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Invited Review Article

INVITED REVIEW ARTICLE

Human adaptation, demography and cattle domestication: an overview of the complexity of lactase persistence in Africa

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Abstract

Lactase persistence (LP) is a genetically-determined trait that is prevalent in African, European and Arab populations with a tradition of animal herding and milk consumption. To date, genetic analyses have identified several common variants that are associated with LP. Furthermore, data have indicated that these functional alleles likely have been maintained in pastoralist populations due to the action of recent selection, exemplifying the ongoing evolution of anatomically modern humans. Additionally, demographic history has also played a role in the geographic distribution of LP and associated alleles in Africa. In particular, the migration of ancestral herders and their subsequent admixture with local populations were integral to the spread of LP alleles and the culture of pastoralism across the continent. The timing of these demographic events was often correlated with known major environmental changes and/or the ability of domesticated cattle to resist/avoid infectious diseases. This review summarizes recent advances in our understanding of the genetic basis and evolutionary history of LP, as well as the factors that influenced the origin and spread of pastoralism in Africa.

Introduction

Lactase persistence (LP)—the ability of adults to digest the lactose present in fresh milk—is a genetically-determined trait that varies in frequency among human populations. Notably, LP is common in European, African and Arab populations that have a tradition of dairy production and consumption (1–8). To date, several derived polymorphisms—located in intron 13 of the *MCM6* gene—have been correlated with the LP phenotype, and it is thought these alleles rapidly increased to high frequency mainly in pastoralist populations due to the action of directional selection occurring within the last 10 000 years (5–7,9–11). Thus, LP represents a recent adaptation that evolved in modern humans likely in response to the cultural development of pastoralism (12,13). Furthermore, LP is a classic example of convergent evolution in humans in which different variants underlying the same phenotype arose independently in geographically distinct populations due to shared selective pressure (i.e. adult milk consumption) (1,2,5,6).

Indeed, the emergence of pastoralism was a cultural innovation that altered the subsistence lifestyle of ancestral populations. In particular, the use of animals as a reliable supply of food products by humans created new circumstances that selected for LP over millennia (14). Thus, the culturally-transmitted practice of milk production and consumption is argued to be an example of niche construction—that is, the process by which organisms alter important components of their local environment introducing novel selective pressures (14). In the end, the evolution of LP was driven by the culture of dairying, and this

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cultural trait was simultaneously favored in lactase persistent populations (i.e. gene-culture coevolution) (15–17).

In addition, demographic events have played a role in the geographic distribution of LP-associated variants in Africa (1,5,6,18–26). For example, studies have shown that the derived C_{-14010} allele—which is thought to have originated in eastern Africa—is present in Khoisan- and Bantu-speaking pastoralist groups in southern Africa (5,20,25). It also has been hypothesized that this functional polymorphism was introduced into southern African populations through admixture with migrating herders within the last 2400 years (5,20–22,25). Furthermore, the timing and routes of migration of ancestral herders were dictated by past changes in climate conditions and/or the ability of domesticated cattle to resist/avoid infectious diseases (27–31), resulting in a dynamic and complex history of pastoralism in Africa.

The Biology of LP

Nutritionally, milk and its derivatives are important sources of carbohydrates, proteins, fats, minerals (e.g. calcium, potassium) and vitamins (e.g. A, B_{12} and D) (32,33). Lactose, the sugar (or main carbohydrate) in milk, provides energy to neonates for their growth and development (34–38). The lactase-phlorizin hydrolase (LPH) enzyme—commonly referred to as lactase—also plays a key role in neonatal nutrition by hydrolyzing lactose into glucose and galactose monosaccharides, which are rapidly absorbed into the bloodstream (39,40). In most mammals, expression of the lactase enzyme is high around the time of birth (produced exclusively in the brush border cells of the small intestine), enabling neonates to digest large quantities of dietary lactose (38,41). However, shortly after weaning, lactase production rapidly declines (though the mechanism for this downregulation is not fully understood), and this decrease in enzymatic activity is known as hypolactasia or lactase non-persistence (15,39,40,42). In this situation, individuals can no longer digest large amounts of lactose, and subsequent ingestion of milk could lead to gastrointestinal problems, such as bloating, diarrhea and abdominal pain (42,43). This digestive response (known as lactose intolerance) occurs because lactose escapes hydrolysis and absorption in the small intestine, entering the colon where it is fermented by bacteria that contribute to the onset of gastrointestinal symptoms (Fig. 1) (42,43). By contrast, a subset of individuals can continue to produce high levels of LPH into adulthood, retaining the ability to digest large quantities of lactose (42); this condition is known as normolactasia or LP (Fig. 1) (44).

