APPLICATIONS OF NEXT-GENERATION SEQUENCING

Harnessing ancient genomes to study the history of human adaptation

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Abstract | The past several years have witnessed an explosion of successful ancient human genome-sequencing projects, with genomic-scale ancient DNA data sets now available for more than 1,100 ancient human and archaic hominin (for example, Neandertal) individuals. Recent 'evolution in action' analyses have started using these data sets to identify and track the spatiotemporal trajectories of genetic variants associated with human adaptations to novel and changing environments, agricultural lifestyles, and introduced or co-evolving pathogens. Together with evidence of adaptive introgression of genetic variants from archaic hominins to humans and emerging ancient genome data sets for domesticated animals and plants, these studies provide novel insights into human evolution and the evolutionary consequences of human behaviour that go well beyond those that can be obtained from modern genomic data or the fossil and archaeological records alone.

Adaptation
A process of phenotypic and corresponding genetic change over time for traits that confer increased reproductive fitness in a given environmental context.

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Reconstructing the history of human biological adaptation has fascinated scientists (and many others) for more than 150 years[1,2]. How did humans evolve in response to the new environments they encountered while expanding across the globe[3]? Did prehistoric human populations adapt biologically to cultural changes such as the dietary shifts associated with agriculture[4]? Do our past adaptations have consequences for health and medicine today, especially given the extent to which some modern human environments and diets differ from those of the past?

With the human reference genome as a cornerstone and benefiting from advances in genotyping and sequencing technology, evolutionary population genetic analyses have greatly aided the study of human biological adaptation. That is, on the basis of patterns of genetic variation observed among living people, researchers can identify genome regions that contain putative 'signatures' of past positive natural selection[5,6]. If the functional consequences of candidate genetic variants can be determined using genotype–phenotype association studies[7] or animal or cell model experiments[8,9], then the plausibility of past adaptation can be evaluated with the comparative method — that is, by asking whether a phenotype evolves repeatedly and independently under similar environmental pressures[10] — or by using other, similarly indirect, approaches.

By contrast, analyses of 'time-stamped' ancient DNA data can provide more direct evidence of past human adaptation by facilitating precise 'evolution in action' tracking of genetic variants before, during and following selection events[11,12]. Excitingly, recent major advances in ancient DNA and sequencing methods (BOX 1) have facilitated a shift in this field from the analysis of mitochondrial genomes for a small number of individuals to the generation of genome-wide data sets (whole nuclear genome, exome, or genome-wide single-nucleotide polymorphism (SNP) data) at the scale of large populations[13,14]. In fact, ancient genomes are now available for >1,100 archaic hominins and anatomically modern humans (FIG. 1a) representing time periods from the Middle Pleistocene (430,000 years before present (BP)) to the early 20th century (FIG. 1b; TABLE 1). Importantly for our understanding of human evolution, analyses of these data sets can provide high-resolution snapshots of the adaptive histories of genetically mediated behaviour, metabolism, soft tissue and other non-skeletal phenotypes not preserved in the fossil or archaeological records.

In this Review, we discuss how the informational content of ancient DNA can be maximized to explore the history of human adaptation at unprecedented depth and precision. We highlight the scope of approaches that enable the detection of selection signatures from ancient genomes, and we use an anthropological lens to explore examples from three major research areas: first, insights from direct analyses of ancient human genomes into adaptations to environmental change and related to the transition from hunter-gatherer to farming lifestyles; second, inferences of adaptive introgression (and the inferred functional effects) of genetic material from archaic hominins to modern humans; and third, ancient DNA-based characterizations of

Box 1 | **Fuelling the ancient genomic explosion**

Before 2010, ancient genome data sets were composed primarily of small numbers of archaic hominin individuals (FIG. 1a) and non-primate mammals[150–153]. This pattern can be explained in part by the intense early excitement about archaic hominin genome sequencing[154]. Yet, perhaps also contributing to this field's history is the difficulty in distinguishing authentic ancient human DNA from contamination introduced, for example, from human excavators, museum staff or laboratory personnel. Although potential contamination was a challenge regardless — as illustrated by analyses of early Neandertal palaeogenomic data[155] — the process of identifying authentic ancient DNA is less onerous when not studying the maximally similar (to those people excavating and handling the material) ancient genomes of anatomically modern humans[98,99]. More recent studies have increasingly applied methodological and bioinformatic strategies that have helped to obviate this issue and to increase the confidence in ancient genomic data sets generated from anatomically modern humans[156]. For example, modern contaminants can be distinguished from authentic ancient molecules based on characteristic damage patterns of cytosine deamination at sequence fragment ends in ancient DNA[27,51]. Some laboratories now also perform a deamination repair step with a subset of each sample and then sequence both the unrepaired and repaired fractions in order to confirm authenticity while minimizing data loss and error[69,157].

Another trend in ancient human genomic studies has been the increasing reliance on relatively low-coverage sequence data (for example, ≤1x coverage, or an average of one or fewer sequence reads mapped to each nucleotide position of interest, per individual; FIG. 1a). This approach may also be combined with methods to enrich the sample for a targeted (but still substantial) fraction of the genome[20,28] (TABLE 1). Depending on the analyses being performed, working with these data sets requires imputation of missing data by comparison with a modern human reference genome panel[19], analytical focus on population allele frequency estimates rather than individual-level genotype calls[20], or other precautions[69]. Such approaches greatly increase the feasibility of population-scale ancient DNA studies as a function of reduced sequencing costs (we note that as sequencing costs continue to decrease, we might eventually expect shifts towards higher proportions of more broadly powerful higher-coverage, whole-genome sequencing of ancient genome data sets). Combined with other laboratory methodological improvements[27,158–160] and continuing sequencing technology advances[161], these analytical innovations have helped fuel the recent rapid growth in the availability of ancient human genome data sets that may now be included in increasingly powerful evolutionary analyses.

human-mediated selection on domesticated plant and animal species that provide insight into past human behaviour and evolution.

Tracking adaptation with ancient DNA

Positive natural selection is a nonrandom, directional process resulting in frequency increases of alleles associated with phenotypes that confer relative fitness advantages in a given spatiotemporal environmental context. Although this process has shaped patterns of modern human genetic diversity in ways that are detectable in present-day genomes[6,15,16], for most traits, it is only by turning to ancient DNA that we can establish precisely when and where such adaptive traits emerged.

The transformative power of ancient genomics for detecting and characterizing the genetic signatures of past human adaptations draws on our ability to access direct radiocarbon (^{14}C) or indirect archaeological (for example, on the basis of pattern changes in tools, pottery or other artefacts associated with burials) estimates of the time period in which a particular individual lived. Armed with these data, researchers can explicitly track the trajectories of genetic variants before, during, and following selection events[11,12,17,18]. Furthermore, ancient genome data can also be used to identify oscillating allele frequency patterns that would otherwise be largely obscured from modern genome records[19,20]. Precise knowledge of the spatiotemporal history of human adaptation can in turn facilitate integrative analyses of the specific environmental and cultural contexts associated with adaptive events and the corresponding implications for models of past human health and fitness.

The general evolutionary ancient genomics approach is straightforward: identify genetic variants with frequency changes significantly greater over a given time period than expected under genetic drift alone and/or relative to the genome-wide distributions of variant frequency changes (FIG. 2). This approach can be used to refine and test longstanding evolutionary hypotheses[20–24] or to develop novel ones on the basis of newly uncovered signatures of selection[25]. These strategies can also be extended to study polygenic adaptation, in which fairly subtle but consistent changes in the frequencies of multiple trait-associated loci can have large phenotypic effects in aggregate[26]. Specifically, ancient genome data can be used to test whether shifts in the collective frequencies of a set of alleles known from a modern genome-wide association study (GWAS) to act directionally on a phenotype of interest — for example, stature — are unusual across a given time period compared with genome-wide backgrounds of frequency-matched alleles[20].

An important consideration to account for in evolutionary ancient genome analyses is that ancient human populations may not necessarily be closely related to subsequent or present-day people living in the same geographic regions. For example, recent ancient DNA-based studies have demonstrated a striking degree of repeated, large-scale human population movement and replacement across the past ~7,000 years in Europe[19,27–30], well beyond that previously predicted by even the most extreme archaeological models of population turnover[31]. Although such complex demographic histories can complicate ancient DNA-based interpretations of allele frequency change across time[11,18], methods to identify genome-wide and genome region-specific population structure can be incorporated into evolutionary ancient genome analyses to help distinguish between models of *in situ* change versus replacement or gene flow from a population with substantial differences in allele frequency[20,32].

