans descend from ancestors who lived in the last hundred thousand years or so in Africa. Based on the rate at which mutations are known to accumulate, Wilson and his colleagues estimated that the most recent African ancestor of all the branches, "**Mitochondrial Eve**," lived sometime after 200,000 years ago.3 The best current estimate is around 160,000 years ago, although it is important to realize that like most genetic dates, this one is imprecise because of uncertainty about the true rate at which human mutations occur."

This finding also "… refuted the "multiregional hypothesis," according to which present-day humans living in many parts of Africa and Eurasia descend substantially from an early dispersal

(at least 1.8 million years ago) of Homo erectus…. The multiregional hypothesis implied that descendants of Homo erectus evolved in parallel across Africa and Eurasia to give rise to the populations that live in the same places today."

In addition to the genetic findings, "Anthropological evidence pointed to a likely scenario for what occurred. The earliest human skeletons with "anatomically modern" features—defined as falling within the range of variation of all humans today with regard to having a globular brain case and other traits—date up to two hundred to three hundred thousand years ago and are all from Africa. Outside of Africa and the Near East, though, there is no convincing evidence of anatomically modern humans older than a hundred thousand years and very limited evidence older than around fifty thousand years."

Reich goes on to describe other archaeological and anthropological artifacts that support the "out of Africa" theory of modern human origin. And he notes that this evidence points to a dramatic acceleration of change in human behavior that occurred fifty thousand years ago. He notes: "The natural explanation for all these changes was the spread of an anatomically modern human population whose ancestors included "Mitochondrial Eve," who practiced a sophisticated new culture, and who largely replaced the people who lived in each place before."

The Siren Call of the Genetic Switch

Reich notes that the success of this genetic analysis led to the view that genetics may provide "**simple explanations**" for human behavior. "The anthropologist best known for embracing the idea that a genetic change might explain how we came to be behaviorally distinct from our predecessors was Richard Klein. He put forward the idea that the Later Stone Age revolution of Africa and the Upper Paleolithic revolution of western Eurasia, when recognizably modern human behavior burst into full flower after about fifty thousand years ago, were driven by the rise in frequency of a **single mutation of a gene affecting the biology of the brain**, which permitted the manufacture of innovative tools and the development of complex behavior."

Our author notes that the traits and behaviors that Klein cites, such as the ability to use conceptual language, among others, were evident from the archaeological record tens of thousands of years before Klein's favored transition periods. "But even if no single behavior was new, Klein had put his finger on something important. The intensification of evidence for modern human behavior after fifty thousand years ago is undeniable, and raises the question of whether biological change contributed to it."

Reich goes on to describe efforts to uncover the biological change: "In 2002, [Svante] Pääbo and his colleagues discovered two mutations in the gene FOXP2 that seemed to be candidates for propelling the great changes that occurred after around fifty thousand years ago. The previous year, medical geneticists had identified FOXP2 as a gene that, when mutated, produces an extraordinary syndrome whose sufferers have normal-range cognitive capabilities, but cannot use complex language, including most grammar. Pääbo and his colleagues showed that the protein produced by the FOXP2 gene has remained almost identical during the more than hundred million years of evolution separating chimpanzees and mice. However, two changes to the protein occurred on just the human lineage since it branched out of the common ancestral population of humans and chimpanzees, showing that the gene had evolved much more rapidly on the human lineage." But these mutations are also present in Neanderthal DNA, so they cannot be the cause of the changes that occurred fifty thousand years ago. Undaunted, "Pääbo and his colleagues later identified a third mutation that is found

in almost all present-day humans and that affects when and in what cells FOXP2 gets turned into protein. This change is absent in Neanderthals, and thus is a candidate for contributing to the evolution of modern humans after their separation from Neanderthals hundreds of thousands of years ago."

Undaunted indeed: "Regardless of how important FOXP2 itself is in modern human biology, Pääbo cites the search for the **genetic basis for modern human behavior** as a justification for sequencing the genomes of archaic humans…. Pääbo's papers highlighted an evolving list of about **one hundred thousand places in the genome** where nearly all present-day humans carry genetic changes that are absent in Neanderthals."

Reich's comment on this search is telling: "There are surely biologically important changes hiding in the list, but we are still only at the very beginning of the process of determining what they are, reflecting a more general problem that we are like kindergartners in our ability to read the genome."

And lastly: "While the scientific question is profoundly important, I expect that no intellectually elegant and emotionally satisfying molecular explanation for behavioral modernity will ever be found."

