Inferring Human Demographic History from Genetic Data

8

Jeffrey D. Wall

Abstract

Genetics and archeology are two fields that provide complementary sources of information on our history as a species. We review what has been learned about human population history from recent genetic studies, including studies of geographic structure, population bottlenecks, and recent population growth. We also describe recent studies that highlight the importance of admixture in human history, from the mixing of different continental populations in the Americas over the past several centuries to ancient admixture between humans and Neanderthals tens of thousands of years ago.

8.1 Introduction

Making inferences about human demographic history has been one of the primary goals of human evolutionary studies for decades. Here demography refers to the history of population relationships, migrations, admixture, and changes in population size if we trace our ancestors back in time over the past 1–2 million years. Archeology and physical anthropology have contributed tremendously to our understanding of past demographic events (e.g., Jones et al. 1994), and the basic outlines of our history are well established. The genus *Homo* first arose in Africa roughly 2–2.5 million years ago, representing ancestors that were bipedal, used tools, and had brain sizes substantially larger than those of chimpanzees. Some of these early hominins then migrated to parts of tropical and temperate Eurasia 1.5–2.0 million years ago, followed by a later migration into southern Europe. More

J. D. Wall (✉)
Institute for Human Genetics, University of California, San Francisco, CA, USA
e-mail: jeff.wall@ucsf.edu

K. E. Lohmueller, R. Nielsen (eds.), *Human Population Genomics*,
https://doi.org/10.1007/978-3-030-61646-5_8

recently, anatomically modern humans first appear in the fossil record 150–200 thousand years ago (Kya) in Eastern and Southern Africa. Modern humans then spread across the rest of the inhabitable world, mostly replacing (but with low levels of hybridization and admixture) the indigenous hominin groups that they encountered. Within this broad outline though, there are many specific details that have yet to be worked out.

In this review, we will focus on what we have learned from genetic data over the past 50 years. Roughly speaking, genetic similarity can be used as a proxy for relatedness—the more similar two sequences are, the more likely they are to share a recent common ancestor. By examining DNA sequences from many individuals at once and by developing computational and statistical models for what these sequences should look like under different scenarios, we can begin to piece together aspects of our species' history in ways that other approaches cannot. This review highlights some of the insights that have come from the study of human genetic data. It is not meant to be comprehensive, but rather a personal opinion on the most important discoveries over the past several decades.

8.2 Human Population Structure

The first large-scale studies of human genetic variation involved classical markers such as blood groups and allozyme polymorphisms (e.g., Brues 1954; Edwards and Cavalli-Sforza 1964). These studies showed that the vast majority of genetic variation (~85–95%) is shared among different populations, while a much smaller fraction differentiates populations (reviewed in Cavalli-Sforza et al. 1994). Subsequent studies of microsatellite, genotype, and resequencing data (e.g., Rosenberg et al. 2002; International HapMap Consortium 2005, 2007, 2010; Wall et al. 2008; 1000 Genomes Project Consortium 2010, 2012, 2015; GenomeAsia 100K Consortium 2019) have found similar levels of population structure between human populations (as measured by F_{ST}). These results have been interpreted as human populations being much more (genetically) similar to each other than different from each other, and we now know that the level of population structure in humans is similar to what is found in many other species. At the time these results formed an important counterweight to the "candelabra model" of Coon (1962), which posited that different continental groups had been mostly isolated for hundreds of thousands of years and which was used to justify segregationist policies in the United States (Jackson 2001).

Despite the overall similarity of different human groups at specific genetic markers, the small differences at many markers in aggregate can be used to accurately distinguish between different human populations (e.g., Pritchard et al. 2000; Patterson et al. 2006). For example, Rosenberg et al. (2002) showed that 377 microsatellite markers were sufficient to distinguish individuals from the major continental groups, such as sub-Saharan Africans, Europeans, Asians, Melanesians, and Native Americans. In addition, for recently admixed individuals, these methods can estimate the proportion of ancestry that comes from multiple ancestral groups

(Pritchard et al. 2000; Falush et al. 2003). When more markers are available, such as from standard SNP genotyping chips or whole-genome sequence data, individuals from closely related populations (e.g., French vs. Spanish, Chinese vs. Japanese) can be distinguished from one another (e.g., Patterson et al. 2006; Jakobsson et al. 2008; Novembre et al. 2008; Tishkoff et al. 2009; Lu and Xu 2013; GenomeAsia 100K Consortium 2019).

The methods and studies described above made no a priori assumptions about the makeup of different human populations. For recently admixed individuals (e.g., African–Americans), more powerful methods can identify the precise portions of their genome that were inherited from different ancestral populations, provided that individuals from each of the ancestral populations have been genotyped (e.g., Sankararaman et al. 2008; Price et al. 2009; Bryc et al. 2010; Wall et al. 2011; Baran et al. 2012). These studies have confirmed the heterogenous nature of Latinos and African–Americans—for example, the estimated proportion of European ancestry in a sample of 181 Mexican controls varied from ~0% to ~100% (Fig. 8.1, Choudhry et al. 2006). In addition, detailed admixture studies have uncovered surprising examples of admixture over the past several thousand years, including low (<5%) levels of West African ancestry in Southern Europeans (Moorjani et al. 2011),

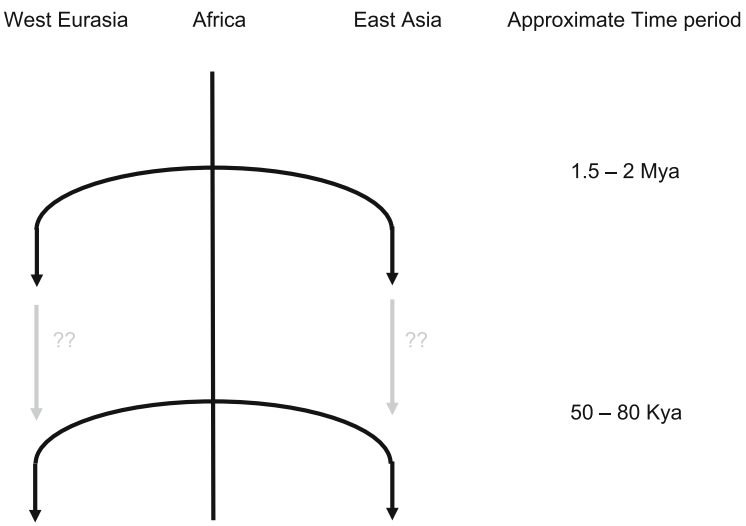

Fig. 8.1 Simplified schematic describing the qualitative differences between historical models of modern human origins. Hominins first evolve in Africa and later colonize temperate Eurasia roughly 1.5 – 2 million years ago. Much later, modern humans evolved in Africa 150–200 thousand years ago and then spread to the rest of the world starting 50–80 thousand years ago. Models differ in the amount of genetic contribution extinct hominins in Eurasia made to the contemporary gene pool. The recent African origin and replacement model predicts that this contribution was negligible, and the recent African origin and hybridization model predicts a small contribution, while the multiregional model predicts that the archaic human contribution was large

substantial Khoesan ancestry in South African Bantu speakers (Henn et al. 2011), and substantial non-African ancestry in the East African Maasai (Wall et al. 2013).