Recent human evolution

The temporal distribution of available human ancient genomes (FIG. 1b) overlaps periods of major environmental and cultural change that are widely hypothesized to have represented significant drivers of recent human biological adaptation[4,33]. For one, the expansion of anatomically modern humans to diverse habitats across the globe resulted in novel exposures to northern latitudes and cold climates[34]. Two, the transition from hunting and gathering lifestyles to agriculture was associated with major dietary shifts[35], the construction of permanent settlements, and population density increases that in combination probably led to novel exposure to some pathogens and increases in the prevalence of others[36,37]. Thus, evolutionary analyses of ancient genomes have

Positive natural selection
A mechanism of evolution in which a genetically mediated trait that confers a relative fitness advantage increases in frequency over time because of that advantage. In this Review, we refer to positive selection as an adaptive process that can act on new or previously existing genetic variants.

Phenotype
Physical traits of an organism; often refers to externally visible traits but may include internal and microscopic or biochemical traits.

Ancient DNA
DNA from palaeontological, archaeological, or historical but pre-modern biological specimens that is often damaged and degraded and recovered in small quantities.

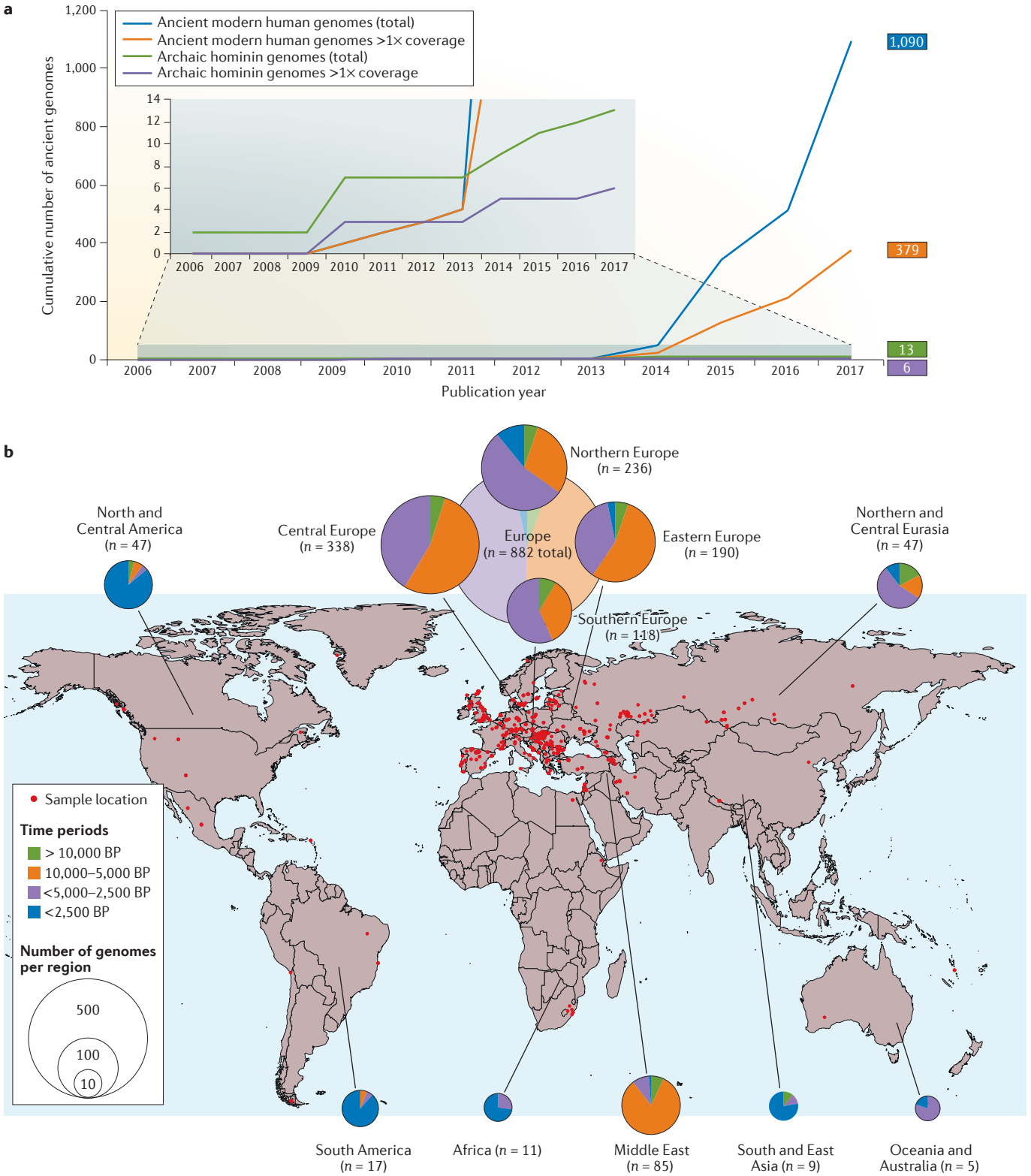


Figure 1 | **The recent (and ongoing) ancient genomic explosion. a** | Cumulative counts of the numbers of ancient human and archaic hominin individuals with available ancient genomic data (whole genome sequences, exomes, and genome-scale single-nucleotide polymorphism data sets), by year of publication. For each category, both the total number of individuals and the subset of that sample with an average of >1 sequence read per targeted site are depicted. **b** | A spatiotemporal distribution of ancient human and archaic hominin genome data sets, where the areas of the circles are proportional to the genome counts. For some archaeological sites, precise geographic coordinates were not indicated in the corresponding publication; longitude and latitude were estimated in these cases. A summary of the published studies and data sets represented in the figure is provided in TABLE 1.

Exome
All or nearly all protein-coding gene regions of the nuclear genome; in humans, representing approximately 1% of the genome.

Table 1 | **Human and archaic hominin ancient genome data sets**

Reference	Year	Number of individuals with new ancient genome data*				Data type	Sample locations‡	Number of individuals per time period§			
		Archaic hominins		Ancient humans				>10,000 years BP	10,000–5,000 years BP	<5,000–2,500 years BP	<2,500 years BP
		Total	>1x	Total	>1x						
Noonan *et al.*[150]	2006	1	0			Direct cloning and WGS	Central Europe	1			
Green *et al.*[151]	2006	1	0			PCR and 454 sequencing	Central Europe	1			
Green *et al.*[98]	2010	4	1			Restriction enzyme-based enrichment	Central, southern and eastern Europe	4			
Burbano *et al.*[167]	2010	0	1			SNP capture	Southern Europe	1			
Reich *et al.*[99]	2010	1	1			WGS	Northern and central Eurasia	1			
Rasmussen *et al.*[156]	2010			1	1	WGS	North America			1	
Rasmussen *et al.*[168]	2011			1	1	WGS	Oceania and Australia				1
Keller *et al.*[169]	2012			1	1	WGS	Southern Europe		1		
Skoglund *et al.*[170]	2012			4	0	WGS	Northern Europe		2	2	
Fu *et al.*[171]	2013			1	1	Chromosome 21 capture	South and central Asia	1			
Castellano *et al.*[108]	2014	1	1			Exome	Central Europe	1			
Prufer *et al.*[102]	2014	1	1			WGS	Northern and central Eurasia	1			
Fu *et al.*[172]	2014			1	1	WGS	Northern and central Eurasia	1			
Schroeder *et al.*[173]	2014			3	0	WGS	North America				3
Gamba *et al.*[19]	2014			13	8	WGS	Central Europe		9	4	
Lazaridis *et al.*[52]	2014			9	3	WGS	Central, northern and western Europe		9		
Malaspinas *et al.*[174]	2014			4	2	WGS	South America				4
Olalde *et al.*[51]	2014			1	1	WGS	Southern Europe		1		
Raghavan *et al.*[175]	2014			1	1	WGS	Northern and central Eurasia	1			
Rasmussen *et al.*[176]	2014			1	1	WGS	North America	1			
Seguin-Orlando *et al.*[177]	2014			1	1	WGS	Eastern Europe	1			
Skoglund *et al.*[178]	2014			7	2	WGS	Northern Europe		4	3	
Allentoft *et al.*[27]	2015			101	19	WGS	Central, northern, eastern and southern Europe; northern and central Eurasia		8	86	7
Fu *et al.*[179]	2015			1	1	Genome-wide SNPs	Eastern Europe	1			
Haak *et al.*[28]	2015			69	41	Genome-wide SNPs	Central, northern, eastern and southern Europe; northern and central Eurasia		45	24	
Mathieson *et al.*[20]	2015			83	31	Genome-wide SNPs	Central, eastern and southern Europe; Middle East; northern Eurasia		34	48	1

