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Taming the Past: Ancient DNA and the Study of Animal Domestication

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Abstract

During the last decade, ancient DNA research has been revolutionized by the availability of increasingly powerful DNA sequencing and ancillary genomics technologies, giving rise to the new field of paleogenomics. In this review, we show how our understanding of the genetic basis of animal domestication and the origins and dispersal of livestock and companion animals during the Upper Paleolithic and Neolithic periods is being rapidly transformed through new scientific knowledge generated with paleogenomic methods. These techniques have been particularly informative in revealing high-resolution patterns of artificial and natural selection and evidence for significant admixture between early domestic animal populations and their wild congeners.

INTRODUCTION

The domestication of plants and animals began at least 15,000 years before present (YBP) with the wolf (*Canis lupus*) and triggered a rapid and profound shift in the evolution, ecology, and demography of both *Homo sapiens* and numerous animal and plant species (1). The appearance of domestic dogs (*Canis lupus familiaris*) in the archaeological record foreshadowed subsequent livestock and crop domestication and the multiple transitions from foraging to farming in geographically and temporally distinct locations across the globe (2, 3). Consequently, approximately 10,000 YBP, a new mode of human existence emerged, which focused on the exploitation of actively managed plant and animal species. Thereafter, the food and other biological resources provided by domestic plants and animals permitted the growth of higher-density populations in domestication centers (4), leading to expansions of increasingly sophisticated agricultural economies and the development of complex hierarchical urban communities (5). Our understanding of the prehistory of modern technological societies may therefore be enriched by deciphering the biological and anthropological processes underlying plant and animal domestication (1, 6).

Animal Domestication Timelines

Zooarchaeological investigations in the early domestication centers of Southwest Asia (the Near East) suggest goats (*Capra hircus*), sheep (*Ovis aries*), humpless cattle (*Bos taurus*), and pigs (*Sus scrofa*) were among the first livestock to be domesticated, approximately 10,000 YBP (1, 7, 8). Parallel work in South Asia (the Indian subcontinent) indicates that humped zebu cattle (*Bos indicus*) and water buffalo (*Bubalus bubalis*) were domesticated approximately 8,000 and 4,500 YBP, respectively (1, 9). It is important to note, however, that the domestication of *B. indicus* may not have been entirely independent and that it may have instead arisen as the result of the translocation of domestic taurine cattle to South Asia, followed by admixture with wild humped cattle (10).

In East and Southwest Asia, pigs (*S. scrofa*) were independently domesticated approximately 9,000 YBP, and chickens (*Gallus gallus*) were likely domesticated in Southeast Asia about 4,000 YBP (11). The horse (*Equus caballus*) was domesticated in Central Asia approximately 5,500 YBP (12), and its close relative the donkey (*Equus asinus*) was domesticated in Egypt at approximately the same time (~5,000 YBP) (13). Following this, the one-humped dromedary camel (*Camelus dromedarius*) was brought under human control on the Arabian Peninsula approximately 3,000 YBP (1). **Table 1** summarizes information on the timing and geography of domestication for the most important domestic vertebrate species.

The Genetics of Domestication

The systematic study of the biological processes underlying the evolution of domestic animals has a long and distinguished history, stretching back to the middle of the nineteenth century AD. Charles Darwin was the first to use the remarkable phenotypic variations wrought by animal breeders to highlight the power of human-mediated artificial selection and support his wider ideas regarding natural selection, biological evolution, and the origins of domestic animals (14, 15). In recent decades, zooarchaeologists, geneticists, and animal scientists have focused on understanding the genetic and phenotypic changes—specifically developmental, anatomical, physiological, and behavioral—that have accompanied the domestication process (16–18), in particular, how many of these traits, such as dramatic coat color variation and depigmentation, floppy and small ears, paedomorphosis with increased tameness and docility, changes in craniofacial morphology and reduction in brain size, alterations to the endocrine system, and significant changes to female estrous cycles—including year-round breeding—may represent a so-called domestication syndrome that is observed across multiple mammalian domestic species (19).

Table 1 The time frame and geography of domestication for key vertebrate domestic species (modified from 1, 160)

Common name	Scientific name	Approximate time frame for domestication (years before present)	Geographical location
Dog	<i>Canis familiaris</i>	15,000	Eurasia
Goat	<i>Capra hircus</i>	10,500	Southwest Asia
Sheep	<i>Ovis aries</i>	11,000	Southwest Asia
Humpless cattle (taurine)	<i>Bos taurus</i>	10,300	Southwest Asia
Pig	<i>Sus scrofa</i>	10,300	Southwest Asia
Cat	<i>Felis catus</i>	9,500	Southwest Asia
Humped cattle (zebu)	<i>Bos indicus</i>	8,000	South Asia
Water buffalo	<i>Bubalus bubalis</i>	4,500	South Asia
Pig	<i>Sus scrofa</i>	8,000	East/Southeast Asia
Chicken	<i>Gallus gallus</i>	4,000	East/Southeast Asia
Duck	<i>Anas platyrhynchos</i>	1,000	East/Southeast Asia
Horse	<i>Equus caballus</i>	5,500	Central Asia
Bactrian camel	<i>Camelus bactrianus</i>	4,500	Central Asia
Dromedary camel	<i>Camelus dromedarius</i>	3,000	Arabian Peninsula
Donkey	<i>Equus asinus</i>	5,500	North Africa
Llama	<i>Lama glama</i>	6,000	South America
Alpaca	<i>Vicugna pacos</i>	5,000	South America

In recent years, it has become possible to investigate the microevolutionary processes underlying animal domestication at the molecular level using the tools of modern genomics. In this regard, deliberate experiments to produce tame silver foxes (a melanistic variant of the red fox *Vulpes vulpes*) and rats (*Rattus norvegicus*), which were initiated during the middle of the twentieth century by Dmitri K. Belyaev at the Institute of Cytology and Genetics in Novosibirsk, Russia, have provided useful insights (20, 21). For example, Frank Albert and colleagues (20) have identified quantitative trait loci (QTLs) and an epistatic network of genes influencing tameness in Belyaev's rats. Two such QTLs include the *Tph1* gene, which is involved in the synthesis of the neurotransmitter serotonin, and the *Gabra5* gene, which encodes a subunit of the receptor for γ -aminobutyric acid, a key inhibitory neurotransmitter (22).