8.3 Effective Population Size

The current human population size is in excess of seven billion and is thought to have been in the millions for all of recorded history (Tellier 2009). However, genetic sequencing studies have found that extant humans are quite similar to each other, with the average sequence divergence between two individuals around 0.1% (Li and Sadler 1991; Wall et al. 2008; 1000 Genomes Project Consortium 2010, 2012, 2015). This corresponds to an effective population size (i.e., time-averaged number of breeding adults) of around 20,000–25,000, which is vastly less than our estimates of the recent census size. While there are reasons why the census size might be more than the effective population size (e.g., nonrandom mating, variance in reproductive success across individuals, unequal sex ratio, natural selection, etc., cf. Caballero 1994), the magnitude of the difference is still surprising. In contrast, great ape species with geographically restricted ranges generally have effective population sizes larger than humans (Fischer et al. 2006; Prado-Martinez et al. 2013). This suggests that despite being able to colonize virtually the whole world, our species must have had a much smaller population size (and likely a more restricted geographic range) for much of its evolutionary history. Researchers have generally considered models of recent exponential population growth from a small initial population to explain the discrepancy between census and effective population size (e.g., Slatkin and Hudson 1991; Marjoram and Donnelly 1994; Gutenkunst et al. 2009; Gravel et al. 2011).

The initial analyses of genetic variation in human mitochondrial DNA (mtDNA) estimated a relatively recent time to the most recent common ancestor (TMRCA) and observed an excess of rare variants over equilibrium expectations (Cann et al. 1987; Vigilant et al. 1991). These data were then used to estimate a time of onset of recent explosive population growth of 60–120 thousand years ago (Kya; Rogers and Harpending 1992). However, mtDNA does not experience recombination so operates as a single genetic locus. As such, the observed patterns of genetic variation are sensitive to the effects of natural selection, and inferences of demographic parameters from mtDNA data are inherently untrustworthy. When comparable sequence polymorphism data was obtained from multiple nuclear regions, the skew toward rare variants was much smaller, suggesting that substantial mid-Pleistocene population growth was unlikely (Wall and Przeworski 2000; Voight et al. 2005; Gutenkunst et al. 2009). Current estimates based on resequencing data from thousands of individuals suggest that population growth started in the late Pleistocene (20–25 Kya) and that the growth rate has accelerated (i.e., super-exponential growth) in the past 5 thousand years (e.g., Coventry et al. 2010; Nelson et al. 2012; Tennessen et al. 2012; Gazave et al. 2014; Chen et al. 2015; Gao and Keinan 2016). This is consistent with the spread of agriculture (and a more steady food supply) being the primary innovation that enabled our recent explosive

population growth. We note in passing though that there are several potential confounding factors that have not yet been adequately accounted for in studies of recent population growth, including the effects of purifying and background selection on the site frequency spectrum and the effects of aggregating different populations into larger groups such as "Europeans" or "African-Americans."

8.4 Population Bottlenecks

The early analyses of human mtDNA variation assumed a founder model, whereby the TMRCA corresponded to the "founding" of a population by a few genetically similar individuals (e.g., Cann et al. 1987). This in part led to the idea that our species had undergone a drastic population bottleneck (i.e., a temporary reduction in effective population size) during the mid- to late-Pleistocene (e.g., Cann et al. 1987; Gibbons 1993). Population genetics theory, though, suggests that the specific TMRCA has very little correlation with the effective population size at that time. In particular, the recent TMRCA of mtDNA might be due to random chance or the action of natural selection. Since demographic events such as bottlenecks are expected to affect genetic variation across the whole genome, it is straightforward to analyze nuclear sequence polymorphism data to assess the strength of evidence for a species-wide bottleneck. Analyses of the HLA region, which has extremely high levels of diversity due to diversifying selection, show that the human effective population size has not dropped much below 10,000 for all of our species' history (Takahata 1993; Ayala 1995), and analyses of unlinked, putatively neutral, autosomal regions came to similar conclusions (Sjödin et al. 2012).

In contrast, there is strong evidence that at least some human populations have experienced a recent population bottleneck. Simulations suggest that population bottlenecks lead to a reduction in levels of nucleotide and haplotype diversity, an increase in levels of linkage disequilibrium (LD), and a skew in the distribution of allele frequencies (Fay and Wu 1999; Reich et al. 2001; Wall et al. 2002). Studies of microsatellite (Tishkoff et al. 1996; Rosenberg et al. 2002), single-nucleotide polymorphism (SNP, e.g., Conrad et al. 2006; Jakobsson et al. 2008), and sequence (Frisse et al. 2001; Livingston et al. 2004; Voight et al. 2005; 1000 Genomes Project 2010, 2012, 2015; Mallick et al. 2016) data consistently show that all non-African populations have less variation and more LD than all sub-Saharan African populations. The simplest explanation for this pattern is that all non-African populations have experienced at least one population bottleneck in their recent history. This is consistent with the recent African origin and replacement model of human evolution (Stringer and Andrews 1988), which posits that modern humans first evolved in sub-Saharan Africa 150–200 Kya and that modern humans later expanded and replaced (without admixture) the indigenous "archaic" humans they encountered in the rest of the world. It is also consistent with the recent African origin and hybridization model (Brauer 1989), which is identical to the previous model but allows for a limited amount of hybridization between modern and archaic humans, but not consistent with some models of modern human evolution such as

the multiregional model (Wolpoff et al. 1984), which claims that modern humans evolved from archaic humans simultaneously in Africa, Europe, and Asia (see Fig. 8.1 for a schematic of these models). Under the multiregional model, there would not be strong systematic differences in levels of LD across continents, and we would expect greater degrees of population differentiation (as measured by F_{ST}) between different human continental groups.

One potential model for explaining global patterns of human genetic variation is the serial bottleneck model (Ramachandran et al. 2005; DeGiorgio et al. 2009), which posits that non-African populations experienced a series of founder bottlenecks as they left Africa and spread across the rest of the world. Under this model, populations that are further away from the putative origin of modern humans (in Eastern or Southern Africa) have experienced more bottlenecks and are expected to have decreasing levels of variation and increasing levels of LD. Genomic data are mostly consistent with these expectations (DeGiorgio et al. 2009; 1000 Genomes Project Consortium 2010, 2012, 2015; Luca et al. 2011; Mallick et al. 2016), but a denser sampling of the world's populations is needed to more fully test this theory. If the serial bottleneck model were mostly correct, it might help explain why inferences of population history based on mtDNA are qualitatively similar to ones based on autosomal data (see also Sect. 8.6).

8.5 Sex Ratio

Human effective population sizes vary not only across time but also between males and females. In principle, this gender-specific difference can be estimated by looking at patterns of genetic diversity on the X chromosome relative to the autosomes. In a randomly mating population with equal numbers of males and females, there are 3 X chromosomes for every four autosomes, and we expect to observe a 3:4 ratio in levels of diversity in X vs. autosome comparisons. However, if the numbers of breeding females and breeding males are unequal, there will be a resulting skew in this 3:4 ratio (Caballero 1994). For example, in polygynous societies, there is greater variation in male reproductive success, since many males have no wives, while some have many. This in turn reduces the male effective population size and leads to an increased ratio of X to autosome diversity.

