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Understanding the Genetic and Evolutionary Basis of Lactase Persistence in Human Populations: A Comprehensive Review

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Abstract: **Lactose intolerance is a prevalent condition characterized by the inability to digest lactose, a sugar in milk and dairy products, due to a deficiency in the lactase enzyme. This condition is influenced by genetic variations near the lactase gene (LCT), particularly single-nucleotide polymorphisms (SNPs) such as -13910 C>T and -22018 G>A, which are associated with lactase persistence. These genetic variants have undergone positive selection in populations with a history of dairy farming, such as Northern Europeans, some African, and Middle Eastern groups, allowing them to digest lactose into adulthood. The prevalence of lactose intolerance varies significantly across populations, with higher rates in groups without a history of dairy farming, such as Native Americans and East Asians. Symptoms include gastrointestinal complaints like bloating, gas, diarrhea, and abdominal pain following lactose consumption. The regulation of the LCT gene involves complex interactions with enhancer sequences and regulators like peroxisome proliferator-activated receptor gamma (PPARγ). Future treatments may include gene editing technologies and modulation of the gut microbiome. Understanding genetic and environmental factors can inform personalized nutrition recommendations and public health strategies, highlighting the dynamic interplay between genes and environment in lactose intolerance**

Keywords: **lactose intolerance, lactase persistence, LCT gene, genetic diagnosis, genetic variations, gene-environment interaction.**

I. INTRODUCTION

Lactose intolerance is a prevailing condition in which a person has difficulties to efficiently digesting lactose, which is the sugar that occurs in milk and dairy products. When this happens, lactase deficiency leads to the disintegration of lactose into sugars that are more readily absorbed (Bogdanova et al., 2020; Leszkowicz et al., 2022). The illness can give rise to various abdominal complaints such as nausea, cramps in the abdomen, and pain when foods containing lactose are eaten. The extent to which it may be inherited has a great influence on the ability of an individual's digestive system in breaking down lactose; some genetic variation near the gene for lactase (LCT) is strongly linked with persistence of this enzyme into adulthood. There exists significant variability in populations' prevalence rates of lactose intolerance, which can be attributed to complex interactions between genetic factors, evolutionary forces and environmental influences (Campbell & Matthews 2005; Buzás 2015).

The main aim of this review is to unravel the genetics and evolution behind lactase persistence among human populations. This will involve examination of genetic variations associated with ability to digest lactose, especially single-nucleotide polymorphisms (SNPs) close to LCT gene. It will also examine how these genetic variants are distributed within different ethnic groups.

II. LACTOSE TOLERANCE AND THE LCT GENE

Lactase, an enzyme that breaks down lactose into glucose and galactose, is absent in those who are lactose intolerant (Bogdanova et al. 2020; Leszkowicz et al. 2022). Lactase, an enzyme encoded by the LCT gene, is a necessary part of lactose tolerance. The LCT gene is located on chromosome 2q21.3 and is substantially conserved in mammals (Spena et al. 2022).

The LCT gene has several genetic variants that are connected to lactose tolerance. For instance, the LCT gene's -13910 C>T polymorphism is one of the most important variations. Because the CC genotype is linked to hypolactasia, a disorder marked by the inability to digest lactose in adulthood, this variant is linked to lactose intolerance (Kowalowka et al. 2023; Sadigova et al. 2024; Morus et al. 2018). On the other hand, lactose persistence—which permits lactose digestion throughout adulthood—is linked to the TT genotype (Kowalowka et al. 2023; Sadigova et al. 2024; Morus et al. 2018). In people with adult-type primary lactase insufficiency, this variant is substantially linked to reduced consumption of milk and dairy products (Kowalowka et al. 2023). Furthermore, Bosnian subjects have the -22018G>A polymorphism, another variant linked to LP (Adler et al. 2017). These genetic variations are frequently employed as markers for lactose tolerance in genetic studies because it has been proven that they are strongly associated with lactose tolerance. (Adler et al. 2017; Valencia et al. 2017).