Lactase activity can be measured either directly from intestinal biopsies or indirectly with a lactose challenge (42,45). Although the direct method is highly accurate, it is expensive, invasive and rarely available (42,45). As a result, lactase activity is usually assessed indirectly from measurements of lactose absorption via the lactose tolerance test (LTT) or the hydrogen breath test (HBT) (42,45,46). In both methods, after fasting overnight, individuals are challenged using an oral dose of lactose (typically 50 g dissolved in water); then, blood glucose concentration or hydrogen (H_2) concentration in expired air is measured over a period of 1–3 h using LTT or HBT, respectively (42,45,47,48). More specifically, after lactose intake, LTT quantifies the rise in blood glucose concentration (mg/dL) from a fasting baseline, while HBT measures the increase in concentration of H_2 (ppm) produced by bacteria during the fermentation of undigested lactose in the colon over a fasting baseline value (42,45).

The Genetic Basis of LP

In nearly one-third of human adults, lactase activity remains at high levels into adulthood, resulting in LP (26). The ability to digest lactose is prevalent in African, European and Arab populations that traditionally incorporated large quantities of milk into their diets (1,7,49–53). Although the lactase enzyme is encoded by the *LCT* gene on chromosome 2, several common single nucleotide polymorphisms (SNPs)—namely, C/T_{-13910} (rs4988235), C/G_{-13907} (rs41525747), T/G_{-13915} (rs41380347), T/G_{-14009} (rs869051967), and G/C_{-14010} (rs145946881) located in intron 13 of *MCM6* upstream of the *LCT* promoter—have been associated with the LP trait in human populations (6,7,10,11,44,54). Furthermore, *in vitro* experiments demonstrated that the derived T_{-13910}, G_{-13907}, G_{-13915}, G_{-14009} and C_{-14010} alleles act as enhancers for *LCT* expression, preventing the downregulation of the lactase gene (1,6,10,44,49,50,55–58). More specifically, studies showed that the T_{-13910}, G_{-13907} and G_{-13915} alleles create new binding sites for the octamer-binding protein 1 (Oct-1) transcription factor which interacts with human hepatocyte nuclear factor 1α (HNF1α) to stimulate *LCT* expression (10,55,59). Additional polymorphisms within intron 13 have also been implicated in LP in several human populations (11,44,60). However, the functional impact of these alleles has not yet been experimentally corroborated (8,44,58).

Although the known common variants (i.e. T_{-13910}, G_{-13907}, G_{-13915}, G_{-14009} and C_{-14010}) are strongly predictive of LP status, studies have indicated that these derived alleles do not fully explain the phenotypic variance observed in African populations (5,6,16). For example, Ranciaro *et al.* (5) reported that the C_{-14010}, G_{-13915} and G_{-13907} loci independently explain no more than ~21% of LP variation in East African pastoralists. Their analyses also showed that these derived alleles in combination account for no more than 45% of the LP variance in Kenyan and Sudanese populations (5). In addition, recent evidence has suggested that loci in other regions of the genome beyond intron 13 might play a role in LP in Africa. Specifically, a preliminary analysis of genome-wide SNPs genotyped in a large set of East African pastoralist populations uncovered strong signals of association with LP in genomic regions outside of the *MCM6* gene (Ranciaro, Campbell and Tishkoff, unpublished data). Moreover, a separate genome-wide analysis of Fulani pastoralists from the Sahel identified prominent peaks of association with blood glucose (glycemia) levels after lactose consumption on chromosomes 2 and 13 (though neither peak reached statistical significance after Bonferroni correction) (26). Not surprisingly, the peak on chromosome 2 overlapped with the genomic region containing the functional T_{-13910} allele; intriguingly, however, the *rs*6563275 SNP on chromosome 13—located in the vicinity of the *SPRY2* gene—showed an even stronger association ($P = 1.03 \times 10^{-6}$) with blood glucose levels (26). As a possible explanation for the latter result, the authors of this study concluded that the observed association might not be related to lactose digestion itself, but rather it may be due to the involvement of the genomic region on chromosome 13 in the subsequent steps of glycemic production (26). Explicitly, more genomic analyses are needed in order to confirm or reject the hypothesis that loci outside of chromosome 2 might contribute to LP in Africa.

Equally as intriguing, several studies have also found that some pastoralist groups in South Sudan (e.g. the Dinka, Nuer and Shilluk) and the Sahel (e.g. the Moors, Tuareg and Zaghawa) have either low frequencies or an absence of the common LP

