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The Evolution of Lactose Tolerance in Dairying Populations

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Abstract and Keywords

Among the biocultural innovations associated with the Neolithic, dairying and the evolution of lactose tolerance is the most studied. Expression of the enzyme lactase, which digests the milk sugar lactose, decreases after weaning in mammals, including most humans. However, some humans express lactase throughout adulthood—a trait known as lactase persistence (LP). Striking observations about LP evolution include: (i) a strong correlation between LP frequency and a history of herding and dairying; (ii) genetic patterns indicating LP-associated variants have increased in frequency through natural selection; (iii) two of these variants have been experimentally shown to affect lactase expression in adults; and (iv) archaeological and ancient DNA data indicate dairying pre-dated the rise of LP-associated variants. This chapter reviews the biology and archaeology of LP, examines some of the hypotheses formulated to explain its distribution, and outlines how simulation modelling has contributed to our understanding of its evolution.

Keywords: lactase persistence, genetic adaptation, dietary transition, Neolithic, milk

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The Neolithic transition—the archaeological period that defines a shift from food-seeking to food-producing (Diamond 1997; Fuller 2007; Fuller and others 2011; Pinhasi and others 2005; Vigne 2008; Whittle 2007; Zeder 2008)—is associated with dramatic changes in human ecology, including changes in diet. Among these changes, a narrowing of dietary range to a few key staples, an increase in carbohydrate, and a reduction in protein and various micronutrients are particularly notable in cereal-based economies (Cordain and others 2000; Konner and Eaton 2010; Losch and others 2006; Luca and others 2010; Richards 2002). These changes have been hypothesized to partly explain the poorer health of early Neolithic individuals compared with those from the Upper Palaeolithic and Mesolithic periods (Eshed and others 2010; Holt and Formicola 2008; Larsen 1995; Richards 2002). It can therefore be hypothesized that after the domestication of animals that may be milked (primarily cows, goats, and sheep), the consumption of milk and dairy products may have provided nutritional complements to the diet of early farmers (Bogucki 1984), as well as protecting against food shortage brought about by crop failure and the seasonality of cereal agriculture (Shennan and others 2013). Indeed, milk contains various nutrients such as lipids, micronutrients (including calcium and vitamin D), proteins, and is an important source of carbohydrates, mainly lactose.

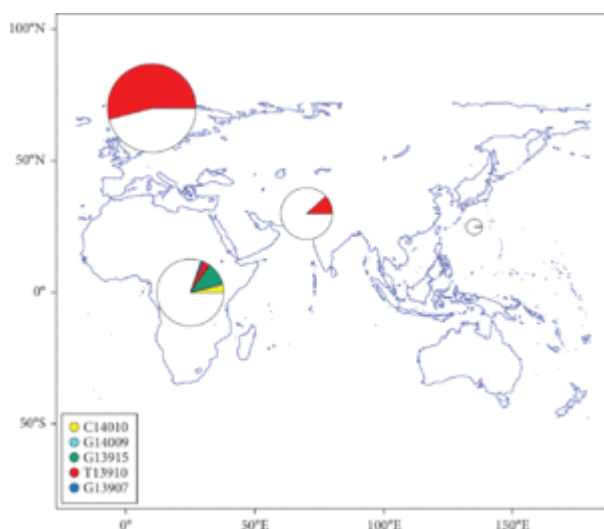
Lactose is a disaccharide comprised of the monosaccharides, galactose and glucose. The enzyme lactase is secreted in the small intestine where it cleaves lactose into its component monosaccharides, which can then be transported across epithelial cell membranes to yield their energetic load. All mammals studied, including humans, express lactase as infants. After weaning, lactase expression typically decreases in comparison to birth levels (Troelsen 2005). This trait is known as lactase non-persistence and is the ancestral state in humans. However, about 32% of humans worldwide continue to express lactase into adulthood (Ingram and others 2009; Itan and others 2010), a trait termed lactase persistence (LP). When a lactase non-persistent individual ingests milk, the lactose is not broken down into glucose and galactose but instead is fermented in the colon by bacteria. This fermentation of undigested lactose produces gases, causing symptoms of lactose intolerance such as bloating, flatulence, and abdominal cramps, and the osmotic effects of colonic lactose can cause diarrhoea. These symptoms may have prevented early lactase non-persistent farmers from benefiting from the nutrient load of fresh milk, thereby affecting their survival in periods of food shortage (Shennan and others 2013). The disciplines of anthropology, archaeology, chemistry, molecular biology, and population genetics have provided some clues about the evolution of LP.

