

Review

Insights into Modern Human Prehistory
Using Ancient GenomesMelinda A. Yang¹ and Qiaomei Fu^{1,*}

The genetic relationship of past modern humans to today's populations and each other was largely unknown until recently, when advances in ancient DNA sequencing allowed for unprecedented analysis of the genomes of these early people. These ancient genomes reveal new insights into human prehistory not always observed studying present-day populations, including greater details on the genetic diversity, population structure, and gene flow that characterized past human populations, particularly in early Eurasia, as well as increased insight on the relationship between archaic and modern humans. Here, we review genetic studies on ~45 000- to 7500-year-old individuals associated with mainly preagricultural cultures found in Eurasia, the Americas, and Africa.

Ancient Genetics of Modern Humans

The period approximately 50–10 thousand years ago (ka) was characterized by significant shifts in human populations, with the radiation of **modern humans** (see [Glossary](#)) throughout Eurasia and the disappearance of **archaic humans** who previously lived in Europe and Asia until ~40 ka [1]. Changes in climate during this period, including several cycles of warming and cooling, likely played a role in the dispersals and interactions of ancient humans across Eurasia, especially in the northern regions [2]. Starting with a relatively warmer interval that began ~60 ka [3], the climate cooled until around 26.5–19 ka during the Last Glacial Maximum (LGM) [4]. After the LGM, it rapidly warmed until ~14.5 ka [4,5], before returning to a colder period called the Younger Dryas ~13–11.7 ka [5], which preceded the warmer interval called the Holocene. These notable climatic shifts, along with potential cultural changes, likely impacted the movement and spread of modern humans, affecting their relationships with archaic humans and each other.

Ancient DNA technology [6–9] now allows direct sequencing of past individuals to address questions related to the biology of modern humans. Who were the ancient modern humans in Eurasia, and how were they related to each other and to present-day humans? How did human populations move and interact with each other during this period, and how does that influence human demography today? When and how often did archaic and modern humans interbreed? Here, we review genomic research on ancient modern humans primarily associated with preagricultural cultures and use these data to (i) articulate the dynamic shifts that occurred in humans from ~45 to 7.5 ka and (ii) summarize and discuss our understanding of how modern and archaic humans interacted.

Modern Humans from ~45 to 7.5 ka

The oldest modern humans in Eurasia may be as old as 120 ka [10], populations that likely used Middle Paleolithic technologies. Subsequent dispersals in western Eurasia were associated with a succession of stone tool industries (i.e., **Aurignacian, Gravettian, Magdalenian**) grouped into the **Upper Paleolithic**, although isolated finds do not always have clear

Highlights

Eurasia ~45–35 ka shows the presence of at least four distinct populations: early Asians and Europeans, as well as populations with ancestry found hardly or not at all in present-day populations.

Europeans from around 34–15 ka show high internal population structure.

Approximately 14–7.5 ka, populations across Eurasia shared genetic similarities, suggesting greater interactions between geographically distant populations.

Ancient modern human genomes support at least two Neanderthal admixture events, one ~60–50 ka in early ancestors of non-African populations and a second >37 ka related to the Oase 1 individual.

A gradual decline in archaic ancestry in Europeans dating from ~37 to 14 ka suggests that purifying selection lowered the amount of Neanderthal ancestry first introduced into ancient modern humans.

¹Key Laboratory of Vertebrate Evolution and Human Origins of Chinese Academy of Sciences, Institute of Vertebrate Paleontology and Paleoanthropology, CAS, Beijing 100044, China

*Correspondence: fuqiaomei@ivpp.ac.cn (Q. Fu).

archaeological associations. We focus on a period spanning ~45–7.5 ka, when most modern humans in Eurasia were associated with tool technologies spanning the Upper Paleolithic. For the review, we divide this time range into three distinct time periods: Ancient Modern A (AMA, ~45–35 ka), Ancient Modern B (AMB, ~34–15 ka), and Ancient Modern C (AMC, ~14–7.5 ka). The age of ancient humans discussed here is based on calibrated radiocarbon dates, both directly and indirectly determined from the sampled specimens (Table 1). A summary of the major patterns is presented in Figure 1 (Key Figure).

Ancient Modern A (AMA): About 45–35 ka

Genetic research on ancient modern humans in Eurasia shows that there were at least four distinct populations in Eurasia during the AMA (Table 1 and Figure 1). The oldest of the specimens is the ~45 000-year-old Ust'-Ishim individual from Central Siberia [11] who shares more alleles with present-day East Asians than with present-day Europeans (Figure 2A). However, when present-day Europeans were replaced with Europeans older than 14 ka – Europeans without 'Basal Eurasian' ancestry (Box 1), the Ust'-Ishim individual is equally closely related to ancient Europeans and to present-day East Asians, suggesting he is from a population that did not contribute to any present-day Eurasian populations [11]. Similarly, the ~42–37 000-year-old Oase 1 individual from Romania shares a similar number of alleles with both Europeans older than 14 ka and present-day East Asians and Native Americans, suggesting that he also belonged to a distinct population that did not contribute substantially to later Eurasians [9]. Between the Ust'-Ishim and Oase 1 individuals, we have growing evidence that some populations in Eurasia during the AMA did not contribute substantial ancestry to present-day populations.

However, during the AMA, individuals that represent early European and Asian populations have also been found. The ~36 000-year-old Kostenki 14 individual from western Siberia and the ~35 000-year-old Goyet Q116-1 from Belgium are more closely related to Europeans than to other Eurasians [12,13] (Figure 2A). Unlike present-day Europeans, ancient Europeans from the AMA do not have Basal Eurasian ancestry [12,13] (Figure 2B and Box 1). Populations with present-day European connections were widespread across West Eurasia at least by 35 ka [13] (Figure 1).