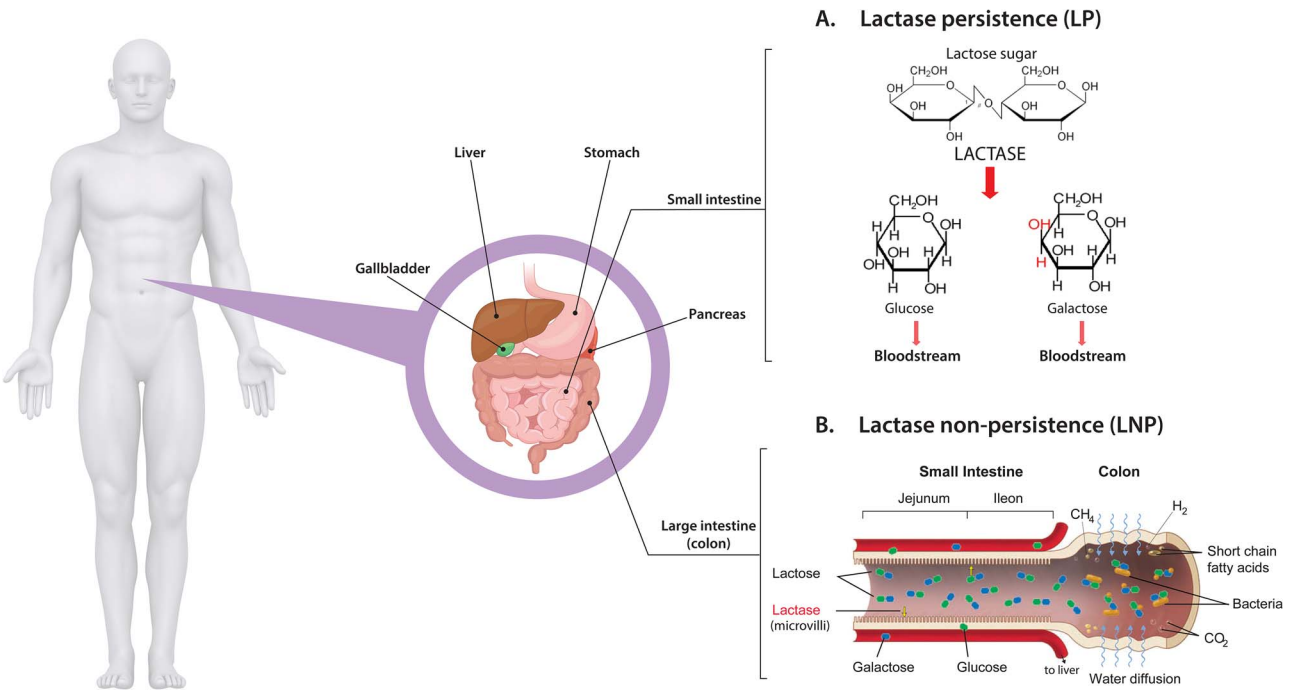

Figure 1. Two possible outcomes for the lactose sugar. When individuals are lactase persistent (A), lactose is hydrolyzed in the small intestine by the enzyme lactase into two monosaccharides, glucose and galactose, which are rapidly absorbed into the bloodstream. In contrast, when individuals are lactase non-persistent and lactose is ingested (B), this sugar escapes hydrolysis in the small intestine and enters the colon (large intestine) where it is fermented by bacteria. Short-chain fatty acids and gases (CO_2, H_2 and CH_4) are the end metabolites of bacterial fermentation of lactose, which contribute to the development of gastrointestinal symptoms of lactose intolerance, such as flatulence, distension, and diarrhea (osmotic or secretory). This figure is adapted from (8).

polymorphisms (5,6,8,11,24,54). As one possible explanation for this phenomenon, it has been proposed that the gut microbiome might facilitate the digestion of lactose without contributing to the development of gastrointestinal symptoms (particularly, if H_2-producing bacteria are absent in the colon) (24,43,61–68). Furthermore, prior studies have reported that some African hunter–gatherer populations with no known LP-associated variants (e.g. the Hadza and Yaaku from Tanzania and Kenya, respectively) have a high frequency of the LP phenotype (5,6,25). It has been hypothesized that lactase activity may have been maintained in these populations due to the secondary role of the enzyme in the hydrolysis of biologically active compounds in dietary plants (5,6,69–71). While these studies suggest that other genetic, biological and/or environmental factors may contribute to LP (5,16,26,56), more systematic research is needed to determine the extent to which these variables affect LP status in African populations.

Signatures of Recent Selection

Prior studies have demonstrated that common LP-associated variants exhibit signatures of recent positive selection (Fig. 2) (1,5,6,9,15,22,26,51,52,72,73). For example, genetic analyses have detected long-range haplotype homozygosity—spanning >2 Megabases (Mbs)—on chromosomes with the derived C_{-14010} allele compared to chromosomes with the ancestral allele primarily in East African pastoralists (Fig. 2) (5,6). Furthermore, Ranciaro *et al.* (5) also identified unusually long haplotype structure around the derived G_{-13907} and G_{-13915} alleles (extending ~1.4 Mbs and ~1.1 Mbs) in Sudanese and Kenyan populations, respectively. These genetic patterns are consistent with a classic selective sweep model in which a single beneficial allele underlying a given trait rapidly rises to high frequency in populations (74). Indeed, the intensity of selection for LP is considered to be amongst the strongest in the human genome, with a selection coefficient ranging from 0.04 to 0.097 in African populations (6,8). In addition, the derived T_{-13910}, C_{-14010}, G_{-13907} and G_{-13915}, G_{-14009} polymorphisms exist on different haplotype backgrounds, implying these functional loci arose independently through convergent evolution (1,2,5–7,10,72).

