

Lactose tolerance and intolerance

Production of lactase in adults as an evolutionary adaptation

INTRODUCTION

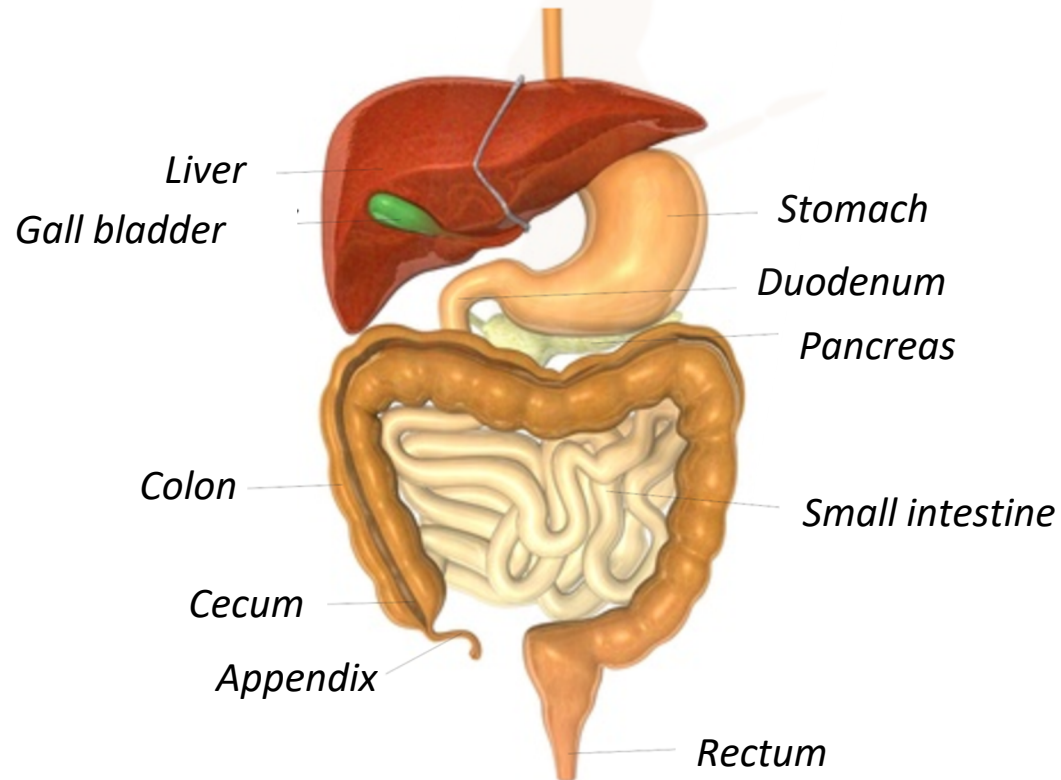
Humans are **one of the few** mammalian species in which many adult individuals retain the ability to absorb **lactose**, a milk sugar.

This ability is the ***result of a mutation*** that occurred millennia ago, which must have granted some adaptive advantage to individuals with this specific trait.

Let's examine how, when, and why this evolutionary event took place.

Biology of the digestive system

- Intestinal cells (which coat the inside of the digestive tract) are responsible for the breakdown and absorption of nutrients from food in the small intestine



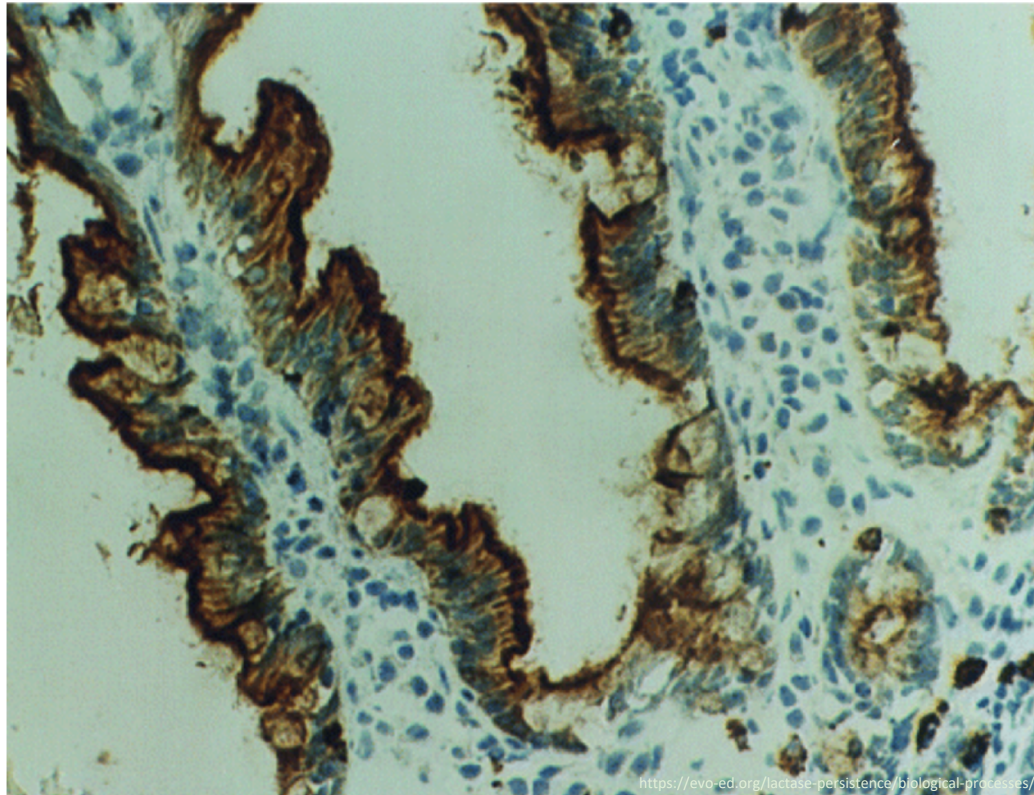
First food: mother's milk

- The intestinal cells of all infant mammals are characterized by high concentrations of the enzyme *lactase* during infancy, when milk is the main source of nutrition.