However, there are many other factors that can affect relative levels of diversity on sex chromosomes versus autosomes. Past changes in population size (e.g., population bottlenecks) can lead to temporary variation in the ratio of sex chromosome to autosome diversity levels (Fay and Wu 1999), while recent positive selection, which decreases levels of genetic variation due to hitchhiking effects, is expected to be more effective on the X chromosome than the autosomes. (This is because recessive advantageous mutations cannot easily spread on the autosomes but can on the X chromosome since their advantageous effect is unmasked in males.) Analyses of human polymorphism data show the effects of both of these evolutionary processes (Hammer et al. 2008, 2010; Keinan et al. 2009; Arbiza et al. 2014). Overall, the ratio of X to autosome diversity increases with increasing distance from genes, consistent

with greater hitchhiking effects on the X chromosome. This result is also apparent from linkage-disequilibrium-based estimates of X and autosome population sizes (Lohmueller et al. 2010). In addition, systematic differences between continental groups are likely the result of shared demographic processes such as a population bottleneck associated with the exodus of modern humans out of Africa (Arbiza et al. 2014). In summary, while it is tempting to speculate on the relative prevalence of polygyny vs. polyandry across human history, it is extremely difficult to separate out the effects of other population processes that differentially affect autosomal and sex-linked levels of diversity.

8.6 Estimating Demographic Parameters

Recently, researchers have started to develop computational and statistical methods for jointly estimating multiple demographic parameters (e.g., split times and migration rates) from DNA sequence data. Generally, these methods must navigate a tradeoff between statistical rigor and biological realism, since the statistically "optimal" approach of full maximum likelihood on autosomal sequence data from multiple individuals is computationally infeasible for the foreseeable future. Below, some of the basic approaches researchers have used are outlined, as well as some recent applications to human data.

The major computational burden of inference methods comes from the modeling of intragenic recombination. One way of reducing the computational burden is to assume a model with no recombination (e.g., Nielsen and Wakeley 2001; Drummond and Rambaut 2007; Gronau et al. 2011) and to apply this model to mtDNA data, data from short autosomal regions without visible evidence of recombination, or single diploid genome sequences. While the no-recombination assumption reduces the usefulness of these methods, this is partially counteracted by the ability to employ full-likelihood techniques (generally using Bayesian Markov chain Monte Carlo algorithms) to efficiently utilize the information contained in the data. For example, Gignoux and colleagues used a large mtDNA sequence data set to infer the rates of recent population growth in different human populations (Gignoux et al. 2011). Their results suggest that most of the population growth happened within the past 8000 years, consistent with recent analyses of autosomal sequence data (described above in Sect. 8.3).

Researchers have also tried the opposite tactic of assuming free recombination between all sites (Nielsen 2000; Marth et al. 2004; Garrigan 2009; Gutenkunst et al. 2009; Nielsen et al. 2009; Kamm et al. 2017, 2019). Under this assumption, sequence data can be summarized by the site frequency spectrum (SFS, the distribution of the number of SNPs with different allele frequencies), and the expected relative values for the SFS can be calculated computationally or analytically for complex demographic models (e.g., Garrigan 2009; Gutenkunst et al. 2009; Bhaskar et al. 2015; Kamm et al. 2017, 2019). These methods have the benefit of being able to handle genome-wide polymorphism data in a computationally efficient manner but at the cost of making a biologically unrealistic assumption and ignoring an

Table 8.1 Comparison of demographic estimates (with confidence intervals in parentheses) from Gutenkunst et al. (2009), Gravel et al. (2011), Malaspinas et al. (2016), and Steinrücken et al. (2019)

Parameter	Gutenkunst	Gravel	Malaspinas	Steinrücken
$T_{EU\text{-}AS}$	21.2 (17.2–26.5)	23 (21–27)	42 (29–55)	54 (52–55)
$T_{EU\text{-}AF}$	140 (40–270)	51 (45–69)	127 (83–171)	NA
$m_{EU\text{-}AS}$	9.6 (2.3–17.4)	3.1 (1.8–3.9)	2.2–3.6 (1.4–6.5)	NA
$T_{PAP\text{-}AS}$	NA	NA	58 (51–72)	113 (110–115)

Here $T_{EU\text{-}AS}$ refers to the split time between European and East Asian populations, $T_{EU\text{-}AF}$ refers to the split time between European and West African populations, $m_{EU\text{-}AS}$ refers to the migration rate ($\times 10^{-5}$) between European and East Asian populations, and $T_{PAP\text{-}AS}$ refers to the split time between Papuan and East Asian populations. NA refers to parameters that were not calculated. Note that Steinrücken have a different parameterization for gene flow between European and East Asian populations which is not directly comparable to the migration rates of the other studies

important component of the data (LD). Application of these methods to human data have generally focused on the demographic history of continental European, East Asian, and West African populations (e.g., Gutenkunst et al. 2009; Gravel et al. 2011; Malaspinas et al. 2016) and occasionally between European, East Asian, and Melanesian populations (Malaspinas et al. 2016; Steinrücken et al. 2019). The parameter estimates obtained by these methods can vary substantially (Table 8.1), but are not directly comparable to each other due to varying demographic and model assumptions. It is also unclear whether dates from ancient DNA studies (e.g., Fu et al. 2013) are consistent with some of the more recent estimates.

Other approaches, which can make more realistic assumptions about intragenic recombination, replace the data with one or more summary statistics in order to achieve computational tractability. These methods then use approximate Bayesian computation (e.g., Patin et al. 2009) or composite likelihood (Voight et al. 2005; Wall et al. 2009) methodology to estimate demographic parameters. Approximate likelihood methods are appealing because, unlike the previously described approaches, they have the potential to exploit the information contained in LD to help estimate demographic parameters. However, there are two main drawbacks that might limit their wider use. First, it is not easy to choose summaries of the data that are both easy to calculate and informative about demographic history. Second, these methods are all extremely computationally intensive, and they are currently unable to handle the analyses of large-scale (e.g., genome-wide) data sets without access to powerful (e.g., hundreds of nodes) computer clusters.

One final promising approach, the pairwise sequentially Markovian coalescent (PSMC) developed by Li and Durbin (2011), uses single diploid genome sequences to estimate the trajectory of past population sizes over time. Population genetics theory predicts that the distribution of coalescent times (i.e., the distribution of times until the two copies of a diploid sequence share a common ancestor) depends directly on the effective population size (both past and present) from which the sample was drawn. While coalescent times cannot be directly observed, they can be estimated using the sequence divergence between two haploid sequences—older

coalescent times generally lead to greater divergence between sequences. Li and Durbin (2011) use a hidden Markov model to estimate the coalescent times between two haploid sequences sequentially across the genome (the times vary across the genome because of recombination). The distribution of times is then used to estimate the trajectory of past population sizes in the history of the population containing the sample. While currently limited to analyses of a single genome, the PSMC provides a novel way of utilizing genome-wide data to make inferences about human history, and the results so far are consistent with previous findings of a population bottleneck in non-Africans and recent growth in all populations (Li and Durbin 2011). More recent work has used the sequentially Markovian assumption in other theoretical frameworks, allowing for the analyses of larger sample sizes and population splits (Sheehan et al. 2013; Schiffels and Durbin 2014; Terhorst et al. 2017; Steinrücken et al. 2019).