Only a single specimen from East Asia has been sequenced that dates to the AMA. The ~40 000-year-old Tianyuan individual from outside Beijing [14] was shown to be more similar to present-day East Asians and Native Americans than to present-day or ancient Europeans [15,16] (Figure 2A). Therefore, by about 40 ka, 'genetically' European populations existed in Europe and 'genetically' Asian populations existed in Asia, indicating that the Asian–European separation likely occurred prior to 40 ka, consistent with recent inferences using *de novo* mutation rates that have pushed back the estimated date of separation from ~40–20 ka to ~80–40 ka [17–19].

Another startling new piece of the puzzle is a connection between the Tianyuan individual from China and the Goyet Q116-1 individual from Belgium (Figure 2C). While the Tianyuan individual is most closely related to East Asians and the Goyet Q116-1 individual is most closely related to Europeans, they share more alleles than would be expected for a simple separation between early Asians and Europeans [16]. Previous methods of demographic inference have inferred some gene flow between Europeans and Asians post separation [20–22], but with the Goyet Q116-1 and Tianyuan individuals, there is direct evidence of a connection between East and West Eurasia as early as the AMA and relatively soon after the Asian–European separation. Given their early dates and large geographic distance, Yang *et al.* [16] proposed a model where

Glossary

Admixture: in genetics, the presence of DNA in an individual from a distantly related population or species, resulting from interbreeding between these two populations or species after an intervening period of reproductive isolation.

Archaic human: early humans from ~500–40 ka across Africa and Eurasia with morphology similar to that found in modern humans but possessing a suite of traits not commonly found in humans today. Here, we largely refer to specimens called Neanderthals or Denisovans that lived in Eurasia and whose genetic patterns fall outside of the variation found in modern humans today.

Aurignacian: archaeological culture found mainly in Europe as early as 43 ka that preceded the Gravettian culture and is associated with ancient modern humans.

Azilian, Epipaleolithic, Epigravettian, and Mesolithic: archaeological cultures or periods that span the interval between the Paleolithic and Neolithic.

Centimorgan: a unit of measurement for genetic linkage, indicating the length of the chromosome over which the average number of chromosomal crossovers expected in a single generation is 0.01.

Gravettian: a widespread Upper Paleolithic culture found mainly in Europe that began around 33 ka and persisted until the Last Glacial Maximum.

Introgession: related to admixture, usually refers to the result after admixture. For instance, the introgressed segment is the DNA sequence belonging to the source population that is found in the admixed population.

Magdalenian: a later culture of the Upper Paleolithic that occurs after the Last Glacial Maximum.

Modern human: the only human species alive on Earth today; they consist of present-day populations and ancient populations whose morphological variation is within the range of that found today.

Neolithic: an archaeological period related to the development of technology associated with farming.

the early Eurasian population that led to Europeans and Asians was structured, and the populations represented by the Goyet Q116-1 and Tianyuan individuals share ancestry from the same early Eurasian subpopulation not shared by other ancient European populations.

Ancient Modern B (AMB): ~34–15 ka

Specimens from the AMB that have been sequenced to date show that by this time modern humans in West and East Eurasia are similar to either Europeans or to Asians. There is also evidence of population structure in both ancient Europeans and Asians, as well as a notable mixture of European- and Asian-like ancestry in North Eurasia.

In Europe, individuals dating to ~34–26 ka associated with the widespread Gravettian culture in West and Central Europe (i.e., Věstonice 16, Ostuni 1) were shown to form a distinct European population [13] (Figure 1 and Table 1). In Russia, partial population replacement seems to have also occurred, as the ~34 000-year-old individuals from the Sunghir site show relationships to both the older Kostenki 14 individual and the Věstonice 16 individual [23]. However, the ~35 000-year-old Goyet Q116-1 associated with the Aurignacian culture that may date to as early as 43 ka [13] shows a close connection to ~19–14 000-year-old individuals associated with the Magdalenian culture found in France and Spain (i.e., El Mirón) that is not observed in Kostenki 14 or individuals associated with the Gravettian culture. Thus, at least two European populations persisted from ~34–26 ka, one associated with individuals belonging to the Gravettian culture and another sharing at least partial ancestry with a population related to Goyet Q116-1. That no sampled individuals from ~34–19 ka share a close relationship to Goyet Q116-1 suggests that the population related to him migrated elsewhere, perhaps to southwestern Europe due to the colder climate leading up to the LGM [13]. Denser sampling of this region is needed to determine whether populations related to Goyet Q116-1 persisted in other parts of Europe.

In Asia, despite low numbers of specimens available for genomic analysis, there are two insights. First, sampling of Siberian individuals from ~24–17 ka from the Lake Baikal region (i.e., Mal'ta 1 and Afontova Gora 3) showed that they share a stronger connection to Europeans than to Asians, but that they share the strongest connection to Native Americans [13,24]. They highlight that Native Americans are a mix of East Asian and North Eurasian ancestry represented by these individuals found in Siberia [24]. These ancient North Eurasians have Asian influences as well [16,25] (Figure 2C). Second, the lack of sequenced individuals dating to the AMB period from East Asia means that population structure and turnover in this region cannot be directly assessed, but indirect evidence from the Tianyuan individual suggests that population structure must also have existed here that dates back to the AMA. Some South American populations, particularly the Suruí and Karitiana, show a connection to Oceanians, the Andamanese Onge, and now the Tianyuan individual, but not to present-day East Asian populations, suggesting that the ancestral Native American population(s) that migrated to the Americas were structured, with different types of Asian influence [16,26]. That this connection exists for the Tianyuan individual means that as far back as ~40 ka, his ancestry is at least partially found in some subpopulations of East Eurasia and must persist in some form until the colonization of the Americas.

