Nutrition & Food

Lactase Persistence

Description of the Event:

Lactase Persistence (LP) frequencies worldwide are not consistent. The prevalence of LP Is much higher is some geographic regions as compared to others.

Essential Questions:

What factors could account for the significantly higher (or lower) rates of LP in certain geographical regions as compared to others?

Stimuli: How will students experience and/or observe the phenomena/problem?

Food and Agriculture

Center for Science Education

Students are given the following data on worldwide frequencies of LP. Additionally, students will be given the worldwide allele frequencies from the most-studied LPassociated genetic variants.

Online Mapping Resources:



Related Phenomena/Problems:

- Differences in the amount of glucose present in milk both before and after being mixed with a Lactaid-type supplement can be compared.
- The presence and relative amounts of lactose and glucose/galactose in milk could be tested on both sides of a filter selecting for small enough particle size (something to represent a rudimentary cell membrane layer for the epithelial cells of the small intestine) that only those small enough to cross the barrier would be detected. (Using lactose-free milk, or something similar could prove useful here as well.)
- Milk can be tested to reveal the presence of major nutrient classes.
- An instructional activity or modeling activity that would allow students to determine LP is the function of positive selection.
- The case study of another, single gene-controlled trait that proves to have a large enough effect on survival over time allowing students to have scaffolded examples for positive and negative selection with examples of influencing factors.
- Historical disease data for geographic locations, that would perhaps have increased selection pressure.



- A typical vaccination schedule for dairy cattle could be examined to point students in a direction of potential cattle diseases that they may want to investigate more for their historical significance and perhaps influence to this phenomenon.
- Comparison of climate and vegetation data by geographic areas over history may reveal possible correlations. Historical seasonal weather patterns would show areas where regions are relatively close to each other.
- Early historical data on the distribution of regions that practiced dairying.
- The typical diets and relative amounts of nutrition available by area vary throughout history.
- What's processes are responsible for the physical symptoms of LI?

Considerations for Instructional Design:

- The particular stimulus students are exposed to will influence what curiosities students may have and perhaps to scope for this phenomenon.
- Could serve as an instructional or lesson-level investigation for broader unit on lactose intolerance as a condition.
- Could serve as the context for a transfer task allowing students to demonstrate their understanding of the associated DCIs.
- The variety in the research methods presented in the citations section, could provide a rich opportunity for comparing and contrasting the research design, scope, and methods of 2 or more different research studies. Students could consider the implications of different methods, participants sizes, etc. and what effects they have on the conclusions that can or cannot be made from them.
- This example provides an opportunity for students to consider how environmental and/or cultural factors play into the biology/genetics and experiences of plants and animals across the globe.
- Students can further study how minor mutations in genes can code for vastly different proteins which varies their structure and the biological functions they are able to (or no longer able to) perform.
- Students can investigate the structure of the different types of cells in digestive tissue and how they are related to the function of nutrient absorption or waste secretion.
- As students learning is scaffolded to a point of understanding basic genetic adaptations, an Elaborate lesson, a Problematizing routine, or an extra instructional sequence would lend itself well to understanding some of the complexities of the inheritance of Heterozygous vs Homozygous for LP phenotypes. Followed by make sense of the wide spectrum of experiences that LNP individuals may experience. These seem to range from no symptoms, to toleration of lactose occasionally within a threshold, or having a very low threshold before experiencing symptoms of or similar to LI. Students could make claims to back up with evidence, they could engineer a biomedical device to quickly and affordably diagnose LI along with the potential impacts for people, for research advances.
- Further opportunity for extension for this phenomenon may be student sense-making around the differences between lactose intolerance and a milk allergy or allergy to particular proteins in milk.

Nature of Science:

As with many contexts, this phenomenon comes with some complexities and areas where some mechanisms are not fully understood. (OTR-M3, ENP-H2, WOK-H4, VOM-H2) Lactose intolerance has the potential to be highly relevant to students and perhaps other family or peers with whom they interact. Given that, below are some of the advances that have been made in our understanding, some of the mechanisms that are not entirely understood at this point, and differentiation amongst some terminology that can be easily misunderstood. "There continues to be research conducted related to this phenomenon and the concepts within it. Before further developing this phenomenon or ideas related, it is advisable to check for new research and reviews.