In addition, following from pioneering functional genomics work using microarray and reverse transcription quantitative real-time PCR analyses of brain tissues from wolves and domestic dogs (23), RNA-sequencing (RNA-seq) transcriptional profiling of rat brains in conjunction with genome mapping have started to be used to identify many putative regulatory variants (expression QTLs) and candidate genes influencing tameness and aggressiveness (24). Finally, RNA-seq has also been used to provide the first tantalizing, though merely suggestive, evidence for a small core group of differentially expressed brain genes in pairwise comparisons of domestic and wild mammalian congeners, including dogs and wolves, pigs and wild boars, domestic and wild rabbits (*Oryctolagus cuniculus*), and domestic and wild cavies (*Cavia* spp.) (25). It is important to note that the critical changes in gene expression associated with domestication are likely to affect particular developmental stages in a tissue-specific manner and will require extensive additional work to be conclusive.

The genetic changes shaped by animal domestication have also recently been explored at high resolution using population genomics tools to compare genome sequence data from living breeds

and wild populations. For example, Carneiro and colleagues (26) generated genome sequence data for six phenotypically distinct domestic rabbit breeds and wild rabbit populations sampled across a geographic transect encompassing the Iberian ranges of two wild subspecies (*Oryctolagus cuniculus algirus* and *Oryctolagus cuniculus cuniculus*) and also the relatively recent (~1,400 YBP) monastic domestication centers for rabbits in southern France (27). Gene set enrichment analysis of the population genomics results indicated that genes affecting neurobiology were overrepresented in loci targeted by directional selection, and proof-of-principle functional assays showed that derived single-nucleotide variants proximal to developmental genes (*SOX2* and *PAX2*) were likely to be embedded within, or close to, regulatory sequences. Most importantly, the authors concluded that domestication was primarily associated with soft selective sweeps acting on regulatory standing genetic variation throughout the rabbit genome, thereby signposting microevolutionary processes relevant during the early stages of domestication for other vertebrate species (26).

A Paleogenomic Approach to Animal Domestication

Our understanding of recent human evolution is currently being revolutionized by the application of powerful new genomics technologies to the study of subfossils from archaic and ancient humans and, in particular, the integration of genetic data from these samples with large genome-wide data sets from modern populations (reviewed in 28, 29). The field of domestic animal paleogenomics is entering a similar phase in which systematic surveys of genome-wide genetic data from domestic animal archaeological material will become the norm, and the vanguard of these efforts is already in sight (30–36). **Figure 1** shows domestication timelines for several key vertebrate species, with relevant paleogenomic information overlaid.

Once paleogenomic information is vertically integrated with very large high-density genomic data sets from widely sampled modern animal populations, several hypotheses related to animal domestication could be addressed. These include hypotheses concerning (*a*) the genetic processes giving rise to domestic animal phenotypes; (*b*) the phylogeographies of predomestic and early domestic populations; (*c*) the extent and tempo of prehistoric and historic gene flow between wild and domestic populations; (*d*) the pattern, mode, and intensity of natural selective processes; and (*e*) the functional, cultural, and economic consequences of genomic variation shaped by many generations of inadvertent and directed selective breeding. In this review, we present the contribution that ancient DNA (aDNA) research has had, thus far, on our understanding of domestication.

ANCIENT DNA: A SHORT INTRODUCTION

The first aDNA to be sequenced was obtained not from an ancient domestic animal but from a museum specimen of an extinct zebra (the quagga, *Equus quagga quagga*), which inhabited South Africa until the end of the nineteenth century (37). Early aDNA studies were based on molecular cloning, in which genomic extracts were end repaired, ligated into plasmids, and replicated within bacteria. The polymerase chain reaction (PCR), which was developed almost simultaneously, provided more direct access to aDNA molecules as it could amplify targeted regions of interest in sufficient quantities prior to sequencing (38). PCR therefore became the standard method until the development of high-throughput DNA sequencing (HTS) approaches 20 years later (39).

PCR was not, however, devoid of limitations. Firstly, several chemical compounds coextracted with archaeological DNA could act as inhibitors of *Taq* DNA polymerases and prevent amplification (40). Secondly, chimeric PCR amplicons recombining sequence information present in multiple templates could be formed (41). Thirdly, aDNA contains many chemical modifications formed postmortem (42), including some that are not traversable by DNA polymerases and, thus, fail PCR attempts (43), and some that lead to copy errors. The most abundant of such modifications

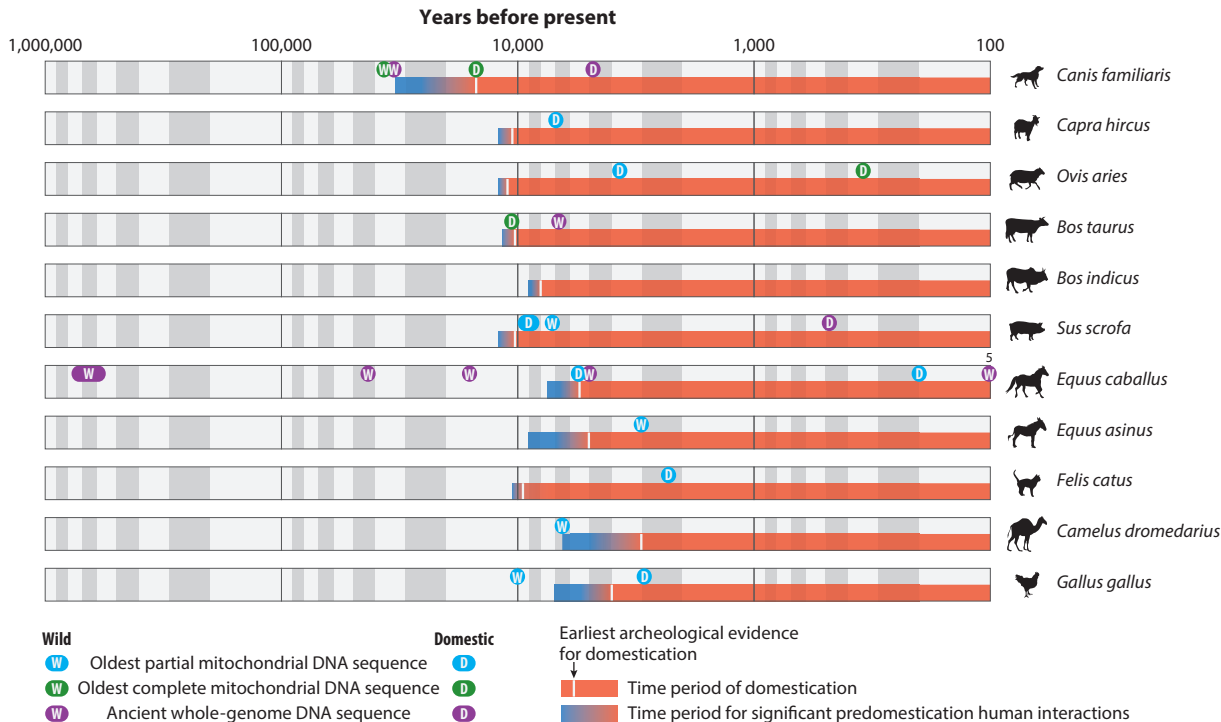


Figure 1

Domestication timelines for a range of domestic species. Paleogenomic information is superimposed showing oldest partial and complete mitochondrial DNA sequences and ancient whole-genome sequences generated to date (ancient DNA and paleogenomic data from 30, 31, 34, 36, 56, 76, 90, 96, 97, 117, 141, 153–159).

consist of uracils that are formed following the deamination of cytosine residues. Copied as thymines, they lead to the introduction of artefactual GC→AT mutations in the amplicon pool (44), which can be revealed through sequencing of amplicons after molecular cloning. Reproducibility across multiple PCR amplifications and/or amplicon clones was therefore required to ensure the quality of the sequence characterized.

