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How Did The Ability For Humans To Digest Lactose Arise And What Are The Genetic And Molecular Mechanisms Behind This Adaptation?

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Introduction

A mammal, by definition, is a species that is fed milk at a young age that is produced by the mother. In the 21st century, the majority of mammals consume lactose, a disaccharide which is hydrolyzed to form glucose and galactose.[1] Lactose, with the molecular formula of $C_{12}H_{22}O_{11}$, can be found in several dairy products, with the most common being milk, yoghurt and cheese.[2] These products are highly consumed by the vast number of the global human population, from a very young age. However, humans are the only mammals known to continue to consume lactose even after infancy. This is because they are lactase persistent, where they tolerate lactose-based foods.

The recent ability for humans to tolerate the presence of lactose in their system during adulthood indicates the occurrence of evolution in the Lactase gene (*LCT*). Hence this generational change is evident through the lack of lactose being consumed during adulthood by our ancient ancestors.

Evolution is the process, leading to changes in the genetic traits of an organism over a period of time.[3] Mutations result in the evolution of new alleles during reproduction as genes are passed from parents to offspring. All genes can undergo mutations, including those somatic and germline cells. This includes mutations in the regulation of the lactase gene '*LCT'* on chromosome 2.[4]

[1]Gutiérrez-Méndez, Néstor. "Introductory Chapter: Lactose." IntechOpen, 11 Nov. 2020, www.intechopen.com/chapters/73316. Accessed 8 July. 2024.

[2]"Lactose." Wikipedia, Wikimedia Foundation, 8 July 2024, en.wikipedia.org/wiki/Lactose. Accessed 14 Aug. 2024.

[3]Nature News, Nature Publishing Group, www.nature.com/scitable/definition/evolution-78/. Accessed 8 Aug. 2024.

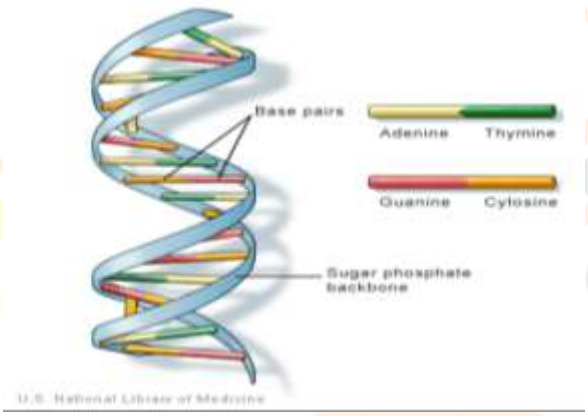
[4]Anguita-Ruiz, Augusto, et al. "Genetics of Lactose Intolerance: An Updated Review and Online Interactive World Maps of Phenotype and Genotype Frequencies." Nutrients, U.S. National Library of Medicine, 3 Sept. 2020, www.ncbi.nlm.nih.gov/pmc/articles/PMC7551416/. Accessed 8 July. 2024.

Literature review

1- Structure of the DNA

The cell is comprised of several components, including the nucleus, mitochondria, ribosome, cell membrane, endoplasmic reticulum, Golgi apparatus and centrosome. The most important is the nucleus. Its nucleus contains the genetic material of the cell in the form of DNA. The DNA contains the specific intrusions which code for the specific proteins which make up a cell[5]. Additionally, the DNA can be subdivided into chromosomes; with a total of 46 chromosomes in the human body, containing several thousands of genes in the overall body.[6] Genes are the "base sequence of the DNA, coding for a specific sequence of amino acids", forming a polypeptide chain.[7] The chain is further folded into a unique tertiary structure and joined with multiple other chains to form a 3D quaternary structure, which is referred to as a protein.[8] The human body contains the lactose gene chromosome 2, encoding for the lactase enzyme. The specific sequence of the amino acids in the lactase protein determines the structure and function of the cell.[9]

Fig 1: Structure of the DNA[10]



DNA, deoxyribonucleic acid, is double-stranded, with four unique bases: Adenine (A), Thymine (T), Guanine (G), and Cytosine (C).[11] These bases join through complementary base pairing and hydrogen bonding, between the bases; with Adenine painting with Thymine and Guanine pairing with Cytosine. The DNA is tightly coiled around histone proteins in the nucleus to form nucleosomes, which are dark patches seen under a

[5]"What Is DNA?: MedlinePlus Genetics." MedlinePlus, U.S. National Library of Medicine, medlineplus.gov/genetics/understanding/basics/dna/#:~:text=DNA%2C%20or%20deoxyribonucleic%20acid%2C%20is,body%20has%20the%20same%20DNA. Accessed 8 July. 2024.