Intriguingly, it also has been inferred that stronger selection for LP occurred in Maasai pastoralists from Kenya (HapMap MKK) compared to individuals of European descent (HapMap CEU) (75). Notably, Schlebusch *et al.* (75) identified a higher peak in iHS score (a measure of haplotype homozygosity) around the *LCT/MCM6* region in MKK than in CEU. Similar results have been observed for the Maasai (Ranciaro, Campbell and Tishkoff, unpublished data) and the Finnish population from the 1000 Genomes Project (Fig. 2). It is important to note, however, that these genetic patterns could be indicators of more recent selection for LP, and associated alleles, in the Maasai relative to populations of European descent. This explanation is supported by other studies that estimated a younger age (~2700–6800 years) for the East African C_{-14010} allele and an older age (~8000–9000 years) for the European C_{-13910} allele (6,9), indicating the C_{-14010} allele arose more recently.

In addition, a targeted resequencing analysis of diverse Africans found that multiple functional loci (specifically, C_{-14010}, G_{-14009}, G_{-13915} and G_{-13907}) co-exist in Ethiopian populations; it was suggested that these variants likely underwent a soft selective sweep—such that alleles of similar benefit were selected for and increased in frequency simultaneously, or in short succession of one another, in response to strong selective pressure (i.e. milk consumption) (51,72). Under this model of evolution, multiple advantageous loci typically segregate at an intermediate frequency, leading to increased genetic