8.7 Ancient Admixture

After modern humans evolved in Africa 150–200 Kya, they quickly expanded to colonize the rest of the inhabitable world. As they did, they encountered other hominin groups that already occupied the rest of Africa and Eurasia. These other groups, often called "archaic" humans, included Neanderthals, Denisovans and *Homo erectus* in Eurasia, *H. floresiensis* in island Southeast Asia, and several unnamed groups within sub-Saharan Africa (Klein 2000; Trinkaus 2005; Rightmire 2009). The extent to which the expanding modern humans interacted and interbred with the various archaic human groups is still unclear, though some interbreeding must have occurred (see below). We first discuss how ancient DNA from archaic hominins has changed our perspective on this issue. Then we describe other indirect methods for inferring the existence of ancient admixture.

Direct Evidence for Ancient Admixture The isolation and sequencing of a portion of the mtDNA hypervariable region from the Neanderthal-type specimen opened up a new avenue of research for human evolutionary studies (Krings et al. 1997). Subsequent work has generated whole mtDNA sequences from several Neanderthals (Briggs et al. 2009) and a putative *H. heidelbergensis* individual (Meyer et al. 2014), low-coverage draft genomes from a Neanderthal (Green et al. 2010) and a Denisovan (Reich et al. 2010), and high-coverage genomes from a Denisovan (Meyer et al. 2012) and two Neanderthals (Prüfer et al. 2014, 2017). Denisovans were a group of archaic humans whose only remains have been found in a single cave in Southern Siberia. They are known almost exclusively from their DNA, with very little morphological information available from the limited fossil remains that have been found (Bennett et al. 2019; Viola et al. 2019). Analyses of the Denisovan genome have shown that they are distant cousins of Neanderthals (Reich et al. 2010).

Studies of Neanderthal mtDNA found that the Neanderthal sequence was outside of the range of normal human variation, suggesting that any Neanderthal contribution to the modern human gene pool was limited (Krings et al. 1997; Serre

et al. 2004). However, an analysis of the initial draft Neanderthal genome showed that Neanderthals were more closely related to all non-African populations than to sub-Saharan African populations (Green et al. 2010). The most likely explanation for this is that Neanderthals and the ancestors of non-African populations interbred and exchanged genes, perhaps in the Middle East 60–90 Kya (Sankararaman et al. 2012), leading to greater genetic similarity. This result was initially surprising, since researchers initially assumed that any interbreeding between Neanderthals and modern humans would have occurred in Europe 30–40 Kya. Instead, more detailed analyses show that East Asian individuals tend to have greater Neanderthal ancestry than do European ones (e.g., Wall et al. 2013). While this could be due to weaker purifying selection in East Asian populations (Sankararaman et al. 2014), it more likely reflects a separate Neanderthal admixture event after the initial divergence of European and East Asian populations or a recent dilution of Neanderthal ancestry in the ancestors of European populations (Kim and Lohmueller 2015; Vernot and Akey 2015). Thus far, a separate Neanderthal admixture event seems more likely (see, e.g., Villanea and Schraiber 2019).

Similar studies using the draft Denisovan genome also turned up a surprising result—aboriginal Australians, Melanesians, and Philippine Negrito groups derived 4–5% of their genome from Denisovans, whereas all other human populations tested showed much smaller levels of Denisovan ancestry (e.g., Reich et al. 2010, 2011; Sankararaman et al. 2016; Vernot et al. 2016; GenomeAsia 100K Consortium 2019). This strongly suggests that the colonization of Melanesia involved a separate migration out of Africa than did the colonization of mainland Eurasia, perhaps along the Southern coast of Asia (the "Southern route" hypothesis, reviewed by Oppenheimer 2009). If so, the historical range of the Denisovans must have stretched far south of the Siberian cave where the fossil remains were found. There is also growing evidence for multiple separate Denisovan admixture events in East and Southeast Asia (Browning et al. 2018; GenomeAsia 100K Consortium 2019; Jacobs et al. 2019).

Indirect Evidence for Ancient Admixture While the direct comparison between modern human DNA and archaic human DNA described above has been extremely informative, it has been limited by the scarcity of archaic human fossils with sufficient amounts of ancient DNA. Other, indirect methods are needed to detect potential ancient admixture between modern humans and other archaic human groups in East Asia and Africa. These methods rely on the observation that ancient admixture, if it occurred, will leave large, discrete chunks of introgressed sequence that are substantially different from orthologous modern human sequences. These chunks can then be detected by searching for unusual patterns of LD (e.g., Wall 2000; Plagnol and Wall 2006; Wall et al. 2009), in an analogous way to how local ancestry is estimated across the genomes of recently admixed individuals (e.g., Price et al. 2009; Baran et al. 2012). Analyses of human polymorphism data have found evidence for ancient admixture in sub-Saharan African populations (Garrigan et al. 2005; Hayakawa et al. 2006; Wall et al. 2009; Hammer et al. 2011; Lachance et al. 2012; Hsieh et al. 2016; Durvasula and Sankararaman 2020; Wall et al. 2019),

though quantifying the amount or the timing of admixture depends on specific assumptions about modern human population structure. Taken at face value, these studies suggest that admixture between modern and archaic humans may have been a relatively common occurrence, involving Neanderthals, Denisovans, and one or more archaic human groups (in sub-Saharan Africa) for which no ancient DNA samples are currently available.

8.8 Other Ancient DNA Studies

The previous section describes what insight has been gained from studies of admixture between modern and archaic human groups. Ancient DNA studies involving only modern human samples have also been very informative about human demographic history. In particular, a comparison between an ancient DNA sample and modern human sequences can provide information on genetic affinities between the population that the ancient sample comes from and extant human groups. For example, Rasmussen et al. (2010) generated a high-coverage whole-genome sequence from a 4000-year-old hair sample from Greenland and found that the genome sequence obtained was most similar to sequences from extant Siberian populations. They concluded that the population from which the hair sample came represented a separate migration than the one that gave rise to modern Native Americans and Inuit. In another example, Rasmussen et al. (2011) sequenced a 100-year-old hair sample from an aboriginal Australian; their analyses provided additional support for the early (>50 Kya) colonization of Melanesia and the Southern route hypothesis. Other studies have also elucidated the recent movements and population affinities of groups across Eurasia (e.g., Lipson et al. 2018; McColl et al. 2018; Harney et al. 2019; Narasimhan et al. 2019; Shinde et al. 2019).

Finally, ancient DNA studies have helped to understand the relationship between Neolithic farmers in Europe and contemporary European Paleolithic hunter-gatherers roughly 6–10 Kya. Specifically, a long-standing debate has centered on the extent to which the Neolithic transition was cultural, with populations adopting farming technologies from their neighbors, versus demic, with farming populations replacing nonfarmers. So far, most of the early ancient DNA studies have suggested that demic diffusion was predominant (e.g., Bramanti et al. 2009; Malmstrom et al. 2009; Haak et al. 2010; Skoglund et al. 2012; but see Sampietro et al. 2007). Later studies have been able to quantify the relative contributions of various ancestral European groups, including ones that were previously unknown, and have highlighted the enormous complexity in European demographic history over the past ~40,000 years (e.g., Lazaridis et al. 2014; Seguin-Orlando et al. 2014; Jones et al. 2015; Lipson et al. 2017).