Ancient Modern C (AMC): ~14–7.5 ka

Around the end of the Paleolithic and the onset of the **Neolithic**, more contact across Eurasia is observed. In West Eurasia, individuals dating to the AMC share more alleles with present-day Asian and Near East populations than older Europeans shared. Individuals from central and western Europe ~14–7.5 ka associated with the **Azilian, Epipaleolithic, Epigravettian, and Mesolithic** cultures (i.e., Villabruna and Loschbour, amongst others, see [13], Table 1) show

Positive selection: a mode of selection describing the process where a new or previously neutral genetic variant becomes advantageous and is swept to high frequency or fixation within a population.

Purifying selection: a mode of selection describing the process where new variants that are deleterious are removed from the population to maintain the old, more advantageous variant found in the majority of the population.

Upper Paleolithic: an archaeological period describing the last subdivision of the Paleolithic. In Eurasia, the tool technologies associated with this period coincide with the dispersal of modern humans throughout this region.

Table 1. Select Ancient Modern Human Individuals from ~45 to 7.5 kBP, with Individuals Grouped into Ancient Modern A (~45–35 ka), B (~34–15 ka), and C (~14–7.5 ka)

Individuals ^a	Dating ^{b,e}	Country	Covg	Refs	Major finds
Ust'-Ishim	47 480–42 560	Russia	42	[11]	Not represented in populations today, used to date Neanderthal admixture.
Oase 1	41 640–37 580	Romania	0.16	[9]	Not represented in populations today, Neanderthal ancestor four to six generations back.
Tianyuan	41 144–39 512	China	4.1	[15,16]	Related to Asians, connections to Goyet Q116-1 and some South Americans.
Kostenki 14	38 680–36 260	Russia	16.1	[12,13]	Oldest individual found to date with close relationship to present-day Europeans.
Goyet Q116-1	35 160–34 431	Belgium	1.05	[13]	Related to Europeans, with connections to Tianyuan from China.
Sunguir (6)	35 283–29 746	Russia	10.75 ^d	[23]	Set of individuals related to Europeans, has connections to both Kostenki 14 and Věstonice 16.
Věstonice 16	30 710–29 310 ^c	Czech Republic	1.31	[13]	Related to Europeans, represents widespread population during LGM in Europe.
Ostuni 1	27 810–27 430	Italy	0.24	[13]	Related to Europeans, close relationship to Věstonice 16.
Mal'ta 1	24 520–24 090	Russia	1.17	[24]	North Eurasian with European and Asian ancestry. Close relationship to Native Americans.
El Mirón	18 830–18 610	Spain	1.01	[13]	Related to Europeans, connection to Goyet Q116-1, suggesting second European population during LGM.
Afontova Gora 3	16 930–16 490 ^e	Russia	0.17	[13]	North Eurasian closely related to Mal'ta 1. Close relationship to Native Americans.
Villabruna	14 180–13 780	Italy	3.14	[13]	Related to Europeans, with stronger Near East connections than older Europeans.
Bichon	13 770–13 560	Switzerland	8.12	[81]	Related to Villabruna but also possesses East Asian connection.
Satsurblia	13 380–13 130	Georgia	1.20	[81]	Related to Europeans, but from the Caucasus with Basal Eurasian ancestry.
Anzick 1	12 707–12 556	US	14.4	[30]	Native American related to present-day Central and South Americans, no extra Tianyuan connection.
Natufian (6)	11 840–9760	Israel	0.53 ^d	[28]	Near Easterner with high Basal Eurasian ancestry from the Levant.
Hotu	9119–8637	Iran	0.14	[28]	Near Easterner with high Basal Eurasian ancestry and closer to the two Caucasus individuals, Satsurblia and Kotias, than Natufians.
Kotias	9890–9550	Georgia	12.2	[81]	Related to Europeans, but from the Caucasus with Basal Eurasian ancestry.
Karelia	8800–7950 ^c	Russia	1.95	[8]	Related to Europeans, but with connection to Mal'ta 1 and Afontova Gora 3.
Hora (2)	8173–7957 ^c	Malawi	0.26 ^d	[31]	Related to ancient and present-day Khoe-San in southern Africa.
Loschbour	8160–7940	Luxembourg	20	[27]	Related to Villabruna but also possesses East Asian connection.
La Brana 1	7940–7690	Spain	3.34	[37]	Related to Villabruna but also possesses East Asian connection.
Kőrös 1	7730–7590	Hungary	1.1	[82]	Related to Villabruna but also possesses East Asian connection.
Motala 12	7670–7580	Sweden	2.18	[27]	Related to Europeans with similar connections as Karelia to Mal'ta 1 and Afontova Gora 3, but weaker.

^aOne sample unless stated otherwise in parentheses.

^bAll dates are in calibrated years before present and estimated directly from the same skeleton unless marked with ^c.