An essential component of lactose digestion is the lactase gene (LCT). Several variables influence the intricate regulation of LCT gene expression. One important regulator of LCT gene expression has been found as peroxisome proliferator-activated receptor gamma (PPARγ). It has been shown that PPARγ agonists enhance LCT expression and function both in vivo and in vitro, indicating that regulating intestinal PPARγ activity could be a potential treatment approach for lactose malabsorption (Fumery et al. 2017). Enhancer sequences, which have undergone numerous separate alterations to achieve high frequency in various groups, also regulate the LCT gene (Leseva et al. 2017). Strong positive selection has been acting on these alterations, because of the health advantages of milk consumption.

Multiple factors have a complex role in the regulation of LCT gene expression. Peroxisome proliferator-activated receptor gamma (PPARγ) is one major regulator that has been demonstrated to control the expression and function of the LCT gene positively. It has been observed that PPARγ agonists enhance lactase activity and LCT gene expression, both in vivo and in vitro, indicating that PPARγ activity modulation may be a viable treatment approach for lactose intolerance (Fumery et al. 2017).

Apart from PPARγ, enhancer regions that have experienced numerous separate alterations in various ethnicities also regulate the LCT gene. Strong positive selection has probably been acting on these mutations because of the advantages of having the ability to digest milk and dairy products. Another important factor in lactose digestion is the interaction between the LCT gene and the gut bacteria.

In most humans, lactase production declines after weaning, leading to the inability to digest lactose as adults. However, certain genetic variations in the LCT gene can allow for continued lactase production and lactose tolerance into adulthood (Fumery et al. 2017; Kowalowka et al. 2023).

Enhancer sequences that have undergone numerous separate mutations in various populations regulate the LCT gene. Strong positive selection has likely been acting on these mutations because of the advantages of having the ability to digest dairy products and milk (Fumery et al. 2017; Kowalowka et al. 2023). Furthermore, the peroxisome proliferator-activated receptor gamma (PPARγ) has been demonstrated to affect the expression and activity of the LCT gene positively, and so has an impact on the regulation of the LCT gene. PPARγ agonists have been reported to boost LCT gene expression and lactase function, both in vitro and in vivo, suggesting that regulating PPARγ activity could be a possible treatment method for lactose intolerance (Fumery et al. 2017; Hankel et al. 2020). The interplay between the LCT gene and the gut microbiota also plays a crucial role in lactose digestion, as the microbiota can compensate for the inability to break down lactose in populations lacking the lactase gene (Fumery et al. 2017; Kowalowka et al. 2023).

The future implications of lactose tolerance research are significant. Advances in gene editing technologies, such as CRISPR, could potentially be used to correct genetic defects leading to lactose intolerance. For instance, CRISPR/Cas9 has been used to edit the LCT gene in mice, resulting in the production of lactase enzymes and improved lactose tolerance (Uddin et al. 2020). Additionally, the development of probiotics and prebiotics could help alleviate symptoms of lactose intolerance by modulating the gut microbiome (Shao et al. 2023). Furthermore, understanding the genetic and environmental factors influencing lactose tolerance could inform strategies for improving public health and reducing the prevalence of lactose intolerance. For instance, identifying genetic variants associated with lactose tolerance could inform personalized nutrition recommendations and help individuals make informed choices about their diet (Sadigova et al. 2024; Leontiadis & Longstreth 2022; Schulz & Rizvi 2021).

III. LACTOSE INTOLERANCE PREVALENCE ACROSS POPULATION

Between 30 and 50 million Americans have the potential for lactose intolerance (Nicklas et al. 2009). The 2005 Dietary Guidelines for Americans states that the "nutrients of concern", essential nutrients, seem to be lacking in adult Americans diets; calcium, potassium, magnesium, and vitamin A (Nicklas et al. 2009). Dairy foods help decrease the risk of multiple chronic diseases and contribute a unique nutrient package to a healthy diet. However, some individuals limit or avoid consuming dairy because of lactose intolerance, which may have long-term effects on diet quality, bone strength, and metabolism, as well as overall health (Nicklas et al. 2009).