8.9 Conclusion

With more than 100,000 modern human genome sequences publicly available and several hundred thousand more genome sequences already generated but not yet public, we are entering a time when the amount of (modern human) genetic data available for demographic inference is essentially unlimited. The computational, statistical, and theoretical methods for dealing with these vast amounts of data are still limited though, and we anticipate that advances on the methodological front will lead to new insights into human demographic history in the coming decade. Since human fossils are rare and appreciable amounts of ancient DNA from fossils rarer still, it is difficult to predict what influence future ancient DNA studies will have on human evolutionary studies. However, based on the results of the past few years, it is safe to assume that occasional future fossil finds (with sufficient amounts of endogenous DNA) will have a major influence on our understanding of human history.

References

1000 Genomes Project Consortium (2010) A map of human genome variation from population-scale sequencing. Nature 467:1061–1073

1000 Genomes Project Consortium (2012) An integrated map of genetic variation from 1,092 human genomes. Nature 491:56–65

1000 Genomes Project Consortium (2015) A global reference for human genetic variation. Nature 526:68–74

Arbiza L, Gottipati S, Siepel A, Keinan A (2014) Contrasting X-linked and autosomal diversity across 14 human populations. Am J Hum Genet 94:827–844

Ayala FJ (1995) The myth of Eve: molecular biology and human origins. Science 270:1930–1936

Baran Y, Pasaniuc B, Sankararaman S, Torgerson DG, Gignoux C, Eng C, Rodriguez-Cintron W, Chapela R, Ford JG, Avila PC et al (2012) Fast and accurate inference of local ancestry in Latino populations. Bioinformatics 28:1359–1367

Bennett EA, Crevecoeur I, Viola B, Derevianko AP, Shunkov MV, Grange T, Maureille B, Geigl EM (2019) Morphology of the Denisovan phalanx closer to modern humans than to Neanderthals. Sci Adv 5:eaaw3950

Bhaskar A, Wang YXR, Song YS (2015) Efficient inference of population size histories and locus-specific mutation rates from large-sample genomic variation data. Genome Res 25:268–279

Bramanti B, Thomas MG, Haak W, Unterlaender M, Jores P, Tambets K, Antanaitis-Jacobs I, Haidle MN, Jankauskas R, Kind CJ et al (2009) Genetic discontinuity between local hunter-gatherers and central Europe's first farmers. Science 326:137–140

Brauer G (1989) The evolution of modern humans: a comparison of the African and non-African evidence. In: Mellars P, Stringer C (eds) The human revolution: behavioural and biological perspectives on the origins of modern humans. Edinburgh University Press, Edinburgh, pp 123–154

Briggs AW, Good JM, Green RE, Krause J, Maricic T, Stenzel U, Lalueza-Fox C, Rudan P, Brajkovic D, Kucan Z et al (2009) Targeted retrieval and analysis of five Neandertal mtDNA genomes. Science 325(5938):318–321

Browning SR, Browning BL, Zhou Y, Tucci S, Akey JM (2018) Analysis of human sequence data reveals two pulses of archaic Denisovan admixture. Cell 173:53–61

Brues AM (1954) Selection and polymorphism in the A-B-O blood groups. Am J Phys Anthropol 12:559–597

Bryc K, Auton A, Nelson MR, Oksenberg JR, Hauser SL, Williams S, Froment A, Bodo JM, Wambebe C, Tishkoff SA et al (2010) Genome-wide patterns of population structure and admixture in West Africans and African Americans. Proc Natl Acad Sci USA 107:786–791

Caballero A (1994) Developments in the prediction of effective population size. Heredity 73:657–679

Cann RL, Stoneking M, Wilson AC (1987) Mitochondrial DNA and human evolution. Nature 325:31–36

Cavalli-Sforza LL, Menozzi P, Piazza A (1994) The history and geography of human genes. Princeton University Press, Princeton, NJ

Chen H, Hey J, Chen K (2015) Inferring very recent population growth rate from population-scale sequencing data: using a large-sample coalescent estimator. Mol Biol Evol 32:2996–3011

Choudhry S, Coyle NE, Tang H, Salari K, Lind D, Clark SL, Tsai HJ, Naqvi M, Phong A, Ung N et al (2006) Population stratification confounds genetic association studies among Latinos. Hum Genet 118:652–664

Conrad DF, Jakobsson M, Coop G, Wen X, Wall JD, Rosenberg NA, Pritchard JK (2006) A worldwide survey of haplotype variation and linkage disequilibrium in the human genome. Nat Genet 38:1251–1260

Coon CS (1962) The origins of races. Alfred A. Knopf, New York

Coventry A, Bull-Otterson LM, Liu X, Clark AG, Maxwell TJ, Crosby J, Hixson JE, Rea TJ, Muzny DM, Lewis LR et al (2010) Deep resequencing reveals excess rare recent variants consistent with explosive population growth. Nat Commun 1:131

DeGiorgio M, Jakobsson M, Rosenberg NA (2009) Out of Africa: modern human origins special feature: explaining worldwide patterns of human genetic variation using a coalescent-based serial founder model of migration outward from Africa. Proc Natl Acad Sci USA 106:16057–16062

Drummond AJ, Rambaut A (2007) BEAST: Bayesian evolutionary analysis by sampling trees. BMC Evol Biol 7:214

Durvasula A, Sankararaman S (2020) Recovering signals of ghost archaic introgression in African populations. Sci Adv 6(7):eaax5097. https://doi.org/10.1126/sciadv.aax5097

Edwards AWF, Cavalli-Sforza LL (1964) Reconstruction of evolutionary trees. In: Heywood VH, McNeill J (eds) Phenetic and phylogenetic classification (systematics association pub. #6). London, pp 67–76

Falush D, Stephens M, Pritchard JK (2003) Inference of population structure using multilocus genotype data: linked loci and correlated allele frequencies. Genetics 164:1567–1587

Fay JC, Wu CI (1999) A human population bottleneck can account for the discordance between patterns of mitochondrial versus nuclear DNA variation. Mol Biol Evol 16:1003–1005

Fischer A, Pollack J, Thalmann O, Nickel B, Paabo S (2006) Demographic history and genetic differentiation in apes. Curr Biol 16:1133–1138

Frisse L, Hudson RR, Bartoszewicz A, Wall JD, Donfack J, Di Rienzo A (2001) Gene conversion and different population histories may explain the contrast between polymorphsim and linkage disequilibrium levels. Am J Hum Genet 69:831–843

Fu Q, Meyer M, Gao X, Stenzel U, Burbano HA, Kelso J, Paabo S (2013) DNA analysis of an early modern human from Tianyuan cave, China. Proc Natl Acad Sci USA 110:2223–2227

Gao F, Keinan A (2016) Inference of super-exponential human population growth via efficient computation of the site frequency spectrum for generalized models. Genetics 202:235–245

Garrigan D (2009) Composite likelihood estimation of demographic parameters. BMC Genet 10:72

Garrigan D, Mobasher Z, Severson T, Wilder JA, Hammer MF (2005) Evidence for archaic Asian ancestry on the human X chromosome. Mol Biol Evol 22:189–192

Gazave E, Ma L, Chang D, Coventry A, Gao F, Muzny D, Boerwinkle E, Gibbs RA, Sing CF, Clark AG et al (2014) Neutral genomic regions refine models of recent rapid human population growth. Proc Natl Acad Sci USA 111:757–762