Table 1 (cont.) | **Human and archaic hominin ancient genome data sets**

Reference	Year	Number of individuals with new ancient genome data*				Data type	Sample locations‡	Number of individuals per time period§			
		Archaic hominins		Ancient humans				>10,000 years BP	10,000–5,000 years BP	<5,000–2,500 years BP	<2,500 years BP
		Total	>1x	Total	>1x						
Gallego Llorente *et al.*[180]	2015			1	1	WGS	Africa			1	
Günther *et al.*[47]	2015			8	3	WGS	Southern Europe			8	
Jones *et al.*[49]	2015			3	3	WGS	Central and eastern Europe	2	1		
Olalde *et al.*[181]	2015			6	1	WGS	Southern Europe		6		
Raghavan *et al.*[182]	2015			23	3	WGS	North and South America		2	1	20
Sawyer *et al.*[183]	2015	2	0			WGS	Northern Eurasia	2			
Rasmussen *et al.*[184]	2015			1	1	WGS	North America	1			
Cassidy *et al.*[30]	2016			4	3	WGS	Northern Europe		1	3	
Martiniano *et al.*[185]	2016			9	6	WGS	Northern Europe				9
Schiffels *et al.*[186]	2016			10	9	WGS	Northern Europe				10
Fu *et al.*[187]	2016			37	6	Genome-wide SNPs	Central, eastern, western and southern Europe; northern and central Eurasia	32	5		
Broushaki *et al.*[50]	2016			5	3	WGS	Middle East		4		1
Lazaridis *et al.*[157]	2016			44	16	Genome-wide SNPs	Middle East and eastern Europe	6	31	7	
Gallego Llorente *et al.*[188]	2016			1	1	WGS	Middle East		1		
Kılınç *et al.*[189]	2016			9	1	WGS	Middle East		9		
Jeong *et al.*[54]	2016			8	5	WGS	South and East Asia			1	7
Hofmanová *et al.*[69]	2016			7	5	WGS	Middle East and southern Europe		7		
Omrak *et al.*[190]	2016			2	0	WGS	Middle East		2		
Meyer *et al.*[191]	2016	1	0			WGS	Southern Europe	1			
Lindo *et al.*[81]	2016			24	25	Exome	North America			1	23
Skoglund *et al.*[192]	2016			4	4	WGS	Oceania and Australia			4	
Jones *et al.*[193]	2017			8	3	WGS	Northern and eastern Europe	1	7		
Unterländer *et al.*[194]	2017			8	0	Genome-wide SNPs and WGS	Northern and central Eurasia			4	4
Lipson *et al.*[195]	2017			127	26	Genome-wide SNPs	Central and southern Europe		93	34	
Lindo *et al.*[196]	2017			1	0	WGS	North America	1			
Kennett *et al.*[197]	2017			6	0	Genome-wide SNPs	North America				6
Mathieson *et al.*[198]	2017			195	95	Genome-wide SNPs	Central, eastern, Western, Northern, and Southern Europe	5	150	40	
Olalde *et al.*[29]	2017			165‖	0	Genome-wide SNPs	Central, Northern, western and southern Europe		15	150	

Table 1 (cont.) | **Human and archaic hominin ancient genome data sets**

Reference	Year	Number of individuals with new ancient genome data*				Data type	Sample locations‡	Number of individuals per time period§			
		Archaic hominins		Ancient humans				>10,000 years BP	10,000–5,000 years BP	<5,000–2,500 years BP	<2,500 years BP
		Total	>1x	Total	>1x						
Martiniano *et al.*[199]	2017			14	7	WGS	Southern Europe		10	4	
Siska *et al.*[200]	2017			5	0	WGS	Northern and Central Eurasia		5		
Haber *et al.*[201]	2017			5	4	WGS	Middle East			5	
González-Fortes *et al.*[48]	2017			6	6	WGS	Eastern and southern Europe		6		
Schuenemann *et al.*[202]	2017			3	1	Genome-wide SNPs	Africa			2	1
Schlebusch *et al.*[203]	2017			7	5	WGS	Africa				7
Mittnik *et al.*[204]	2017			24	16	Genome-wide SNPs	Northern Europe, northern and central Eurasia		7	12	5
Slon *et al.*[205]	2017	1	1			WGS	Northern and central Eurasia	1			
Günther *et al.*[25]	2017			7	4	WGS	Northern Europe		7		

The authors apologize for any accidental omissions of published ancient human or archaic hominin genomic data sets. These data are otherwise intended to be current as of 25 July 2017. SNP, single-nucleotide polymorphism; WGS, whole-genome sequencing. *>1× indicates an average of greater than one sequence read mapped to each targeted site. If a new study generated additional DNA sequencing data for the same individual as included in a previous study, a new genomic data set was not recorded for that individual[20,29,81,103,108,178,196,198,206]. However, for cases in which coverage was newly increased to >1×, this update was recorded[20,81,167]. ‡Geographic region definitions: central Europe: Croatia, the Czech Republic, Hungary, Austria, Poland, Germany, Switzerland, Serbia; eastern Europe: Belarus, the Ukraine, eastern Russia, Bulgaria, Montenegro, Caucasus, Romania; northern Europe: Estonia, Denmark, Sweden, Lithuania, Latvia, Ireland, United Kingdom, Norway, Netherlands, Belgium, France, Luxembourg; southern Europe: Spain, Portugal, Italy, Greece, Macedonia; South and East Asia: Nepal, China; northern and central Eurasia: Russia, Kazakhstan; Middle East: Iran, Israel, Turkey, Jordan, Lebanon; North America: Canada, United States, Greenland, Central America, the Caribbean; South America: Brazil, Chile; Africa: Ethiopia, Egypt. §For small subsets of samples without reported specific dates[27,48,50,81,181,190], cultural periods were used to estimate time periods. ||For this study[29], sequence coverage per targeted SNP per sample was not provided. Among the samples, a range of 5,722–936,369 SNPs (of 1.24 million targeted SNPs) was covered by one or more sequencing reads. We recorded all samples as <1×; however, a small proportion of samples could actually cross this threshold.

the potential to confirm, refine, and expand our current understanding of the history of recent human biological adaptation.

Adaptation to novel environments. The roughly latitudinal gradient of ultraviolet A and B (UVA and UVB) radiation is thought to have been the principal evolutionary driver of modern human skin colour variation, with dark pigmentation in tropical latitudes protecting folate from photolysis, and depigmented skin in more northern and southern latitudes allowing for higher proportions of the fewer UVB rays to penetrate the skin to facilitate adequate vitamin D production[38]. Vitamin D can also be acquired through a limited number of dietary sources, with fatty fish being one of the richest sources and smaller amounts found in beef liver, dairy products and egg yolk; however, this nutrient is largely absent from most agricultural plants[39–41]. Vitamin D insufficiency is associated with cardiovascular disease, musculoskeletal disorders (for example, rickets), pre-eclampsia in pregnancy and other health concerns[42,43].