Lactose is a disaccharide sugar found in milk, which is broken down into glucose and galactose by the enzyme lactase (Anguilla-Ruiz et al. 2020). Congenital lactase deficiency and lactase non-persistence are two different conditions that affect the ability of a person to digest lactose (Sollid 2024).

Lactose intolerance is a gastrointestinal symptom, such as cramps, abdominal discomfort, and nausea, all associated with lactose maldigestion, which occurs when more lactose is consumed than the existing lactase enzyme can hydrolyze (Fisher 2018). It is crucial to understand that lactose intolerance is not the same as having a food allergy to milk (Hopkins 2024). Based on studies, lactose intolerance in Americans occurs in about 15% of whites, 50% of Mexican Americans, and 80% of African Americans (Nicklas et al. 2009).

Congenital Lactase Deficiency

Congenital lactase deficiency is a rare genetic disorder caused by variants in the LCT gene, which encodes the lactase enzyme. These variants interfere and mess with the processing of lactase, resulting in an impaired ability to digest lactose. The LCT gene is responsible for the production of lactase, which is needed for the digestion of lactose (Fisher 2018; Wanes 2019). Variants in the LCT gene can lead to a range of lactose intolerance, from mild to severe (Robayo-Torres et al. 2007).

Lactase Non-Persistence

Lactase non-persistence is a condition characterized by the gradually decreasing activity of the LCT gene after infancy (Labrie et al. 2016; Fisher 2018). This decrease is because of the genetic variations in the MCM6 gene, which encodes a transcription factor that regulates lactase expression (Labrie et al. 2016). People with these variations have lactase production in the small intestine, which allows them to digest lactose throughout life. However, individuals without these variations have a reduced ability to digest lactose as they get older, resulting in the signs and symptoms of lactase non-persistence (Labrie et al. 2016).

The prevalence of lactose intolerance varies significantly across different populations. A recent study estimated that 68% of the world's population is lactose intolerant, with the highest prevalence found in the Middle East and the lowest in Western Europe (Storhaug et al. 2017). Another study found that in a national Canadian survey, 16% of participants perceived that they had lactose intolerance (Barr 2013).

Evolution and Variants Associated with Lactose Intolerance

The LCT gene on chromosome 2 encodes the lactase enzyme. Regulatory regions near the LCT gene, particularly within the MCM6 gene, play a key role in lactase expression. Single nucleotide polymorphisms (SNPs) within these regulatory regions act as genetic switches, influencing the level of lactase production (Anguita-Ruiz et al. 2020).

The most well-studied polymorphisms associated with lactase persistence include C/T−13910 and G/A-22018. The ancestral allele (C) at the C/T−13910 locus is linked to a decrease in lactase expression after weaning, while the derived

allele (T) is associated with continued lactase production (Baffour-Awuah et al. 2016). Similarly, the G allele at the G/A-22018 locus promotes lactase persistence (Enattah et al. 2008).

Researchers have identified additional lactose persistence-related polymorphisms, such as G/C*-14010, C/G*-13907, and T/G*-13915. These variants often appear together in specific populations, forming a compound allele that acts as a stronger genetic determinant for lactase persistence (Hassan et al. 2016). The inheritance pattern of lactase persistence is complex, exhibiting characteristics of both dominant and codominant inheritance. While some individuals with just one copy of the lactase persistence allele have sufficient lactase activity, others may require two copies for full lactose tolerance (Wells et al. 2021). This explains the observed spectrum of lactase levels, ranging from very low in individuals homozygous for the non-persistence variants to high levels in those with the persistence variants (Smith et al. 2006).