[6]"Chromosome." Mount Sinai Health System, www.mountsinai.org/health-library/special-topic/chromosome. Accessed 10 July. 2024.

[7]"Codon." Genome.Gov, www.genome.gov/genetics-glossary/Codon. Accessed 10 July. 2024.

[8]Ibid

[9]Emily Henderson, B.Sc. "What Is Lactase Persistence, and How Did It Evolve?" News, 3 May 2023, www.news-medical.net/news/20230503/What-is-lactase-persistence-and-how-did-it-evolve.aspx. Accessed 10 July. 2024.

[10]"What Is DNA?: MedlinePlus Genetics." MedlinePlus, U.S. National Library of Medicine, medlineplus.gov/genetics/understanding/basics/dna/. Accessed 10 July. 2024.

[11]"Base Pair." Genome.Gov, www.genome.gov/genetics-glossary/Base-Pair. Accessed 10 July. 2024.

microscope.[12] This structure forms chromatin; protein complexes which are dark patches seen under a microscope. Specifically, the chromatin plays the crucial role of ensuring the DNA is compact in order to ensure it fits within the cell wall.[13] If the DNA does not fit perfectly between the walls of the cell, there is risk of damage.[14] Additionally, the chromatin also regulates gene expression through the modification of histone and by limiting transcription factors such as RNA polymerase. This minimises any changes to the DNA sequence, as transcription cannot occur. During protein synthesis, specifically, transcription and translation, the DNA is transcribed into RNA. Ribonucleic acid (RNA), is a single-stranded molecule that, unlike the DNA, contains Uracil (U) instead of Thymine (T).[15] RNA then acts as a template strand for protein synthesis where free bases are attached to. The template determines the sequence of the DNA, and in turn the type, structure and function of protein formed.

Proteins are synthesised in the ribosome, with each individual protein having a unique structure and function, which determines the role of the protein. This process of protein synthesis occurs due to the transcription and translation. Protein synthesis involves the formation of a polypeptide chain, which is held together by peptide bonds between the carboxyl group of one amino acid to another neighbouring amino acid.[16] Initially, a stem cell is formed, such as totipotent and pluripotent cells; which has the ability to differentiate into various cell types based on the activation or deactivation of specific genes.[17] This is caused by the neighbouring organ cells, as they act as a stimuli causing the activation/deactivation of certain genes. Additionally, there can be different versions of genes, called alleles, which are located on the same locus on a chromosome. The locus is the specific location on a chromosome where a gene is found.

2 - Central dogma

Central Dogma is a theory that states that "genetic material flows on in one direction" from DNA to RNA to the protein.[18] This process includes three key stages of: DNA replication, transcription and translation; in turn leading to the formation of new proteins.[19] During replication, the DNA is copied and identical versions of the DNA are produced. The next process is transcription, where the DNA is transcribed into messenger RNA (mRNA) to make a template strand. Finally, in translation, using the transfer RNA (tRNA), the RNA is translated into amino acids and joined to form a polypeptide chain (figure 3).[20] The unique polypeptide chain is folded

[12]Simpson, Brittany. "Genetics, DNA Packaging." StatPearls [Internet]., U.S. National Library of Medicine, 29 May 2023, www.ncbi.nlm.nih.gov/books/NBK534207/. Accessed 17 July . 2024.

[13]Ibid

[14]Ibid

[15]"Uracil." Genome.Gov, www.genome.gov/genetics-glossary/Uracil. Accessed 17 July. 2024.

[16]Alberts, Bruce. "From RNA to Protein." Molecular Biology of the Cell. 4th Edition., U.S. National Library of Medicine, 1970, www.ncbi.nlm.nih.gov/books/NBK26829/. Accessed 17 July. 2024.

[17]www.fcav.unesp.br/Home/departamentos/tecnologia/marcostuliooliveira/translation_-dna-to-mrna-to-protein-_-learn-science-at-scitable.pdf. Accessed 17 July. 2024.

