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## HYPOTHESES

### Insights & Perspectives

# Proposed mechanism for the selection of lactase persistence in childhood

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#### Abstract

Lactase persistence/persistent (LP), the ability to express the lactase enzyme in adults, is one of the most strongly selected phenotypes in humans. It is encoded by at least five genetic variants that have rapidly become widespread in various human populations. The underlying selective mechanism is not clear however, because dairy products in general are well tolerated in adults, even by lactase non-persistence/persistent (LNP) individuals. Cultural adaptations to milk consumption, notably fermentation and transformation, which can provide most of the energy (protein, fat) to both LP and LNP individuals without any associated cost seem to have been common in ancient societies. Here, we propose that selection for LP occurred through increased glucose/galactose (energy) from fresh milk intake in early childhood, a crucial period for growth. At the age of weaning indeed, lactase activity has already begun to decline in LNP individuals so the gain in energy from fresh milk by LP children represents a major fitness increase.

#### KEYWORDS

lactase persistence, lactose, lactose intolerance

## INTRODUCTION

Lactase persistence/persistent (LP) is often described as a textbook example of human niche construction, given that it results from the coevolution of genes and culture.<sup>[1]</sup> At least five functional genetic variants in a regulatory region about 14 kb upstream of the lactase gene have been independently and strongly selected for in various human populations following the incorporation of animal milk into their diet, around 7000 years ago.<sup>[2]</sup> However, it is not clear how the cultural changes associated with the beginning of animal domestication could have led to such a high level of selection in some populations but not in others. Indeed, it seems that lactose-containing dairy products can be consumed in large quantities by lactase non-persistence/persistent

(LNP) individuals, without the need for genetic adaptation, as exemplified by Central Asian herders, whose diet consists chiefly of dairy products despite their being LNP.<sup>[3]</sup> Similarly, ancient human populations clearly consumed dairy products for millennia before beneficial mutations could reach appreciable frequencies,<sup>[4–6]</sup> suggesting that technical innovations such as the production of fermented milk, yogurt, and/or cheese were sufficient to exploit at least some of the dietary benefits of animal milk.<sup>[4]</sup>

A recent large-scale study found no association between ancient milk usage and LP variant frequency.<sup>[7]</sup> This is not unexpected given that it takes time for mutations to increase in frequency and become correlated with consumption practices. Nevertheless, the question remains how the selective pressure could be so strong in these populations given that LNP adults can drink reasonable amounts of raw milk without major symptoms and can in any case access milk proteins and fats through other dairy products. One possible explanation for this

**Abbreviations:** LI, lactose intolerance/intolerant; LNP, lactase non-persistence/persistent; LP, lactase persistence/persistent.

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apparent contradiction is that selection for LP mainly took place during infancy. In LNP populations indeed, lactase levels begin to decline as early as the second year of life<sup>[8,9]</sup> and by the age of nine, 85% of children are lactose intolerant.<sup>[10]</sup> Different rates of lactase decline between individuals should allow for fitness selection during infancy, a crucial period for growth and exposure to pathogens. Variations in glucose intake and in symptoms associated with milk drinking may have constituted an important substrate for natural selection. To explore the idea of LP selection in childhood, we first consider what is known about ages of weaning, of first animal milk drinking, and of lactase decline. We then describe the effects of LP on lactose digestion and assimilation and review the clinical manifestations of milk drinking in LNP children.

## MAIN TEXT

Several factors could promote selection in childhood: weaning practices, animal milk consumption, decline in lactase activity, and the ages at which these transitions occur, but also children's (small) size, which means that even small differences in milk consumption can correspond to significant differences in energy intake.

## AGE OF WEANING AND USE OF ANIMAL MILK IN CHILDREN

At what age did prehistoric children begin to drink animal milk? It seems likely that animal milk was introduced alongside or in replacement of breastmilk. The age of weaning in ancient human populations is hard to assess. However, data from 113 preindustrial societies suggest that children are weaned at around  $29 \pm 10$  months in these societies,<sup>[11]</sup> that is, at a younger age than other primates (chimpanzees are weaned at about 4.5 years of age, and orangutans at 7 years).<sup>[12]</sup>