Where is **lactase** detected?

- In the protrusions below, we can observe the so-called “brush border”, the inner side of the small intestine, facing its content. It is there that lactase is detected.



Lactase is labeled brown.

Lactase “unlocks” an energy source

- **Lactose** is a disaccharide found in milk.
- **Lactase** breaks down **lactose** into two monosaccharides, **glucose** and **galactose**.
- These simple sugars can be absorbed by small intestine cells and used as an energy source.



Lactase regulation



- Nearly all known mammals -including **65% of humans**- show a decrease in **lactase** biosynthesis in the years after weaning.
- The regulation of **lactase** biosynthesis after weaning is the main factor that distinguishes individuals with **lactose tolerance** from those with **lactose intolerance**.

Lactase regulation



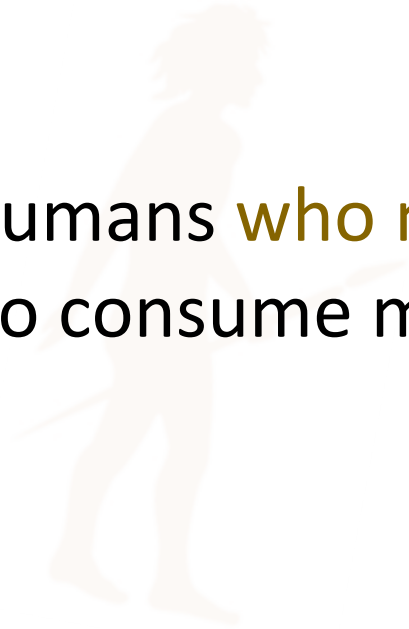
The **decrease** in **lactose synthesis** after weaning is probably a matter of cellular-level energy conservation:

- 1) Energy is needed to produce any enzyme, including **lactase**, the enzyme required for digestion of milk.
- 2) Mammals do not usually consume milk after weaning.
- 3) Without milk consumption, the energy expended to produce **lactase** would mean a waste of energy on the cellular level.

Therefore, over time, the energy-saving option was selected: reducing **lactase** production after weaning.

Lactase is not produced in adults

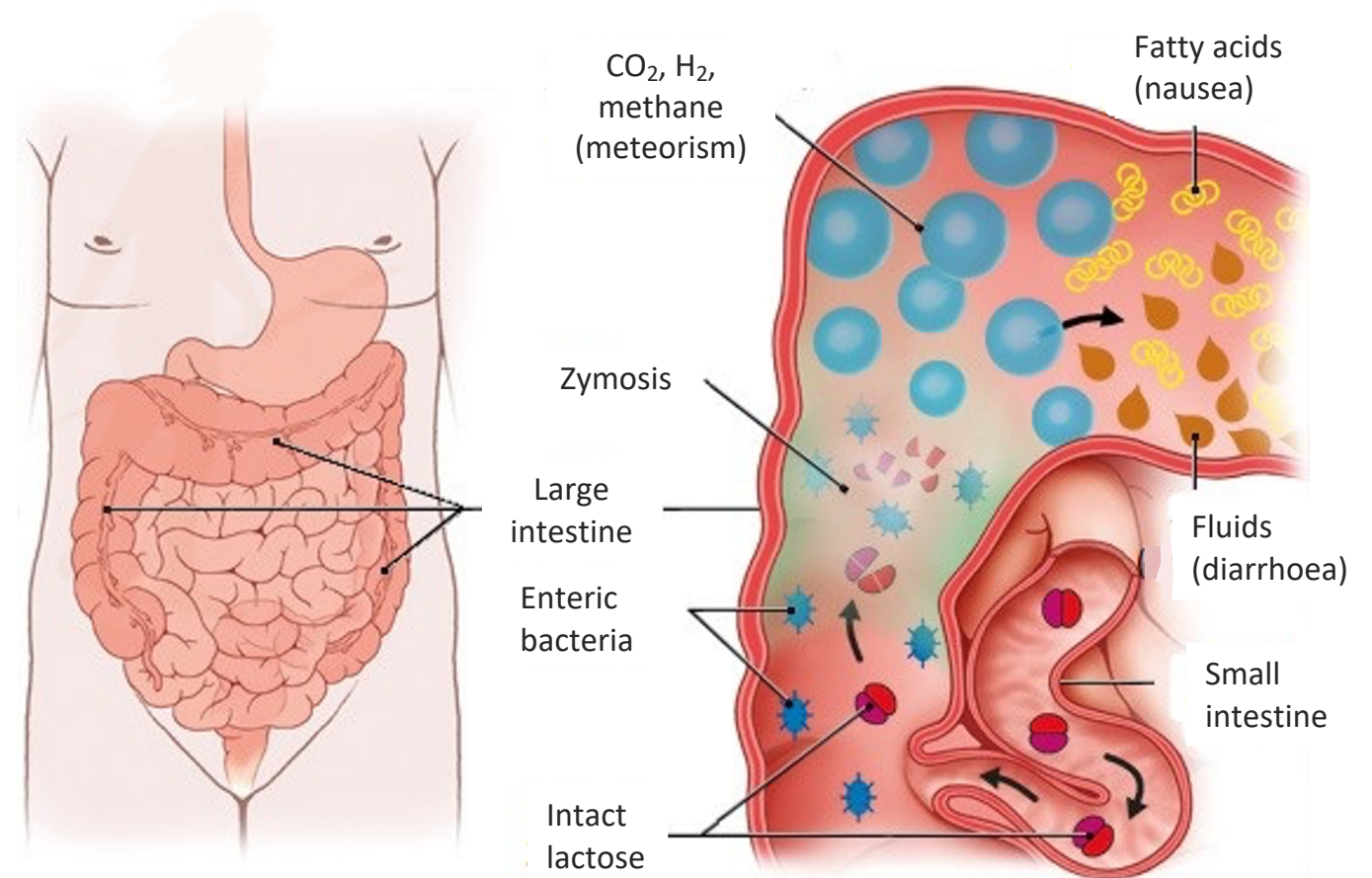
What will happen to humans who no longer produce lactase if they continue to consume milk in adulthood?