[18]"Central Dogma." Genome.Gov, www.genome.gov/genetics-glossary/Central-Dogma. Accessed 17 July 2024.

[19]www.fcav.unesp.br/Home/departamentos/tecnologia/marcostuliooliveira/translation_-dna-to-mrna-to-protein-_-learn-science-at-scitable.pdf. Accessed 14 Aug. 2024.

[20]"Transfer RNA (tRNA)." Genome.Gov, www.genome.gov/genetics-glossary/Transfer-RNA. Accessed 17 July. 2024.

into a tertiary structure. Several polypeptide chains in their tertiary structure are joined using disulphide bridges, hydrogen bonding and hydrophobic/hydrophilic interactions to form a 3D quaternary structure. This 3D structure is also known as a protein.[21] These three processes occur in the nucleus and the ribosome and contribute to the production of new cells.

Fig 2: Central dogma [22]

In the DNA, the regulatory region also plays a vital role in controlling gene expression.[23] This occurs due to the region's interactions between transcription factors during protein production to control RNA synthesis and therefore influencing the specific genes that are expressed. In turn the expressed genes will impact the structure and type of protein as it affects the folding of the polypeptide chain formed. For example, the *MCM6* gene is a regulatory region responsible for the expression of the *LCT* gene. This affects the phenotype of the person such as their ability to withstand and digest lactose. [24]

3 - Evolution

The theory of evolution explains the "changes in the genetic material of a population over time", such as the lactose gene. [25] The changes occurring in the genotype of a species may lead to changes in its phenotype, as the genes expressed differ. Over time, species adapt to these changes. For example, the evolution of the lactose gene enabled the tolerance of lactose by humans. Hence, humans adapted to this trait by increasing their daily lactose intake, through a wide range of dairy products. In turn, the galactose absorbed into the bloodstream after lactose is metabolised, is highly useful for humans, aiding in the overall energy production.[26]

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[21]Alberts, Bruce. "The Shape and Structure of Proteins." Molecular Biology of the Cell. 4th Edition., U.S. National Library of Medicine, 1970, www.ncbi.nlm.nih.gov/books/NBK26830/. Accessed 17 July. 2024.

[22]"Intro to Gene Expression (Central Dogma) (Article)." Khan Academy, www.khanacademy.org/science/ap-biology/gene-expression-and-regulation/translation/a/intro-to-gene-expression-central-dogma. Accessed 18 July. 2024.

[23]Doane, Ashley S, and Olivier Elemento. "Regulatory Elements in Molecular Networks." Wiley Interdisciplinary Reviews. Systems Biology and Medicine, U.S. National Library of Medicine, www.ncbi.nlm.nih.gov/pmc/articles/PMC5400678/. Accessed 18 July. 2024.

[24]Labrie, Viviane, et al. "Lactase Nonpersistence Is Directed by DNA-Variation-Dependent Epigenetic Aging." Nature Structural & Molecular Biology, U.S. National Library of Medicine, www.ncbi.nlm.nih.gov/pmc/articles/PMC4899171/. Accessed 18 July. 2024.

[25]science, Wellcome connecting. "What Is Evolution?" New_your_genome, www.yourgenome.org/theme/what-is-evolution/. Accessed 18 July. 2024.

[26]www.fil-idf.org/wp-content/uploads/2017/05/Factsheet-002_2017-Reasons-why-galactose-is-good-for-you.pdf. Accessed 18 July. 2024.

This process occurs due to various factors and processes. Mutation and natural selection and two of the most common processes influencing the evolution of traits. Mutations occur whilst genes are passed commonly during fertilisation, and may be both advantageous or disadvantageous. Whereas, due to natural selection, over a period, species with the advantageous alleles to a given environment reproduce and pass on their advantageous alleles to their offsprings.[27] Those with these superior alleles are more likely to survive and reproduce, hence their population increases gradually. Another factor causing a rise in the mutated genes such as the lactase enzyme producing gene are selection pressures. In this case an increase in the availability of lactose rich products acts as a selection pressure and an environmental interaction as these products are commonly found from natural sources, for example cows. Overall, evolution leads to the introduction of new traits.