Along the same lines, a number of stable isotope studies from various Eurasian post-Neolithic sites suggest that weaning was a multistage process involving various milk products beginning around 6–12 months of age and completed between the ages of 2 and 4 years.<sup>[13–15]</sup> On the other hand, children from ancient forager populations (the Kitoi and Serovo in the western Lake Baikal region), who could not benefit from non-human milk, were exclusively breastfed for longer, until 12–24 months of age, and were totally weaned at 4 years.<sup>[16]</sup> Comparisons of Mesolithic and Neolithic toddlers from the Iron Gates sites in the Danube Valley suggest that weaning may have occurred slightly earlier in the latter.<sup>[17]</sup>

While stable carbon and nitrogen isotope data can indicate the incorporation of animal products into diets, they do not discriminate between meat, milk, and dairy products. The diversity of food used for weaning may even participate in blurring the signal.<sup>[18]</sup> New approaches based on stable calcium isotope ratios are promising, but are still to be applied on Neolithic children.<sup>[19,20]</sup> Isotope analyses of European Neolithic cattle show that calves were weaned early, possi-

### In summary

Literature data indicate that:

1. LNP can appear as early as the first year of life and occurs in about 50% of 5-year-olds.
2. LNP is often associated with LI and with decreased milk intake.
3. LNP is associated with zero to low glucose/galactose calorie intake from milk and very little in the form of fermented dairy products

And our analysis indicates that:

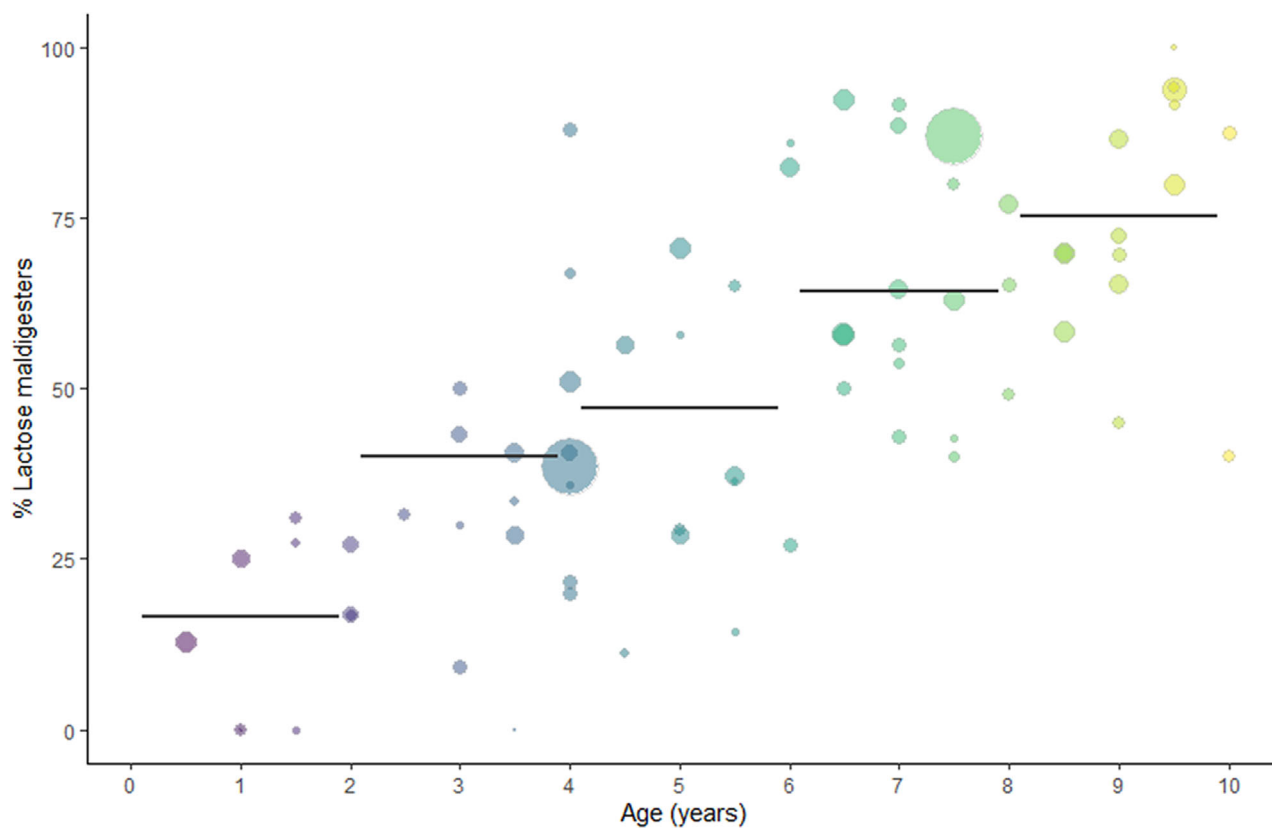
1. The energy gap between LNP and LP children increases steadily with the share of milk in the diet.

bly because herders wished to increase the amount of milk available for human consumption.<sup>[21]</sup> Traces of ruminant milk have been found in vessels that were used to feed infants in Neolithic, Bronze Age, and Iron Age Europe.<sup>[22,23]</sup> All this suggests that as early as the Neolithic, animal milk was used early in childhood for weaning and possibly later too.