Lactase is not produced in adults

If undigested lactose passes into the large intestine, the individuals will show symptoms of lactose intolerance:

1. Increased concentration of saccharides in the large intestine creates an osmotic gradient, during which water enters the intestine. This causes cramps and diarrhea.
2. Large intestine bacteria absorb lactose as food, creating gaseous byproducts like methane, carbon dioxide and hydrogen. This leads to accumulation of gases and meteorism.



Continuous production of lactase

On the other hand, **35% of humans** continues to produce **lactase** after weaning, and are therefore capable of consuming milk and other dairy products in adulthood.

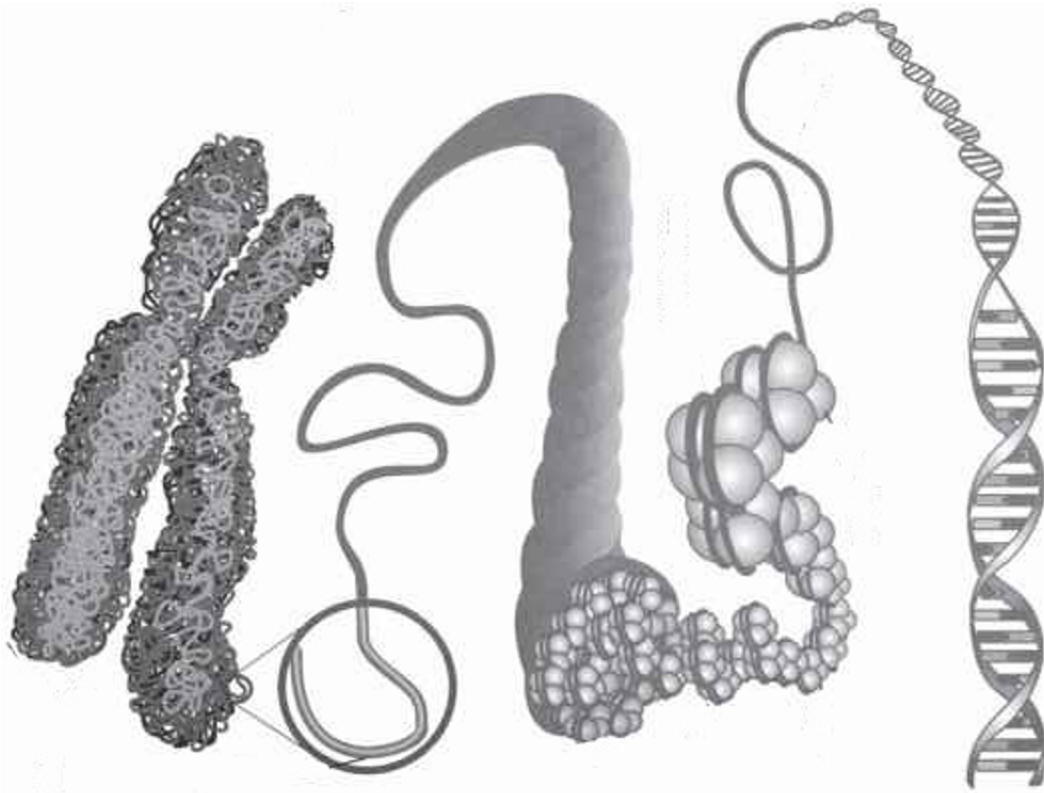


What happens on molecular level?

- **Retaining of lactase production**, the opposite of lactose intolerance, is the result of an evolutionarily preserved *mutation* in the regulatory mechanisms for the production of lactase mRNA.
- This mutation, which is connected to the continuation of lactase production into adulthood, consists of a change in a single nucleotide (SNP, single nucleotide polymorphism).