These early approaches to studying aDNA were not particularly high throughput, which considerably limited the amount of accessible information as large fractions of the DNA extracts were required to characterize even a single DNA segment. Amplifying mitochondrial DNA (mtDNA) templates, which are present in hundreds to thousands of copies per cell, was generally easier than nuclear fragments, and (hyper-)variable mtDNA regions represented, until the mid-2000s, the almost sole focus for aDNA researchers. This technological limitation explains why the vast majority of studies in the first 20 years of aDNA research emphasized reconstruction of the phylogenetic relationships among extinct and extant species and the characterization of phylogeographic and/or demographic population patterns (reviewed in 45).

The first functional information retrieved from ancient nuclear gene fragments was obtained following the development of so-called two-round multiplex PCRs, where multiple loci are coamplified in a first round to restore sufficient material for a second amplification targeting each of them individually (46). This provided access to biological characters that do not fossilize, such as skin pigmentation (47), but was in practice limited to a few loci and phenotypic traits at best. However, soon after this period, HTS began to revolutionize aDNA research by allowing parallel

sequencing of millions to billions of DNA templates, thereby dramatically increasing the amount of genetic information that could be obtained from each microliter of extract (48). The first HTS platforms became commercially available in 2006, and relatively soon afterward a draft of the first woolly mammoth (*Mammuthus primigenius*) genome was generated (49). The first ancient human genome and the first Neanderthal genome were sequenced a few years later (50, 51). Another fruitful area of research has been paleomicrobiology, and scientists have already tackled the genomes of ancient bacterial pathogens, such as *Yersinia pestis* (the etiological agent of plague), that have significantly impacted human health over the last ~6,000 years (52, 53).

So far, hundreds of ancient genome sequences (or dense genome-wide SNP data sets) have been generated, most of which are from anatomically modern humans or archaic human relatives (reviewed in 28). However, a small number of other mammalian taxa are represented, including mammoths (49, 54, 55), horses (32, 33, 35, 36), aurochs (*Bos primigenius*) (30), pigs (56), and wolves and dogs (31, 34).

Despite the presence of postmortem DNA damage, the quality of ancient genomes can rival that of modern genomes (reviewed in 48, 57); novel molecular and computational methods have improved our ability to (a) access ultrashort and highly damaged aDNA molecules (58–62), (b) align sequence reads from these molecules against the reference genomes of closely related organisms (63–65), and (c) identify and/or remove damage-related sequencing errors (66, 67). Molecular methods have also been developed to target enrich preselected regions of interest using probe-library annealing. Currently, the latter approaches can retrieve up to a few millions of preselected SNPs across the whole genome (68), entire exomes (69) and individual chromosomes (70), and even complete genomes (71, 72). In summary, based on recent progress in human paleogenomics and assuming that caution is taken to avoid (or correct for) the effects of SNP ascertainment bias—whereby polymorphic sites segregate preferentially in the panel of breeds or populations used for SNP discovery (see **Figure 2**)—presently there are no obvious technological limitations to comparable high-resolution studies of domestic animal and wild progenitor population genomics throughout the Holocene and beyond. **Figure 3** shows a schematic illustrating the types of high-resolution evolutionary genomics analyses that can be performed using genome-wide data from domestic animal subfossils and modern breeds and populations.

Notwithstanding the remarkable technical progress in recent years, the optimistic outlook for domestic animal paleogenomics is somewhat tempered by climate and geography. The local environmental conditions of several key animal and plant domestication centers, particularly those such as the Fertile Crescent, are not conducive to the preservation of archaeological DNA (73). However, it is important to note that ~400,000-year-old genomic information has been successfully retrieved from material preserved in non-Arctic environments (58, 74), and mtDNA fragments have already been successfully sequenced from the Levant (75), the Arabian peninsula (76), Iran (77), and the tropics (78, 79). The first genome-scale data sets from early farmers in the Levant have recently been characterized (80–83). In addition, with archaeological material that can favor preservation of aDNA, particularly inner ear bones, the petrous part of the temporal bone (84), and tooth cementum (59), the focus on the Fertile Crescent region is likely to increase in the very near future.

TRACKING ANIMAL DOMESTICATION CENTERS AND EARLY MIGRATION ROUTES

The Phylogeography of Animal Domestication

If we assume that animal domestication emerged in a limited number of centers from which domesticates expanded outward, then as Nikolai Vavilov (85) originally proposed for crops, geographical