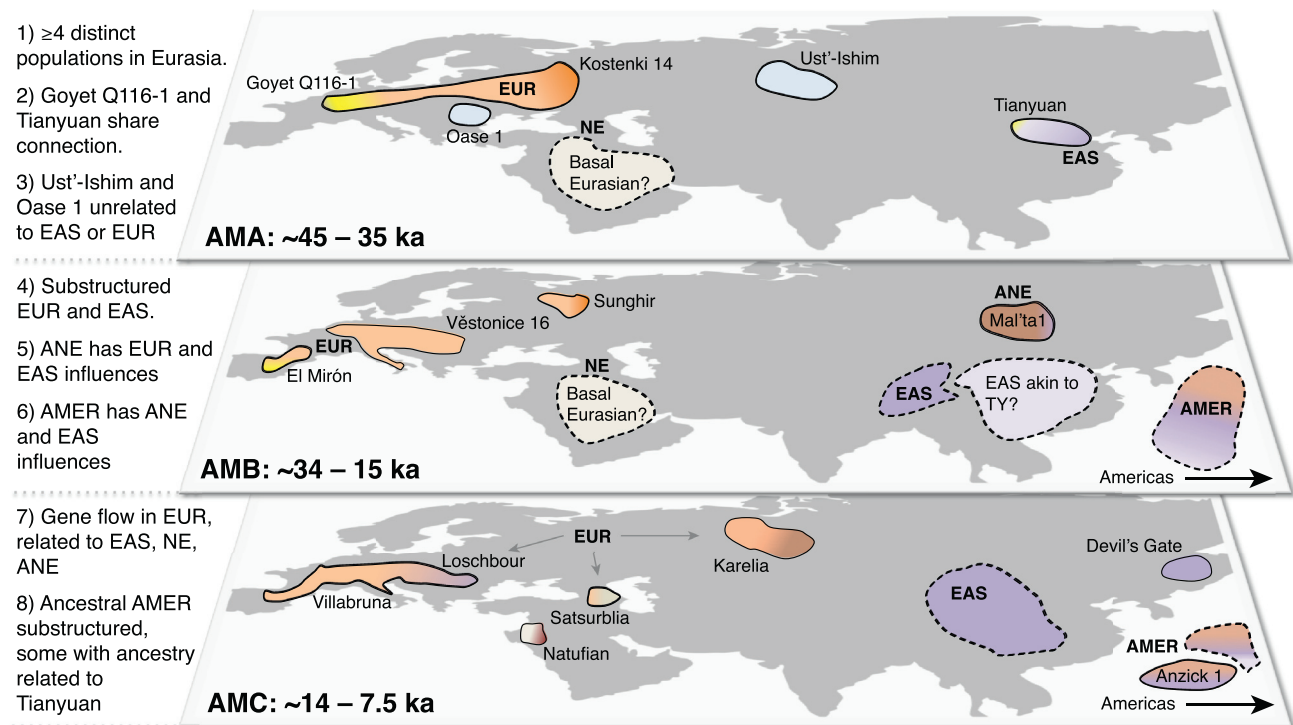
^cThese are indirect dates based on associated archaeological layers.

^dHighest coverage from set of multiple individuals from same site.

^eDate ranges were provided in Fu *et al.* [13] or the original study, see 'Refs'.

Key Figure

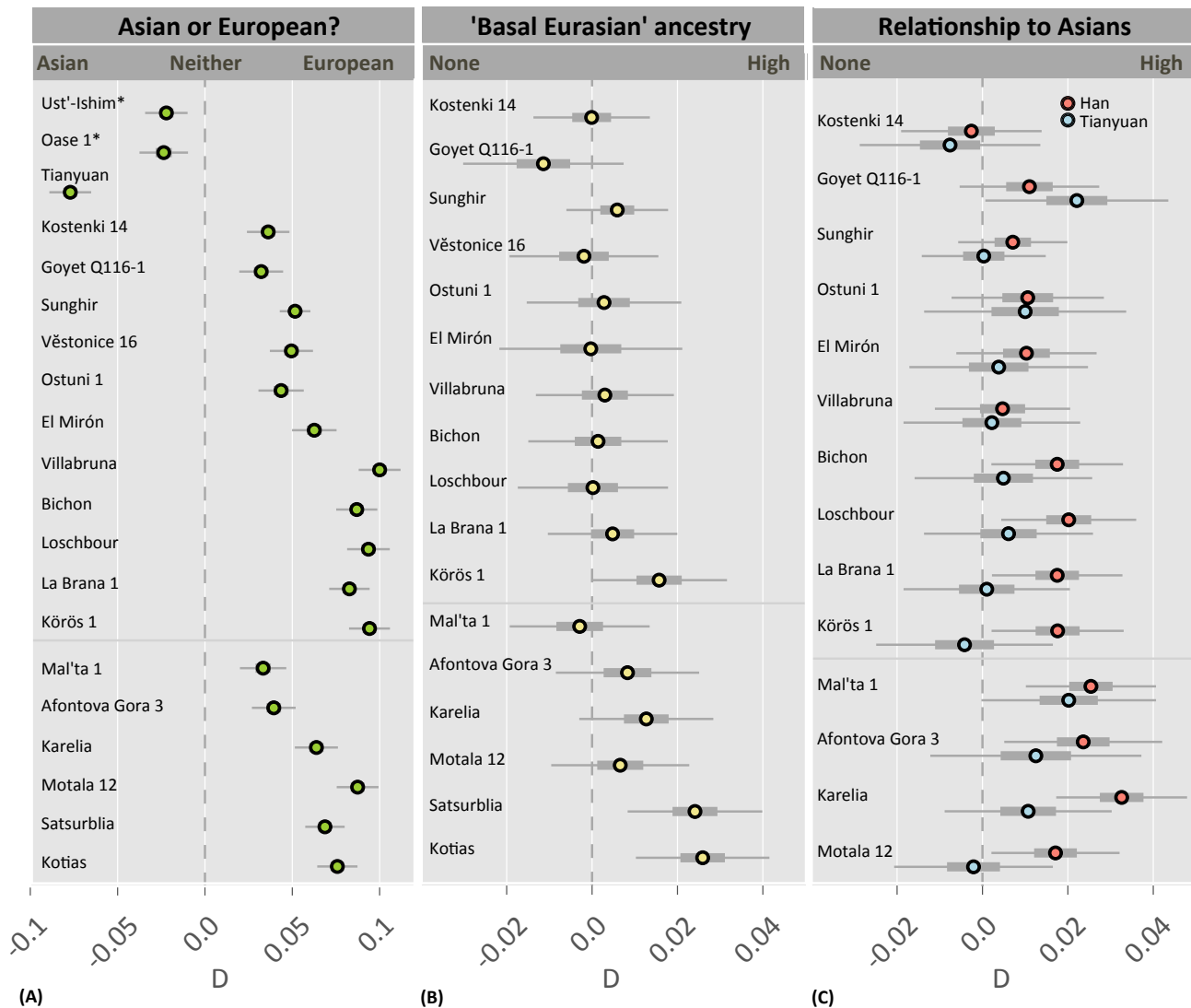
Schematic of Populations in Eurasia and the Americas (Bottom Right) during Ancient Modern A (AMA, ~45–35 ka), Ancient Modern B (AMB, ~34–15 ka), and Ancient Modern C (AMC, ~14–7.5 ka)