Given the predicted strong negative fitness effects of insufficient vitamin D production, it is interesting that recent ancient genome analyses have revealed a very gradual evolution of depigmentation among European modern humans following their expansion into this region. Specifically, derived alleles associated with lighter skin pigmentation in the genes *SLC45A2*, *SLC24A5*, *TYR* and *HERC2* are nearly fixed or are observed at their highest frequencies worldwide among living Europeans[44,45], with modern-human genome-based analyses estimating that selection acted on the major-effect alleles *SLC45A2* and *SLC24A5* 19,000–11,000 years BP[46]. However, ancient genome data demonstrate that although the *SLC45A2* allele was present as early as ~9,000 years BP in Scandinavia[25], it was absent or found at only fairly low frequencies at most sites across Europe before the onset of the Copper Age ~5,300–4,800 years BP[19,20,27,47,48]. Meanwhile, although the *SLC24A5* allele was slightly more widely distributed by the Neolithic (that is, before ~7,000 years BP) in central and northern Europe[19,20,25,27,30,49] and in the Middle East[50], the ancestral allele was predominant in hunter-gatherers who lived ~13,000–7,000 years BP in what are now Spain ($n = 3$ individuals), Romania ($n = 3$), Switzerland ($n = 1$) and Luxembourg ($n = 1$)[48,49,51,52]. Finally, *TYR* and *HERC2* variants associated with lighter skin colour also experienced major frequency increases only fairly recently (for example, from 0.04 to 0.37 and from 0.16 to 0.65, respectively, between 6,500 and 4,000

Single-nucleotide polymorphism
(SNP). A single position in the reference genome at which the specific nucleotide present (thymine, guanine, cytosine, or adenine) varies among individuals in a population or species.

Archaic hominins
Now-extinct populations or species that are distinct from anatomically modern humans but that share a more recent common ancestor with modern humans than with chimpanzees — for example, Neandertals and Denisovans.

Anatomically modern humans
Hominins recognizable phenotypically as early members of our own species, *Homo sapiens*, first appearing >200,000 years BP in Africa.

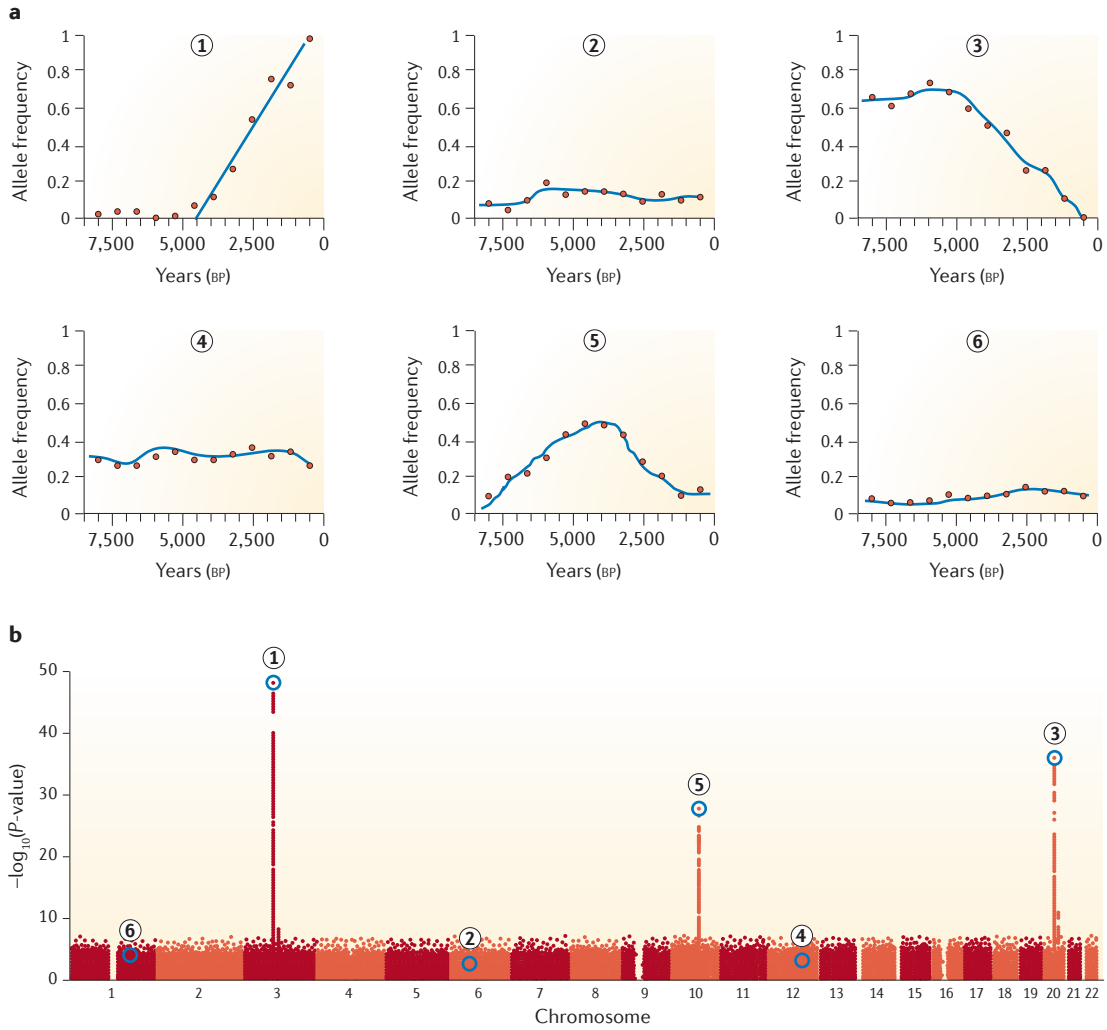


Figure 2 | **Ancient genomic signatures of positive natural selection. a** | Illustrative examples of derived allele frequency trajectories over time for a human population. At most loci in the genome, genetic variants are subject to genetic drift or purifying selection and are not observed to have changed substantially in frequency over the investigated time period. Relatively rarely, a new mutation (or an existing mutation following environmental or cultural change resulting in different evolutionary pressures) confers a fitness benefit and may rapidly increase in frequency. **b** | Each variant across the genome is tested for an unexpectedly large temporal frequency shift. The statistical significance of each variant is shown as an individual point (due to the density of variants, most points cannot be individually differentiated) arranged by human chromosome position on the *x* axis and negative log *P*-value on the *y* axis.

Adaptive introgression
The process of a genetic variant that was originally introduced into a population via admixture increasing in frequency by positive natural selection because it confers a fitness advantage.

Genetic drift
Changes in genetic variation over time that are due to random (chance) processes, apart from natural selection.

Gene flow
Movement of genetic variation between populations, for example, through migration or admixture.

Neolithic
A cultural period in human prehistory characterized by early technological and demographic shifts associated with the transition to farming and pastoralism, occurring at different times across regions.

years BP in Ukraine)[19,53]. Interestingly, in one study, the derived *HERC2* variant was observed at higher frequency in earlier hunter-gatherer samples than in later agriculturalist samples[20], perhaps reflecting the substantial European population turnover processes mentioned above.

In a South Asian ancient genome study, Jeong *et al.*[54] observed a similarly staggered history of physiological adaptations to the low-oxygen, high-altitude environment of the Himalayan Arc in Nepal ($n = 5$ individuals from 3,150 to 1,250 years BP). Specifically, whereas a derived *ELGN1* allele associated with maintaining oxygen homeostasis under high-altitude stress[55] was represented in every sequence read mapped to this position for all five individuals, derived *EPAS1* variants associated with reduced haemoglobin levels that help limit high-altitude sickness[56] were absent in the earliest individuals from this region and were only variably present in the most recent period (1,750–1,250 years BP; $n = 2$)[54].

The gradual evolutionary histories of skin depigmentation and high-altitude-related adaptations among ancient Europeans and Himalayans, respectively, as revealed by ancient genomic analyses, may have several explanations. First, the random process of mutation is likely to play a part; that is, natural selection can only act on variation once it exists. Second, a time lag between the origin and geographic spread of an adaptive allele is to be expected[57,58], especially when considering the variability of ancient human migration patterns. Regardless, these ancient DNA-based evolutionary insights have implications for our understanding of prehistoric human

health and fitness. For example, does the finding of a relatively slow depigmentation process suggest that ancient Europeans were fairly susceptible to musculoskeletal or cardiovascular conditions associated with low levels of vitamin D? Alternatively, pre-agricultural Europeans could have ingested substantially more dietary vitamin D through hunting and fishing, as suggested by at least some archaeological evidence[59,60], to at least partially offset the expected reduction in skin-based production of this critical vitamin. Indeed, skeletal evidence of vitamin D insufficiency from the archaeological record is rare before the origins of agriculture, when it then begins to increase over time[40]. Future integrative studies that directly combine ancient genomic, archaeological and palaeopathological data sets might help researchers to more thoroughly characterize temporal variation in human health in the context of environmental change.