The topic of lactose intolerance offers an opportunity for students to see the changing nature of science and a responsibility for educators/developers to recognize. (WOK-H4) One

Universally, nearly all humans are born with and maintain the ability to produce adequate amounts			
of lactase. It is natural for lactase activity to decrease after a child has been weaned. Typically, if symptoms			
of decreased lactase appear, they don't appear often before the age of eight.			
Genetic Types	Associated Terminology		
Lactose Non-Persistence (LNP):	Lactose Malabsorption: a term meaning lactose is		
The genotype that is characteristic is reduced	not properly absorbed in the small intestine. <u>An</u>		
expression of the gene that codes for the	individual with lactose malabsorption may or may		
translation of the enzyme lactase. LNP does not	not experience uncomfortable gastrointestinal		



	Candidate Pheno	ome
 individuals with the LNP genotype do produce dramatically less lactose than individuals with the LP genotype. This genotype is and has traditionally been the most prevalent globally. Individuals with the LNP genotype are not necessarily lactose intolerant/experience gastrointestinal symptoms after consuming lactose 	 Lactose Intolerance: a condition in which an individual who is LM does experience uncomfortable gastrointestinal symptoms after ingesting lactose, but who does not would not experience those symptoms with the same amount of placebo. The same symptoms associated with lactose intolerance can be caused by a variety of other conditions. In general, there appears to be a threshold of lactose which most LI individuals can tolerate without experiencing symptoms. Most can tolerate up to 12 grams of lactose at once and up to 24 g spread out over the course of a day. (Informedhealth.org 2018) Though LI can be tested for clinically using breath tests, and placebo compared trials, it is not standard clinical practice. (ETS1.B-H1) Commonly someone is predicted to be LI or has self-diagnosed themselves and this makes the true prevalence difficult to predict. 	
Lactose Persistence (LP): Lactose Persistence is a term encompassing several genotypes with a dominant trait mutation in which the enzyme lactase continues to be produced at high levels throughout adulthood. Research indicates that an individual can be homozygous for the trait or heterozygous. Current research suggests those homozygous produce about 10X as much lactase as someone with the LNP genotype and those heterozygous produced intermediate amounts more than those with the LNP genotype. (Enatin 2017)		

Explanation:

What factors could account for the geographical differences in LP?

There are two complimentary theories that currently offer the most-complete explanation: *Please note that naming of these theories isn't critical in developing a casual explanation. The theories have been labeled for your information and scaffolding as a teacher. The same is true of other specific vocabulary labels; the actual labels are not needed to provide a complete and acceptable explanation from a student.*

 Advantage for LP phenotypes in areas where fresh milk was readily available to adults in populations that traditionally practiced domestication of dairy animals. (Augusto, Antuita-Ruiz. 2020). In other words, populations that had regular access to milk began experiencing natural selection that was positive for those who were easily able to digest and absorb the nutrients from the milk. Historically, those who experienced the symptoms associated with lactose intolerance (regardless of the cause) were at a disadvantage for survival and procreation. (MS-LS4-6)

What nutritional advantages does milk offer? Milk provides hydration and is nutrient-rich with a mixture of carbohydrates, proteins, fat, as well as vitamins and minerals.

- Carbohydrates and fats can be broken down by the body and used for energy while the proteins are broken-down into the amino acids. The amino acids are then utilized by the body to build the proteins it needs at any given time to carry out nearly all life processes.
- Proteins serve as enzymes to that facilitate bio-chemical reactions of all sorts in the body (digestion, energy production, blood clotting, muscle contraction), as hormones which to send feedback throughout the body, as buffer systems to maintain pH, and to balance fluids. Proteins provide the raw materials for growth and repair, provide cells and tissues



with structure, help form antibodies for the immune system, transport and store nutrients, and can also be used to produce energy.

Other essential vitamins and minerals including calcium, phosphorus, selenium, iodine, and vitamins A, D, B12, B2, B3, and B5 (Dairy Innovation 2021)

2. Dairying Barrier hypothesis: This hypothesis addresses the question, "Why is dairying in some areas but not others?" The hypothesized barriers, supported by research (Bloom 2005) are that Lactose Malabsorption (LM) has the following correlations in data. (Additional sources include Campbell 2021, Dairy Innovation 2021, Lang 2005) Please note that the correlation here is noted LM verses Lactose Persistence (LP) which is essentially the opposite of LP. If looking at LP, these relationships would be inverse. (MS-LS4-6)

- <u>1.</u> LM and latitudes had a highly significant, negative correlation.
- 2. LM and mean temperatures had a significant positive correlation.
- 3. LM and historical presence of deadly cattle diseases had a significant and positive correlation.

The data from Africa was likely influenced by nomadism as some tribes migrated seasonally to avoid harsh climates and conditions where dairy would likely struggle to survive. (Bloom 2020) In other researchers' data sets, there are some African outliers where there is dairying, but lower levels of LP (higher instances of LM). The outliers appear to tribes that were more sedentary and where dairying is relatively new (20th century). (Bloom 2020) (MS-LS4-6)

Figure 3 Climate change and routes of migration of domesticated cattle in Africa. Maps (A–C) show changes in climatic ...