The Genetics of LP

LP is inherited in an autosomal dominant manner (Ferguson and Maxwell 1967; Sahi 1974; Swallow and Hollox 2000). A single gene (*LCT*) located on chromosome 2q21 encodes lactase. To date, five variants (*-13,907*G*, *-13,910*T*, *-13,915*G*, *-14,009*G* and

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-14,010*C) have been found to associate with lactase persistence, indicating convergent evolution (Enattah and others 2002; Imtiaz and others 2007; Ingram and others 2007, 2009; Jones and others 2013; Tishkoff and others 2007). These variants are located about 14kb upstream of the *LCT* promoter, in the first intron of the neighbouring *MCM6* gene. This genomic region contains various transcription factor binding sites (Troelsen 2005) and these five substitutions have been reported to enhance lactase expression *in vitro* (Jensen and others 2011; Jones and others 2013; Lewinsky and others 2005; Olds and Sibley 2003; Tishkoff and others 2007; Troelsen and others 2003). A recent functional study (Fang and others 2012) has confirmed the effect of one of these alleles *in vivo* (-13,910*T). Importantly, these variants are not evenly distributed among populations where LP is observed (Figure 28.1). In Africa, all five LP-associated alleles have been identified, whereas in Europe and Southern Asia only a single major variant (-13,910*T) has been found (Gallego Romero and others 2012).



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Figure 28.1 Distribution of the five genetic variants that have been shown to be associated with LP and to affect lactase expression *in vitro*. Pie chart radii are proportional to sample sizes. Population and allele frequency information can be found at <http://www.ucl.ac.uk/mace-lab/resources/glad>

The age of an allele can be estimated by studying patterns of genetic variation in surrounding genomic regions. For the Eurasian -13,910*T allele, an age range of between 2,188 and 20,650 years (Bersaglieri and others 2004) has been estimated using extended haplotype homozygosity (EHH), and between 7,450 and 12,300 years ago (Coelho and others 2005), or between 7,475 and 10,250 years ago (Mulcare 2006), estimated using variation in closely linked

microsatellites. A similar age range of between 1,200 and 23,200 years has been estimated for the major African allele, -14,010*C, using EHH (Ranciaro and others 2014; Tishkoff and others 2007) and over 4,500 years using closely linked microsatellite variation (Macholdt and others 2014). These age estimates for LP-associated variants are remarkably young for alleles found at such high frequencies in multiple populations.

The combination of recent age and high frequency implies that the variants have increased in frequency rapidly. Allele frequencies can change over time through genetic drift, but these changes tend to be slow—unless in very small populations—and directionless. However, the rapid increase in frequency of LP-associated alleles is unlikely to have been caused by drift alone, and positive selective pressures are typically invoked. The strength of natural selection can be estimated by measuring the extent of haplotype

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conservation, or microsatellite diversity, along the chromosomal region carrying LP-associated alleles, together with the frequency of the allele itself, by modelling the population history and natural selection processes in space (Gerbault and others 2009; Itan and others 2009), or by comparing allele frequencies in ancient and modern population samples (Sverrisdottir and others 2014; Wilde and others 2014). The strength of selection needed to explain the distribution of the *-13,910*T* allele ranges between 0.8 and 19% (Bersaglieri and others 2004; Gerbault and others 2009; Itan and others 2009; Sverrisdottir and others 2014). Similarly, the estimates for the *-14,010*C* allele range between 0.02 and 15% (Macholdt and others 2014; Tishkoff and others 2007). These selection coefficients are among the highest estimated for any human gene in the last 30,000 years (Sabeti and others 2006), and yet the reasons why LP has been favoured are debated (Gerbault and others 2011).