Biocultural adaptation to agricultural diets. Although some domestication processes probably had earlier roots[61,62], the archaeological record demonstrates that full transitions to agriculture for human societies were under way by ~12,000 years BP in the Middle East and not long after in Southeast Asia, the Americas and sub-Saharan Africa[63]. The subsequent near-worldwide spread of this technology led to novel evolutionary pressures associated with innumerable lifestyle, demographic and dietary changes. For example, one major dietary consequence of the agricultural transition was reduced nutritional diversity relative to the diets of many hunter-gatherer societies; starch alone comprises up to 70% of the caloric intake for some modern agriculturalist populations[64]. Such specialization may have simultaneously resulted in new or increased evolutionary pressures on increasing digestive capacity for newly dominant food sources and maximizing metabolic efficiency for critical nutrients now deficient in some subsistence agricultural diets.

A classic example of biocultural adaptation is the co-evolution of the persistent production of the milk sugar lactose-digesting enzyme lactase into human adulthood with the cultural practice of collecting and consuming milk and dairy products from domesticated animals such as sheep, goats and cattle[65]. Without lactase persistence, human adults who consume lactose can have intestinal symptoms including diarrhoea, resulting in nutritional loss even beyond not receiving direct energetic benefits from lactose digestion[66]. Human lactase persistence has evolved independently in multiple regions worldwide[67]. In Europe, the regulatory mutation conferring lactase persistence has been modelled based on modern human genetic data to have undergone selection beginning ~7,500 years BP[68], coincident with the spread of Neolithic (farming) cultures into this region. However, ancient DNA data clearly demonstrate a substantially more recent frequency increase and geographic spread of this adaptive variant only within the past ~5,000 years[19,20,27,30,69,70] (FIG. 3; Supplementary table S1). Once again, this result has important implications for our models of prehistoric human health and behaviour, given that convincing archaeological evidence of dairy production in Europe predates this new understanding of the emergence of the lactase persistence phenotype by more than two millennia[71,72]. Before the spread of the adaptive allele, milk drinking behaviour by adults may have been more limited, and/or early dairy processes may have emphasized lactose-reducing processing techniques (for example, some cheese-making and fermentation processes), for which there is archaeological evidence from multiple European sites between 7,400 and 6,800 years BP[73,74] (FIG. 3c).

Amylase, which is produced in humans by genes expressed in both the saliva (*AMY1*) and pancreas (*AMY2A* and *AMY2B*), is the enzyme responsible for the initial stages of starch digestion. Most present-day humans have an expanded number of *AMY1* gene copies relative to chimpanzees, a difference associated with higher levels of salivary amylase protein expression[75]. Human *AMY1* duplications are associated with signatures of positive natural selection[76]. The original *AMY1* duplications post-date our divergence with the Neandertal and Denisovan lineage but pre-date modern human origins[77]. At least some modern human populations with traditionally high-starch diets have higher average *AMY1* copy numbers than low-starch populations[75], suggesting potential biocultural adaptation for expansion of the *AMY1* locus following the agricultural transition. The few ancient DNA results reported to date are inconclusive with respect to this hypothesis; three European hunter-gatherers are estimated to have had five, six, and 13 diploid *AMY1* gene copies[51], whereas a Neolithic farmer from Germany (~7,000 years BP) had ~16 copies[52]. This test is an opportunity for future ancient genome analyses, even of existing data sets.

Current models of compensatory adaptations to nutritional deficiencies putatively associated with the transition to agriculture are also incomplete, but ancient DNA has an important role in our developing understanding of this evolutionary dynamic. For example, relative increases in the consumption of plants in some agricultural diets may have placed indirect evolutionary pressure on metabolic pathways of long-chain polyunsaturated fatty acids. These nutrients, which are consumed at higher levels in diets incorporating more animal protein (for example, from meat, fish or marine mammals), are critical for inflammatory responses and brain development[78]. Human ancient genome data were used to identify a haplotype encompassing the fatty acid desaturase genes *FADS1* and *FADS2* that experienced marked frequency changes over the past ~4,000 years[20,22,23]. Functional alleles in this haplotype can convert plant-based short-chain polyunsaturated fatty acids to long-chain fatty acids, thereby potentially compensating for the reduced dietary intake of these nutrients[22].

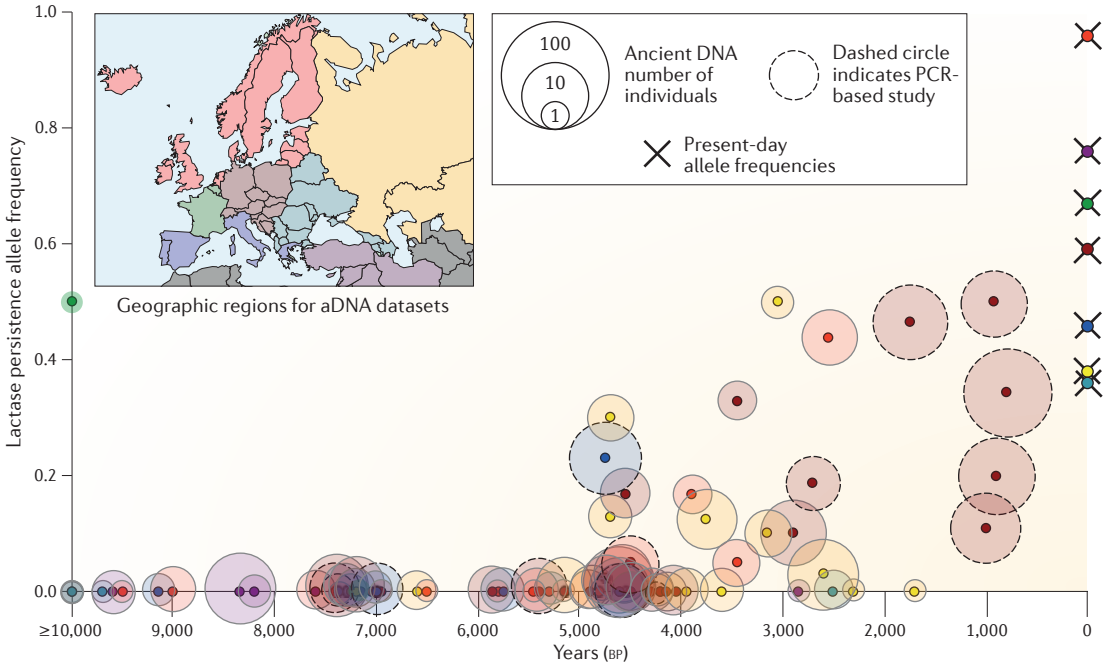
Similarly, the amino acid ergothioneine, which is involved in protecting cells from oxidative stress and in the inflammatory response[79], must be obtained through dietary sources but is found at only very low quantities in domesticated cereal grains (for example, wheat and barley)[80]. A functional variant in the ergothioneine transporter gene *SLC22A4* is hypothesized to have

Domestication
A process of plant and animal evolution mediated by human selection for particular phenotypes (artificial selection), sometimes combined with commensal adaptation to human-constructed niches.

Biocultural adaptation
The process of interaction between human cultural and adaptive biological change (for example, dairying and the ability of adults to digest milk sugars).

a Archaeological evidence of early Neolithic (7,500–5,000 BP) dairying in Europe

b Frequency of the European lactase persistence allele over time, by region



c Early archaeological evidence of lactose-reducing dairy processing techniques

Figure 3 | **Biocultural adaptation to dairying and milk consumption. a** | In addition to the early Neolithic presence of cattle and other domestic animals commonly milked for human consumption[163], early archaeological evidence of dairying practices in Europe include cattle-, sheep- and goat-specific β-lactoglobulin milk proteins recovered from human dental calculus and pottery fragments containing milk fat residues. **b** | Ancient DNA-based allele frequency estimates over time for the regulatory variant that confers the lactase persistence phenotype in Europe. For each population, the circle size represents ancient DNA sample size, and shading indicates geographic region. Centre time points reflect the midpoints of the date range estimates for each population sample. Allele frequencies estimated with PCR-based methods rather than from ancient genomic data sets are indicated with dashed circles; detecting and accounting for DNA damage and contamination is more difficult in PCR-based studies, potentially resulting in higher error rates. For reference, lactase persistence allele frequencies for present-day European populations are also indicated. A summary of the data used for this plot is provided in Supplementary table S1. **c** | Archaeological evidence of an early Neolithic dairy processing technique that would have resulted in reduced lactose contents for consumption by adults without lactase persistence. Shown is an ~7,200 years BP (before present) sieve fragment from Poland used for the production of lactose-reduced cheeses. Also shown is an ~3,800 years BP preserved piece of kefir (lactose-free) cheese from China made via fermentation. Part **a** (left panel) is reproduced with permission from REF. 162, CC-BY 4.0. Part **a** (middle panel) is reproduced with permission from REF. 164, CC-BY 4.0. Part **a** (right panel) is reproduced with permission from REF. 165, Macmillan Publishers Limited. Part **c** (left panel) image courtesy of Mélanie Roffet-Salque, University of Bristol, UK. Part **c** (right panel) is reproduced with permission from REF. 166, Elsevier.