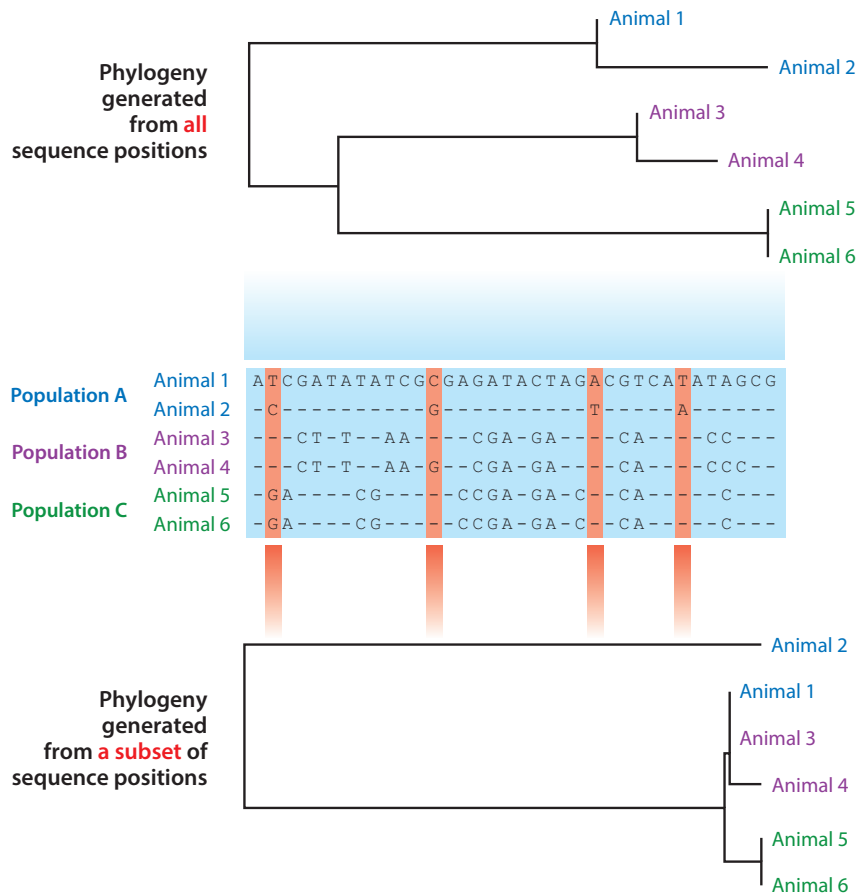


Figure 2

Ascertainment bias with single-nucleotide polymorphisms used for phylogenetic reconstruction.

hotspots of extant genetic diversity should reflect the location of these original domestication centers. This should also be evident as an isolation-by-distance pattern resulting from serial founder events accompanying the expansion of early domestic populations as they migrated radially from these centers (86, 87). Following this rationale, the strong phylogeographic structure observed for certain domestic animal populations, most notably cattle (88) and Eurasian pigs (89, 90), supports domestication models based on archaeological evidence. In cattle, for instance, mtDNA shows a strong phylogeographic structure, with four macrohaplogroups (T, T1, T2, and T3) found in the Near East at comparable frequencies, which is in contrast to Europe, where T3 is dominant (88). This, and the starlike T3 mtDNA haplotype network in Europe, mesh satisfyingly with the archaeological evidence for a Near Eastern domestication center for taurine cattle.

Further characterization of ancient bovine mitochondrial diversity from almost 200 ancient specimens sampled across Europe, Anatolia, and the Near East has refined the tempo and mode of cattle domestication (91, 92). These analyses support a population model in which domestication emerged ~10,000 YBP from a local and limited stock of female founders in the Near East and Southeast Anatolia, after which the process expanded to Anatolia and the Aegean approximately

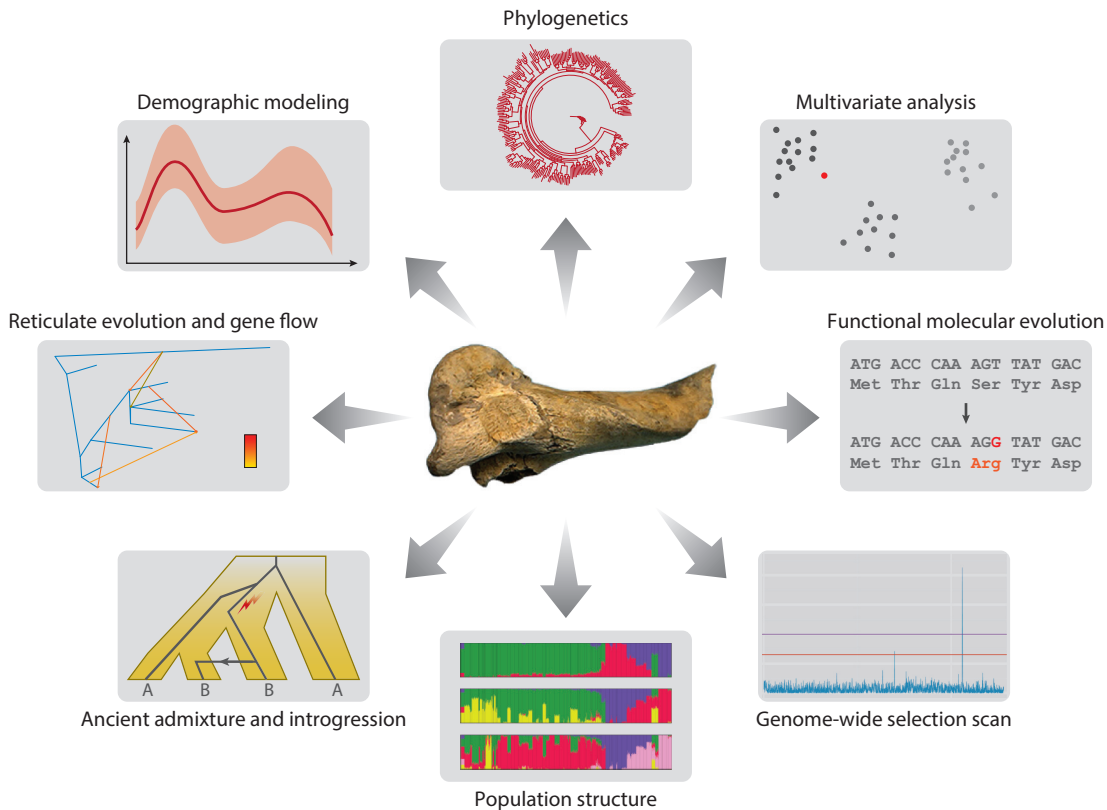


Figure 3

Evolutionary and population genomic analyses that can be performed with genome-wide data from domestic animal subfossils and modern populations (some graphic elements modified from Reference 30 under the terms of the Creative Commons Attribution 4.0 International License, <http://creativecommons.org/licenses/by/4.0>).

9,000 YBP, and then throughout Europe following a northern continental route along the Danube River and a southern maritime route via the shores of the Mediterranean (91, 92).

Tracking the Origins and Spread of Domestic Animals

Modern domestic animal populations do not, however, always display strong phylogeographic structure. For example, this is the case at both the mitochondrial and microsatellite level for horses (93, 94) and dromedaries (76), where the capacity for large-scale dispersal and human-driven population movements along transcontinental trade routes have homogenized geographic population structure in these species. Additionally, despite compelling archaeological evidence for a Near-Eastern origin for European pigs, wild boar mtDNA lineages found in the Middle East are not observed in domestic pig populations from Europe (89). In this regard, as described below, analyses of ancient Anatolian and European pigs demonstrate that trade and multiple importations have obscured and reshuffled the genetic composition of domestic pig and wild boar populations.