Hypotheses on the Advantage of Being Lactase Persistent

The substrates of lactase may provide some insights into the benefits of expressing the enzyme as adults. The full name of the enzyme is lactase-phlorizin hydrolase (LPH). It takes its name from its two primary activities (Arribas and others 2000; Swallow 2003): the β -galactosidase activity, responsible for the hydrolysis of lactose, and the β -glucosidase activity hydrolysing plant glucosides (Day and others 2000; Jager and Saaby 2011; Mackey and others 2002) including phlorizin (Arribas and others 2000), which is a 2'-glucoside of phloretin (a type of flavonoid, i.e. a plant secondary metabolite) found in roots and bark of plants from the Rosaceae family (e.g. pear and apple trees) and of some seaweeds. The substrates of LPH β -glucosidase activity, such as flavonoids, have known beneficial health effects (Jager and Saaby 2011), but the relationship between the consumption of substrates requiring this activity in lactase persistent versus non-persistent individuals has not been well studied. It may be hypothesized that this LPH β -glucosidase activity, by enabling the intake of deglycosylated substrates, was positively selected because it benefited the health of lactase persistent individuals. However, another intestinal enzyme, cytosolic β -glucosidase (CBG), performs the same deglycosylation (Jager and Saaby 2011; Nemeth and others 2003), and therefore the expression of lactase for this purpose appears redundant, and needs further investigation.

In contrast, LPH is the only mammalian enzyme that has the ability to cleave lactose. When lactose is consumed but not broken down by lactase into its constituent monosaccharides, it can cause symptoms of lactose intolerance. It has been shown that the severity of these symptoms can vary between individuals (Gerbault and others 2011, 2014; Ingram and others 2007; Ingram and Swallow 2009). Nonetheless, lactase non-persistent individuals may lose fluids and minerals when drinking fresh milk, while lactase persistent individuals can fully benefit from the carbohydrates and the many other nutrients milk contains. Even though lactose is also found in very small quantities in forsythia flowers and in the Sapotaceae family (Holsinger 1997), fresh milk, along with some milk products, are the major natural sources of lactose. It thus seems unlikely that LP would confer any advantage without a supply of fresh milk. This is supported by the observed correlation between populations with a history of dairying practices and a high frequency of lactase persistent individuals (Holden and Mace 1997).

Despite the association of LP and milk consumption, no consensus has been reached regarding the specific selective advantage(s) it conferred to ancestral populations. Cook and al-Torki (1975) hypothesized that milk may have provided a relatively pathogen-free liquid during periods when water was scarce and/or in an arid climate. However, when water is scarce, livestock are as likely to suffer from drought as humans and therefore milk production may be impaired. Some authors have suggested LP may have provided some protection against malaria (Anderson and Vullo 1994; Cordain and others 2012;

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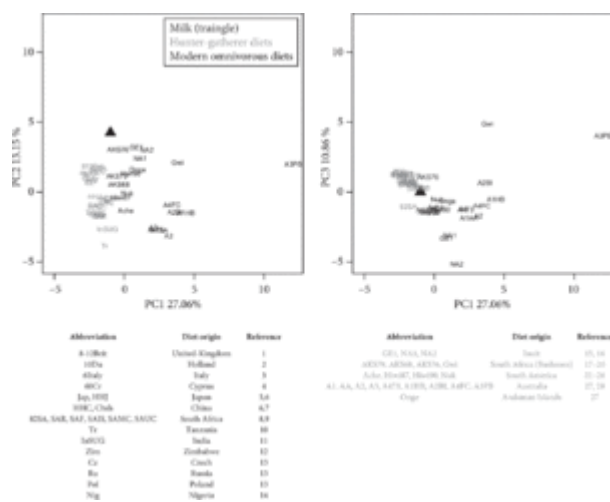
Ranciaro and others 2014). While this has not yet been investigated in African populations, there is no evidence of a protective effect of LP against malaria in a Sardinian population where malaria was prevalent (Meloni and others 1996, 1998). Other authors have suggested that LP evolved as a by-product of the diffusion of milk drinking as a socially elite behaviour (Durham 1991a; Simoons 1970).