## AT WHAT AGE DOES LACTASE DECREASE IN ACTIVITY?

Lactase decline does not seem to occur at the same age in all LNP populations. Hypolactasia has indeed been observed in children as young as 1 or 2 years old in some populations.<sup>[8,9]</sup> Data retrieved from 22 studies of lactose malabsorption in healthy children from a range of LNP populations (Mediterranean, African, South Asian, East Asian, and American) indicate that the proportion of lactose maldigesting children increases up to 10 years. Although these studies are very heterogeneous in terms of time periods and tests used (mainly hydrogen breath tests with 1 or 2 g/kg lactose loads); they nevertheless present a coherent picture. Pooled results show that the proportion of lactose malabsorbing children increases from about 20% in the very first years of life up to 50% at age five, and roughly 80% at age 10 (Figure 1).<sup>[10,24–39]</sup> The same trend is observed when only considering studies with a breakdown by year of age (Figure S1).<sup>[10,25,28,29,33,38,39]</sup> Lactase therefore seems to decline early, in more than a third of children by the age of four.

It has been suggested that LNP does not automatically lead to lactose intolerance/intolerant (LI), the appearance of symptoms depending rather on levels of lactose intake and on individual differences in tolerance. In the five studies to date that have evaluated both LNP and LI,<sup>[24,30,35,40,41]</sup> LNP was identified in 42.5% (interquartile range [IQR], 18.2%–56.5%) of children aged 2–6 years whereas LI was only found in 22.3% (IQR, 11.0%–26.5%) of this age group. In other words, in these populations, just under a half of 2–6-year-olds were LNP and just under a quarter were LI.



**FIGURE 1** Bubble plot of literature data<sup>[10,24–39]</sup> on the prevalence of lactose malabsorption as a function of age in populations with lactose malabsorption rates >70% in adults (adult rates reported in Table S1).<sup>[51]</sup> The bubbles appear at the mean age of the reported age bracket. Bubble size (color) represents the number (age) of patients in each bracket. The horizontal lines are the weighted means by 2-year age bracket.