The genetic signature of the earliest domestic pigs from Eastern Anatolia was masked by local introgression from wild boars when they expanded to Western Anatolia (95). This particular domestic mtDNA signature then spread to Europe (96) as far as present-day France, until it was lost through admixture with local boars. Following this, during the early Bronze Age, back migrations

of European domestic pigs replaced the native mtDNA signature in Anatolian pigs. Additionally, in ancient Israel, the introgression of maternal lineages of domestic ancestry was not limited to domestic pigs but also involved wild boars that acquired European haplotypes during the Iron Age (2,900 YBP) (75). A major implication of this work is that past turnover and complete replacement of mtDNA lineages such as these are not detectable in surveys of modern pig mtDNA diversity.

In dogs, most phylogeographic analyses of canine genetic diversity indicate that the domestication process occurred only once; however, the location of the original domestication center is still in dispute, with Europe (97), Central Asia (98), and East Asia (99) proposed as plausible candidates. This picture is further complicated by other recent studies, which instead suggest two domestication centers (31), such that Western European and East Asian dogs form two distinct groups that diverged between 14,000 and 6,400 YBP. The time of this split was estimated using a genome-wide mutation rate calibrated from the genome sequence of a ~4,800-year-old domestic dog excavated at Newgrange, a Neolithic passage tomb in eastern Ireland (31).

Additionally, mtDNA sequencing of 59 ancient dogs revealed that haplogroups C and D, which were the most abundant in Europe prior to ~3,000 YBP, have now been replaced by haplogroups A and B (31). This is consistent with a scenario in which dogs were independently domesticated in Europe and East Asia but dispersed later alongside humans from Asia to Europe, replacing the early native European dogs. This interpretation is also in agreement with earlier work on ancient Scandinavian dog mtDNA (100).

If the paleogenomics of dog domestication is not already sufficiently confusing, another ancient genome has introduced an additional layer of complexity. This sequence was obtained from a gray wolf that lived in the Taymir Peninsula, Central North Siberia, ~35,000 YBP (34) and was found to belong to a wolf population whose descendants contributed to domestication, in particular to the genetic makeup of Greenland sledge dogs and other Arctic breeds. This suggests that descendants of the Taymir wolf survived until dogs were domesticated in Europe, arriving at high latitudes where they mixed with local wolves and contributed to the substratum of modern Arctic breeds.

Based on the most widely accepted oldest zooarchaeological remains, domestic dogs are therefore most likely to have arrived at high latitudes within the last ~15,000 years. However, earlier canid remains (~32,000 YBP from Goyet, Belgium) have been tentatively assigned as proto-dogs (but see below), and mutation rates calibrated from both the Newgrange dog (31) and the Taymir wolf genomes suggest modern wolves and modern dog populations diverged between 20,000 and 60,000 YBP. These dates could be used to support a superficial interpretation that either dogs were domesticated much earlier than their first appearance in the archaeological record would suggest or they arrived in the Arctic early, or both.

However, the chronologies estimated for primary evolutionary divergences between wild and domestic lineages do not necessarily correspond to the start of the domestication process; they provide only upper boundaries. This phenomenon is perhaps best illustrated using the example of horses, for which the time of divergence between the population leading to all known domesticated horses and the lineage leading to the last truly wild horses—Przewalski's horse (*Equus przewalskii*)—is currently estimated to be ~45,000 YBP (32). This is in contrast to the earliest archaeological evidence for horse domestication, which dates to at most 5,500 YBP (12).

The discrepancy between divergence and domestication times results from several factors. Firstly, contemporary wild populations are not the direct ancestors of domesticated animals and do not necessarily descend from them, as significant population structure may have existed prior to the onset of the domestication process. Secondly, the divergence time estimate can reflect other population processes rather than a singular domestication, for example, an allopatric split owing to climatic, topographical, or other environmental factors. Therefore, in the case of domestic canids, wolf-dog divergence times of within a 20,000–60,000 YBP time frame (31, 34) do not

imply that dogs were domesticated during this specific period, even though the skull morphology of the Belgian Goyet Cave canids, dated to approximately 32,000 YBP, has been interpreted as evidence that dogs were first domesticated much earlier than previously thought (101).

Recent 3D geometric morphometric analyses now demonstrate that this material, and the 13,000-year-old cranium from the Upper Paleolithic Eliseevichi site in Russia, also first assigned to dogs (102), more likely originates from wolves (103), casting doubt on earlier claims for a human-dog relationship stretching back more than 30,000 years (104). Additionally, aDNA analyses revealed that the Goyet Cave canids have left no traces of mtDNA in modern dogs (97), suggesting that this population did not play a role in dog domestication and may instead represent an extinct morphologically and genetically divergent wolf population.

Underappreciated Admixture Between Wild and Domestic Populations

Patterns of genomic diversity present in domestic populations are forcefully demonstrating that livestock and companion animals have not evolved in complete isolation, pointing instead to significant admixture with wild congeners. This is very evident for domestic pigs (105), in particular suggesting that domestic phenotypes can be maintained despite extensive homogenizing gene flow from the wild. This has led Frantz and colleagues (105) to propose the hypothesis of domestication islands in the porcine genome, which are refractory to gene flow, thereby preventing back introgression of maladaptive wild boar haplotypes. An analogous, albeit much older phenomenon has been described for regions of the human genome that were measurably resistant to archaic admixture (106, 107).

In cases where wild progenitors of domestic animals have gone extinct, aDNA provides the only method to assess genetic contributions from wild congeners. For example, ancient mtDNA work on the dromedary, which became extinct in the wild ~2,000 YBP, supports domestication models involving wild restocking (76). Similarly, as the last surviving wild cattle—the aurochs (*B. primigenius*)—became extinct in the seventeenth century, the genetic contribution of native European aurochs to domestic herds can be evaluated only using paleogenomics. In this regard, genetic characterization of many specimens, for both partial (88, 108–110) and complete mitochondrial genomes (111), has revealed divergent mtDNA haplotypes in German and British aurochs, which are virtually absent from modern livestock except in remote Landrace cattle from Korea. However, Italian aurochs specimens exhibit haplotypes currently found in European Landraces (112–114), suggesting admixture between domestic cattle and their wild predecessors in some regions of Europe. Taken together, however, mitochondrial variation in aurochs archaeological material suggests that, outside of the Italian Peninsula, local domestication made no major contribution to the establishment of cattle agriculture in Europe.

mtDNA, it is important to emphasize, represents a single nonrecombining locus, and therefore has limited utility for reconstructing complete evolutionary histories (115). This is illustrated by Neanderthals and anatomically modern humans, which show fully sorted mitochondrial phylogenies but significant levels of nuclear genomic admixture (reviewed in 116). Therefore, nuclear genome information is required before the hypothesis of local admixture between aurochs and cattle in Europe outside Italy can be rejected. Relevant to this question is the first recently published complete genome sequence of an aurochs that inhabited central Britain ~6,750 YBP. Population genomics analyses of this specimen in conjunction with a large database of extant cattle have revealed an excess of shared derived polymorphisms with native British and Irish cattle breeds (30), supporting the hypothesis—contrary to mtDNA data—that local aurochs contributed significantly to the development of agro-pastoralism in Europe. **Figure 4** shows a map of aurochs genomic admixture in modern European cattle breeds.