Alternative hypotheses include that LP was advantageous because of the nutritional benefits milk provides in the absence of lactose intolerance symptoms. In particular, one of the most widely cited explanations for the evolution of LP is the '*calcium assimilation hypothesis*', first proposed by Flatz and Rotthauwe (1973). They suggested that milk—which is a modest source of vitamin D and an excellent source of calcium—supplemented the expected deficient levels of calcium and vitamin D of early farmers as they moved to the higher latitudes of northern Europe. While fish and some other foods are good sources of vitamin D, which is required for calcium absorption, most people in the world produce sufficient vitamin D by UVB photoconversion of 7-dehydrocholesterol into cholecalciferol (vitamin D₃) in the skin. In northern Europe, however, UVB levels are usually too low for this (Jablonski and Chaplin 2010), and cereal-based diets are a poor source of vitamin D, so early farming populations may have had elevated rates of rickets. However, the Mesolithic and Neolithic archaeological record has, thus far, not provided any evidence of a higher risk of rickets in early Neolithic populations (Larsen 1995) to support this theory. In addition, ancient DNA data indicate that selection favouring LP was strong even in lower latitude Europe, such as Iberia, where sunlight exposure should have been sufficient for vitamin D synthesis (Sverrisdottir and others 2014). Thus, while the '*calcium assimilation hypothesis*' may provide an important explanatory component of LP evolution in some regions (Cramp and others 2014; Gerbault and others 2009), it does not in others.

Although the '*calcium assimilation hypothesis*' is concerned with specific nutrient components, milk is in fact a generally nutrient-dense and nutrient-diverse food. Advocates of the Palaeolithic diet hypothesis (Konner and Eaton 2010) have noted that modern hunter-gatherer diets, and inferred Palaeolithic diets, were also nutrient-dense and nutrient-diverse when compared to modern and inferred post-Neolithic transition diets (Cordain and others 2000; Konner and Eaton 2010; Kuipers and others 2010; Losch and others 2006; Luca and others 2010; Richards 2002). This may have had negative health implications for early farmers (Eshed and others 2010; Holt and Formicola 2008; Larsen 1995; Richards 2002), raising the possibility that a key benefit of milk consumption was that it contains a diversity of nutrients that supplemented those severely reduced in the transition from hunter-gathering to farming. We have examined this hypothesis further using principal component analysis. To do so, we decomposed twenty-one modern agriculturalist and twenty modern hunter-gatherer diets, using the USDA National Nutrient Database for Standard Reference (US Department of Agriculture 2013), to their composite twenty-nine macro- and key micronutrients, normalized for total calories. For the first and third principal components of variation in nutrient profiles among these diets (Figure 28.2), milk occupies a position midway between hunter-gatherer and modern agriculturalist diets. This suggests that it may have acted as a

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bridging food between hunter-gatherer and early Neolithic diets. Interestingly, an immediate replacement of fishing with dairying by the earliest farmers of the north-east Atlantic archipelagos has recently been observed (Cramp and others 2014). One way of examining this hypothesis further would be to reconstruct early Neolithic diets to assess their nutrient breadth and compare their positions on the principal component plots described above.