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Figure 1. Abbreviations: AMER, ancestry related to present-day Native Americans and Anzick 1; ANE, ancestry related to ancient North Eurasians represented by Mal'ta 1; EAS, ancestry related to present-day East Asians and the Tianyuan and Devil's Gate individuals; EUR, ancestry related to ancient Europeans and found partially in present-day Europeans; NE, ancestry related to an unsampled population known as Basal Eurasian and found in partial amounts in ancient and present-day populations of the Near East and in present-day Europeans. Broken lines indicate no ancient genetic samples have been found for a population with the inferred ancestry. Colors loosely indicate genetic groupings between or within a region, with color gradients showing the connections (i.e., gene flow) that may exist between different ancient populations. A summary of major events in each of the time periods is on the left.

connections to present-day Near Easterners and/or East Asians [13,16,25] (Figure 2C). In the Caucasus, ~13–10 000-year-old individuals (i.e., Satsurblia and Kotias) show a close relationship to ancient individuals in West Eurasia, but they also possess the Basal Eurasian ancestry observed in populations from Europe and the Near East [13,27,28] (Figure 2B). Basal Eurasian ancestry is highest in the Near East, with estimates as high as 66% in Epipaleolithic Natufian individuals from the Levant ~12–9.8 ka, and 44% in a Mesolithic individual from Iran from ~9.1 to 8.6 ka (i.e., Hotu) [28]. Further sampling will help to determine whether the gene flow between populations in the AMC began during this time period or extends back into the AMB.



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Figure 2. Major Affinities Found in Ancient Eurasians, Determining whether the Individual Was (A) More Genetically Similar to Present-Day Asians or Europeans, (B) Possesses 'Basal Eurasian' Ancestry, or (C) Shows a Connection to Asians (Either the Tianyuan Individual or the Present-Day Han Chinese). (A) shows $D(\text{French, Han}; X, \text{Mbuti})$, (B) shows $D(\text{Han, X}; \text{Ust}'\text{-Ishim, Mbuti})$, and (C) shows $D(X, \text{Věstonice 16}; \text{Han or Tianyuan, Mbuti})$. In (A), the starred (*) individuals show similar relationships to Asians and Europeans (see Box 1). In (B), all included individuals show a close relationship to present-day Europeans. In (C), the red points indicate a shared connection between the individual and the present-day Han, while the blue points indicate a shared connection between the individual and the ~40 ka Tianyuan individual. Thick bars are within one standard error of the estimate (in A, these are too small to be observed), and thin bars are within three standard errors of the estimate (99.7% confidence interval), and the broken vertical line indicates $D = 0$.

Regardless of the timing of gene flow between East and West Eurasia, some amount of either Near Eastern ancestry, Asian ancestry, or both has been observed in all West Eurasians sampled from the AMC. The East Asian and Near East connections seem to be distinct, as not all West Eurasians from this time period show a connection to East Asians, whereas all of them show a connection to Near Easterners [13]. Some ancient individuals with European ancestry, such as the ~8500-year-old Karelia individual from Russia and the ~7500-year-old Motala 12 individual from Sweden, exhibit ancestry related to ancient North Eurasians [16]. Other West

Box 1. The ‘Basal Eurasian’ Ghost Population

Lazaridis *et al.* [27] sequenced hunter-gatherers from Luxembourg and Sweden (~8–7.5 ka), as well as a Neolithic farmer from Germany (~7 ka) to compare them with present-day European populations and found that the Neolithic farmer and present-day Europeans share an ancestral component not found in earlier Europeans. They concluded that this ancestral component dates to an unsampled population that separated from other non-African populations early in non-African ancestry, and referred to this component as ‘Basal Eurasian’. Later work [28] showed that this ancestry can be found in higher proportions in Near East individuals from ~12–1.4 ka, and that this population likely separated from other non-Africans before the introduction of archaic admixture. However, no ancient specimen or present-day population sampled thus far shows evidence of being from a Basal Eurasian population. The earliest evidence of individuals with this ancestry are hunter-gatherers from the Caucasus region ~13 ka who also possess European ancestry and the Natufians from the Levant region ~12 ka (see Figure 1 and Table 1 in main text).

Because of the old separation time argued for the Basal Eurasian population, statistical analyses using populations that possess their ancestry are likely to be biased. For instance, tests comparing ancient Europeans without this ancestry and present-day Europeans with this ancestry may give different results. In comparisons of the Ust'-Ishim and Oase 1 individuals with the present-day French and Han populations, these two individuals share more genetic similarities with the Han than they share with the French (see Figure 2A in main text). However, they share similar levels of genetic similarity with Asians and ancient Europeans [9,11]. Because ancient European samples without this ancestry are available, we know that these two individuals are not more closely related to either Europeans or Asians, suggesting they are not represented in any present-day populations today.

European individuals from ~14–7.5 ka (i.e., Bichon, Loschbour, La Brana 1, Körös 1) exhibit ancestry potentially related to East Asians [16], though all but the Bichon individual also share a relationship to a population related to the admixed Karelia individual [28]. These results hint at a rich and complex history of gene flow between West and East Eurasia.