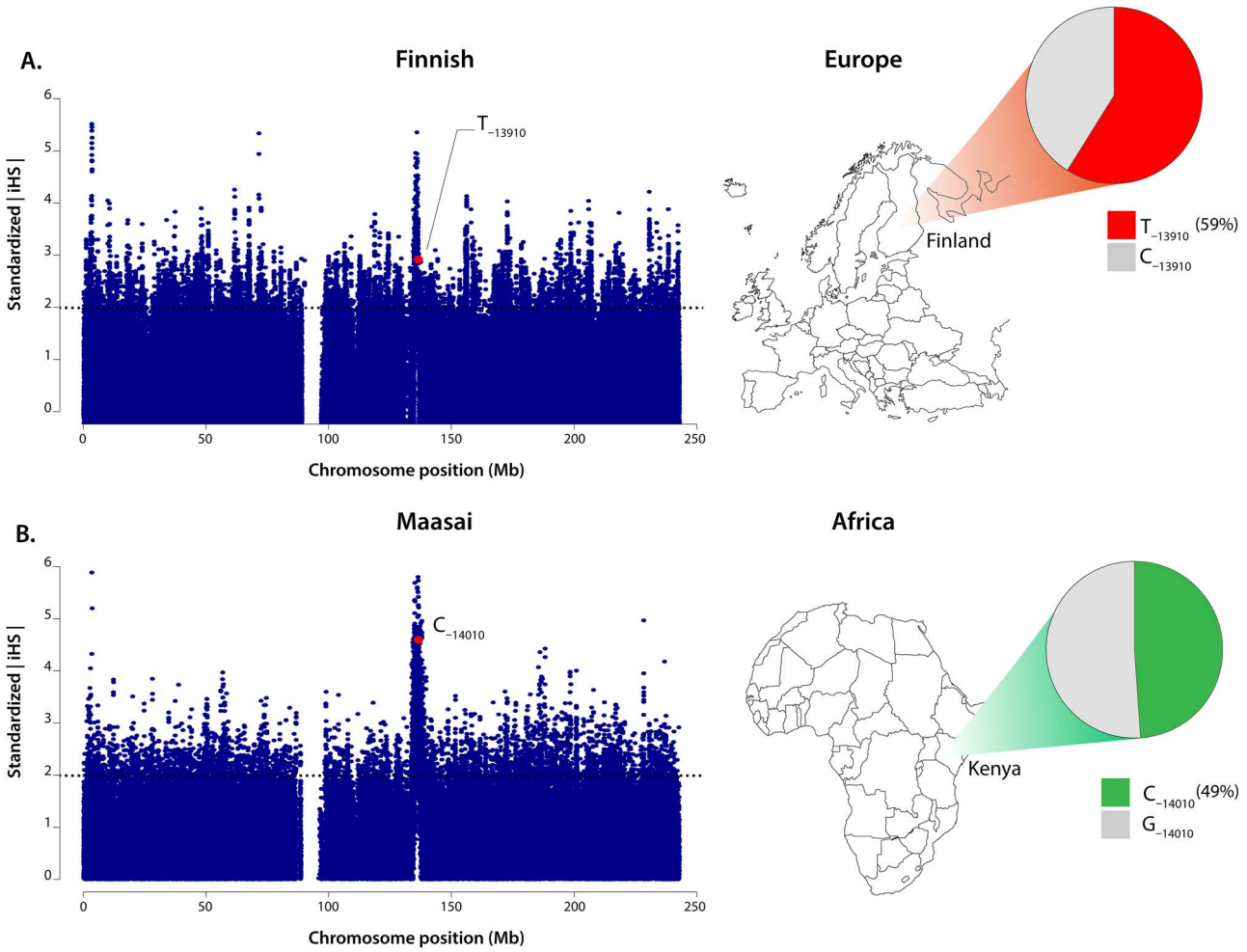

Figure 2. Integrated haplotype score (iHS) plots and frequency of derived LP-associated variants for selected populations. Manhattan plots of standardized | iHS | statistics for the Finnish (Europe) and Maasai (African) populations are given. The dashed horizontal lines indicate the cut-off for extreme | iHS | scores; | iHS | > 2 represents the most extreme 5% of empirical | iHS | values. The red dots in the plots represent outlier SNPs (either the derived T_{-13910} or C_{-14010} allele) in intron 13 of the *MCM6* gene. The frequencies of the derived LP-associated alleles in both Finnish and Maasai populations, along with their geographic locations, are also shown in the figure.

diversity (76–80) in populations, which is distinct from a classic selective sweep.

Although the fitness advantage of milk consumption in populations remains unclear (3), it has been hypothesized that fresh milk may have served as a source of uncontaminated water and electrolytes, particularly in ancestral populations inhabiting more arid environments, such as some African and Arab pastoralists (3,8,81). Alternatively, it has been proposed that milk digestion beyond infancy could contribute to higher circulating levels of insulin-like growth factor (since milk intake is associated with an increase of this hormone), leading to accelerated growth and larger body size (82). Irrespective of the true fitness advantage of milk consumption, however, it is clear that the genetic variation underlying the LP trait was functionally important during recent human evolution in Africa.

Geographic Distribution of LP-associated Alleles

Northern Africa and Sahel/Savannah belt

Indeed, human migration and admixture were integral to the rise and spread of pastoralism in Africa. One of the most important events in recent history was the geographic expansion of individuals from the Near East into northern Africa ~6500–7400 years ago (ya) during the African Humid Period (AHP) and their subsequent movement to the Central Sahara (27,83,84). Archaeological evidence (such as rock art, pastoralist cemeteries and the chemical residue of milk in pottery vessels) confirmed the presence of domesticated cattle in the region and the incorporation of milk into the diet of these migrating individuals (85,86). However, progressive desertification of the Sahara—resulting in the retreat of grasslands to the Sahel/Savannah belt—marked the end of the AHP ~5000–5500 ya (29,87). In response to this climatic shift (and increased herding of livestock), individuals migrated southward along river bed systems to the Sahel/Savannah region ~4500 ya (29). When these migrants arrived in the Lake Chad Basin, they were not the first inhabitants in the region, which was also occupied by populations of Niger-Congo, Afroasiatic and Nilo-Saharan ancestry (53,88–91).

Notably, several studies have identified striking geographic structure in the distribution of LP-associated loci across the Sahel/Savannah region (24,92–94). More specifically, the T_{-13910} variant is common in populations (e.g. the Bulala from Chad and the Fulani from Cameroon) west of Lake Chad, while pastoralists

east of the lake mainly carry the G_{-13907}, G_{-13915}, G_{-14009} and C_{-14010} alleles (5,24). Moreover, analyses indicated that the Fulani pastoralists—who possess the T_{-13910} allele—share the same haplotype background with Europeans, suggesting the ancestors of modern-day Fulani may have acquired this variant through admixture with a non-African source population rather than by convergent evolution (5,26,95,96). In addition to the migration of individuals from the Near East into Africa, it is known that Bedouin pastoralists also dispersed across northern and eastern Africa and into the Sahel from the Arabian Peninsula >1300 ya (93,97,98). This event likely introduced the G_{-13915} allele into these regions of Africa, contributing to contemporary patterns of genetic variation in populations (1,98,99). Further analysis also showed that the age of the derived T_{-13910} allele in Fulani pastoralists is much older (7534–9686 years) than the G_{-13915} allele (~1274–1782 years), implying the T_{-13910} mutation appeared earlier in the Sahel/Savannah belt relative to G_{-13915} (100).

Finally, studies have reported the presence of the G_{-14009} variant in Somali, Sudanese, Kenyan and Ethiopian populations, with the highest frequency occurring in the Sudanese Beja (up to 42.6%) (5,11,50,51,54,93). This variant also exists at a much lower frequency in the Arabic Baggara from Cameroon (1.6%) and in Middle Eastern populations (1.0%) (5,98). Given the prevalence of the G_{-14009} mutation in the Beja, it has been speculated that this functional allele may have originated in Sudan (93,98,101,102).