provided protection against ergothioneine deficiency via increased absorption of this amino acid in European agriculturalists[80]. However, although this allele was present at low frequencies in earlier stages of the Neolithic, ancient genome data have revealed that major frequency increases occurred only within the past 4,000 years[20]. Thus, any farmers in this region who specialized in cultivating cereals earlier than 4,000 years BP would have been doing so without the widespread presence of this potentially compensatory allele. Alternatively, dietary diversity may have been greater in earlier time periods, limiting evolutionary pressure on the efficiency of this metabolic pathway until more recently.

Adaptation to a changing pathogen landscape. The human burden of infectious diseases is hypothesized to have changed dramatically following the transition to agriculture[36,37]. This phenomenon is thought to be explained by multiple factors, including the shift from small-group-based mobile hunting and gathering lifestyles to inhabiting permanent settlements with increasing population densities, being surrounded by human-modified habitats favoured by vector insects, and living in close proximity to livestock, which act as reservoirs of zoonotic pathogens. This period of novel exposure to some pathogens and increases in the prevalence of others was probably associated with intense new evolutionary pressure on the human immune system, including dynamic changes to the fitness spectrum (detrimental to neutral to beneficial) of functional alleles involved in pathogen defence.

Multiple ancient genome analyses have already helped to identify and characterize the trajectories of numerous adaptive alleles located within or near pathogen response and immune system genes in human populations worldwide[20,50,51,69,81]. At present, equating particular ancient genome changes with evolved resistance to particular pathogens represents a major challenge due to both the broad immune system functions of many genes and uncertainty in the spatiotemporal distribution of exposure to multiple pathogens that were themselves also evolving. Yet, such inference may become increasingly possible with the improving power of modern disease–genotype association studies and the identification of subsets of alleles with relatively specific disease resistance effects, as for example with a number of *Plasmodium falciparum* and *Plasmodium vivax* malaria-resistance alleles[21].

A different form of ancient genome data could ultimately provide major analytical benefits to these analyses by reducing the spatiotemporal uncertainty of past disease presence or absence and of disease prevalence. Specifically, beyond reconstructing endogenous genomes from ancient human skeletal remains, researchers can also characterize the ancient genomes of various pathogens that may have infected individuals during life[82], as recently done for tuberculosis (*Mycobacterium tuberculosis*)[83], leprosy (*Mycobacterium leprae*)[84], plague (*Yersinia pestis*)[85], malaria (*P. falciparum*)[86,87], smallpox (Variola virus)[88], cholera (*Vibrio cholerae*)[89], *Staphylococcus saprophyticus*[90] and others[82,91].

It is also possible with ancient DNA data to reconstruct the virulence characteristics of pathogen strains as they evolved over time[89]. For example, Rasmussen *et al.*[92] sequenced the genomes of seven Eurasian *Yersinia pestis* strains from 5,000–2,800 years BP and analysed these data with those from other published ancient and modern *Y. pestis* strains. Interestingly, all strains from before 3,600 years BP were missing the *ymt* gene, which encodes a protein needed for the viability of the pathogen in the gut of its vector, the flea[93]. By contrast, nearly all *Y. pestis* strains from ~2,900 years BP to today contained an intact *ymt* gene copy, thus marking one of the key factors probably associated with the bubonic plague transmission cycle. Conversely, a ~660 years BP *Y. pestis* genome sequence recovered from London Black Death victims did not contain any derived nucleotide changes not also observed in present-day *Y. pestis* genomes, suggesting a potentially important role for concomitant human behaviour and ecology in the Black Death pandemic rather than genetic changes in the pathogen itself[94].

Continued expansion of these efforts will help to more precisely define the spatiotemporal distributions of ancient pathogens and to model their effects on host morbidity and mortality, knowledge that is in turn important for testing human immune system co-evolution hypotheses with endogenous ancient genome data, potentially even on local scales[95].

Archaic adaptive introgression

A rich history of intrigue surrounds the potential genetic contributions of archaic hominins to present-day modern humans. Hypotheses on this topic have ranged from the *in situ* evolution of anatomically modern humans from archaic hominin ancestors such as Neandertals in multiple continental regions, requiring extensive long-term gene flow[96], to a single sub-Saharan African origin of modern humans followed by widespread worldwide dispersal and the complete replacement of remnant archaic hominin populations, with no interbreeding[97].

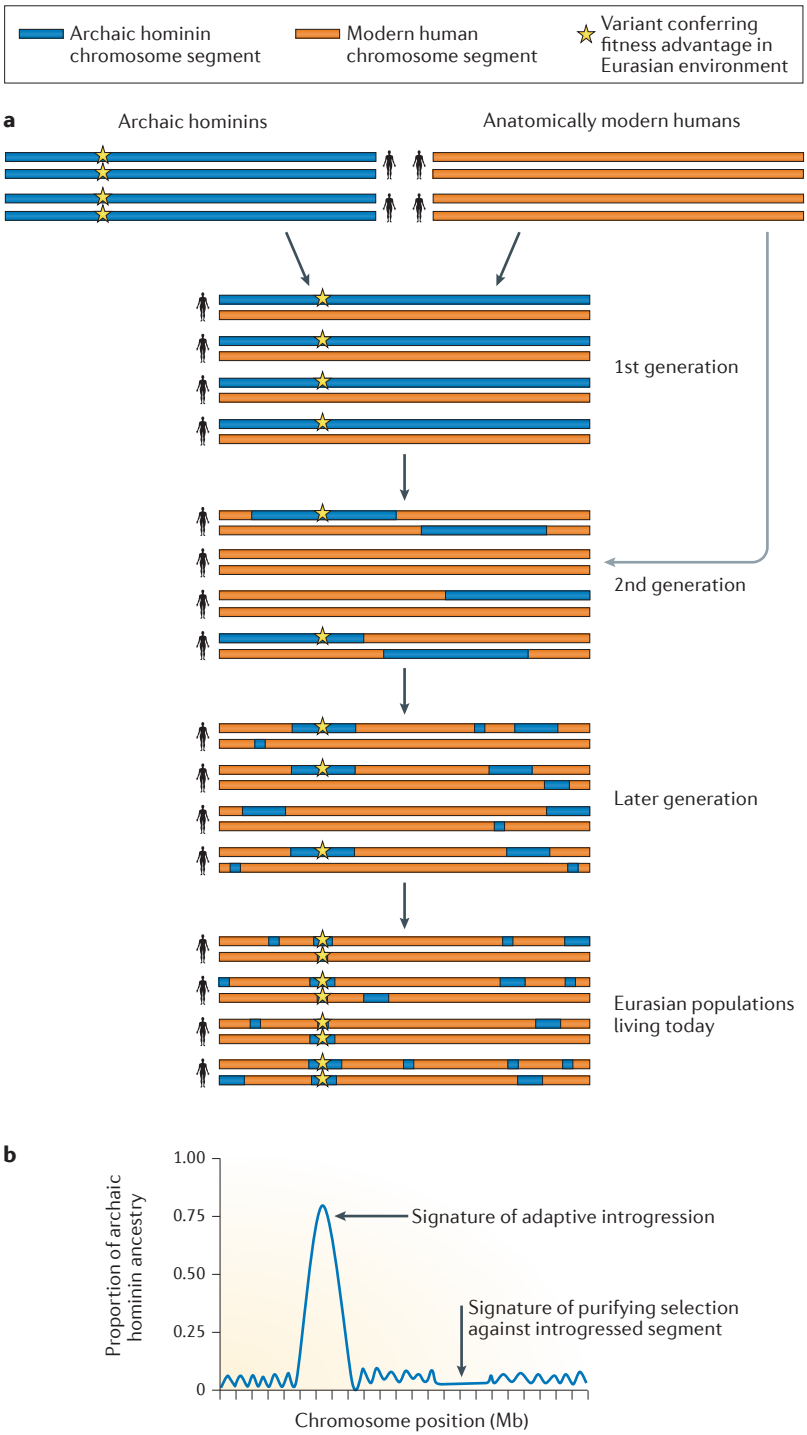
Excitingly, not only have archaic hominin 'palaeogenomic' data helped to provide a definitive answer to this question — the correct model is intermediate between the two hypotheses[98] — but this field has also uncovered evidence of an additional, previously unsuspected contemporary archaic hominin lineage, the Denisovans[99]. We now know that modern humans did largely replace non-African archaic hominin populations after expanding across the globe, but not before multiple interbreeding and admixture events, which have left a legacy of an average of ~1–4% Neandertal DNA in the genomes of Eurasian and Native American humans living today[98,100–102] and of up to ~6% Denisovan ancestry in the genomes of indigenous Australians, Melanesians and some other Southeast Asian populations[99,103–107].