Lactase biosynthesis

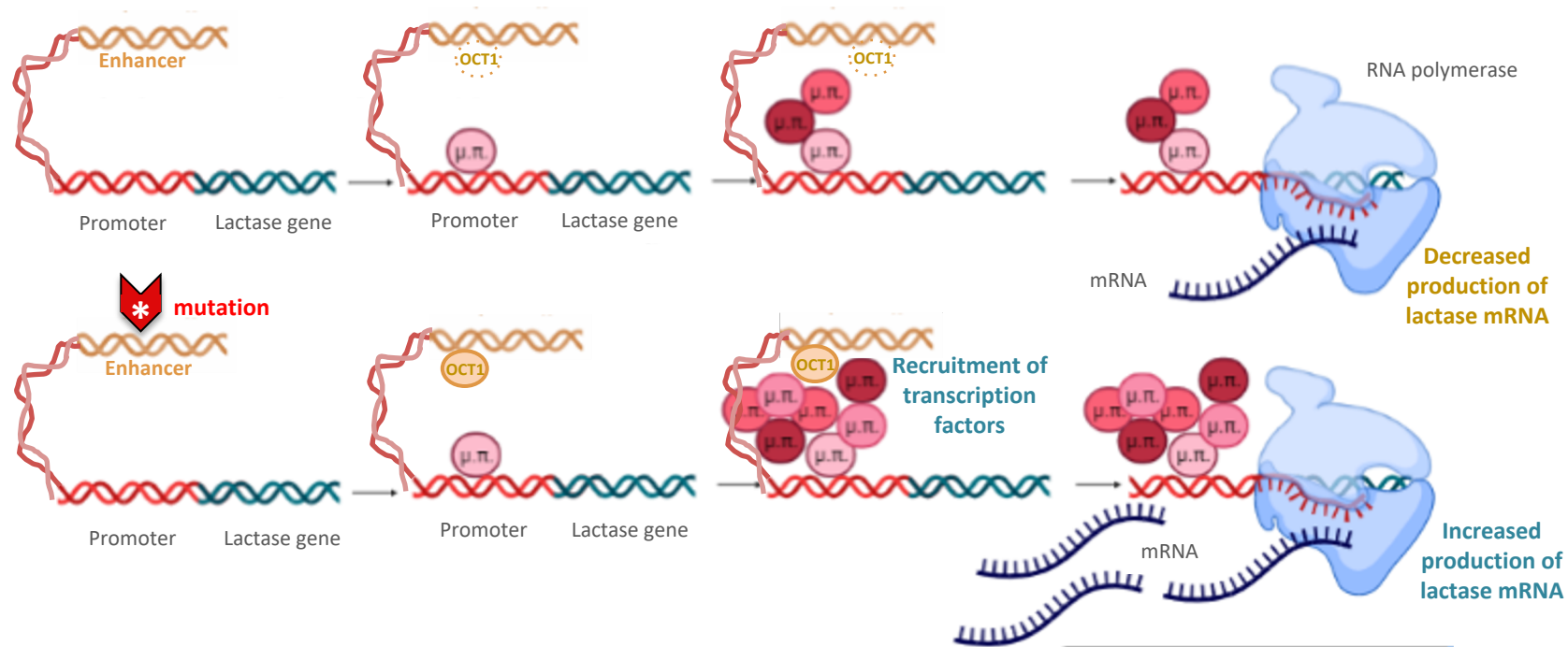
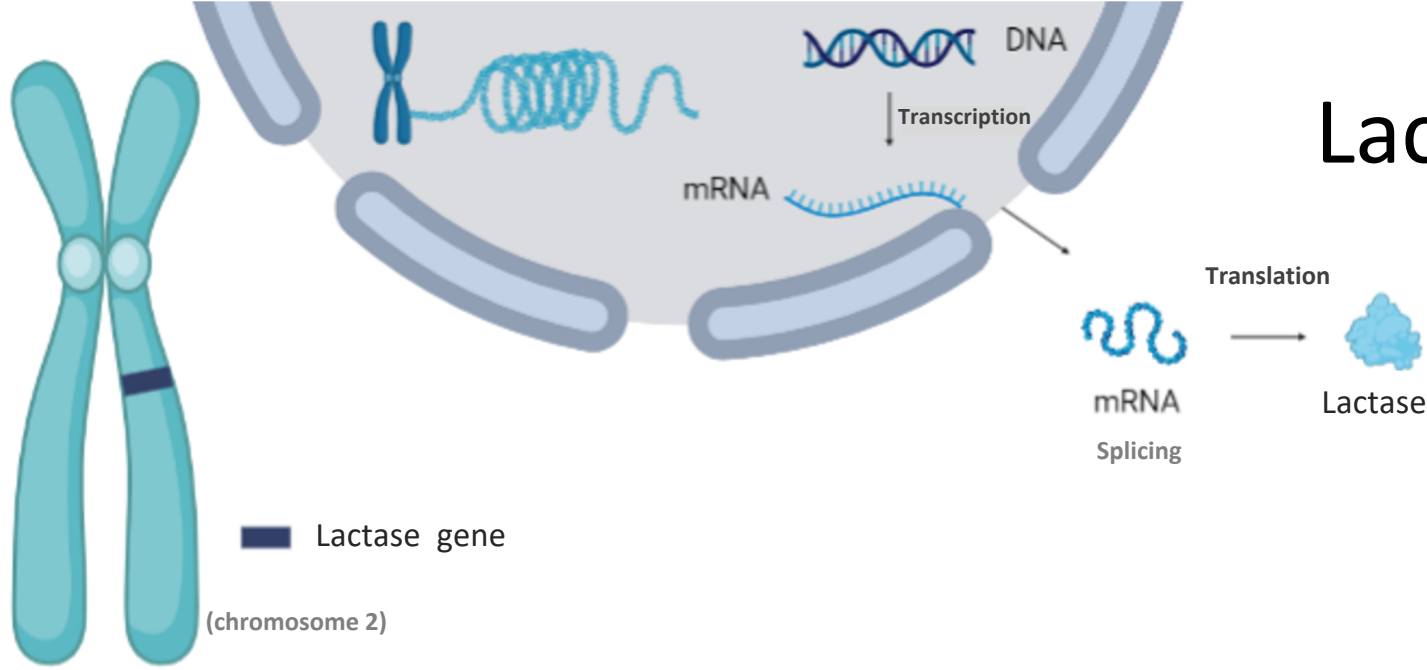
The human lactase gene (LCT), composed of 55 thousand base pairs, is part of the second chromosome, with 17 exons.