And this brings him back to the subject of this book: "… the great surprise of the genome revolution is the explanations it is starting to provide from another perspective—that of history. By comprehending the entire genome—by going beyond the tiny slice of the past sampled by our mitochondrial DNA and Y chromosome and embracing the story of our past told by the multiplicity of our ancestors that is written in the record of our whole genome—we have already begun to sketch out a new picture of how we got to be the way we are."

One Hundred Thousand Adams and Eves

That picture is highly diverse and complex. And it doesn't help to have such simplifications as "Mitochondrial Eve". "… the name has been more misleading than helpful. It has fostered the mistaken impression that all of our DNA comes from precisely two ancestors and that to learn about our history it would be sufficient to simply track the purely maternal line represented by mitochondrial DNA, and the purely paternal line represented by the Y chromosome."

"The truth is that the genome contains the stories of many diverse ancestors—tens of thousands of independent genealogical lineages, not just the two whose stories can be traced with the Y chromosome and mitochondrial DNA…. one needs to realize that beyond mitochondrial DNA, the genome is not one continuous sequence from a single ancestor but is instead a mosaic." Reich likens the mosaic to "tiles" made up of the chromosomes, 23 from each parent, 46 total.

But "… the chromosomes themselves are mosaics of even smaller tiles. For example, the first third of a chromosome a woman passes down to her egg might come from her father and the last two-thirds from her mother, the result of a splicing together of her father's and mother's copies of that chromosome in her ovaries. Females create an average of about forty-five new splices when producing eggs, while males create about twenty-six splices when producing sperm, for a total of about **seventy-one new splices** per generation. So it is that as we trace each generation back further into the past, a person's genome is derived from an ever-increasing number of spliced-together ancestral fragments."

"This means that our genomes hold within them a multitude of ancestors. Any person's genome is derived from 47 stretches of DNA corresponding to the chromosomes transmitted by mother and father plus mitochondrial DNA. One generation back, a person's genome is derived from about 118 (47 plus 71) stretches of DNA transmitted by his or her parents. Two generations back, the number of ancestral stretches of DNA grows to around 189 (47 plus 71 plus another 71) transmitted by four grandparents."

While the number of stretches of DNA we inherit from our ancestors increase arithmetically, the number of ancestors increases exponentially. "Twenty generations in the past, the number of ancestors is almost a **thousand times greater** than the number of ancestral stretches of DNA in a person's genome, so it is a **certainty** that each person has not inherited any DNA from the great majority of his or her actual ancestors."

So no "Mitochondrial Eve", no "Y Chromosome Adam": "Tracing back fifty thousand years in the past, our genome is scattered into more than one hundred thousand ancestral stretches of DNA, greater than the number of people who lived in any population at that time, so we inherit DNA from **nearly everyone** in our ancestral population who had a substantial number of offspring at times that remote in the past."

Reich notes the power of "whole genome" analysis for discovering our deep history: "There is a limit, though, to the information that comparison of genome sequences provides about deep time. At **each place in the genome**, if we trace back our lineages far enough into the past, we reach a point where everyone descends from the same ancestor, beyond which it becomes impossible to obtain any information about deeper time from comparison of the DNA sequences of people living today. From this perspective, the common ancestor at **each point in the genome** is like a black hole in astrophysics, from which no information about deeper time can escape. For mitochondrial DNA this black hole occurs around 160,000 years ago, the date of "Mitochondrial Eve." For the great majority of the rest of the genome the black hole occurs between five million and one million years ago, and thus the **rest of the genome** can provide information about far deeper time than is accessible through analysis of mitochondrial DNA. Beyond this, everything goes dark."

The Story Told by the Multitudes in Our Genomes

Reich next notes that the cost of sequencing DNA dropped precipitously by 2006. The result: "Scientists could gather orders of magnitude more data, and test whether the **history of our species suggested by the whole genome** was the same as that told by mitochondrial DNA and the Y chromosome."