GenomeAsia100K Consortium (2019) The GenomeAsia 100K project enables genetic discoveries across Asia. Nature 576:106–111

Gibbons A (1993) Pleistocene population explosions. Science 262:27–28

Gignoux CR, Henn BM, Mountain JL (2011) Rapid, global demographic expansions after the origins of agriculture. Proc Natl Acad Sci USA 108:6044–6049
Gravel S, Henn BM, Gutenkunst RN, Indap AR, Marth GT, Clark AG, Yu F, Gibbs RA, 1000 Genomes Project, Bustamante CD (2011) Demographic history and rare allele sharing among human populations. Proc Natl Acad Sci USA 108:11983–11988
Green RE, Krause J, Briggs AW, Maricic T, Stenzel U, Kircher M, Patterson N, Li H, Zhai W, Fritz MHY et al (2010) A draft sequence of the Neandertal genome. Science 328:710–722
Gronau I, Hubisz MJ, Gulko B, Danko CG, Siepel A (2011) Bayesian inference of ancient human demography from individual genome sequences. Nat Genet 43:1031–1034
Gutenkunst RN, Hernandez RD, Williamson SH, Bustamante CD (2009) Inferring the joint demographic history of multiple populations from multidimensional SNP frequency data. PLoS Genet 5:e1000695
Haak W, Balanovsky O, Sanchez JJ, Koshel S, Zaporozhchenko V, Adler CJ, Der Sarkissian CS, Brandt G, Schwarz C, Nicklisch N et al (2010) Ancient DNA from European early neolithic farmers reveals their near eastern affinities. PLoS Biol 8:e1000536
Hammer MF, Mendez FL, Cox MP, Woerner AE, Wall JD (2008) Sex-biased evolutionary forces shape genomic patterns of human diversity. PLoS Genet 4:e1000202
Hammer MF, Woerner AE, Mendez FL, Watkins JC, Cox MP, Wall JD (2010) The ratio of human X chromosome to autosome diversity is positively correlated with genetic distance from genes. Nat Genet 42:830–831
Hammer MF, Woerner AE, Mendez FL, Watkins JD, Wall JD (2011) Genetic evidence for archaic admixture in Africa. Proc Natl Acad Sci USA 108:15123–15128
Harney E, Nayak A, Patterson N, Joglekar P, Mushrif-Tripathy V et al (2019) Ancient DNA from the skeletons of Roopkund Lake reveals Mediterranean migrants in India. Nat Commun 10:3670
Hayakawa T, Aki I, Varki A, Satta Y, Takahata N (2006) Fixation of the human-specific CMP-N-Acetylneuraminic acid hydroxylase pseudogene and implications of haplotype diversity for human evolution. Genetics 172:1139–1146
Henn BM, Gignoux CR, Jobin M, Granka JM, Macpherson JM, Kidd JM, Rodriguez-Botigue L, Ramachandran S, Hon L, Brisbin A et al (2011) Hunter-gatherer genomic diversity suggests a southern African origin for modern humans. Proc Natl Acad Sci USA 108:5154–5162
Hsieh P, Woerner AE, Wall JD, Lachance J, Tishkoff SA et al (2016) Model-based analyses of whole-genome data reveal a complex evolutionary history involving archaic introgression in central African pygmies. Genome Res 26:291–300
International HapMap 3 Consortium (2010) Integrating common and rare genetic variation in diverse human populations. Nature 467:52–58
International HapMap Consortium (2005) A haplotype map of the human genome. Nature 437:1299–1320
International HapMap Consortium (2007) A second generation human haplotype map of over 3.1 million SNPs. Nature 449:851–861
Jackson JP (2001) In ways unacademical: the reception of Carleton S. Coon's the origin of races. J History Biol 34:247–285
Jacobs GS, Hudjashov G, Saag L, Kusuma P, Darusallam CC, Lawson DJ, Mondal M, Pagani L et al (2019) Multiple deeply divergent Denisovan ancestries in Papuans. Cell 177:1010–1021.e32
Jakobsson M, Scholz SW, Scheet P, Gibbs JR, VanLiere JM, Fung HC, Szpiech ZA, Degnan JH, Wang K, Guerreiro R et al (2008) Genotype, haplotype and copy-number variation in worldwide human populations. Nature 451:998–1003
Jones S, Martin RD, Pilbeam DR (eds) (1994) The Cambridge encylopedia of human evolution. Cambridge University Press, Cambridge
Jones ER, Gonzalez-Fortes G, Connell S, Siska V, Eriksson A et al (2015) Upper Palaeolithic genomes reveal deep roots of modern Eurasians. Nat Commun 6:8912
Kamm JA, Terhorst J, Song YS (2017) Efficient computation of the joint sample frequency spectra for multiple populations. J Comp Graph Stat 26:182–194
Kamm J, Terhorst J, Durbin R, Song YS (2019) Efficiently inferring the demographic history of many populations with allele count data. J Am Stat Assoc 115:1472–1487

Keinan A, Mullikin JC, Patterson N, Reich D (2009) Accelerated genetic drift on chromosome X during the human dispersal out of Africa. Nat Genet 41:66–70

Kim BY, Lohmueller KE (2015) Selection and reduced population size cannot explain higher amounts of Neandertal ancestry in East Asian than in European human populations. Am J Hum Genet 96:454–461

Klein RG (2000) The earlier Stone age of southern Africa. S Afr Archaeol Bull 55:107–122

Krings M, Stone A, Schmitz RW, Krainitzki H, Stoneking M, Paabo S (1997) Neandertal DNA sequences and the origin of modern humans. Cell 90:19–30

Lachance J, Vernot B, Elbers CC, Ferwerda B, Froment A, Bodo JM, Lema G, Fu W, Nyambo TB, Rebbeck TR et al (2012) Evolutionary history and adaptation from high-coverage whole-genome sequences of diverse African hunter-gatherers. Cell 150:457–469

Lazaridis I, Patterson N, Mittnik A, Renaud G, Mallick S et al (2014) Ancient human genomes suggest three ancestral populations for present-day Europeans. Nature 513:409–413

Li H, Durbin R (2011) Inference of human population history from individual whole-genome sequences. Nature 475:493–496

Li WH, Sadler LA (1991) Low nucleotide diversity in man. Genetics 129:513–523

Lipson M, Szécsényi-Nagy A, Mallick S, Pósa A, Stégmár B et al (2017) Parallel palaeogenomic transects reveal complex genetic history of early European farmers. Nature 551:368–372

Lipson M, Cheronet O, Mallick S, Rohland N, Oxenham M et al (2018) Ancient genomes document multiple waves of migration in Southeast Asian prehistory. Science 361:92–95

Livingston RJ, von Niederhausern A, Jegga AG, Crawford DC, Carlson CS, Rieder MJ, Gowrisankar S, Aronow BJ, Weiss RB, Nickerson DA (2004) Pattern of sequence variation across 213 environmental response genes. Genome Res 14:1821–1831

Lohmueller KE, Degenhardt JD, Keinan A (2010) Sex-averaged recombination and mutation rates on the X chromosome: a comment on Labuda et al. Am J Hum Genet 86:978–980

Lu D, Xu S (2013) Principal component analysis reveals the 1000 genomes project does not sufficiently cover the human genetic diversity in Asia. Front Genet 4:127