4 - Mutation

A mutation is a "change in the base sequence of the DNA which contributes to genetic diversity and evolution".[28] However, there are 2 main types of mutations including: chromosomal mutations and point mutations (which are insertion, deletion and substitution).[29]

Chromosomal mutations are changes in the number or structure of the chromosome. This can influence a molecular change as the number of copies of each chromosome can be increased or decreased after a mutation. There are four types of chromosomal mutations: deletion, duplication, inversion, and translocation.[30] In deletion, a part of the chromosome is deleted causing a change in the sequence as the chromosome length is shortened. Duplication can increase the length of the DNA as an extra copy of the chromosome is produced.[31] In an inversion, the chromosome is directly inverted and the sections of the chromosome are now read back to front. Finally, translocation occurs when there is a movement of one section of the chromosome to another. This shortens one genetic sequence and increases the length of another. Point mutations are composed of substitutions, insertions and deletions (figure 2); and are random mutations occurring through environmental factors or DNA replication.[32]

During processes such as DNA replication, there may be changes in the base sequence of the DNA, leading to a mutation in the gene. A mutation alters the final structure of the protein produced as the folding between the changed polypeptide chain changes, and a new mutated and altered protein is formed.[33] This results in the growth of an abnormal type of cell which may grow rapidly, hence classified as cancerous. Additionally, the type of cell mutated can influence the extent to which a person is affected. For example, a somatic cell mutation commonly leads to a local effect; whereas a germline mutation may affect the entire being and have a lifelong effect.[34] Regardless, the mutation can be life-threatening and permanent. The mutated genes are then

[27]Gregory, T. Ryan. Evolution: Education and Outreach, vol. 2, no. 2, 9 Apr. 2009, pp. 156–175, doi:10.1007/s12052-009-0128-1.

[28]What Is Mutation?, learn.genetics.utah.edu/content/basics/mutation/. Accessed 18 Julyg. 2024.

[29]Nature News, Nature Publishing Group, www.nature.com/scitable/topicpage/genetic-mutation-441/. 18 July. 2024.

[30]www.etsu.edu/uschool/faculty/tadlockd/documents/bio_mutations_show_2019.pdf. Accessed 22 July. 2024.

[31]Pös, Ondrej, et al. "DNA Copy Number Variation: Main Characteristics, Evolutionary Significance, and Pathological Aspects." Biomedical Journal, U.S. National Library of Medicine, www.ncbi.nlm.nih.gov/pmc/articles/PMC8640565/. Accessed 22 July. 2024.

[32]"Point Mutation." Encyclopædia Britannica, Encyclopædia Britannica, Inc., www.britannica.com/science/point-mutation. Accessed 22 July. 2024.

[33] ibid

[34]What Is Mutation?, learn.genetics.utah.edu/content/basics/mutation/. Accessed 14 Aug. 2024.

passed on to future offspring, only if these mutations occur within germline cells.[35] This is because germline cells are cells that will give rise to the gametes (sperm and egg); therefore mutations to these cells are passed to the organism's offspring. The mutation can contribute to a generational trait such as lactose tolerance in adulthood.

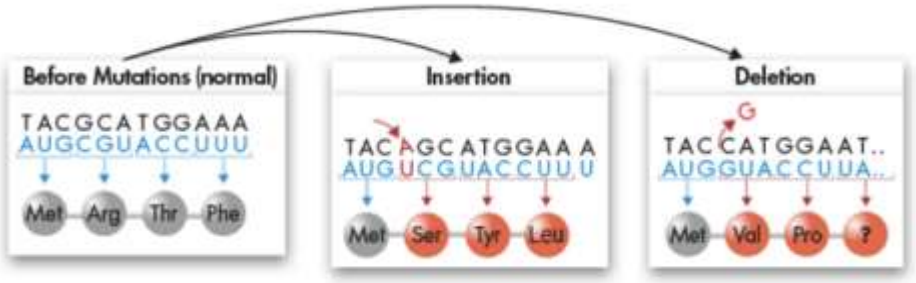

Fig 3: Mutations caused by Insertion and Deletion [36]

Over time a mutation can lead to evolution. Mutations can lead to organisms developing characteristics or features which aid them in survival. When the populations of certain species increase, a mutation can occur that leads to variation between different individuals in the population.[37] In the lactose gene, the mutations occurring over certain periods of time have had no effect on the overall enzyme shape; instead only affected the regulatory region, which influenced the amount of the lactase enzyme being produced by the human body of an individual.[38] Hence due to the different mutations occurring between ancestors, different individuals in the human population have a different tolerance to lactose, due to a different level of lactase production.