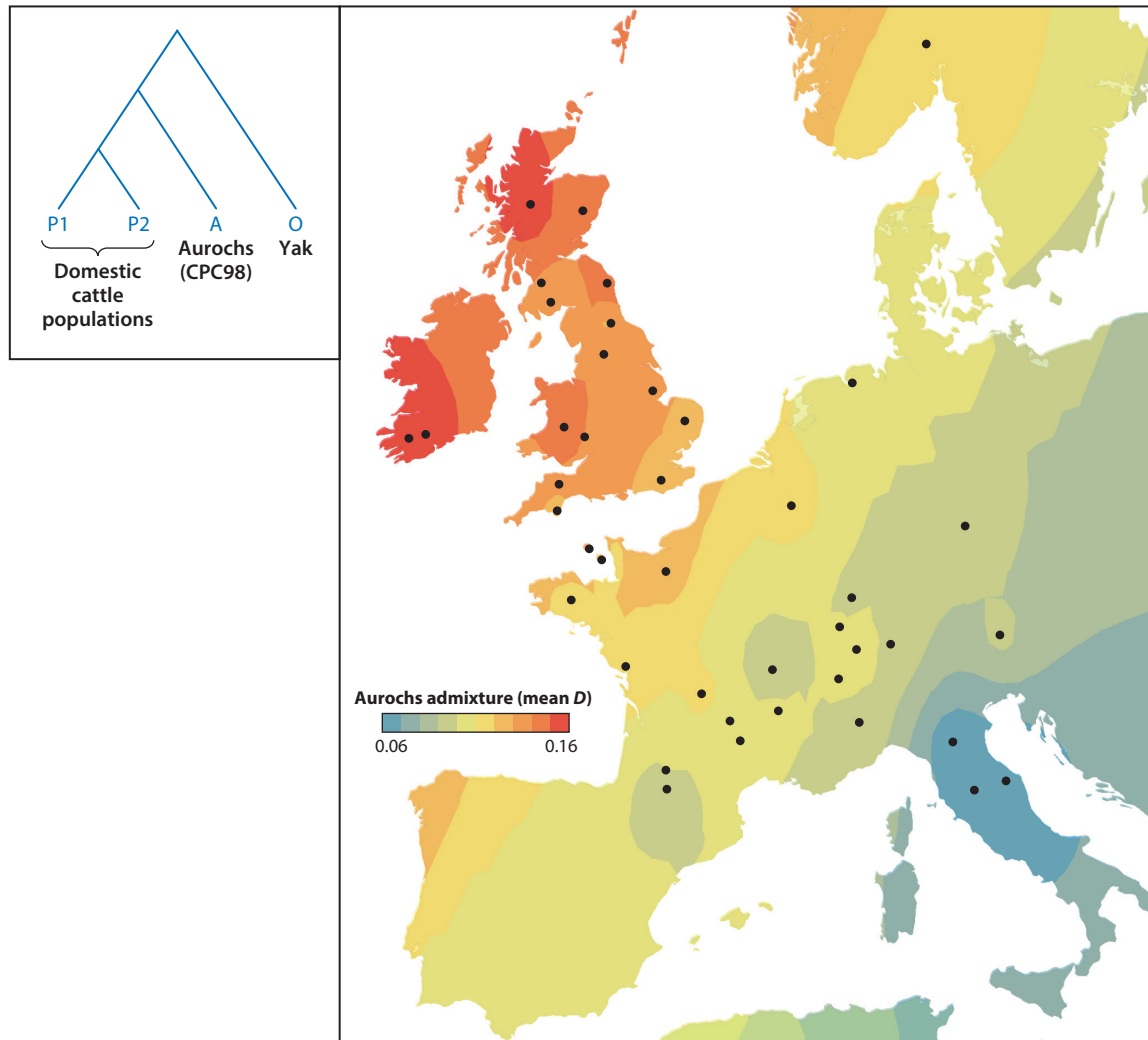


Figure 4

Geographic contour map of ancient British aurochs (*Bos primigenius*) genomic admixture with modern European cattle breeds. The ABBA/BABA test tree topology for detecting genomic admixture is also shown (modified from Reference 30 under the terms of the Creative Commons Attribution 4.0 International License, <http://creativecommons.org/licenses/by/4.0>).

Patterns of mtDNA variation in modern and ancient horses have also suggested extensive gene flow from wild into domesticated horses (93, 117, 118), which was confirmed through complete genome sequencing of living and ancient Przewalski's horses (32). The genomic information showed a reticulate pattern of recent evolution, with both lineages maintaining partial genetic contact since they diverged, and also that domestication has not reduced levels of restocking. Interestingly, complete genome sequencing of two predomestic Siberian horses from the Late Pleistocene revealed the existence of a hitherto unknown and now extinct population of wild horses, not related to Przewalski's horses, which significantly contributed to the genetic makeup of domesticated horses (35). This example clearly illustrates the power of paleogenomics, in which

MODELING DOMESTICATION WITH ANCIENT DNA DATA

Temporal sampling improves the statistical power for detecting past demographic changes (115, 119) and facilitates direct estimation of molecular rates of evolution (120). However, the temporal structure of paleogenomic data sets, if not properly modeled, can also confound classical population genetic tests, resulting in false signatures of population differentiation and expansion (121–123). Serial coalescent simulators have thus been developed to accommodate the temporal structure and predict patterns of genetic variation through space and time, according to a range of user-defined population scenarios (124, 125). Once a particular history can be identified for best fitting the patterns of genetic diversity observed in the archaeological record, a range of possible demographic and admixture parameters can be estimated using approximate Bayesian Computation (126). These modeling approaches, which account for the stochastic nature of the transmission of neutral alleles from one generation to the next, are strongly recommended in population genetics and are more likely to recover the true complexity of domestication processes (127). They have, for instance, revealed that the domestication of dromedaries involved substantial restocking from the wild (80). The temporal structure present in ancient DNA data sets, which provides direct measurements of allelic frequencies at different time points, also facilitates precise estimation of selection coefficients for loci underlying phenotypes that were preferred in a given sociocultural context and/or domestication stage. Current approaches coestimate selection coefficients and the age of the allele under selection (128, 129). In horses, when the method was applied on a realistic demographic population model, selection at the *MC1R* locus was inferred to act in an overdominant fashion in contrast to the *ASIP* locus, which was found to have evolved under positive, nearly additive selection (129).

sequencing of even a limited number of genomes can provide crucial information, which, although not apparent in patterns of modern genetic variation, is key to a fuller understanding of the true genetic foundations of domestic animals (see sidebar titled Modeling Domestication with Ancient DNA Data).