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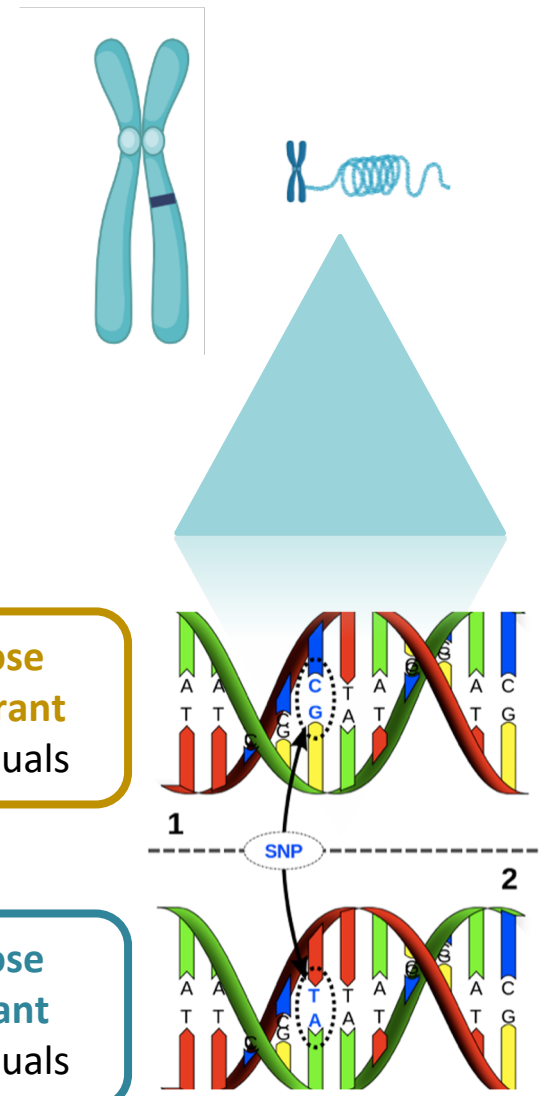
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LFDSYADFCF QTFGDRVKFW MTFNEPMYLA WLG YSGSEFP PGVKDPGWAP YRIAHAVIKA HARVYHTYDE KYRQE QKGV I
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Lactase biosynthesis



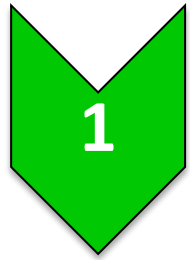
Lactose intolerant individuals

Lactose tolerant individuals



T-13910 mutation in the Enhancer of lactase gene (common in Europe)

Lactose intolerant adults



After weaning, there is a decrease in effectiveness of the transcription factors controlling the lactase gene.



This decreased effectiveness of the transcription factors leads to reduced transcription of the lactase gene.



This results in lower lactase levels in intestinal cells and **inability to digest lactase** in milk.

Lactose tolerant adults



A **mutation** at an Enhancer site upstream of the **lactase** gene increases binding of an Activator called Oct1, which participates in the regulation of lactase gene transcription.



The Oct1 activator attracts more general transcription factors to the lactase gene throughout adult life.



This increased attraction of transcription factors prevents the decreased transcription of the lactase gene that would normally happen, and thus lactase production continues into adulthood.



This results in steady lactose levels in intestinal cells, and a **retained ability to digest lactose** in milk throughout adulthood.

Anthropology and Biogeography of lactose tolerance



<https://evo-ed.org/lactase-persistence/biological-processes/>

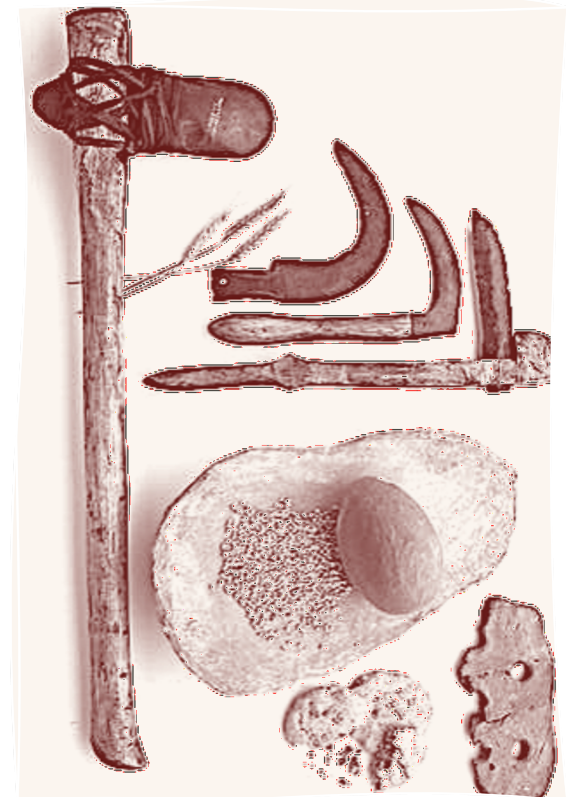
The Neolithic Revolution

The neolithic revolution describes a time period about 12.000-6.000 years ago, during which humans throughout the world began the transition from a hunter-gatherer lifestyle to a **farmer-herder** lifestyle.



The Neolithic Revolution

During this period, humans developed new ways of interacting with their environment, such as planting and harvesting **tools**, **mills** for grinding corn, and **pottery** for food storage.



Pastoralism and milking

One of the major innovations of the neolithic revolution was pastoralism and the the practice of milking livestock (such as goats, sheep, cows and camels).

This practice was adopted by different civilizations in the period between 12.000 and 7.000 years ago.