He cites a "… 2011 paper by Heng Li and Richard Durbin… " that showed that a single person's genome contained information about a multitude of ancestors. "To decipher the deep history of a population from a single person's DNA, Li and Durbin leveraged the fact that any single person actually carries not one but two genomes: one from his or her father and one from his or her mother. Thus it is possible to count the number of mutations separating the genome a person receives from his or her mother and the genome the person receives from his or her father to determine when they shared a common ancestor at each location. By examining the range of dates when these ancestors lived—plotting the ages of one hundred thousand Adams and Eves—Li and Durbin established the size of the ancestral population at different times. In a small population, there is a substantial chance that two randomly chosen genome sequences derive from the same parent genome sequence, because the individuals who carry them share a parent. However, in a large population the chance is far lower. Thus,

the times in the past when the population size was low can be identified based on the periods in the past when a disproportionate fraction of lineages have evidence of sharing common ancestors." This demonstrated "… that a whole population history is contained within a single person as revealed by the multitude of ancestors whose histories are recorded within that person's genome."

An unanticipated finding of this study: "… evidence that after the separation of non-African and African populations, there was an extended period in the shared history of non-Africans when **populations were small**, as reflected in evidence for many shared ancestors spread over tens of thousands of years." This is a phenomenon known as a population "bottleneck event… when a small number of ancestors gave rise to a large number of descendants today…"

"… prior to Li and Durbin's work, there was no good information about the duration of this event, and it seemed plausible that it could have transpired over just a few generations—for example, a small band of people crossing the Sahara into North Africa, or from Africa into Asia. The Li and Durbin evidence of an **extended period** of small population size was also hard to square with the idea of an unstoppable expansion of modern humans both within and outside Africa around fifty thousand years ago. Our history may not be as simple as the story of a dominant group that was immediately successful wherever it went."

How the Whole-Genome Perspective Put an End to Simple Explanations

Reich continues to argue against the idea of a "genetic switch."

"The newfound ability to take a **whole-genome view** of human biology… has allowed reconstruction of population history in far more detail than had been previously possible. In doing so it revealed that the simple picture from mitochondrial DNA, and the **just-so stories** about one or a few changes propelling the Later Stone Age and Upper Paleolithic transitions when recognizably modern human behavior became widespread as reflected in archaeological sites across Africa and Eurasia, are no longer tenable."

As evidence for this claim, he cites the ancestry of the "… San hunter-gatherers of southern Africa." Adapting the Li and Durbin methodology, Reich and colleagues found that the separation of the San lineage from other modern human lineages "… had begun by **around two hundred thousand years ago** and was mostly complete by more than one hundred thousand years ago. The evidence for this is that the density of mutations separating San genomes from non-San genomes is uniformly high, implying few shared ancestors between San and non-San in the last hundred thousand years." Thus: "The extremely **ancient isolation** of some pairs of human populations from each other conflicts with the idea that a single mutation essential to distinctively modern human behavior occurred shortly before the Upper Paleolithic and Later Stone Age. A key change essential to modern human behavior in this time frame would be expected to be at high frequency in some human populations today—those that descend from the population in which the mutation occurred—and absent or very rare in others. But this seems hard to reconcile with the fact that all people today are capable of mastering conceptual language and innovating their culture in a way that is a hallmark of modern humans."

Reich goes on: "A second problem with the notion of a genetic switch became apparent when we applied the Li and Durbin method to search for places where all the genomes we analyzed shared a common ancestor in the period before the Upper Paleolithic and Later Stone Age. At FOXP2—the gene that seemed the best candidate for a switch based on previous studies—we

found that the common ancestor of everyone living today (that is, the person in whom modern humanity's shared copy of FOXP2 last occurred), lived more than **one million years ago.**"

"Expanding our analysis to the whole genome, we could not find any location—apart from mitochondrial DNA and the Y chromosome—where all people living today share a common ancestor less than about 320,000 years ago. This is a far longer time scale than the one required by Klein's hypothesis. If Klein was right, it would be expected that there would be places in the genome, beyond mitochondrial DNA and the Y chromosome, where almost everyone shares a common ancestor within the last hundred thousand years. But t**hese do not in fact seem to exist.**"

While not ruling out the hypothesis of a single critical genetic change, Reich still believes that "… If we are going to try to search the genome for clues to what makes modern humans distinctive, it is likely that we cannot look to explanations involving one or a few changes."

Reich goes on: "The whole-genome approaches that became possible after the technological revolution of the 2000s also soon made it clear that **natural selection** was not likely to take the simple form of changes in a small number of genes, as Klein had imagined." Working with whole-genome datasets, researches began looking for mutations affected by natural selection; they were looking for "… low-hanging fruit - instances in which natural selection had operated strongly on a few mutations…", such as "mutations allowing people to digest cow's milk into adulthood…. As a community, we have been successful in identifying selection on mutations like these because they have risen rapidly from low to high frequency, resulting in a large number of people today sharing a recent ancestor or striking differences in mutation frequency between two otherwise similar populations. Events like these leave great scars on patterns of genome variation that can be detected without too much trouble."