East Africa

Following the end of the AHP, herders from Sudan, Ethiopia and possibly Somalia, who spoke proto-Southern Cushitic languages (103–105) migrated with their domestic cattle to northwest Kenya. Archaeological monuments and faunal assemblages near Lake Turkana, dating to 4300–5000 ya, are said to represent the earliest evidence of livestock in East Africa (106,107). Moreover, lipid residue analysis detected chemical evidence of meat, plant and milk in pottery vessels found at settlement sites near Lake Turkana dating to around the same time (108).

Genetic and archaeological data also indicated that pastoralism became more geographically widespread (23,31,109). In particular, Nilotic-speaking pastoralists are argued to have migrated southeastward to Kenya and northern Tanzania from eastern Sudan within the last 3500 years (110). Furthermore, Cushitic agro-pastoralists are thought to have expanded into the same geographic regions from Ethiopia around the same time, engaging in cultural exchange and intermarriage with southern and eastern Nilotic-speakers (111). This inferred gene flow between Nilotic- and Cushitic-speakers is consistent with genetic data that showed the shared presence of the East African-specific C_{-14010} mutation in these linguistically distinct populations (5,6,112,113). Given the high frequency of the C_{-14010} allele in Tanzanian populations and its virtual absence in southern Sudanese Nilo-Saharan-speakers (5,6), it has been argued that the C_{-14010} mutation likely arose first in Afroasiatic Cushitic-speaking populations and then was introduced into Nilo-Saharan Nilotic-speakers through admixture. However, regardless of population origin, it is thought that the C_{-14010} allele spread rapidly throughout East Africa together with the cultural practice of herding consistent with a demic diffusion model (5,6). Archaeological data also suggested that a more specialized reliance on milk arose in herding communities throughout southern Kenya and northern Tanzania after 3300 ya (108). In addition, the G_{-13907} allele is found mainly in Afroasiatic-speakers from northern Sudan, northern Kenya and Ethiopia (1,3,5,6,10) but is absent in southern Cushitic-speakers from Tanzania. Although it has been speculated that G_{-13907} allele arose in eastern Cushitic-speakers from Ethiopia (5,91), the geographic origin of this mutation remains unclear.

Finally, the recent migration of non-Africans into Africa is argued to have contributed to the gene-pool of eastern African populations. In particular, studies have suggested that the derived G_{-13915} allele—found mainly in populations from the Arabian Peninsula, Sudan, Kenya, and the Horn o f Africa (5)—arose in the Arabian Peninsula ~4100 ya and was brought to eastern Africa by migrating Arabic-speaking herders >1300 ya (1,5,98).

Southern Africa

Studies also have described additional migration events across Africa (5,114–117). In particular, the southward migration of East African pastoralists is thought to be the source of LP-associated variants in southern Africa (5,20–22,25,118–120). While the precise details of this dispersal are still unclear, it has been speculated that the C-14010 allele might have been brought to southern Africa by migrant East African Nilo-Saharan and/or Afroasiatic pastoralists who admixed with Khoekhoe-speaking groups ~2400 ya (5,21,121). The Khoekhoe-speakers subsequently spread to the western parts of South Africa, introducing the mutation through admixture to pastoralist communities (5,21,121). By contrast, genomic analyses of contemporary and ancient populations have uncovered East African/Eurasian ancestry in southern African Khoekhoe herders and San hunter–gatherers; moreover, this ancestry was present at higher frequency in Khoekhoe herders (20,22,25,116,117,122,123). Thus, it has been argued that herding practices along with the C_{-14010} allele may have been introduced into southern Africa, prior to ~1300 ya, by migrants with East African/Eurasian ancestry who admixed with southern African hunter–gatherers to form the ancestors of the Khoekhoe herders (that is to say, Khoekhoe herders descended from previously admixed ancestors) (20,25).

Alternatively, it has been proposed that the C_{-14010} variant could have been introduced ~1400 ya by eastern African Bantu-speaking populations who acquired the variant through admixture and subsequently migrated along the East coast to southern Africa (25,124–127). Genetic studies have also reported the presence of the T_{-13910} allele in southern African groups with European ancestry, such as the 'Wellington Colored' (17.5%) and Nama Khoisan–speaking populations (6.8%) (20,123,128), reflecting ongoing admixture within this geographic region.

The Dispersal of Domesticated Cattle Within the Context of Climate Change and Disease

Archaeological and genetic data indicate that the ancestors of modern *Bos taurus* (taurine cattle) were domesticated from *B. primigenius primigenius* in the Fertile Crescent (the Near East) >10 000 ya (129–135). The domestication of *B. primigenius nomadicus* also occurred independently in the Indus Valley in present-day Pakistan, giving rise to the extant *Bos indicus* (humped zebu cattle) >8000 ya (136–139).