## EFFECT OF LP PHENOTYPE ON MILK INTAKE

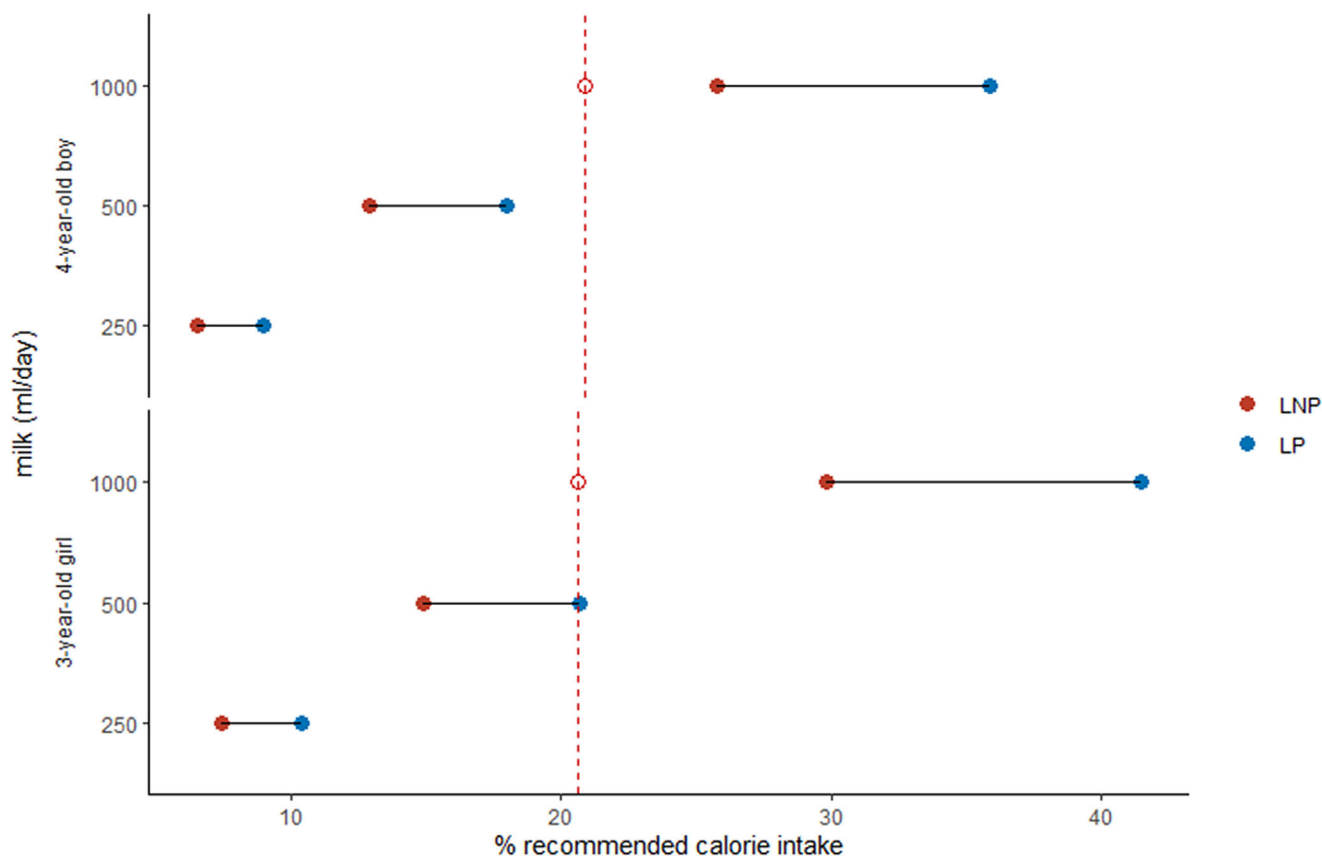
If LNP leads to LI in a substantial number of cases, a corresponding decrease in milk consumption could be observed and thus explain some of the advantage of LP. In that regard, Leberthal et al. found that 89% of LP and 83% of LNP children above the age of 5 years had consumed more than 1 L/day of milk before 4 years of age, but that 14% of LP and 83% of LNP children consumed less than 250 mL/day after 5 years old, with 4 of the 12 LNP children being LI.<sup>[42]</sup> Paige et al.<sup>[39]</sup> found that LNP was associated with lower milk consumption, even among 3–5-year-olds, with LP children being significantly more likely to consume more than 120 mL of milk per day. Similarly, Bolin et al.<sup>[31]</sup> found that while 75% of LP children aged 1–5 years drank milk, only 22% of those with LNP also did. Thus, even though milk consumption has not often been studied in terms of LP and LNP status, the available data suggest that LP is associated with greater milk intake after the age of 4–5 years.

In older children, Almon et al.<sup>[43]</sup> showed using Mendelian randomization that LP children (aged 9–10 years) and adolescents (aged 15–16 years) consumed significantly more milk than LNP children/adolescents of the same age (e.g., 70% more for LP boys aged 9–10 years and 24% for LP girls of the same age). Meanwhile, milk avoidance was found to be associated with LNP among adolescents but not among children. The same association has been observed in adults,

for instance, Bergholdt et al.<sup>[44]</sup> found in Denmark that LP adults had a median milk intake of five glasses per week whereas LNP adults had a median milk intake of three glasses per week, and UK Biobank data suggest that LP is weakly associated with greater milk consumption in adults.<sup>[7]</sup> Overall therefore, there seems to be a constant association between LP/LNP status and increased/decreased milk consumption from infancy to adolescence.

## ENERGY INTAKE OF LNP AND LP CHILDREN

Lactase activity could be evaluated by monitoring blood glucose levels after lactose intake, lactase being required to break down lactose into galactose and glucose. An increase from baseline of 1.1–1.4 mmol/L (19.8–25.2 mg/dL) 30 min after lactose intake is indicative of LP. The results of these tests in LNP individuals indicate that even in the absence of symptoms, most of the sugar content of milk is not absorbed.<sup>[45]</sup> When the same tests are performed with fermented dairy products such as yoghurt and fermented milk, LNP individuals show increased glycemia, but only by 15 mg/dL for yogurt and quark<sup>[46]</sup> and less than 15 mg/dL (a similar level as observed in LP subjects) for acidophilus milk (Alm, 1982).<sup>[47]</sup> It therefore seems as if fermented dairy products are better tolerated, but at the cost of carbohydrate energy intake for both LNP and LP consumers.