TRACKING FUNCTIONAL GENOMIC VARIATION AND SELECTION

Candidate Gene Approaches

As described in the Introduction, pioneering work on experimental domestication in silver foxes has shown that strong selection for tameness can substantially modify behavioral, physiological, and morphological traits over relatively few generations (21). Coat color is one such trait, and the wide spectrum of coat color diversity observed in domestic animals suggests this character was a target during the early phases of animal domestication (130). This was first demonstrated for ancient Neolithic horses, for which six genes could be genotyped for eight mutations that modulate coat color variation (131).

Although allelic diversity was found to be limited in wild Pleistocene horse populations, a rapid increase in the number of coat color gene variants was observed from 5,000 YBP, only a few centuries after horses were first domesticated (12). Two of these genes (*ASIP* and *MC1R*) showed positive selection coefficients, suggesting that chestnut and black colorations appeared early during the process of horse domestication. Further work revealed that some of the variants selected during domestication, especially a *TRPM1* allele that is responsible for leopard spotting, were already present by the time Paleolithic cave paintings were being produced (132, 133). This demonstrated, certainly for coat color, that human-mediated selection during domestication acted on standing genetic variation.

Interestingly, mapping *TRPM1* variation through space and time further revealed that the leopard spotting mutation was present at high frequencies in Turk horses from the early Bronze Age (4,700–4,200 YBP) (134). However, the variant apparently disappeared until the late Bronze Age, approximately 1,500 years later, when it reappeared in Western Siberia. This suggests that human herders have not maintained constant selective pressures on their domestic animals but, depending on the sociocultural context, have instead favored different traits in different places and at different times.

These and other recent findings imply that the true breeding history underlying domestic phenotypic characters was extremely dynamic and cannot be reconstructed from patterns of genetic variation found in modern livestock and companion animals. Therefore, ubiquity of a particular trait in modern breeds does not necessarily mean that the trait was an early domestication target, contrary to what is usually assumed. This is perhaps best demonstrated in the case of the yellow skin phenotype, which is common to the vast majority of commercial chicken breeds and was proposed to have been selected prior to the arrival of domestic chickens in Europe, approximately 2,700–2,900 YBP (135).

When a large number of European chickens spanning ~2,000 years prior to the eighteenth century were genotyped for the *BCDO2* locus, however, it was found that no animals could express the yellow skin phenotype (135). This trait, therefore, became prominent only during the late domestication history of chickens, presumably through the development of modern commercial breeds after the Industrial Revolution. This work builds on previous studies highlighting the limitations of using extant phylogeographic patterns to infer the domestication processes that shaped modern animal genomes. The true complex nature of animal domestication and subsequent artificial selective processes can really only be fully understood using vertical prehistoric or historic aDNA time series.

These molecular chronologies are crucial, not only for investigating early domestication processes but also for understanding the recent history of managed selective animal breeding, thereby complementing both long-term genealogical records in studbooks compiled since the eighteenth and nineteenth centuries and high-resolution genome/phenome studies in contemporary breeds. This is illustrated by the origin of one economically important gene variant in Thoroughbred racehorses: the C variant of the myostatin gene (*MSTN*), which is associated with shorter sprint-type race events (136). This variant could not be found in 12 historically important stallions, all related to the Darley Arabian sire line (to which ~95% of all living Thoroughbreds can trace their paternal lineage). Bower and colleagues (136) therefore hypothesized that the *MSTN* C-allele entered the Thoroughbred pedigree from local mares of British origin at the foundation stage in the seventeenth and eighteenth centuries, but has risen in frequency relatively recently as a consequence of the increased popularity of shorter race events that require greater speed and athletic precocity.

Genome-Wide Scans of Positive Selection

Despite providing important functional insights into the domestication process, focusing on a restricted number of gene candidates inevitably introduces ascertainment bias and may cause important genes to be overlooked. The domestication process has likely involved artificial and natural selection at a very large number of genomic loci (1, 26). Therefore, only recently, with the shift to analyses that encompass complete genome sequences, has it become possible to investigate the domestication process at high resolution to determine how it has shaped modern domestic animals.

This approach was first taken with horses, where the genomes of two animals predating domestication and one living wild Przewalski's horse were used to survey the genomes of modern domestic horses for signatures of positive selection (35). In this study, a total of 125 genomic loci

were found to represent good candidates for positive selection in at least two of the four tests implemented. Interestingly, these genomic regions were enriched for genes involved in locomotion (muscles and myotendons, articular junctions, balance, and motor coordination), the regulation of blood pressure, the development of the skeleton and limbs, and cognition and behavior (neural growth, guidance, and plasticity but also learning ability, response to fear, and social behavior).

Comparisons of the first aurochs genome with genome-wide data from modern taurine and indicine cattle also revealed several genomic loci putatively under selection, for example, the *DGAT1* gene, which is known to contain a major quantitative trait nucleotide associated with lactation traits (30). In addition, 106 selection candidates detected using population genomics methods were notably enriched for genes involved in neurobiology, muscle development and function, growth, metabolism, and immunity. This supports the hypothesis that behavior and meat traits represented key targets of domestication in cattle, and also that the environmental niche created by humans led to new pathogen challenges.

This first round of genome-wide analyses of selection is encouraging because the genes detected fulfill the requirements expected of domestication candidates. However, it is important to note that these results are provisional pending appropriate functional validation. Additionally, comparing the genomes of wild ancient progenitors and modern domesticates is unlikely to reveal the full complexity of microevolutionary processes that have been dynamic through space and time (134). However, as methods become available to routinely sequence ancient genomes and/or retrieve and genotype hundreds of thousands of genomic loci, and as sequencing costs reduce further, we are confident that paleogenomic diversity will soon be investigated at population scales to track when, where, and how quickly adaptive alleles spread in domestic populations.

Recent work has highlighted the importance of regulatory variants in driving fast adaptive responses to extreme environments (33). Consequently, it is important that future studies do not solely focus on protein-coding variants but also encompass structural and regulatory variants. Once these data are collected on a wide scale, across many species, a picture may emerge of the core biological pathways and gene networks that underlie the domestication process in vertebrate animals.