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Figure 28.2 Principal Component Analysis of the quantities of twenty-nine major and key micronutrients in milk (red triangle), twenty-one modern agriculturalist (orange) and twenty modern hunter-gatherer (green) diets. The first two principal components (left, PC1 and PC2) and the first and third principal components (right, PC1 and PC3) are considered. Diets were obtained from: 1 Family Food (DEFRA 2013); 2 van Rossum and others (2011); 3 Sette and others (2011); 4 Kafatos and others (2000); 5 Iso and others (2005); 6 Zhou and others (2003); 7 Cai and others (2004); 8 Langenhoven and others (1988); 9 MacIntyre and others (2002); 10 Mazengo and others (1997); 11 Reddy and Rao (2000); 12 Merchant and others (2005); 13 Boylan and others (2009); 14 McFie (1967); 15 Binford (1978); 16 Sinclair (1953); 17 Silberbauer (1980); 18 Lee (1979); 19 Lee and DeVore (1976); 20 Lee and DeVore (1968); 21 Hurtado and others (1985); 22 Hurtado and Hill (1990); 23 Hill and others (1984); 24 Hawkes and others (1982); 25 Hurtado and Hill (1987); 26 Politis (2009); 27 Meehan (1982); 28 Anderson and others (2001). Diets were then decomposed into twenty-nine macro- and key micronutrients: total protein, total fat, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, cholesterol, total carbohydrates, fibre, alcohol, calcium, iron, zinc, magnesium, sodium, potassium, phosphorus, selenium, manganese, thiamine, riboflavin, niacin, vitamin B6, vitamin B12, total folic acid, vitamin C, total vitamin A, vitamin D, and vitamin E. Nutrient quantities for each diet were first normalized by the recommended daily calorie intake (2000 calories per day). We then calculated the twenty-nine arithmetic means of these normalized nutrient quantities over all the forty-one diets and milk. We finally divided these normalized nutrient quantities by their respective mean, so that the forty-one diets and milk could be compared. Principal component analysis was performed using the R (<https://www.r-project.org>) package FactoMineR (<http://cran.r-project.org/web/packages/FactoMineR/index.html>).

Evidence from the Archaeological Record

The age estimates of the LP-associated mutations bracket dates for the domestication of animals that can be milked and the spread of agriculture and herding, for which the earliest evidence dates to around 10,500 years (Bollongino and others 2012). Evidence for the use of milk in the archaeological record comes from two major sources: kill-off profiles of domestic animals and the detection of dairy fat residues in potsherds, both identified in Neolithic assemblages.

Kill-off profiles are the age and sex distribution of animals in archaeological assemblages (i.e. at death) and show that weaned animals are more frequent in Near Eastern sites dated from 10,000 years before present (BP) onwards, than in earlier (Late-Mesolithic) sites (Balasse and Tresset 2002; Vigne 2008; Vigne and others 2003). This has been interpreted as evidence for early dairying practices, where more females were kept alive and their milk could be used for human consumption while their offspring were slaughtered.

Further archaeological evidence for the intensification of dairying during the Neolithic comes from the detection of dairy fat residues in potsherds, using a combination of individual fatty acid discrimination and measurements of stable isotope ratios (Gerbault and others 2013). Using this approach, the presence of dairy products has been demonstrated in north-west Anatolia as early as 8,500 years BP (Evershed and others 2008), the Libyan Sahara between 7,150 and 5,750 years BP (Dunne and others 2012), at Neolithic sites in Romania and Hungary dating to around 7,900–7,450 years BP (Craig and others 2005), and in Britain around 6,100 years BP (Copley and others 2005). These dates fall near to or at the time when farming arrived in those regions, indicating that dairying was an early feature of the Neolithic lifestyle in Europe. Though less commonly performed than detection of lipid residues, the detection of milk proteins (e.g. alpha bovine casein) in potsherds can also be used to infer whether ancient populations processed milk (Craig and others 2000).