**FIGURE 2** Percentage of recommended daily calorie intake covered by 250, 500, and 1000 mL of milk in lactose intolerance/intolerant (LP) and lactase non-persistence/persistent (LNP) children (top: a 3-year-old girl; bottom: a 4-year-old boy). The dashed lines and empty circles correspond to the lactose loads (2 g/kg), above which clinical symptoms of lactose intolerance are considered to appear,<sup>[52]</sup> and therefore represent the presumed maximum milk calorie intakes of the LNP children. Milk volumes were converted to calorie contents based on a cow milk composition of 32.5 g/L fat, 40.2 g/L lactose, and 30.5 g/L protein,<sup>[48]</sup> omitting the caloric value of lactose for LNP individuals. The values obtained were then divided by the children's recommended calorie intakes, assuming median weights for the children obtained from WHO growth charts, and per-kilogram calorie requirements from the United Nations Food and Agriculture Organization.

Rough estimates of the energy content of milk suggest that moderate amounts of milk can cover a significant fraction of recommended daily calorie intakes in LP children, up to 40% for the highest consumers. At that time period, the energy gap between LP and LNP children thus represents a significant difference, of 12% of the recommended daily intake (Figure 2). These estimates are based on a cow milk composition of 32.5 g/L fat, 40.2 g/L lactose, and 30.5 g/L protein,<sup>[48]</sup> a median weights for the children (WHO growth charts), and calorie requirements from the FAO. For adults in comparison, the difference in calorie intake from 1000 mL milk between LP and LNP individuals would only be of 6.7% of the recommended daily intake (2400 kcal).

## PROPOSED MODEL FOR THE SELECTION OF LP IN CHILDHOOD

The proposed model largely depends on cultural traits, as it is strongly affected by the amount of raw milk consumed in childhood, during and after weaning but with selection operating more progressively than has

previously been proposed. Indeed, given that most children are lactose tolerant in the first 2–3 years of life, consuming raw milk is unlikely to have caused discomfort and would presumably have been offered to all children in prehistoric societies. Milk consumption would have decreased as LNP and LP phenotypes began to be expressed as children aged, but progressively and at different rates between children. Children with the LP phenotype would have extracted more energy from milk and would have consumed milk for longer, potentially increasing fitness and survival. (In children, 0.5–1 L of milk per day can cover between a quarter and a third of their daily caloric needs.) An increasing prevalence of the LP phenotype could also have promoted raw milk consumption in adolescence and adulthood, further promoting selection. Since fermented dairy products do not appear to provide much carbohydrate energy, even in LP individuals, this advantage would only have arisen in populations that consumed raw milk. In terms of the different genotypes associated with LP (T/T and C/T), one can speculate that post-infection hypolactasia<sup>[49]</sup> may be reduced in homozygotes, who seem to have higher lactase activity,<sup>[50]</sup> adding a further layer of selection. This would be consistent with recent results indicating that LNP individuals were disadvantaged in prehistoric periods of

diseases.<sup>[7]</sup> However, selection in childhood as proposed here, during and outside periods of crises, better explains the observed strength of selection, since children are more prone to infections and are more likely to have consumed raw milk than adults.

## CONCLUSION AND FUTURE DIRECTIONS

We propose that LP could have been selected through the consumption of raw milk in infancy and childhood during and after weaning. This mechanism is culture-dependent since it would only have arisen in populations where raw animal milk was consumed after weaning. The proposed model could be tested in present-day pastoralist populations, by studying lactose tolerance (functionally and genetically) and comparing levels of raw milk and dairy product consumption during infancy and childhood between the different genotypes. If our hypothesis is correct, LP individuals should be seen to drink more raw milk and have better overall health parameters. Our hypothesis also implies that toddlers with the T/T genotype should have reduced post-infection hypolactasia compared with C/T peers.

## AUTHOR CONTRIBUTIONS

Alexandre Fabre: acquisition of data, drafting the manuscript, study conception and design, data analysis; Anne Fabre: study conception and design, and data analysis; Céline Bon: critical revision of the manuscript; Paul Guerry: data analysis, revision of the manuscript, figure and table creation; Laure Segurel: study conception and design, revision of the manuscript.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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