The story in Asia is not clear, in part because little to no genetic data from specimens dating to the AMC have yet been recovered. Two individuals from ~7.7 ka sampled from the Primorye region of Russia (Devil's Gate) show the closest relationship to the Ulchi who occupy the same region today, suggesting population continuity in that area [29]. However, their low coverage and the lack of other samples from this time period in Asia make it difficult to understand the genetic prehistory in Asia. Further south, present-day East Asian populations show remarkable homogeneity relative to ancient samples from other regions, both when used as a potential source population for Asian gene flow into Europe and when treated as the admixed population with gene flow from Europe, which current models do not seem to support [16]. This homogeneity suggests that the diversity in Asia during the AMC is non-existent or difficult to find when analyzing only present-day populations. Clarifying the connection between Europe and Asia during the AMC will require direct sampling of ancient individuals from this time period in Asia.

While very few samples have been sequenced outside of Eurasia in this time period, there is one ~12 500-year-old individual from Montana in North America (Anzick 1, [30]) and two ~8100-year-old individuals from Malawi in Africa (Hora, [31]). In the Americas, the Anzick 1 individual shows a closer relationship to central and southern Native Americans, rather than the geographically closer northern Native Americans, suggesting at least two distinct Native American populations by this time period in the Americas [30]. In Africa, the Hora individuals share the closest relationship with ancient Malawi individuals dating to ~6.1–2.5 ka, suggesting a long-standing population that persisted for at least 5000 years. These ancient individuals do not share a close relationship with present-day Malawians but show partial ancestry related to ~2000-year-old southern Africans and the present-day Khoe-San. The present-day Khoe-San show subdivision between northern and southern populations estimated to have manifested ~26–21 ka [32–34], and the ancient Malawi show symmetric relationships to both Khoe-San populations, suggesting at least three populations in southern and eastern Africa that

separated from each other at least 20 ka [31]. Outside of Eurasia, individuals from both Africa and the Americas hint at population subdivision that dates to at least the AMC if not earlier, suggesting that a rich genetic prehistory will be uncovered with future sampling.

Phenotypic Changes in Ancient Modern Humans

As we understand more about human demographic history, we are increasingly able to address questions regarding the timing of phenotypic changes in humans over time, potentially due to **positive selection**. Some studies have tackled these questions in samples from younger time periods [31,35,36], but much sparser sampling earlier in time makes it more difficult to systematically explore positive selection in modern humans from ~45 to 7.5 ka. However, studies exploring variants with known functions [13,37] highlight that ancient human sequences can provide information about the timing of specific phenotypic changes.

The ~7500-year-old La Brana 1 individual possesses the ancestral skin pigmentation alleles for the genes *SLC45A2* and *SLC45A5*, which are strongly associated with dark skin and hair, but he possesses the derived allele in the gene *HERC2* associated with blue eye color. This combination is not observed today, suggesting that light skin pigmentation was not fixed in European populations by ~7.5 ka [37]. The allele for blue eye color was widespread across Europe even earlier, as ancient Europeans ranging from ~14 to 7.5 ka (i.e., Villabruna, Loschbour) also possess the blue eye color allele [13], though it is not observed in more ancient Europeans sampled to date. Allele frequency differences in functional regions have not been well studied, but a growing body of analyses is being developed to include ancient DNA in tests of selection, while accounting for uncertainty in dating of samples and potential external gene flow [38,39].

The Relationship between Modern and Archaic Humans

Comparison of genome-wide data from Neanderthals to present-day humans showed that all non-African populations today have a Neanderthal **admixture** proportion of ~1.8–2.6% [6,40], but the population dynamics leading to archaic admixture was not clear. Ancient DNA from modern humans have played an important role in providing deeper insights into the timing and number of admixture events with archaic humans, and into the selective pressures that have acted on **introgressed** DNA.

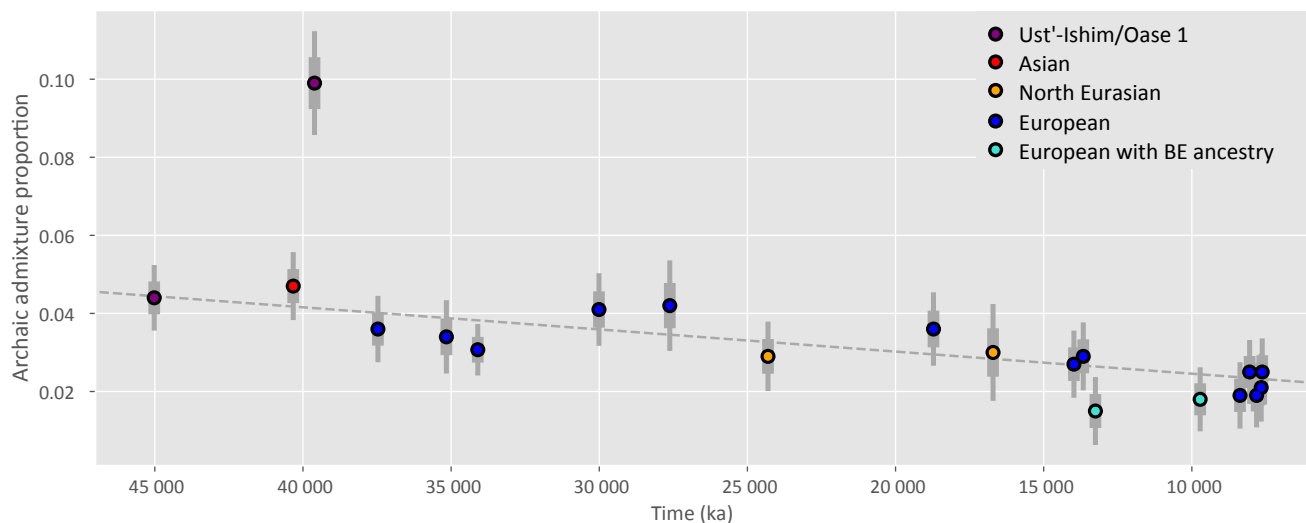
Dating to ~45 ka, the Ust'-Ishim individual [11] (Table 1) lived at a time when Neanderthals were still present in Eurasia, making his genome an exciting prospect for better understanding how Neanderthals and ancient modern humans interacted. Like present-day populations in Eurasia he carried Neanderthal DNA, but these stretches of Neanderthal DNA in his genome were on average 1.8–4.2 times longer than those found in present-day populations, a feature expected from an ancient individual if recombination had less time to fragment the introgressed Neanderthal segments than in populations today [11,41]. His genome therefore provided unequivocal support for Neanderthal admixture into ancient modern humans, as previously proposed models without admixture [6,42–47] do not explain longer Neanderthal segments in the Ust'-Ishim individual relative to present-day populations. His genome was also used to refine a previous estimate [45] of the date of admixture to between ~60 and 50 ka (or ~430–232 generations before the Ust'-Ishim individual lived [11]), which was corroborated by similar estimates for the ~37 000-year-old Kostenki 14 individual and the ~34 000-year-old Sunghir individuals from Russia [12,23].