Hum Mol Genet, Volume 30, Issue R1, 1 March 2021, Pages R98–R109, <u>https://doi.org/10.1093/hmg/ddab027</u> The content of this slide may be subject to copyright: please see the slide notes for details. (Augusto, Antuita-Ruiz. 2020) Accessible in larger format at <u>https://academic.oup.com/view-large/figure/237746135/ddab027f3.tif</u>.

Why do some people have lactase persistence?

Lactase persistence is due to a genetic polymorphism. A polymorphism is the term for a mutation with two or more variant forms and occur in more than 1% of the general population. (Gunter, Chris. 2023) The gene that regulates the production of lactase levels is called the LTC gene. The LTC gene provides the instructions for making lactase. In adulthood, the functioning of the LCT gene can start to decrease, leading to lactose malabsorption and possibly lactose intolerance later in life. Those who continue to produce sufficient levels of lactase may have inherited specific changes to their MCM6 gene, which acts as a regulatory element for the LCT gene (MS-LS3-1) (HS-LS1-1). (Swallow, Dallas. 2003.) This element causes the body to continue elevated lactase production, whereas those without experience lowered lactase production. This variation is autosomal dominant; only one parent needs to carry the mutation for the offspring to receive it and have increased lactase production throughout life (Medline Plus, n.d.). (MS-LS3-2)

At present there are 23 genetic variations of the LP gene. Six of those are widely studied genetic variations that account for the majority of LP globally and all are located on chromosome 2, genomic region MCM6, which is just upstream from the LTC. When looking at the worldwide geographical distribution of the different allele frequencies for six most common LP variations, some patterns can be seen. This includes certain variations being more prevalent in certain areas. That said, there are also instances where more than one variations can be found within the same community. Currently, the data is not strong enough to adequately explain the distribution of variations.

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PAGE 4

Candidate Phenomena



Enlarged Map of MCM6 and LCT, Located on Chromosome 2, and Locations of the Genomic Regions Sequenced and the Four Genotyped Microsatellites LCT and MCM6 have both been mapped to the long arm of chromosome 2 at position q21. Intron 13 of MCM6, upstream of LCT, carries the primary variants associated with the LP trait in the current study (C-14010, G-13915, T-13910, and G-13907), whereas intron 9 contains the A-22018 variant, which is in strong LD with T-13910 in Europeans and Africans. Relative positions of the four linked microsatellites and their repeat motifs typed in the study are also shown.

(Ranciaro 2014)



(Augusto, Antuita-Ruiz. 2020). Interactive variation available at http://bionit.ugr.es/pages/investigacion/software/bioinformatics-methods-software.

Below are concepts which may prove useful for students to understand as they approach their explanation for this phenomenon. The need will vary depending on students' past experience and the scope of unit or task.

Lactase vs. Lactose:

Lactase is an enzyme that helps to break down lactose (the main carbohydrate found in milk). Lactose (a disaccharide sugar) is broken down by the enzyme lactase to turn lactose into glucose and galactose — two sugars that the body can metabolize and use for cellular respiration (MS-LS1-3).

Where in the body is lactose digested and how is it digested?

Different nutrients are digested, or broken down into smaller units, throughout different organs along the digestive tract. For lactose, that organ is primarily the small intestine. Lactase, the enzyme that breaks down lactose into its smaller components of glucose and galactose, is typically encountered in the small intestine.

Where and how is the resulting glucose absorbed to be used in the body?

Most nutrients are absorbed into the blood stream in the small intestine. The unique structure of the small intestine helps facilitate the absorption of nutrients. Stretched out, the small intestine ranges between 10 – 15' in length and are surrounded by smooth muscle. The cavity where the intestines are located isn't very big. To fit, they are scrunched as they fold and twist. You can imagine the inside of the small intestine to be full of peaks and valleys packed together. Along the peaks and valleys are microscopic finger-like projects that packed along the entire surface. The larger folds are referred to as villi and the microscopic layer covering the villi, are referred to as micro-villi.

Remember that in dairy products, lactose is generally the sugar that first enters the small intestine. Lactose is a large sugar, too large to be absorbed. The membranes along the surface of the microvilli are packed with enzymes, which can include



Candidate Phenomena

lactase. When present, the lactase breaks lactose into two smaller sugars: glucose and galactose. Broken down, the sugars are ready to be absorbed when conditions are right.