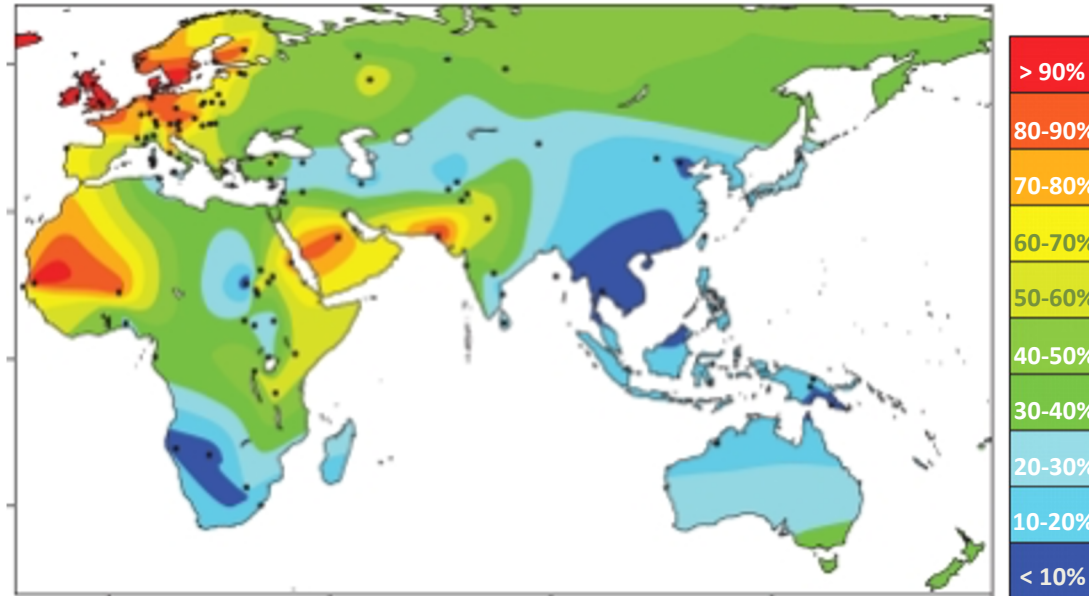


Milking livestock and milk consumption

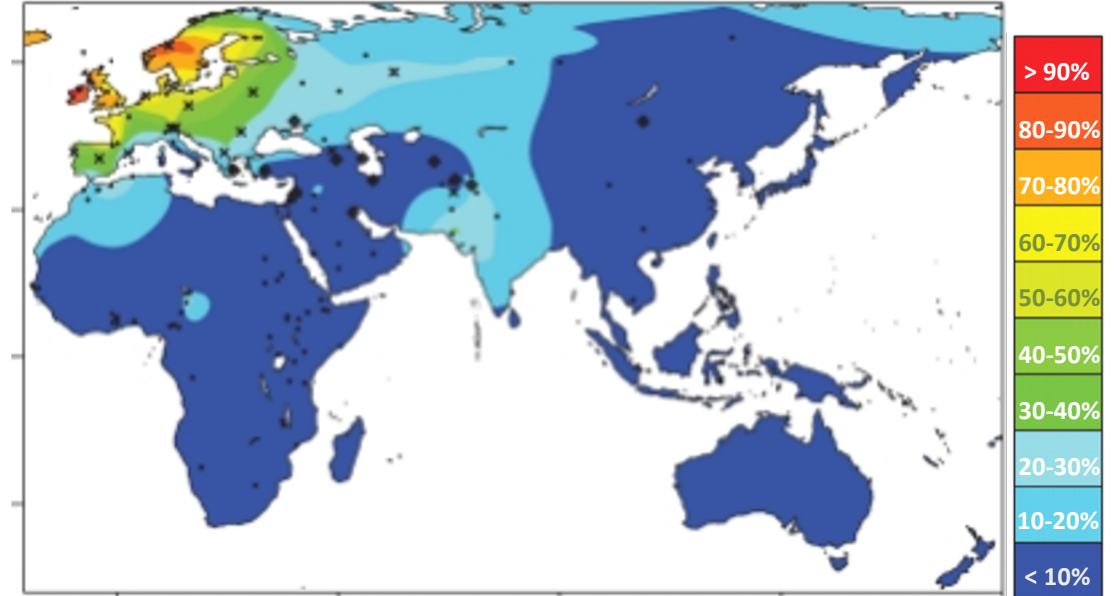
- The **Biocultural Coevolution theory** suggests that livestock milking and lactase production coevolved.
- This means that they arose around the same time, and their relationship is reciprocal: milk consumption led to the prevalence of lactose tolerance and, conversely, lactose tolerance enabled increased milk consumption.

How are human populations distributed today based on lactose tolerance?

Geographic distribution of lactose tolerance



Percentage of adults with lactose tolerance



Percentages of the T-13910 mutation upstream of the lactase gene

[modified image from Gerbault *et al.* (2011) *Phil. Trans. R. Soc. B* 366, 863-877]