Comparison with genomic data from multiple Neanderthal individuals across West Eurasia and in Siberia allows a better understanding of how the introgressing population was related to

Neanderthals sampled to date. This population is more closely related to recent Neanderthals than to the Siberian Altai Neanderthal who separated from more recent Neanderthals ~ 150 ka. This population is also similarly related to more recent Neanderthals, who share a common ancestor ~ 90 ka, suggesting that they separated from more recent Neanderthals at least 90 ka [40,48].

A second modern human contemporaneous with Neanderthals also provided new insight on archaic admixture. The Oase 1 individual from Romania dating to ~ 42 – 37 ka was sequenced in 2015 and shown to carry Neanderthal ancestry of ~ 6 – 11% [9,13], higher than in present-day non-African populations (~ 1 – 4% [6,13]) and ancient modern humans sampled to date (~ 2 – 5% [13], Figure 3). He possessed at least three segments of Neanderthal DNA that were >50 centiMorgans in size, indicating a Neanderthal relative four to six generations earlier [9]. Previous analysis [6] suggested that a single admixture event occurred soon after modern humans entered Eurasia, due to relatively similar amounts of Neanderthal admixture in all present-day non-African populations. The Oase 1 specimen's early age, his location in Romania, and his recent Neanderthal ancestor indicate that additional, perhaps more localized, admixture must also have taken place in Europe following this [9].

Today, East Asians show more Neanderthal ancestry than is observed in Europeans [7,32,41,49,50], with the most recent estimate of ~ 2.3 – 2.6% in East Asians and ~ 1.8 – 2.4% in Europeans [40]. One argument to explain this is more Neanderthal admixture events into East Asians [7,50–53]. Another is dilution of recent European populations from a population with little to no Neanderthal ancestry [7,52], perhaps the Basal Eurasians who separated from all other non-African populations prior to the introduction of archaic admixture [27,28] (Box 1). A third argument is more efficient purifying selection in European populations [41] due to their larger effective population size [54]. However, evaluation of demographic models accounting for differences in population size suggests that efficiency of selection alone cannot explain the



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Figure 3. Archaic Admixture Proportion in Eurasian Individuals Dating to ~ 45 – 7.5 ka. The proportion of archaic admixture estimated for several ancient Eurasians using an f_4 -ratio test [83], adapted from analyses from [13] and [16]. Thick bars are within one standard error (SE) of the estimate, while thin bars are within 1.96 SE of the estimate (95% confidence interval). Colors represent the predominant ancestry associated with each individual (see Table 1). The broken, gray regression line is calculated from all individuals but Oase 1 (purple, highest point) and Satsurblia and Kotias (teal), with a significantly negative slope ($p = 0.000001$).

observed differences in Neanderthal ancestry [52]. Currently, the verdict is still out on which model or combination of models is best supported, and greater understanding of archaic admixture in ancient modern humans from different time periods will help clarify the variation in Neanderthal ancestry in present-day humans.

Denisovans are a group of archaic humans who are more closely related to Neanderthals than either group is related to modern humans and overlapped geographically with Neanderthals, at least in the Altai region of Russia [7,55]. Analysis of the genome of a Denisovan individual showed that some present-day Oceanian populations carry ~4–6% ancestry from a population related to the Denisovan [55,56] from an admixture event that occurred ~54–44 ka [57]. Ancestry related to the Denisovan individual is also observed in Philippine Negrito populations (~1%) [58], as well as East Asian and American populations [11,59,60] and South Asian and Himalayan populations [32,57] who show a smaller but significant signal of admixture (~0.05–0.2% [57,60,61]). Either a single admixture event with dilution from populations with no Denisovan-like gene flow, recent backflow from Oceanian populations into Asia carrying Denisovan-related introgressed regions, or at least three episodes of admixture are needed to account for the differing levels of admixture observed in Oceanians, Negritos, East Asians, and South Asians [57,58,60]. Further review on when and where archaic admixture occurred can be found in [62]. Overall, study of the genomes of modern and archaic humans shows that multiple archaic admixture events occurred in human prehistory.