Luca F, Hudson RR, Witonsky DB, Di Rienzo A (2011) A reduced representation approach to population genetic analyses and applications to human evolution. Genome Res 21:1087–1098

Malaspinas AS, Westaway MC, Muller C, Sousa VC, Lao O, Alves I, Bergström A, Athanasiadis G, Cheng JY, Crawford JE et al (2016) A genomic history of Aboriginal Australia. Nature 538:207–214

Mallick S, Li H, Lipson M, Mathieson I, Gymrek M, Racimo F, Zhao M, Chennagiri N, Nordenfelt S, Tandon A, Skoglund P et al (2016) The Simons Genome Diversity Project: 300 genomes from 142 diverse populations. Nature 538:201–206

Malmstrom H, Gilbert MTP, Thomas MG, Brandstrom M, Stora J, Molnar P, Andersen PK, Bendixen C, Holmlund G, Gotherstrom A et al (2009) Ancient DNA reveals lack of continuity between Neolithic hunter-gatherers and contemporary Scandinavians. Curr Biol 19:1758–1762

Marjoram P, Donnelly P (1994) Pairwise comparisons of mitochondrial DNA sequences in subdivided populations and implications for early human evolution. Genetics 136:673–683

Marth GT, Czabarka E, Murvai J, Sherry ST (2004) The allele frequency spectrum in genome-wide human variation data reveals signals of differential demographic history in three large world populations. Genetics 166:351–372

McColl H, Racimo F, Vinner L, Demeter F, Gakuhari T et al (2018) The prehistoric peopling of Southeast Asia. Science 361:88–92

Meyer M, Kircher M, Gansauge MT, Li H, Racimo F, Mallick S, Schraiber JG, Jay F, Prufer K, de Filippo C et al (2012) A high-coverage genome sequence from an archaic Denisovan individual. Science 338:222–226

Meyer M, Fu Q, Aximu-Petri A, Glocke I, Nickel B, Arsuaga JL, Martinez I, Gracia A, Bermudez de Castro JM, Carbonell E, Pääbo S (2014) A mitochondrial genome sequence of a hominin from Sima de los Huesos. Nature 505:403–406

Moorjani P, Patterson N, Hirschhorn JN, Keinan A, Hao L, Atzmon G, Burns E, Ostrer H, Price AL, Reich D (2011) The history of African gene flow into Southern Europeans, Levantines, and Jews. PLoS Genet 7:e1001373

Narasimhan V, Patterson N, Moorjani P, Rohland N, Bernardos R et al (2019) The formation of human populations in South and Central Asia. Science 365:eaat7487

Nelson MR, Wegman D, Ehm MG, Kessner D, St Jean P, Verzilli C, Shen J, Tang Z, Bacanu SA, Fraser D et al (2012) An abundance of rare functional variants in 202 drug target genes sequenced in 14,002 people. Science 337:100–104

Nielsen R (2000) Estimation of population parameters and recombination rates from single nucleotide polymorphisms. Genetics 154:931–942

Nielsen R, Wakeley J (2001) Distinguishing migration from isolation: a Markov chain Monte Carlo approach. Genetics 158:885–896

Nielsen R, Hubisz MJ, Hellmann I, Torgerson D, Andres AM, Albrechtsen A, Gutenkunst R, Adams MD, Cargill M, Boyko A, Indap A, Bustamante CD, Clark AG (2009) Darwinian and demographic forces affecting human protein coding genes. Genome Res 19:838–849

Novembre J, Johnson T, Bryc K, Kutalik Z, Boyko AR, Auton A, Indap A, King KS, Bergmann S, Nelson MR et al (2008) Genes mirror geography within Europe. Nature 456:98–101

Oppenheimer S (2009) The great arc of dispersal of modern humans: Africa to Australia. Quat Int 202:2–13

Patin E, Laval G, Barreiro LB, Salas A, Semino O, Santachiara-Benerecetti S, Kidd KK, Kidd JR, Van der Veen L, Hombert JM et al (2009) Inferring the demographic history of African farmers and pygmy hunter-gatherers using a multilocus resequencing data set. PLoS Genet 5:e1000448

Patterson N, Price AL, Reich D (2006) Population structure and eigenanalysis. PLoS Gene 2:e190

Plagnol V, Wall JD (2006) Possible ancestral structure in human populations. PLoS Genet 2:e105

Prado-Martinez J, Sudmant PH, Kidd JM, Li H, Kelley JL, Lorente-Galdos B, Veeramah KR, Woerner AE, O'Connor TD, Santpere G et al (2013) Great ape genetic diversity and population history. Nature 499:471–475

Price AL, Tandon A, Patterson N, Barnes KC, Rafaels N, Ruczinski I, Beaty TH, Mathias R, Reich D, Myers S (2009) Sensitive detection of chromosomal segments of distinct ancestry in admixed populations. PLoS Genet 5:e1000519

Pritchard JK, Stephens M, Donnelly P (2000) Inference of population structure using multilocus genotype data. Genetics 155:945–959

Prüfer K, Racimo F, Patterson N, Jay F, Sankararaman S, Sawyer S, Heinze A, Renaud G, Sudmant PH, de Filippo C et al (2014) The complete genome sequence of a Neanderthal from the Altai Mountains. Nature 505:43–49

Prüfer K, de Filippo C, Grote S, Mafessoni F, Korlevic P, Hajdinjak M, Vernot B, Skov L, Hsieh P, Payregne S et al (2017) A high-coverage Neandertal genome from Vindija cave in Croatia. Science 358:655–658

Ramachandran S, Deshpande O, Roseman CC, Rosenberg NA, Feldman MW, Cavalli-Sforza LL (2005) Support from the relationship of genetic and geographic distance in human populations for a serial founder effect originating in Africa. Proc Natl Acad Sci USA 102:15942–15947

Rasmussen M, Li Y, Lindgreen S, Pedersen JS, Albrechtsen A, Moltke I, Metspalu M, Metspalu E, Kivisild T, Gupta R, Bertalan M et al (2010) Ancient human genome sequence of an extinct Palaeo-Eskimo. Nature 463:757–762

Rasmussen M, Guo X, Wang Y, Lohmueller KE, Rasmussen S, Albrectsen A, Skotte L, Lindgreen S, Metspalu M, Jombart T et al (2011) An aboriginal Australian genome reveals separate human dispersals into Asia. Science 334:94–98

Reich DE, Cargill M, Bolk S, Ireland J, Sabeti PC, Richter DJ, Lavery T, Kouyoumjian R, Farhadian SF, Ward R et al (2001) Linkage disequilibrium in the human genome. Nature 411:199–204

Reich D, Green RE, Kircher M, Krause J, Patterson N, Durand EY, Viola B, Briggs AW, Stenzel U, Johnson PL et al (2010) Genetic history of an archaic hominin group from Denisova cave in Siberia. Nature 468:1053–1060

Reich D, Patterson N, Kircher M, Delfin F, Nandineni MR, Pugach I, Ko AMS, Ko YC, Jinam TA, Phipps ME et al (2011) Denisovan admixture and the first modern human dispersals into Southeast Asia and Oceania. Am J Hum Genet 89:516–528