5 - The lactose gene

In humans, the enzyme responsible for digesting lactose is lactase, found on the *LCT* gene. This enzyme breaks down lactose, a sugar found in dairy products, into its simpler forms: glucose and galactose.[39] Once hydrolyzed, these sugars are reabsorbed into the bloodstream, acting as a vital source of energy during the metabolic processes that occur in the body.[40] The *LCT* is located on chromosome 2, however, the regulation of the gene is managed by the *MCM6* gene, neighbouring to the *LCT* gene. This activation and deactivation of certain alleles on this gene affects the amount of lactase being produced, hence a person's level of tolerance to lactose. In humans the phenotype shown by the lactase genotype is the level of tolerance of lactose. Commonly,

[35]"Discovering Cancers of Epigenetic Origin without DNA Mutation." ScienceDaily, 24 Apr. 2024, www.sciencedaily.com/releases/2024/04/240424111523.htm. Accessed 14 Aug. 2024.

[36]Team. "Mutation Examples and How They Happen." Agriculture, 14 Nov. 2023, www.canr.msu.edu/news/mutation-examples-and-how-they-happen. Accessed 22 July. 2024.

[37]Learning, Lumen. "Biology for Majors I." Mutations and Evolution | Biology for Majors I, courses.lumenlearning.com/suny-wmopen-biology1/chapter/mutations-and-evolution/. Accessed 22 July. 2024.

[38]Forsgård, Richard A. "Lactose Digestion in Humans: Intestinal Lactase Appears to Be Constitutive Whereas the Colonic Microbiome Is Adaptable." The American Journal of Clinical Nutrition, U.S. National Library of Medicine, 1 Aug. 2019, www.ncbi.nlm.nih.gov/pmc/articles/PMC6669050/. Accessed 22 July. 2024.

[39]Emily Henderson, B.Sc. "What Is Lactase Persistence, and How Did It Evolve?" News, 3 May 2023, www.news-medical.net/news/20230503/What-is-lactase-persistence-and-how-did-it-evolve.aspx. Accessed 27 July. 2024.

[40]"LCT Gene: MedlinePlus Genetics." MedlinePlus, U.S. National Library of Medicine, medlineplus.gov/genetics/gene/lct/. Accessed 27 Julyg. 2024.

the *LCT* gene is primarily active in the cells lining the surface of the small intestine, where it facilitates the digestion of lactose. [41]

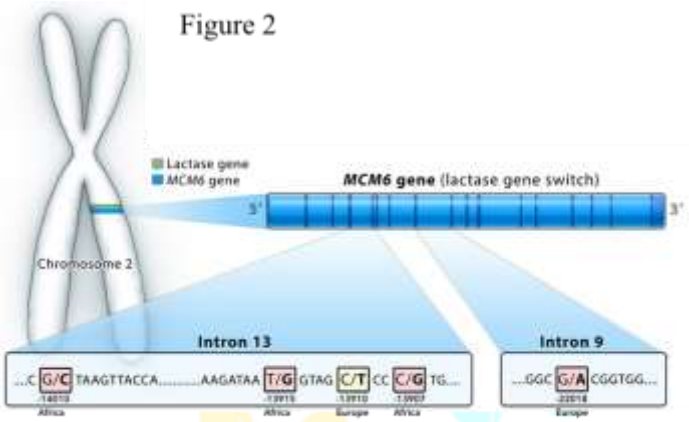

Fig 4: Location of MCM6 gene on Chromosome 2 [42]

6 - Evolution of the Lactose Gene

After infancy, most mammals naturally reduce their intake of lactose, usually received from the mothers milk. Humans are unique among most mammals, being considered the only mammals continuing to consume lactose after infancy. This continued consumption of lactose is due to mutations in the LCT gene, where a change in the base sequence of this gene has occurred over long periods of time. Specifically, mutations in the *MCM6* gene are responsible for the overall production of the lactase enzyme. This is because the regulatory region of the *MCM6* gene controls the activation and deactivation of other genes hence influencing the level of effective digestion of lactose into glucose and galactose before their reabsorption into the bloodstream. Overall, this process leads to the advantageous contribution to metabolic processes as well as other factors such as strengthening bones.