The distribution of Neanderthal DNA in present-day humans provides evidence that both purifying and positive selection have affected introgressed archaic DNA. Large ‘deserts’ in the modern human genome with fewer archaic alleles than one would expect under a neutral demographic model suggest reduced fitness of some archaic alleles in modern humans [41,50]. Such deserts on the X chromosome and enrichment of regions with low Neanderthal ancestry on testes-specific genes have been used to argue that Neanderthal DNA had a direct impact on male fertility [41,63,64]. Comparing ancient Eurasian individuals ranging in age from ~45 ka to the present day, a gradual decline in archaic ancestry is observed (Figure 3) [13]. Notably, this pattern is found in Europeans dating to ~37–14 ka. Dilution cannot explain this decline in these ancient Europeans, as they mostly show no evidence of external influences related to non-European populations. Instead, the decline is likely related to purifying selection acting to reduce archaic ancestry in modern humans over time in ~37–14 ka. Neanderthals underwent a population decline, resulting in much lower genetic diversity than modern human populations [61] and the accumulation of weakly deleterious alleles [63,64]. These alleles were likely carried by archaic gene flow into modern human populations, upon which more efficient selection in larger modern human populations led to a reduction in archaic ancestry over time [63,64]. Adaptive archaic introgression is also found; a Denisovan-like variant of the *EPAS1* gene affecting the occurrence of hypoxia at high altitudes is found in high frequency in Tibetan populations [65,66]. Genes associated with skin pigmentation, diet, cerebral development and immunity, amongst others [41,50,67] also show evidence of adaptive introgression. A detailed review is available in [68,69].

Ancient modern humans have provided a valuable resource for clarifying the number and types of archaic introgression that must have occurred and have aided in illustrating how archaic and modern human populations interacted in Eurasia. In addition, genomic data for multiple Neanderthal individuals have not only helped to better characterize the introgressing Neanderthal population who contributed to the ancestors of all non-African populations, but they also suggest that the Siberian Altai Neanderthal [70] and the more recent Vindija Neanderthal [40] both possess gene flow from ancient modern humans. Thus, interactions between modern

and archaic humans likely occurred prior to the separation of the Altai and Vindija Neanderthals [40].

Concluding Remarks

Studying the genomes of modern humans from ~45 to 7.5 ka reveals an incredibly rich human prehistory in Eurasia that is only hinted at in present-day genomes. They have increased our understanding of the nature and timing of early archaic admixture events and emphasized the role of population turnover and movement. These findings, and evidence of pervasive past population structure in Eurasia and high amounts of gene flow connecting more recent Eurasian populations, show the valuable contribution that ancient DNA makes to unraveling human history.

Using genetic data from ancient humans allow the correlations between biology and culture to be explored; for example, ~34–26 000-year-old individuals from the Gravettian culture are closely related to each other, despite their distribution across much of Europe. Examples where biology cannot be inferred from culture are also found; the Mal'ta 1 specimen and the Gravettian cultural complex are associated with female figurines, but no special genetic relationship is observed [13]. Comparison of the ~34 000-year-old Sungir individuals from Russia to each other indicates limited kinship and small effective population sizes similar to that found in present-day hunter-gatherer populations, suggesting that the social organization of at least the Sungir is like that found in present-day hunter-gatherers [23]. Furthermore, methods are being developed that assess human mobility in the past by comparing genetic, spatial, and temporal distance of sampled ancient modern humans, potentially showing that human populations after the LGM during the AMB show a decline in mobility followed by a sharp increase at the end of the AMC, related to populations associated with the Neolithic culture [71].

It is likely that our understanding of ancient humans will become more complex with more sampling. With no Denisovan ancestry in currently sampled ancient modern humans, we do not yet know when and where admixture related to Denisovans occurred in human history (see Outstanding Questions). In addition, while we have focused on modern humans younger than 45 ka, tantalizing new fossils attributed to ancient modern humans in China [10] and Sumatra Island, Indonesia [72] that date to ~120–80 ka and ~73–63 ka, respectively, immediately beg the question of when the oldest modern humans can be found in areas of Eurasia outside of the Near East, and how they are related to archaic humans and other modern humans.

Greater temporal and spatial resolution in genomic data from ancient humans will increase understanding of the biology of modern humans in many more geographic regions. Many current questions regarding archaic admixture and population structure in Eurasia have been addressed, but they highlight how little we know about other regions of the world. We are only just beginning to sequence ancient individuals from the African continent, particularly in the east [31,73] and south [31,74], where modern humans originated and interbreeding between archaic and ancient modern humans may have also occurred [75]. We also know little about the ancient continent of Sahul (consisting of Australia, New Guinea, and Tasmania) that shows evidence of human occupation by ~65 ka [76–78]. As the field of ancient DNA matures, sampling of archaic or ancient modern humans from Africa or Australia will allow us to expand beyond Eurasia when studying the population structure of early humans and characterizing the role archaic admixture played in human evolution. More recent history since the Neolithic has also been studied, particularly in Europe [8,27], the Near East [28], and the Americas [79], but these studies are beyond the scope of this review, though they have been discussed by others

Outstanding Questions

What is the relationship of ancient modern humans older than 45 ka to archaic and more recent modern humans?

What were the interpopulation dynamics ~14–7.5 ka leading to signals of gene flow between populations across Eurasia?

What were the possible selective pressures on modern humans ~45–7.5 ka?

Where was the introgressing Neanderthal population that contributed to the ancestors of non-African populations and when and where did gene flow occur from ancient modern humans to Neanderthals?

When and where did admixture between a Denisovan-like population and ancient modern humans occur?

What is the history of archaic admixture and demographic change in modern humans from the African or ancient Sahul continents?

Who were the 'Basal Eurasians', and what was their history?

[62,69,80]. It is an exciting time to be in the field of human evolutionary genetics, with both new answers and new questions generated by retrieval of human DNA from long ago.

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Supplemental Information

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