Rightmire GP (2009) Out of Africa: modern human origins special feature: middle and later Pleistocene hominins in Africa and Southwest Asia. Proc Natl Acad Sci USA 106:16046–16050
Rogers AR, Harpending H (1992) Population growth makes waves in the distribution of pairwise genetic differences. Mol Biol Evol 9:552–569
Rosenberg NA, Pritchard JK, Weber JL, Cann HM, Kidd KK, Zhivotovsky LA, Feldman MW (2002) Genetic structure of human populations. Science 298:2381–2385
Sampietro ML, Lao O, Caramelli D, Lari M, Pou R, Marti M, Bertranpetit J, Lalueza-Fox C (2007) Palaeogenetic evidence supports a dual model of Neolithic spreading into Europe. Proc Biol Sci 274:2161–2167
Sankararaman S, Sridhar S, Kimmel G, Halperin E (2008) Estimating local ancestry in admixed populations. Am J Hum Genet 82:290–303
Sankararaman S, Patterson N, Li H, Pääbo S, Reich D (2012) The date of interbreeding between Neandertals and modern humans. PLoS Genet 8:e1002947
Sankararaman S, Mallick S, Dannemann M, Prüfer K, Kelso J et al (2014) The genomic landscape of Neanderthal ancestry in present-da humans. Nature 507:354–357
Sankararaman S, Mallick S, Patterson N, Reich D (2016) The combined landscape of Denisovan and Neanderthal ancestry in present-day humans. Curr Biol 26:1241–1247
Schiffels S, Durbin R (2014) Inferring human population size and separation history from multiple genome sequences. Nat Genet 46:919–925
Seguin-Orlando A, Korneliussen TS, Sikora M, Malaspinas AS, Manica A et al (2014) Genomic structure in Europeans dating back at least 36,200 years. Science 346:1113–1118
Serre D, Langaney A, Chech M, Teschler-Nicola M, Paunovic M, Mennecier P, Hofreiter M, Possnert G, Paabo S (2004) No evidence of Neandertal mtDNA contribution to early modern humans. PLoS Biol 2:E57
Sheehan S, Harris K, Song YS (2013) Estimating variable effective population sizes from multiple genomes: a sequentially Markov conditional sampling distribution approach. Genetics 194:647–662
Shinde V, Narasimhan V, Rohland N, Mallick S, Mah M et al (2019) An ancient Harappan genome lacks ancestry from steppe pastoralists or Iranian farmers. Cell 179:729–735
Sjödin P, Sjöstrand AE, Jakobsson M, Blum MGB (2012) Resequencing data provide no evidence for a human bottleneck in Africa during the penultimate glacial period. Mol Biol Evol 29:1851–1860
Skoglund P, Malmstrom H, Raghavan M, Stora J, Hall P, Willerslev E, Gilbert MT, Gotherstrom A, Jakobsson M (2012) Origins and genetic legacy of Neolithic farmers and hunter-gatherers in Europe. Science 336:466–469
Slatkin M, Hudson RR (1991) Pairwise comparisons of mitochondrial DNA sequences in stable and exponentially growing populations. Genetics 129:555–562
Steinrücken M, Kamm J, Spence JP, Song YS (2019) Inference of complex population histories using whole-genome sequences from multiple populations. Proc Natl Acad Sci USA 116:17115–17120
Stringer CB, Andrews P (1988) Genetic and fossil evidence for the origin of modern humans. Science 239:1263–1268
Takahata N (1993) Allelic genealogy and human evolution. Mol Biol Evol 10:2–22
Tellier LN (2009) Urban world history: an economic and geographical perspective. Presses de l'Universite du Quebec, Montreal
Tennessen JA, Bigham AW, O'Connor TD, Fu W, Kenny EE, Gravel S, McGee S, Do R, Liu X, Jun G et al (2012) Evolution and functional impact of rare coding variation from deep sequencing of human exomes. Science 337:64–69
Terhorst J, Kamm JA, Song YS (2017) Robust and scalable inference of population history from hundreds of unphased whole genomes. Nat Genet 49:303–309
Tishkoff SA, Dietzsch E, Speed W, Pakstis AJ, Kidd JR, Cheung K, Bonne-Tamir B, Santachiara-Benerecetti AS, Moral P, Krings M (1996) Global patterns of linkage disequilibrium at the *CD4* locus and modern human origins. Science 271:1380–1387

Tishkoff SA, Reed FA, Friedlaender FR, Ehret C, Ranciaro A, Froment A, Hirbo JB, Awomoyi AA, Bodo JM, Doumbo O et al (2009) The genetic structure and history of Africans and African Americans. Science 324:1035–1044

Trinkaus E (2005) Early modern humans. Annu Rev Anthropol 34:207–230

Vernot B, Akey JM (2015) Complex history of admixture between modern humans and Neandertals. Am J Hum Genet 96:448–453

Vernot B, Tucci S, Kelso J, Schraiber JG, Wolf AB et al (2016) Excavating Neandertal and Denisovan DNA from the genomes of Melanesian individuals. Science 352:235–239

Vigilant L, Stoneking M, Harpending H, Hawkes K, Wilson AC (1991) African populations and the evolution of human mitochondrial DNA. Science 253:1503–1507

Villanea FA, Schraiber JG (2019) Multiple episodes of interbreeding between Neanderthal and modern humans. Nat Ecol Evol 3:39–44

Viola BT, Gunz P, Neubauer S, Slon V, Kozlikin MB, Shunkov MV et al (2019) A parietal fragment from Denisova cave. Am J Phys Anthropol 168(S68):258

Voight BF, Adams AM, Frisse LA, Qian Y, Hudson RR, Di Rienzo A (2005) Interrogating multiple aspects of variation in a full resequencing data set to infer human population size changes. Proc Natl Acad Sci USA 102:18508–18513

Wall JD (2000) Detecting ancient admixture in humans using sequence polymorphism data. Genetics 154:1271–1279

Wall JD, Przeworski M (2000) When did the human population size start increasing? Genetics 155:1865–1874

Wall JD, Andolfatto P, Przeworski M (2002) Testing models of selection and demography in *Drosophila simulans*. Genetics 162:203–216

Wall JD, Cox MP, Mendez FL, Woerner A, Severson T, Hammer MF (2008) A novel DNA sequence database for analyzing human demographic history. Genome Res 18:1354–1361

Wall JD, Lohmueller KE, Plagnol V (2009) Detecting ancient admixture and estimating demographic parameters in multiple human populations. Mol Biol Evol 26:1823–1827

Wall JD, Jiang R, Gignoux C, Chen GK, Eng C, Huntsman S, Marjoram P (2011) Genetic variation in native Americans, inferred from Latino SNP and resequencing data. Mol Biol Evol 28:2231–2237

Wall JD, Yang MA, Jay F, Kim SK, Durand EY, Stevison LS, Gignoux C, Woerner A, Hammer MF, Slatkin M (2013) Higher levels of Neanderthal ancestry in east Asians than in Europeans. Genetics 194:199–209

Wall JD, Ratan A, Stawiski E, GenomeAsia 100K Consortium (2019) Identification of African-specific admixture between modern and archaic humans. Am J Hum Genet 105:1254–1261

Wolpoff MH, Wu X, Thorne AG (1984) Modern *Homo sapiens* origins: a general theory of hominid evolution involving the fossil evidence from East Asia. In: Smith FH, Spencer F (eds) The origins of modern humans: a world survey of the fossil evidence. Liss, New York, NY, pp 411–483