He notes that excitement over this early success was tempered by "… work led by Molly Przeworski, who studied the types of patterns that natural selection is likely to leave on the genome as a whole. A 2006 study… showed that genome scans of present-day human genetic variation will miss most instances of natural selection because they simply will not have the **statistical power** needed to detect it, and that scans of this type will also have more power to detect some types of selection than others. A study she led in 2011 then showed that only a small fraction of evolution in humans has likely involved intense natural selection for advantageous mutations that had not previously been present in the population. Thus, intense and easily detectable episodes of natural selection such as those that have facilitated the digestion of cow's milk into adulthood are an exception."

Reich asks: "So what has been the dominant mode of natural selection in humans if not selection on newly arising single mutation changes that then rocket up to high frequency? An important clue comes from the study of height. In 2010, medical geneticists analyzed the genomes of around 180,000 people with measured heights, and found **180 independent genetic changes** that are more common in shorter people." After noting "…that at the 180 changes, southern Europeans tend to have the versions that reduce height…", and that natural selection is the only possible explanation for this phenomenon, Reich describes a further study: "In 2015, an ancient DNA study led by Iain Mathieson in my laboratory revealed more about this process. We assembled DNA data from the bones and teeth of 230 ancient Europeans and analyzed the data to suggest that these patterns reflected natural selection for mutations that decreased height in farmers in southern Europe after eight thousand years ago, or increased height in ancestors of northern Europeans who lived in the eastern European steppe lands before five thousand years ago. The advantages that accrued to shorter people in southern Europe, or to taller people in far eastern Europe, must have increased the number of

their surviving children, which had the effect of systematically changing the frequencies of these mutations until a new average height was achieved."

Reich notes that there have been many successful studies of the effect of natural selection on complex human traits since the one on height. "These examples demonstrate that by leveraging the power of the whole genome to examine **thousands of independent positions** in the genome simultaneously, it is possible to get beyond the barrier that Molly Przeworski had identified—"Przeworski's Limit"—by taking advantage of information that we now have about a **large number of genetic variations at many locations** in the genome that have similar biological effects." After noting both the value and contentiousness of "genome-wide association studies", he observes that "… what is often overlooked is that genome-wide association studies have provided a powerful resource for investigating human evolutionary change over time. By testing whether the mutations identified by genome-wide association studies as affecting particular biological traits have all tended to shift in frequency in the same direction, we can obtain evidence of natural selection for specific biological traits."

Reich next circles back to the "genetic switch" concept: "As genome-wide association studies proceed, they are beginning to investigate human variation in cognitive and behavioral traits, and studies like these—such as the ones for height—will make it possible to explore whether the shift to behavioral modernity among our ancestors was driven by natural selection. This means that there is new hope for providing genetic insight into the mystery that puzzled Klein—the great change in human behavior suggested by the archaeological records of the Upper Paleolithic and Later Stone Age."

Nevertheless, "… even if genetic changes—through coordinated natural selection on combinations of many mutations simultaneously—did enable new cognitive capacities, this is a very different scenario from Klein's idea of a **genetic switch**. Genetic changes in this scenario are not a creative force abruptly enabling modern human behavior, but instead are **responsive to nongenetic pressures imposed from the outside….** Thus, even if it is true that increases in the frequency of mutations were important in allowing modern humans to match their biology to new conditions during the Upper Paleolithic and Later Stone Age transition, what we now know about the nature of natural selection in humans and about the genetic encoding of many biological traits means it is unlikely that the first occurrence of these mutations triggered the great changes that followed. If we search for answers in a small number of mutations that arose shortly before the time of the Upper Paleolithic and Later Stone Age transitions, we are unlikely to find satisfying explanations of who we are."

How the Genome Can Explain Who We Are

Reich concludes: "It is in the area of shedding light on human migrations—rather than in explaining human biology—that the genome revolution has already been a runaway success. In the last few years, the genome revolution—turbocharged by ancient DNA—has revealed that human populations are related to each other in ways that no one expected. The story that is emerging differs from the one we learned as children, or from popular culture. It is full of surprises: massive mixtures of differentiated populations; sweeping population replacements and expansions; and population divisions in prehistoric times that did not fall along the same lines as population differences that exist today. It is a story about how our interconnected human family was formed, in myriad ways never imagined."