Cells lining the outside of the microvilli are flat and thin which is convenient for absorption. These cells are called endothelial cells. Endothelial cells are also found along the linings of all organs containing smooth muscle. Epithelial cells have channels in their membranes that allow certain nutrients to pass through them. With some assistance, the glucose can exit the small intestine into the microvilli where it immediately encounters a tangle of capillaries. Capillaries are also lined epithelia cells meaning that when conditions are right, nutrients can be transported across the membrane into the bloodstream. Here they can be carried off to where they are needed for cellular respiration or to be stored for later. (Kong, S. 2018.) (MS-LS1-3)



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Image Source: Kong, Shanshan & Zhang, Yanhui & Zhang, Weiqiang. (2018). Available in larger format at <u>https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5966675/figure/fig1/</u>.

What does someone who is lactose intolerant experience after consuming lactose? When lactose is not broken down in the small intestine, it passes to the large intestine where its presence creates a higher concentration gradient and therefore an influx of fluid via osmosis into the large intestine. This can result in diarrhea,

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PAGE 6

cramping, and gas. The gas production actually comes from bacteria in the colon that digest the lactose as a food source for themselves. (MS-LS1-7) The severity of symptoms varies from one individual to another.

It should be noted that diarrhea, cramping, and gas are common symptoms of several conditions that are unrelated to LI.

Terminology

There are terms that sound similar, but have different meanings. They are worth clarifying as teachers or students will likely run across them in literature and data. The definitions below are from the National Institute of Health.

- Lactase-Persistence (LP): a genetic trait (autosomal dominant) in which humans continue to produce lactase
 through adulthood
- Lactase-Non-persistence (LNP): a genetic trait (autosomal recessive) that leads to the down-regulation of lactase activity
- Lactose-Intolerant (LI): characterized by digestive symptoms—such as bloating, gas and/or diarrhea, after consuming food or drinks containing lactose
- **Lactase Malabsorbtion (LM):** the inability of a person to absorb lactose in the small intestine due to an underlying cause, with the most common cause being lactase non-persistence

Figure 1 Two possible outcomes for the lactose sugar. When individuals are lactase persistent (A), lactose is ...



(Campbell, Michael C. 2021.)

Why is the incidence of infant lactose intolerance/malabsorption so low?

Globally, nearly all infants can digest lactose efficiently. Their bodies produce plenty of lactase, which is an enzyme in our digestive system that breaks down lactose into two other sugars that can easily be digested/absorbed. This makes sense given that, whether it be breast milk or formula, the top source of carbohydrate for infants is lactose.

Why do many people produce less lactase after weaning?

Newborns have a high concentration of lactase that can start to decline once breastfeeding stops. After breastfeeding and/or formula are replaced by other nutritional sources, levels of lactase tend to decrease. To at least some degree, this is true for a large segment of the global population. The timing of this can vary but usually begins between 2 and 3 years of age and is done between 5 and 10 years of age. (Swallow, Dallas. 2003). If levels of lactase decrease significantly, a person won't be able to efficiently breakdown or absorb lactose. Those individuals may experience symptoms, including gastrointestinal issues like diarrhea, gas, nausea, gut distension, and stomach pain. Lactose intolerance can occur when the lactase level in your small intestine is too low (MS-LS1-3).

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Student and teacher generated questions about this phenomenon/problem that could be instructionally productive:

Generic questions about this topic:

- What is lactose intolerance?
- Is lactose intolerance an allergy to lactose?
- What is the difference between lactose intolerant and lactase persistent?
- Do people take lactase pills every day or just before they eat dairy or right after?
- Are there foods besides dairy that have lactose in them?
- Does milk without lactose taste different?
- How do they make the milk or dairy products that say "lactose free"?
- Why are some people lactose intolerance?
- Are people born with lactose intolerance?
- Can someone who is lactose intolerant become lactose persistent and vice versa?
- How do those lactase (Lactaid) pills work?
- If my parents are lactase persistent, does that mean that I am or will be as well?
- If my parents are lactose intolerant, does that mean I am or will be as well?
- If someone drinks a lot of milk as a child, will it prevent them from becoming lactose intolerant?
- Do older people become more sensitive to lactose as they age?
- Are younger people less likely to be lactose intolerant than older people?
- Is there lactose in all mammal's milk?
- Is there lactose in human milk?
- Is there lactose in almond/soy/coconut milk?
- How do they make milk or ice cream that is lactose free or lower in lactose?
- Is lactose healthy?