Deleterious Mutation Loads

In addition to identification of functional genetic variation that has been advantageous during and following domestication, ancient genomes have started to reveal the consequences of domestication for deleterious genetic variation. As it is often associated with repeated demographic bottlenecks, domestication is expected to reduce the efficacy of negative selection in eliminating weakly deleterious genetic variants from the population. The genome sequences from domestic animals will therefore, on average, contain a higher fraction of deleterious mutations than those of wild congeners. This hypothesis has been tested in tomatoes (*Solanum lycopersicum*) and African rice (*Oryza glaberrima*), where modern genomes from wild and domestic plants were compared (137, 138), and also in dogs (138, 139).

This approach is, however, ill-suited to animals such as cattle and dromedaries, for which wild populations have become extinct, or horses, for which wild populations survived but experienced a severe demographic collapse; for example, only 12–15 Przewalski's horses, the last remaining truly wild horses, founded the current population (32). In such cases, unbiased estimates of the deleterious mutation loads observed in wild animals can be measured only in ancient specimens predating extinction or recent demographic collapses. To date, this has been possible only for the horse, for which mutational loads were estimated by leveraging genomic conservation across mammalian taxa and accounting for inbreeding, a possible confounding factor. These analyses confirmed the expectation of the cost-of-domestication hypothesis, revealing significantly higher deleterious mutational loads in the genomes of domestic horses compared with ancient wild

congeners (35). Future work, using extensive time series of ancient domestic genomes, will help test whether the effect was most pronounced in the early domestication stages or more recently, for example, as a result of intensive modern breeding practices.

FUTURE DIRECTIONS

Paleogenomics research in domestic animals is undergoing a paradigm shift. During the last decade, the field has been revolutionized by spectacular improvements in the scope and capacity of high-throughput genomics technologies (reviewed in 39), which, coupled with increasingly sophisticated computational methods for analyzing and interpreting recovered genome-wide aDNA sequence information, has led to significant discoveries regarding the recent evolutionary history of domestic animal species, including horses (32, 33, 35, 36), cattle (30), and dogs (31, 34). In this section, we summarize recent research work that illuminates the likely course of the coming decade for paleogenomics, while also anticipating the impact of new methods and approaches for understanding the biology of domestication and human-mediated artificial selection and management of livestock and companion animals.

The introduction of HTS methods to genomics in 2006 led to a dramatic upsurge in aDNA research activity (reviewed in 48, 57, 73, 140). In this regard, suitable sample types and extraction methods are being explored to maximize the yield and purity of endogenous aDNA from archaeological material and museum specimens. For example, the observation that particular osteological specimens exhibit high yields of endogenous aDNA (84) will encourage identification of similarly useful skeletal elements in domestic animals. Also, novel sources of aDNA, such as parchment made from processed animal skins, will play a major role in future studies of livestock genomic diversity and functional microevolution across historical time frames (141). Simple modifications of existing aDNA extraction methods, such as the inclusion of a bleach-based (142) or an EDTA-based (59) enzymatic predigestion step, can also markedly improve DNA yields for preparation of sequencing libraries. In addition, systematic modeling of aDNA survival based on environmental temperature histories, geochemistry, and depth of preservation will help guide future efforts to identify promising locations for paleogenomics research work (73). These developments will therefore help to systemize and expand the range and types of archaeological subfossils that can be used for population genomics studies of ancient domestic animals and their wild congeners.

The rapid evolution of methods for targeted sequence capture by hybridization (reviewed in 143) will dramatically improve enrichment of specific genomic regions for high-resolution paleogenomic analyses from very large numbers of specimens across wide time depths. In addition, the increasing sequencing capacity of HTS platforms, coupled with new methods for aDNA library preparation (60), robotics, and large-scale sample multiplexing, will significantly decrease costs and facilitate higher throughput for paleogenomics. This is particularly relevant to studies of animal domestication, because at many important sites zooarchaeological material can be obtained in relatively large quantities across many stratigraphic layers (144). These developments will therefore facilitate high-resolution genomic studies of multiple samples from individual animals that capture population genetic and functional microevolutionary processes in domestic and wild populations across transects in space and time.

A model for future studies of paleogenomic variation in domestic animals is provided by surveys of aDNA across a range of time depths from Adélie penguins (*Pygoscelis adeliae*) in the Ross Sea region of Antarctica, which show great promise for shedding light on spatial and chronological microevolutionary processes simultaneously (145). Another example is provided by a survey of temporal genome-wide variation in humans sampled across 5,000 years of European prehistory during the Neolithic (146, 147), which reveals a genetic transition toward lighter

pigmentation and suggests that the lactase persistence trait did not emerge until the late Bronze Age (~3,000 YBP). Fu and colleagues (68) have taken a similar approach to human genome-wide data from Eurasian samples spanning 45,000 to 7,000 YBP, showing that Neanderthal admixture has decreased over this time, leading to the hypothesis of consistent natural selection against Neanderthal genomic variants in Paleolithic human populations. An example of genome-wide microevolution in livestock, albeit across a much smaller time scale, is provided by the 1000 Bull Genomes Project (148), whereby functional genomic variation can be tracked in great detail over the past half-century for key ancestors of modern cattle breeds. In particular, analyses of these data have revealed loss of genetic diversity owing to intensive artificial selection in the global Holstein-Friesian dairy cattle population (149).

Although it is at an early stage of development, paleoepigenomics will have a major role in future studies of animal domestication and the history of animal husbandry. In this regard, epigenetic analyses of genome-wide aDNA sequence data have already begun. For example, Gokhman and colleagues (150) have reconstructed genome-wide methylation maps for Neanderthals and Denisovans and observed differential methylation between modern and archaic humans for a homeobox gene cluster that is a key regulator of limb development, which brings into focus the role of the epigenome in shaping phenotypic variation. In a similar fashion, Pedersen and coworkers (151) generated a nucleosome occupancy map and genome-wide cytosine methylation levels for 4,000-year-old human hair and were able to infer the age of death using methylation patterns at specific CpG sites. It was also possible to reconstruct expected patterns of gene expression for proteins such as keratins, which are important components of hair follicles.

If epigenomic information can be reconstructed from ancient domestic animal genomes, it is therefore tempting to speculate that this may reveal previously unknown epigenetic phenomena that relate to animal domestication, in particular, those triggered by environmental stressors, such as altered social dominance relationships, new infectious diseases, confinement, and restriction of movement. Comparable studies of early domestic animal and progenitor microbiomes—for example, from dental plaque preserved in ancient teeth (152)—may also provide important information regarding changing diets as wild animals transitioned to domestic livestock and companion animals.

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Errata

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