As a brief aside (but one that is of major interest for palaeoanthropologists), the presence of Neandertal and Denisovan alleles in modern humans living today means that there are two genomics-based pathways to help reconstruct archaic hominin evolutionary biology: one, through direct analyses of archaic hominin

Zoonotic
The ability of a pathogen to be directly or indirectly transmitted to humans from animals sharing the same habitat.

Admixture
Interbreeding between previously isolated populations.

palaeogenome sequences for loci where function can be inferred or tested[77,108–110]; two, and perhaps much more powerfully, through GWAS or functional analyses conducted in modern humans that characterize the phenotypic effects of Neandertal or Denisovan ancestry alleles[111,112]. These analyses will become increasingly informative as future GWAS are performed on increasing numbers of non-disease phenotypes and if more studies are conducted in populations with appreciable proportions of Denisovan ancestry.



Admixture with Neandertals and Denisovans played an important part in the history of modern human biological adaptation. In particular, these archaic hominins and their ancestors inhabited Eurasia for hundreds of thousands of years before the migration of anatomically modern humans out of Africa, with assumed long-term histories of biological adaptation to their local environments. Modern humans did not have this long history of ecological adaptation to the diverse habitats of Eurasia, but the genetic legacy of archaic hominin admixture could have provided fitness benefit opportunities for carriers of Neandertal or Denisovan alleles associated with environment-specific adaptive phenotypes[113]. Indeed, numerous signatures of adaptive introgression can be found in the genomes of Eurasian populations living today, identified as regions of the genome with unexpectedly large proportions (>0.50 in multiple cases) of Neandertal- or Denisovan-ancestry haplotypes relative to the much lower background levels of genome-wide archaic hominin ancestry[100,114,115] (FIG. 4).

The benefits of Neandertal admixture for Eurasian modern humans may have included the immediate acquisition of alleles associated with lighter skin pigmentation, potentially benefiting vitamin D production in northern-latitude habitats with relatively low UVB levels. Among the genomic regions with the strongest signatures of adaptive introgression from Neandertals are genes involved in skin development and pigmentation, including a *BNC2* gene haplotype now observed at 70% frequency in present-day European populations and a *POU2F3* haplotype now observed at >60% frequency in East Asian populations[100]. Nonetheless, this process certainly did not reflect an evolutionary end point for depigmentation in Eurasians (as discussed above).

Figure 4 | **Adaptive archaic introgression.** An illustration of genetic admixture between archaic hominins (that is, Neandertals or Denisovans) and anatomically modern humans including an example of adaptive introgression that is ultimately detectable from patterns of variation in modern human genomes. **a** | Chromosomes (or chromosome segments) with ancestry originally from archaic hominins and anatomically modern humans are represented in blue and orange, respectively. For illustrative purposes, only one pair of autosomal chromosomes is depicted. Chromosomes experience recombination with each generation; thus, archaic hominin ancestry segments become reduced in size over time. The location of an archaic hominin variant conferring a fitness advantage is indicated with a star. Following admixture and introgression, this variant (and the surrounding chromosome segment not broken down by recombination) increases in frequency over time in humans via positive natural selection. **b** | Representation of the proportion of haplotypes with archaic hominin ancestry (*y* axis) at points along this chromosome (*x* axis) observed in the descendent human population living today. The proportion of archaic hominin ancestry in the region containing the adaptively introgressed variant is exceptional. In other regions of the genome depauperate of archaic hominin haplotypes, archaic hominin alleles may have been deleterious and removed by purifying selection[100].

Meanwhile, the *EPAS1* haplotype associated with high-altitude tolerance in Tibetan populations was found to reflect adaptive introgression from Denisovans[104], even though the genome-wide proportion of Denisovan ancestry is much higher in other modern human populations[107,116]. Similarly, a haplotype containing the *WARS2* and *TBX15* genes that is fixed at 100% frequency in Greenland Inuit populations[117] also originated in Denisovans[105]. The protein encoded by *TBX15* is involved in the differentiation of brown and inducible (brite) adipocytes, which have critical roles in heat production during cold exposure[118], suggesting a potential evolutionary mechanism for this adaptive introgression event in populations inhabiting cold climates.

Genes involved in pathogen defence and immune response are also significantly enriched within adaptively introgressed regions of modern human genomes[119,120], with specific cases including *MHC*[121], *OAS*[122] and *TLR*[113,119] gene loci. Multiple non-mutually exclusive scenarios might explain the inferred fitness benefits of these haplotypes upon their introgression to modern humans. First, some of these alleles could have co-evolved with archaic hominin-specific pathogens ultimately transferred to modern humans during the period of direct contact between populations[123,124]. Second, this result may reflect the general pathogen defence benefit of increased individual genetic diversity (heterozygosity) that is known for many immune loci[125]. Third, some immune system variants that originated by random mutation in the Neandertal or Denisovan lineages may simply have been particularly effective relative to ancestral or human lineage-specific alleles at the same loci. Continued experimental characterization and computational prediction of the functional effects of introgressed alleles at immune system loci[120,126,127] could help researchers both distinguish among these scenarios and advance our general understanding of how our history of adaptive introgression affects the health of human populations living today.

Genomic signatures of domestication

Beyond ancient humans and archaic hominins, ancient genome data sets are also rapidly emerging for many other species, including human-domesticated animals and plants[128–131]. In our opinion, evolutionary ancient genome analyses of domesticated taxa offer multiple extremely valuable windows into the history of human behaviour and evolution (FIG. 5). Specifically, ancient genome analyses that characterize the evolutionary origins and spreads of various domestication-associated traits provide indirect insight into the human choices that favoured their selection across different cultural periods[132]. Such work also yields information on the nutritional return of investments in crops and livestock from farming and pastoralism at various points in history[129,131], providing valuable data for models of past human–environment interaction, health and demography. Finally, this line of research can help to identify how and when domestic species may have adapted commensally (that is, with traits not directly selected for by humans) to environmental and human niche habitats they shared with ancient people[133,134], thereby simultaneously advancing our understanding of evolutionary pressures faced by past humans themselves.

Recent ancient genome results for domesticated species have highlighted substantial temporal spacing in the emergence of key traits. For example, the analysis of ancient maize cobs from Mexico and the southwestern USA revealed that maize from 5,310–4,400 years BP already carried multiple functional, derived variants found in present-day varieties; these variants are associated with the complex traits of seed storage, flowering time and exposed edible kernel (rather than a hard shell). However, other ancestral variants associated with ear shattering (whereby seeds do not remain attached when ripened) and some starch production phenotypes were simultaneously present[131,135].

Ancient genome analyses of domestic chickens in Europe have demonstrated that selection for variants associated with yellow skin colour, reduced fear of humans and increased egg production occurred only over the past 1,100–500 years[129,136], counter to previous inferences of ~6,000 years[137]. Interestingly, consistent with the timing of the emergence of these adaptive traits as demonstrated by ancient genome analysis, archaeological and historical evidence supports the notion that chicken husbandry intensified in medieval Europe as a result of religious fasting practices during this period that limited the consumption of four-legged animals[129].