Geography and Demographics:

- Why is the frequency of LP highest in Europe?
- Why does the frequency of LP seem to decrease as you move south?
- Why does the eastern part of the Middle East have higher frequency but is surrounded by areas of lower frequency?
- Why are Australia and Asia's frequency lower?
- Are there more mountains in the areas with high (or low) frequencies?
- What is similar about the places with high (or low) frequencies?
- Did the areas with higher frequencies tend to be areas where people had more money?
- Do the areas with higher frequencies have more dairies?
- Are cows sacred in the areas where the frequency is low?
- Is there not enough space for cows in the areas with low frequency?

Explaining the phenomenon/problem or related phenomena could lead students toward developing the following DCIs:

LS1.A: Structure & Function

- Organisms reproduce, either sexually or asexually, and transfer their genetic information to their offspring. (secondary to MS-LS3-2) Built toward the concept that different frequencies of LP across the world have developed due to those with LP have a survival and reproductive advantage in areas where dairy has been available throughout history.
- In multicellular organisms, the body is a system of multiple interacting subsystems. These subsystems are groups
 of cells that work together to form tissues and organs that are specialized for particular body functions. (MS-LS1-3)
 Built toward Lactase presence on the brush border enterocytes where it is anchored into the membrane at its Cterminal end. Additionally built toward specialized cells forming the tissue in the small intestine serve key digestive
 functions from absorption of amino acids, to secreting enzymes that break down food into smaller, absorbable
 nutrients.

LS1.A: Structure and Function

• All cells contain genetic information in the form of DNA molecules. Genes are regions in the DNA that contain the instructions that code for the formation of proteins, which carry out much of the work of cells. (HS-LS1-1) Built toward if students include information about the LTC gene, including that it provides the instructions for making



lactose. Additionally in understanding that the variations in the gene that regulates the LTC gene, is responsible for promoting the production of lactose by activating the LTC gene.

LS1.C: Organization for Matter and Energy Flow in Organisms

• Within individual organisms, food moves through a series of chemical reactions in which it is broken down and rearranged to form new molecules, to support growth, or to release energy. (MS-LS1-7) Built toward with the concept of lactase acting as an enzyme to break down lactose and with the lack of lactase leading to uncomfortable digestive symptoms.

LS3.A: Inheritance of Traits

- In sexually reproducing organisms, each parent contributes half of the genes acquired (at random) by the offspring. Individuals have two of each chromosome and hence two alleles of each gene, one acquired from each parent. These versions may be identical or may differ from each other. (MS-LS3-2) Built toward in understanding LP is dominant trait and causes by a change in one of the allele pairs on a particular location on a particular gene.
- In addition to variations that arise from sexual reproduction, genetic information can be altered because of
 mutations. Though rare, mutations may result in changes to the structure and function of proteins. Some changes
 are beneficial, others harmful, and some neutral to the organism. (MS-LS3-1) Built toward in understanding that LP
 is caused by polymorphism (technically a mutation).

LS4.C Adaptation

 Adaptation by natural selection acting over generations is one important process by which species change over time in response to changes in environmental conditions. Traits that support successful survival and reproduction in the new environment become more common; those that do not become less common. Thus, the distribution of traits in a population change. (MS-LS4-6) Built toward as students make sense of how variations in the frequency of LP came about due to LP being advantageous for those to whom dairy was readily accessible. Similarly, built toward in understanding the disadvantages of lactose intolerance throughout history, particularly under conditions of famine or plague.

ETS1.B-H

When evaluating solutions it is important to take into account a range od constraint including cost, safety, reliability, and aesthetics and to consider social, cultural, and environmental impacts. There is an opportunity to build toward this if a student were to take on an engineering problem related to the efficacy of how we could test people easier for LI. There currently are tests, they just not yet considered needed in standard clinical practice. Weighing the constraints of costs, distribution, etc..

Science of Nature

ENP-M2: Scientific Knowledge is Open to Revision in Light of New Evidence.

• Science theories are based on a body of evidence developed over time. This can build toward in discussion on what we have known or believed over time has changed with new research. A good example is the article that brough the pottery evidence to light. Another example is the suggestion of a third phenotype being the heterozygous for LP and has there been enough research in that area? What were the sample sizes, the procedures and have other replicated with similar evidence?

Notes about relevance and authenticity (funds of knowledge, interests, identity) Why might students be engaged?

- Students may have other food allergies or food sensitivities they can relate to the symptoms or management of lactose intolerance.
- Students may have traveled to or have friends or family from different geographical regions on the maps.
- All humans start as infants and nearly all infants can efficiently digest lactose.
- Students may have been born prematurely or know of someone born prematurely.
- Students might relate climate and changes in weather to people migrating seasonally.
- Students may recognize that animal and/or plant species that once thrived in a particular geographical area no longer thrive there due to climate changes or prevalence of disease.



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