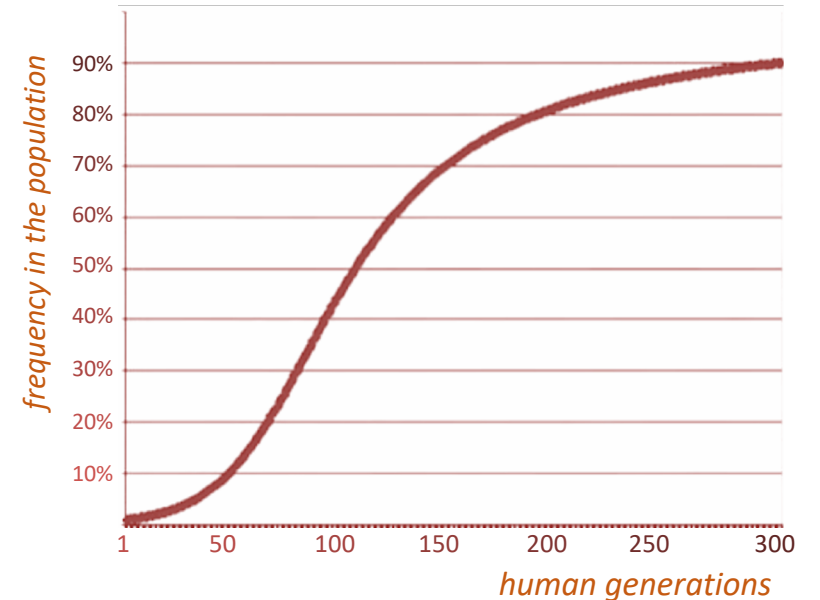
For complete data, see: <https://www.ucl.ac.uk/biosciences/gee/molecular-and-cultural-evolution-lab/global-lactase-persistence-association-database-glad>; Ingram *et al.* (2022) Lactose malabsorption, in *Advanced Dairy Chemistry*, vol. 3, Lactose, water, salts and minor constituents, Springer, <https://link.springer.com/book/10.1007/978-3-030-92585-7>

The T-13910 mutation (most common in Europe) enables **continuation of lactase production after weaning**. Other mutations G-13915, G-13907, G-14009, C-14010) are connected to the same phenomenon in regions of Africa or Northwestern Asia (not shown here).

What led to this geographic distribution?

Mutations allowing lactose tolerance developed in human populations after the neolithic revolution (10.000 years ago), with different areas of the Earth showing different development rates.

Depending on the area, and considering population migrations, the archaeological record and the modern picture, the **selective advantage** from retaining expression of effective lactase in adults is calculated at a rate of 0.5% to >3%.



Theoretical curve of the increase in frequency of a mutation allowing lactose tolerance in a population, assuming a selective advantage of 5%. Frequency may rise from 1% to 90% of the population within 8.000 years (that is, 300 human generations).

Two different stories

- Lactose tolerance and pastoralism arose and spread independently in Europe and Africa (an example of convergent evolution).
- Convergent evolution is the independent evolution of similar traits along separate evolutionary paths.
- In other words, we have two different stories explaining how pastoralism and lactose tolerance emerged in Europe and Africa, respectively.

History of lactose tolerance in Europe

- The first evidence of pastoralism were discovered in the Middle East: the bones of juvenile bovines, killed before their first birthday, prove that humans in the area had begun taming and milking cattle.



<https://evo-ed.org/lactase-persistence/biological-processes/>

- The bovine remains found in the Middle East were roughly 10,500 years old.

Migration (a)

The first tame bovines in Greece and the Balkans (8.000 years ago) were more closely related to Middle Eastern tame bovines than to wild European bovines...



This observation shows that the pastoralists who migrated to Europe from the Middle East brought their cattle with them.

Migration (b)

Middle Eastern pastoralists, being skilled and specialized food producers, spread rapidly, prevailing over the local hunter-gatherers they encountered in Central and Northern Europe.



The diffusion of migrating pastoralists from the Middle East in Europe led to the spread of mutations (mainly T-13910) allowing lactose tolerance.

History of lactose tolerance in Africa

In Africa, lactose tolerance evolved independently from the European origin. The mutations responsible for continuous lactose production are different.

<i>Wild Type:</i>	...AAGATAA T GTAG C CC C TG...	
Europe:	...AAGATAA T GTAG T CC C TG...	(T-13910)
Kenya:	...AAGATAA G GTAG C CC C TG...	(G-13915)
Sudan:	...AAGATAA T GTAG C CC G TG...	(G-13907)

A gap of a few thousand years

- Anthropological studies date the emergence of pastoralism and the practice of **livestock milking** to **10,500-6,500 years ago**.
- However, genetic research shows that the trait of **continuous lactase production**, and thus lactose tolerance, only became widespread in Europe between **7,000-5,000 years ago**.
- This find means that, for several thousand years, many humans must have milked sheep, goats, cows, or camels without being able to absorb the milk they fed on.

How can we explain this paradox?

A theory explaining the paradox

It is possible that neolithic humans fermented milk to make cheese, a process that significantly reduced its lactose content, making it more digestible.

Pottery shards unearthed in Northern Europe likely served as sieves for the straining and fermentation of milk to make cheese.



Short history of cheese

- Many paleolithic and neolithic civilizations stored and transported food and water in animal skins and intestines.
- When milk was first introduced to the neolithic diet in the Middle East, it was probably stored in inflated cow stomachs, causing the curds to separate from the whey.
- Cheese is thought to have accompanied pastoralism ever since its cultural beginnings, and is still very popular among European cultures today.



Benjamin Rabier (1926), *La vache qui rit*
(La grande marque française)



<https://evo-ed.org/lactase-persistence/biological-processes/>

Interpreting the spread of lactose tolerance

- The original theory for the prevalence of lactose tolerance included the processing of milk into forms that were **more digestible energy sources, like cheese**
- Later studies attempted to interpret the coevolution of milk consumption and lactose tolerance based on the **potential dietary advantages** offered by milk consumption.