Zooarchaeological remains suggest that *B. taurus* was the first domesticated cattle species introduced into Africa from the Near East. Some of the earliest taurine cattle sites in Africa are argued to be found in the Acacus Mountains in Libya and in the Nabta-Keseiba region of southern Egypt dating to ~7000–8000 ya and ~6500–7700 ya, respectively (27,28,140–142). These cattle subsequently expanded across the Sahara, southeast to Sudan,

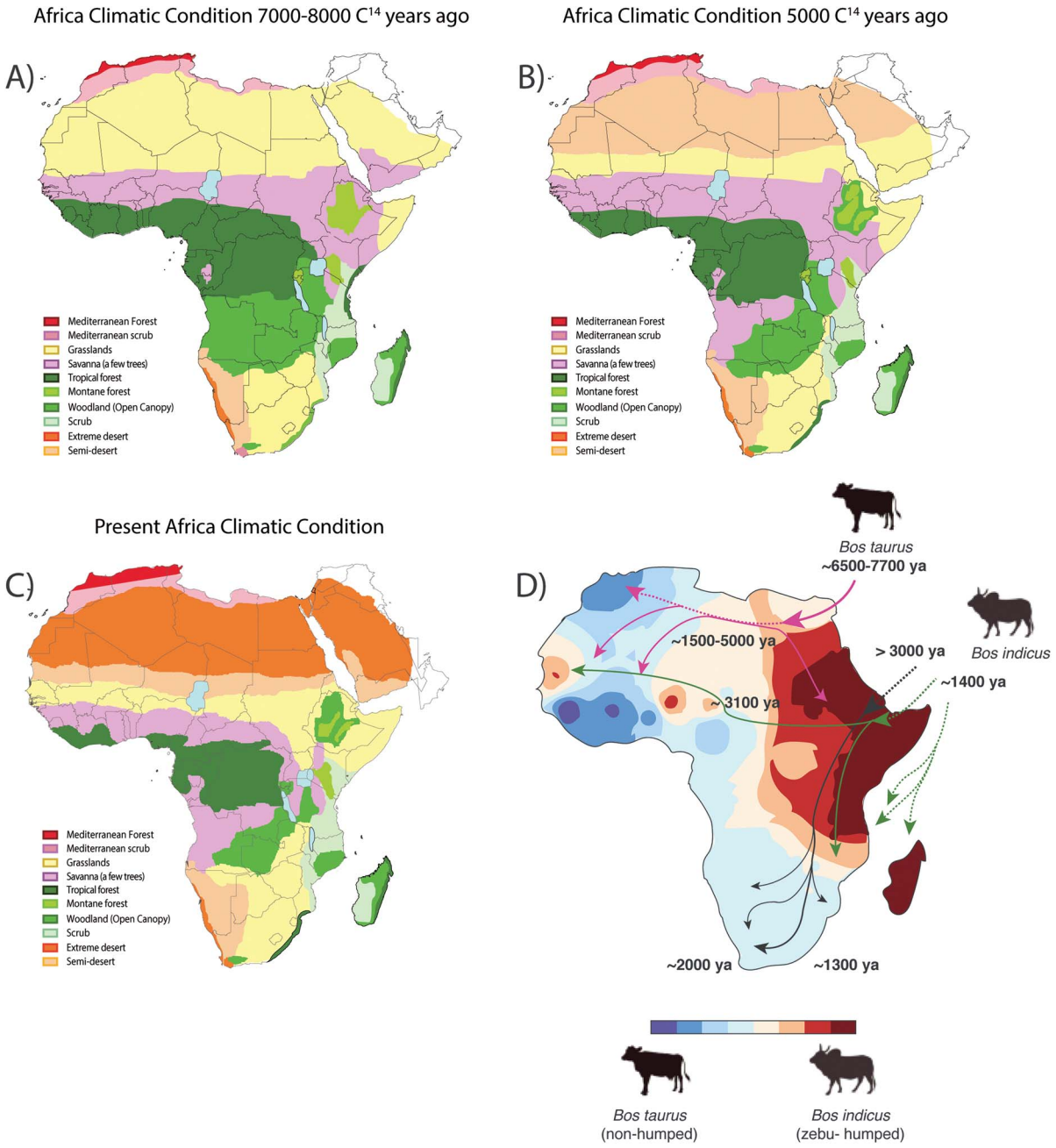

Figure 3. Climate change and routes of migration of domesticated cattle in Africa. Maps (**A–C**) show changes in climatic conditions from 8000 ya until the present, which played important roles in the introduction and spread of domesticated cattle in Africa. In (**D**), the different colored arrows on the map indicate the migratory routes of two bovine species, *Bos taurus* and *Bos indicus*, that were domesticated in the Near East and South Asia, respectively (adapted from (151,172)). *B. taurus* migrated via a northern Africa route ~6500–7700 ya; whereas *B. indicus* was introduced into Africa mainly through an eastern route in two waves ~3000–4000 ya and ~1400 ya. Different domestic cattle types were also repeatedly interbred to form new populations of hybrids that spread across the continent. Today, ~150 breeds of indigenous cattle are recognized in sub-Saharan Africa (151).

southwest to West Africa and later to Lake Turkana and the Horn of Africa (Fig. 3) (110,143–147). By contrast, genetic and faunal data indicated that *B. indicus* migrated into Africa primarily from South Asia in two waves ~3000–4000 ya and ~1400 ya (the main arrival of *B. indicus* that occurred in association with the spread of Islam) (Fig. 3) (129,145,146,148–152). After entering eastern Africa, *B. indicus* dispersed to western Africa through the Sahel corridor (between the Sahara desert to the north and the tsetse fly-infested forests to the south) and along the East African coast (Fig. 3) (135,139,148,149,151,153). Although there is still some debate about whether or not cattle domestication took place in northern Africa, mounting evidence suggests that both *B. taurus* and *B. indicus* cattle were brought by migrants onto the African continent after their domestication in other regions of the world (53,135,154).