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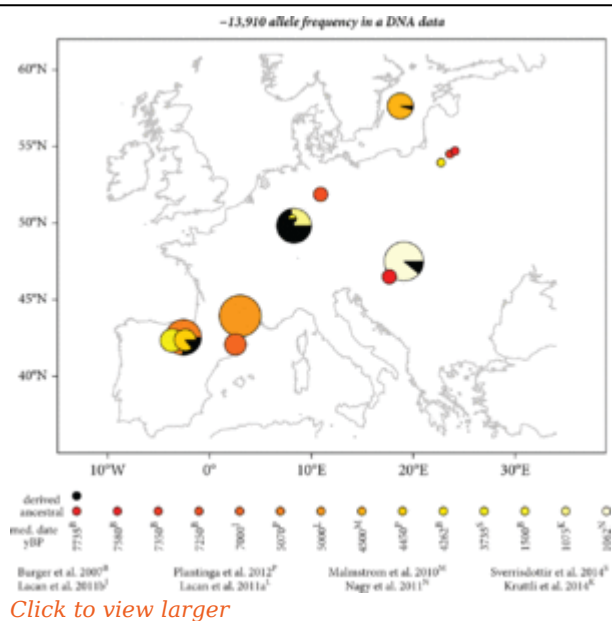


Figure 28.3 Distribution of published lactase persistence-associated allele ($-13,910^*T$) frequencies in European ancient DNA samples, as of March 2014. Pie chart radii are proportional to sample sizes. The derived allele frequency ($-13,910^*T$) is shown in black, while the ancestral allele frequency ($-13,910^*C$) is shown in shades of red to cream, where the closer to red the colour is, the more ancient the aDNA sample.

In ancient DNA (aDNA) samples (Figure 28.3), the earliest evidence for the presence of $-13,910^*T$ in European populations is from late Scandinavian hunter-gatherers dating from 5,400–3,400 years BP, with an estimated frequency of 5%, (Malmström and others 2010). This allele has been found in early Neolithic farmers from north-western Iberia between 5,000 and 4,500 years BP with an estimated frequency of 26% and 11% (Plantinga and others 2012). While the $-13,910^*T$ allele is absent from contemporaneous early Neolithic farmer samples

from other regions (Burger and others 2007; Lacan and others 2011a, 2011b; Sverrisdottir and others 2014), it has been found in a single heterozygous individual from a Medieval sample in north-eastern Europe dated to 400–600 years AD (Burger and others 2007). In Central Europe and south-eastern Europe, aDNA samples dated to 950–1200 years AD (Kruttl and others 2014) and to 1012–1112 years AD (Nagy and others 2009) yielded frequency estimates of 72% and 11%, respectively. This rarity of the $-13,910^*T$ allele in older aDNA samples, together with the evidence of early dairying practices in the archaeological record, suggest that LP did not become common until after dairying was widespread in Europe. Furthermore, the correlation between LP—and more precisely the LP-associated alleles identified so far—and pastoralist/milk-drinking populations (Holden and Mace 1997; Itan and others 2010; Simoons 1970) provides strong support for a co-evolutionary process between a cultural (dairying) and a genetic (LP-associated alleles) trait. This highlights the evolution of LP as a prime example of gene–culture co-evolution (Durham 1991a, 1991b; Gerbault and others 2011; Itan and others 2009; Laland 2008; Laland and others 2010).

Simulation Modelling and Future Directions

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Because only one major LP-associated allele has so far been identified in indigenous Europeans, while five have been identified in African and Middle Eastern populations, modelling the evolution of LP in Europe is more straightforward. To this end, computer simulation has been used to generate genetic data sets under a range of evolutionary scenarios of varying complexities. For example, a demic simulation model illustrated that while natural selection may be required to explain the high observed allele frequencies in Northern Europe, it may not be for the lower observed allele frequencies of Southern Europe (Gerbault and others 2009). Furthermore, using a coalescent approach, Peter et al. (2012) suggested that the pattern of genetic variation surrounding *LCT* observed in the Finnish population, one of the populations showing the highest frequencies and most recent ages for *-13,910*T* (Bersaglieri and others 2004), could have been produced by selection acting on a *de novo* mutation rather than on standing variation. This implies that the ecological conditions that eventually favoured LP existed before LP arose.