Interpreting the spread of lactose tolerance

Prevailing Theories

- Calcium and Vitamin D absorption
- Increase of the IGF-1 factor (Insulin-like Growth Factor 1) in circulation
- Increased fertility

Systematic comparison of lactose tolerant and intolerant individuals showed that:

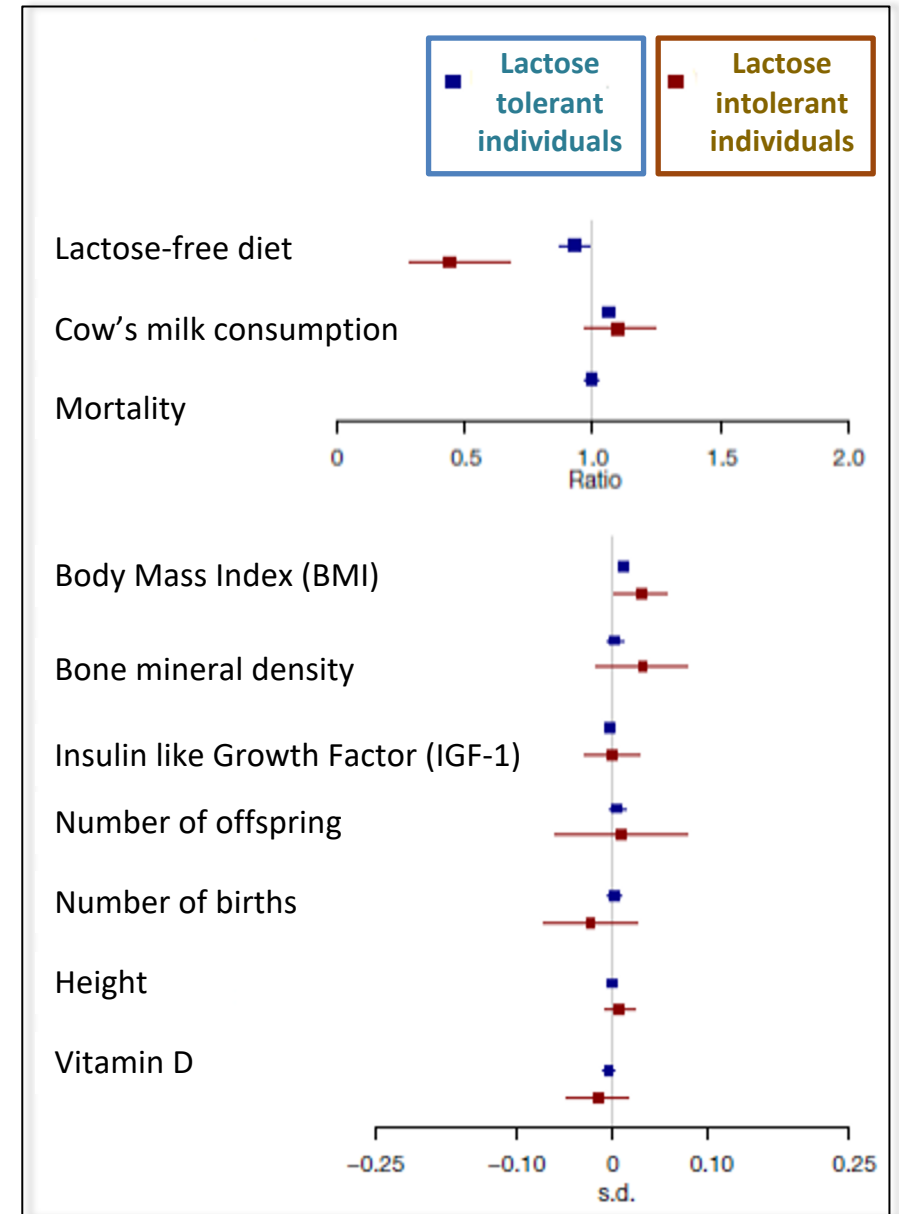
- No significant difference in vitamin D concentration or bone density
- No significant difference in Body Mass Index (BMI) or age of sexual maturity
- No significant impact on the number of births or offspring



CONCLUSION:

Coevolution of milk consumption and lactose tolerance and the spread of the lactose tolerance trait is not related to the dietary advantages that led to further milk consumption.

Effect of lactose tolerance alleles on different phenotypic traits:



Interpreting the spread of lactose tolerance

Alternative (more recent) interpretations:

Crisis Mechanism

- **In times of hunger**, the lack of food would turn people towards other sources of nutrition, such as milk consumption.
- The symptoms of lactose intolerance (e.g. diarrhea) would be more intense in malnourished individuals who had a hard time obtaining other food due to the shortages.
- Lactose intolerant individuals would not survive.
- Lactose tolerant individuals would have a survival advantage (positive selection of the lactose tolerance trait).

Chronic Mechanism

- **Increased pathogen load**, mostly zoonoses, connected to pastoralism and rising population density and mobility.
- Pathogen-induced mortality in lactose intolerant individuals that would consume dairy products, due to dehydration and intestinal disorders.
- Survival of lactose tolerant individuals, since they did not experience any symptoms from milk consumption (positive selection of the lactose tolerance trait).

Sources

- ❑ Evo-Ed: Making evolution education relevant and accessible: Case study *Lactase persistence* (Michigan State University, 2023). <https://evo-ed.org/lactase-persistence/biological-processes/>
- ❑ Evershed, R.P., Davey Smith, G., Roffet-Salque, M. *et al.* (2022). Dairying, diseases and the evolution of lactase persistence in Europe. *Nature* **608**, 336–345. <https://doi.org/10.1038/s41586-022-05010-7>
- ❑ Ségurel, L., and Bon, C. (2017). On the evolution of lactase persistence in humans. *Annu. Rev. Genom. Hum. Genet.* **18**, 297-319. <https://doi.org/10.1146/annurev-genom-091416-035340>