To date, more evolutionary ancient DNA analyses have been published on horses than on any other domestic species. This collective body of work is providing strong insight into artificial selection behaviour by humans. For example, Librado *et al.*[138] studied 13 ancient genomes of domestic horses from 2,700–2,300 years BP in the Kazakh Steppe in Asia, observing enrichment for genes expressed in mammary and pituitary tissues within genomic regions with signatures of positive selection. The authors suggest that this pattern might reflect a history of human-directed selection for phenotypes related to horse milking[138], a practice conducted for millennia in the region according to archaeological pottery lipid analysis and ethnographic records[139].

Based on knowledge of the relationship between genetics and coat colour and pattern variation in modern horses, it is possible to make inferences about prehistoric horse phenotypes by using ancient DNA. Ludwig *et al.*[140] reported a marked increase in the diversity of coat colours and patterns in European early domesticated horses (6,000–2,000 years BP; $n = 73$ individuals) relative to horses before the onset of domestication (>6,000 years BP; $n = 16$), with inferred black, white, chestnut, silver and spotted patterns in domesticated horses compared with bay and dun colourations in pre-domestic animals[140]. Librado *et al.*[138] inferred similarly extensive coat colour diversity in the Kazakh Steppe horses, with cream, chestnut and spotted variants present in their sample, and a third study identified the increased frequency of a genetic variant associated with leopard-spotted coat patterns (from 0.06 to 0.35 in 16 pre-domestic and 83 domestic horses, respectively),

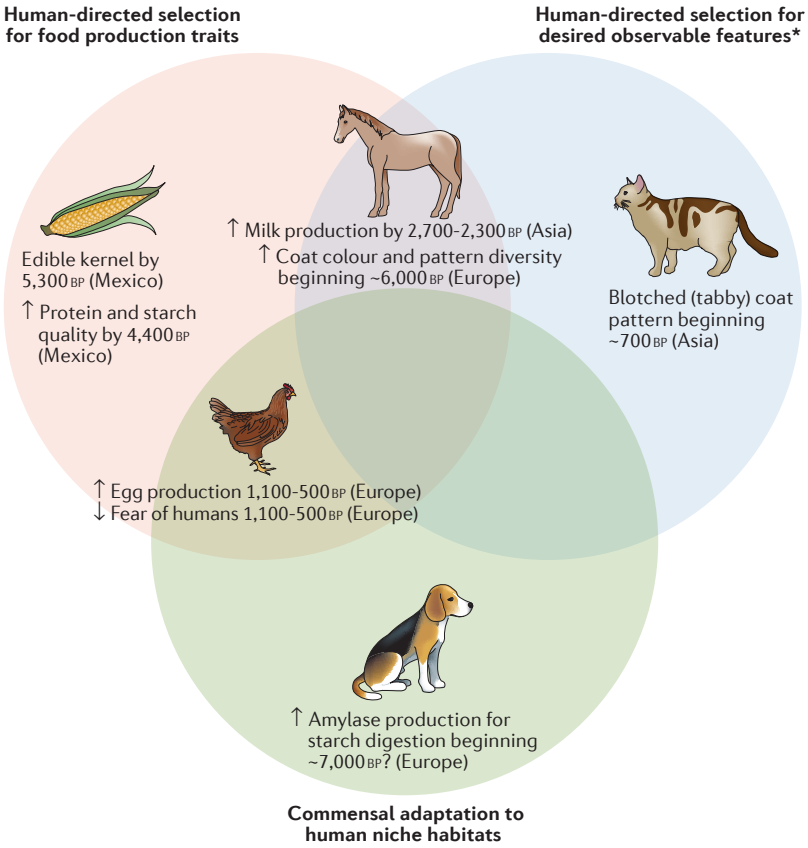


Figure 5 | **Insights into the timing of different trait evolution processes for domesticated species based on ancient DNA.** Domestic plant and animal ancient DNA studies can inform our understanding of past human behaviour and ecology. Shown are selected published examples for maize, horse, dog, cat, and chicken. The asterisk indicates that for some observable feature evolution examples, it has yet to be determined whether changes reflect human-directed selection or the relaxation of selective constraint related to changes in harvesting pressure from natural predators or other ecological processes (see text). As domestic plant and animal ancient genome data sets continue to expand, we expect increasing numbers of taxa to have multiple ancient-DNA-characterized traits that together intersect two or even all three of these categories of trait evolution processes.

despite this variant also being associated with nervousness and night blindness traits[141]. At least some of these changes were shown to reflect human-directed artificial selection as opposed to relaxation of functional constraint (which could have occurred, for example, via reduction in harvesting pressure from visual predators)[141]. In contrast to the coat changes associated with the early stages of domestication for horses, a recent ancient DNA study of African, European and Asian domestic cats (~8,500–100 years BP; $n = 67$ individuals) reported a fairly recent emergence of only ~700 years BP for the blotched (tabby) coat pattern now common in present-day domestic cats[142].

Dogs have an even longer-term co-evolutionary relationship with humans than do horses or cats[61]. Results from evolutionary genomic analyses seem to reflect this history; for example, signatures of positive selection in dog genomes are enriched for genes involved in starch digestion[143], suggesting commensal biological adaptations to a human-like starch-rich diet. In fact, one selection signature surrounds the pancreatic amylase gene (*AMY2B*), for which dogs were found to have an average of ~15 diploid gene copies ($n = 136$ individuals) versus only two copies for all tested wolves ($n = 35$)[143]. Subsequent studies have reported a greater average number of *AMY2B* copies in breeds with long-term associations with agriculturalists versus those associated with hunter-gatherer societies[144], suggesting remarkable potential convergence with human *AMY1* copy number variation[75]. As with humans, dog ancient genomics studies would help to clarify the precise history of this adaptation. Early results have thus far been mixed; a maximum of three diploid *AMY2B* copies were observed among three total European Neolithic dogs (~7,000–5,000 years BP) in two studies[145,146], whereas another study reported a substantial average copy number increase beginning ~7,000 years BP ($n = 13$ Eurasian dogs from 15,000–4,000 years BP)[133]. Future studies and expanded spatiotemporal sampling will be necessary to fully characterize the timing and pace of dog *AMY2B* expansion and the potential relationship of this process to human cultural change.

Conclusions and future perspectives

We have illustrated the power of ancient genomics for studying processes of human biological adaptation. Potential insights from this approach complement, yet can also reach beyond, those from studies based on analyses of modern human genomes or based on the fossil and archaeological records alone. In particular, multiple high-precision temporal snapshots of human adaptation already provided by ancient genomics demonstrate substantial time lags between environmental or cultural changes and related biological adaptations — for example, skin depigmentation and lactase persistence in ancestral Europeans. Although these timelines are in some respects unsurprising given the random process of mutation, these results nonetheless have implications for our models of human health and fitness and hypotheses of compensatory cultural behaviours (FIG. 3). With increasing numbers of ancient genome data sets becoming available (FIG. 1), we anticipate expanded insights into the spatiotemporal dynamics of human adaptation, deeper analyses of the evolutionary histories of polygenic traits, and the transition from a primary focus on characterization of known human adaptations to the discovery of new ancient genomic signatures of past natural selection.

We note that existing ancient genome data sets are biased heavily towards Europe (especially) and parts of Asia (FIG. 1). Although this pattern partly reflects environment-based differences in ancient DNA preservation[147], disparities in global science funding and emphasis are also likely to play a part. Initial evolutionary ancient-genomic analyses on data sets from regions elsewhere have already delivered exciting insights[54,81,148]. Concerted efforts to help close the geographical ancient genome data gap would lead to a more comprehensive picture of the history of human biological adaptation, including in response to a broader diversity of worldwide habitats and cultural and population history changes.

Finally, direct study of ancient human genomes is not the only useful approach for obtaining novel evolutionary anthropology insights using DNA. The domestication examples highlighted in this Review and the associated implications of these results for understanding past human behaviour are cases in point. As the generation of ancient genome data becomes increasingly feasible, we can look forward to dramatic increases in the taxonomic reach and spatiotemporal precision of domesticated plant and animal analyses and insights. Moreover, the population and evolutionary histories of many non-domesticated, non-human species have been affected long term by human size-selective hunting and harvesting pressures, habitat modifications, accidental or purposeful translocations, and other behaviours[149]. Evolutionary ancient genomic analyses of affected taxa could thus help to indirectly reconstruct the intensities of various human behaviours at different points in time as a valuable component of a broader, ecosystem-level view of human evolutionary history.

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Competing interests
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