The pattern and timing of domestic cattle dispersal within Africa were strongly dictated by environmental changes (Fig. 3) (155). For example, archaeological and paleoclimate data have shown that the presence of domestic cattle in northern Africa coincided with the occurrence of humid conditions

> 6500 ya. Furthermore, after the arrival of more arid conditions ~5000 ya, it is thought that herders migrated with their cattle to other parts of Africa (27,28,30,156). Notably, infectious disease also influenced the geographic range of different cattle types. Currently and historically, zebu cattle are common in eastern Africa (where there is an abundance of tick species), while taurine cattle are found mainly in West Africa (which is rife with tsetse flies, the known carriers of the African trypanosome protozoan) (151). Moreover, zebu and taurine cattle possess distinct genetic/phenotypic adaptations that enable them to survive and reproduce in their environments. For example, recent genetic studies of zebu cattle have reported long-distance haplotype homozygosity—indicative of a recent selective sweep—in chromosomal regions containing genes associated with biological traits, such as milk-production, thermotolerance, and parasite resistance (149,157–159). By contrast, analyses of taurine cattle genomes detected long-range haplotype structure around variation in the MHC region that may be associated with trypanotolerance (i.e. tolerance to the protozoal disease, trypanosomiasis) (160). Due to these genetic traits, zebu and taurine cattle flourished within their respective environments. Specifically, taurine cattle (e.g. N'Dama longhorn cattle), which can withstand the effects of trypanosomiasis, expanded their geographic range to West and equatorial Africa over time (161,162); whereas tick-resistant zebu cattle were able to move into the grasslands of Kenya and Tanzania, and then to South Africa via newly-developed tsetse fly-free environments (163,164). In the end, the geographic distribution of zebu and taurine cattle is consistent with the unique adaptations that these two bovine species possess.

Genetic studies also uncovered evidence of admixture between different cattle types. For example, zebu and taurine cattle were interbred to form populations of sanga cattle that migrated to central, eastern and southern Africa (Fig. 3) (148,149,151); other cattle hybrids, with different parental types, also can be found across Africa (Fig. 3).

Future Directions

Although we have learned a considerable amount about LP, more comprehensive research is required to shed further light on the genetic architecture and evolutionary history of this trait. With newly increased capacity to generate whole-genome sequencing data and the corresponding advancements in computational methods, scientists now have a unique opportunity to explore new avenues of research in ways that were previously inaccessible. For example, the analysis of genomic and phenotypic data collected from diverse African pastoralist populations will be invaluable for identifying novel loci associated with LP, including alleles with small to moderate effect sizes (together with their epistatic effects). Furthermore, it will be important to test for signals of selection (e.g. long-range haplotype homozygosity and outlier F_{ST} values) at associated loci to determine whether a few adaptive alleles at high frequency underlie LP (a classical selection model) or selective events occurring at many loci contribute to LP variation (a polygenic adaptation model) (165–167), providing new information regarding human biological evolution. Additionally, genomic sequence data from fossil remains (when more are discovered), spanning thousands of years, could be highly informative for directly investigating increases in LP allele frequency and the timing of selection in Africa. These DNA analyses can yield novel insights into the process of adaptation and population change over time.

Intriguingly, researchers have also speculated that the gut microbiome may play a role in lactose digestion in some populations (168). Future studies that examine human genotype–phenotype data (including *in vitro* experiments using human cells) along with the gut microbiome could be highly informative for clarifying the degree to which host genetics and other biological factors individually or jointly influence LP in Africans. Additional studies that integrate archaeological, linguistic, paleoclimatic, and geographical information with genetic data will be useful for reconstructing historical events related to the origin and spread of pastoralism, providing a more nuanced view of recent human evolution.

Despite nearly half a century of debate (3,8,15,73,74,169–171), researchers still do not fully understand the selective advantage of milk consumption in African populations. Explicitly, more cultural anthropological studies that examine the intimate relationship between African herders, cattle and milk are needed. In addition, increased residue testing of archaeological remains will lead to a better understanding of past dietary practices (including milk processing and the amount of milk consumption). These analyses will enable investigators to infer why and when ancestral populations began to incorporate fresh milk into their diet and, by extension, characterize the nature of the selective pressure that drove LP and associated variation to high frequency in Africa (8,27).

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