Itan et al. (2009) used a high-resolution spatially explicit model to simulate the spread of the LP-associated allele (*-13,910*T*) with farmers diffusing from the Near East and throughout Europe. This model accommodated natural selection, various processes of migration and gene flow, and the possibility of allele surfing—a process by which rare genetic variants undergo sequential genetic drift on the wave front of an expanding population and end up at highest frequencies in regions far removed from their location of origin (Currat and others 2006; Edmonds and others 2004; Excoffier and others 2009; Klopstein and others 2006). While allele surfing of neutral variants can produce patterns of genetic variation similar to those obtained under a selective sweep (Currat and others 2006; Excoffier and others 2009), Itan and colleagues (2009) inferred similar selection coefficients on the *-13,910*T* variant to those obtained previously (Bersaglieri and others 2004), and that selection started in Central Europe about 7,500 years ago. These location and time estimates bracket the origins of the Linearbandkeramic (LBK), an early Neolithic culture where an increase in the frequency of cattle bones has been noted when compared to earlier Neolithic economies (Benecke 1994). Elsewhere around the Mediterranean, other contemporaneous cultures mainly used goats and sheep (Vigne 2006), which yield less milk, and so potentially lower selection pressure favouring LP.

Simulation modelling is a powerful method for testing evolutionary hypotheses (Belle and others 2009, 2006a, 2006b; Bollongino and others 2012; Bramanti and others 2009; Fagundes and others 2007; Gerbault and others 2014, 2012; Murray and others 2010; Ray and others 2009). In particular, because the likelihood of observed data sets under various scenarios can be quantitatively assessed and compared, this approach is likely to provide a deeper understanding of the evolution of LP.

All of the modelling studies mentioned in the previous paragraph indicate that demographic history may have important effects on the evolution of LP, and some indicate that selection pressures favouring LP were spatially heterogeneous. However, it also seems likely that selection pressures favouring LP were episodic, perhaps responding to fluctuations in the availability of non-dairy foods or other factors (Shennan and others

2013). To date, episodic selection on LP has been hypothesized (Gerbault and others 2011) but not demonstrated using empirical data. Advances in the analysis of aDNA data now make this a possibility (Sverrisdottir and others 2014; Wilde and others 2014).

Concluding Remarks

The continuous expression of the enzyme lactase throughout adulthood (LP) is a recent trait on the human evolutionary timescale. So far, at least five genetic variants have been found to associate with LP, indicating convergent evolution. These LP variants are unevenly distributed worldwide; they are concentrated in geographical regions with a history of pastoralism and dairying, and broadly encompass the period when agriculture and dairying became prevalent. Simulation modelling and other lines of evidence suggest that the geographic distribution of LP-associated genetic variants is likely to have been partly shaped by the demographic history, and that the specific selective advantages conferred by LP may have differed between geographic locations. It is also likely that selection favouring LP acted episodically through time, although resolution of these episodes will require more aDNA data than is currently available (Sverrisdottir and others 2014).

A range of hypotheses exist on why LP conferred such high selection coefficients on ancestral dairying populations (Flatz and Rotthauwe 1973; Gerbault and others 2011, 2009; Itan and others 2009; Sverrisdottir and others 2014). While no single advantage is likely to explain LP evolution in all regions where it is prevalent, and at all time periods, an often neglected consideration is the sheer range, as well as the density, of nutrients in milk. It has been argued that modern diets and, indeed, post-Neolithic diets more generally, are mismatched with the ancestral hunter-gatherer diets to which our metabolism should be optimized (Cordain and others 2000; Konner and Eaton 2010; Kuipers and others 2010). In this chapter we suggest that—to some extent—milk can be considered as a bridging food between the nutrient compositions of hunter-gatherer and modern diets (Cramp and others 2014). A more detailed analysis of the nutrient compositions of reconstructed early Neolithic diets is required to examine this hypothesis further.

LP illustrates how a new component of our diet, i.e. milk and dairy products, has affected our biological evolution. The changes in diet and lifestyle introduced during the Neolithic period, including animal and plant domestication together with the associated human metabolic responses, created new adaptive pressures and environments. It is likely that further studies investigating the relationship between dietary change and genetic diversity will highlight how our behaviours have shaped our evolution, and will ultimately shed light on the ongoing evolutionary processes which continue to shape our species.

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