While galactose is crucial for the development of infants, it also plays an essential role in adult metabolism. The persistence of lactase production in adults is a result of evolutionary pressures, which in turn result in the large dairy consumption by humans. Natural selection favoured individuals with mutations that allowed them to digest lactose into adulthood, leading to the spread of these traits in the population.[43] The mutations in the base sequence of the germline cells influence a change in trait, including the lactose tolerability across several generations. Over time, these mutations ensure that individuals can continue to benefit from the nutritional value of dairy products throughout their

The mechanisms of genetic variation, including crossing over and independent assortment during meiosis, contribute to the variations in the *LCT* gene amongst humans. Hence influencing the range of lactose tolerance that can be observed in the current global human population. These evolutionary processes due to mutations have led to the adaptation of lactose digestion as an advantageous trait in various environments, enhancing the survival and reproductive success of individuals who can metabolise lactose effectively.

[41] Ibid

[42] "The Evolution of Lactose Tolerance." LEO, 19 Nov. 2019, smleo.com/2019/11/19/the-evolution-of-lactose-tolerance/. Accessed 27 July. 2024.

[43] Understanding Evolution, evolution.berkeley.edu/evo-news/got-lactase/. Accessed 4 Aug. 2024.

The figure 4 below, demonstrates the impact of lactose on the growing human population from 1992-2021.[44] The graph shows the greatest increase in dairy consumption of over 130 points per capita during this time period. Hence, implying the increase in the number of people with the evolutionary trait of the *LCT* gene producing the lactase enzyme. This phenotype is beneficial and is predicted to grow amongst the human population.

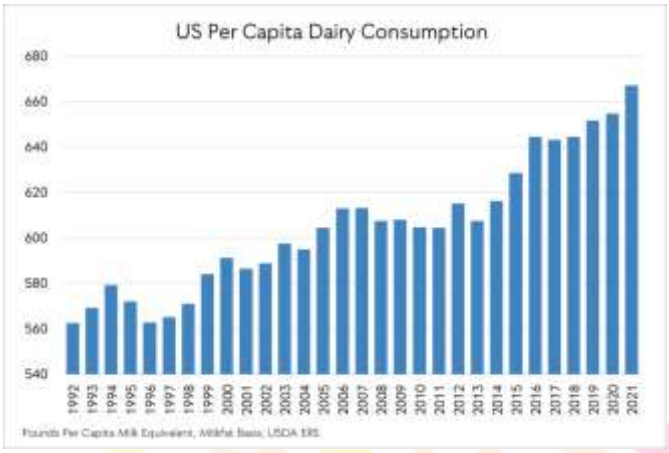

Fig 4: Graph showing dairy consumption in the US from 1992-2021[45]

Conclusion:

On a macro and micro level, the lactose gene illustrates how environmental evolutionary pressure and genetic mutations have led to the development of a new trait; which in this case is lactose persistence. The increase in the availability of lactose based products acts as a selection pressure contributing to the increase in the mutation in the *LCT* gene, as it allows humans to digest lactose. The increase in availability is a factor leading to the increase in consumption of lactose. Hence a greater portion of the global population has the mutated *LCT* gene.

Over time, the human dependency on lactose increases due to evolution, specifically influenced by the adaptability of the human genome. This is demonstrated through the changes that have occurred in the regulation of the lactose gene instead of any changes in the structure of the lactase enzyme.[46] The overall structure of the enzyme remains constant despite mutation such as insertion and deletion in its primary base sequence. The process of mutations may occur during transcription and translation of the gene in the nucleus and the ribosome, when contributing the production of a new protein.[47]

In conclusion, the lactose gene in humans illustrates the advantageous influence of genetic and molecular changes that result in modifications in a day to day human diet. Generational mutations due to evolution influence the frequent consumption of large quantities of lactose rich foods.

[44]"U.S. Dairy Consumption Hits All-Time High in 2021 as Growing Category Evolves Toward Yogurt, Cheese, Butter." IDFA, 30 Sept. 2022, www.idfa.org/news/recorddairyconsumption. Accessed 4 Aug. 2024.

[45] *Ibid*

[46]Emily Henderson, B.Sc. "What Is Lactase Persistence, and How Did It Evolve?" News, 3 May 2023, www.news-medical.net/news/20230503/What-is-lactase-persistence-and-how-did-it-evolve.aspx. Accessed 10 Aug. 2024.

[47]Ibid