The global geographical diversity in the genetic foundations of the LP phenotype indicates that this trait emerged independently multiple times throughout human history. Moreover, various independent mutations associated with regional social dynamics, local cultural practices, behavior, and pre-existing genetic diversity have contributed to its present-day multiethnic distribution (Jackson 2014). By utilizing genetic data and historical knowledge, the researchers can enhance and broaden our understanding of the social implications of these behavioral and cultural changes and their impact on regional development and health, underscoring the dynamic interplay between "genes" and "environment" (Jackson 2014).

Lactose Intolerance and Evolution History

Lactose intolerance is closely linked to the evolution of lactase persistence, the ability to produce the lactase enzyme into adulthood. The prevalence of lactose intolerance varies among different populations and is thought to have evolved in populations with a history of dairy farming (Campbell & Matthews 2005; Buzás 2015).

The genetic variants associated with lactase persistence have undergone positive selection in certain populations, such as Northern Europeans and some African and Middle Eastern groups, as it provided a selective advantage by allowing them to obtain nutrients from milk throughout their lifespan (Campbell & Matthews 2005; Buzás 2015).

The evolution of lactase persistence is believed to have occurred relatively recently, within the last 10,000 years, coinciding with the development of dairy farming in these regions (Campbell & Matthews 2005; Buzás 2015). Populations without a history of dairy farming, such as Native Americans and East Asians, generally have a higher prevalence of lactose intolerance (Campbell & Matthews 2005; Buzás 2015; Lukito et al. 2015).

Lactose intolerance is caused by the inability to produce enough lactase, the enzyme responsible for breaking down lactose (Buzás 2015; Mărginean et al. 2017).

In individuals with lactose intolerance, undigested lactose can cause symptoms such as bloating, gas, diarrhea, and abdominal pain after consuming dairy products (Buzás 2015; Mărginean et al. 2017).

Interestingly, Charles Darwin's mystery illness, which he suffered from for over 40 years, has been suggested to be a case of systemic lactose intolerance (Campbell & Matthews 2005). His symptoms, including vomiting, gut pain, headaches, and severe tiredness, matched those of lactose intolerance, and he only got better when he stopped taking milk and cream (Campbell & Matthews 2005; Geoghegan & Webb 2017).

Gene-Environment Interactions in Lactose Intolerance

To understand the etiology of a disease, genetic-environment interactions are one of the most interesting and very complex factors that contribute to a given disease or phenotype via the molecular process (Virolainen et al. 2023).

Gene-environment interaction review

According to Carolyn M. Hutter, the Division of Genome Sciences director, "Gene-environment interaction refers to the interplay of genes and the physical and social environment". For instance, Environmental risk factors include physical elements like radiation and temperature, chemical substances such as polycyclic aromatic hydrocarbons, and biological agents like viruses. Additionally, behavioral patterns like delayed age at first pregnancy and significant life events such as job loss or injury contribute to this complex landscape of risk factors. Comparably genetic risk factors can involve an autosomal or X-linked major gene, a polygenic model, or an epistatic model (Ottman 2010).

Explain lactose intolerance via genetic-environment interaction

In humans, the ability to digest milk lactose is governed by an enzyme called lactase-phlorizin hydrolase (LPH), specifically a β-galactosidase enzyme (Montgomery 1991). Following the weaning phase, approximately two-thirds of humankind experience a drastic decline in the levels of this enzyme, a trait known as lactase non-persistence (LNP). However, some individuals can maintain high levels of LPH throughout their lives, a condition called lactase persistence (LP) (Rossi 1997). Remarkably, it has been hypothesized that LP may arise independently due to the influence of five or more single nucleotide polymorphisms (SNPs) within a regulatory region known as MCM6 (minichromosome maintenance complex component 6). This region, positioned upstream of the LCT gene, serves as a transcriptional enhancer, potentially contributing to the sustained expression of lactase in individuals with LP (Liebert et al. 2017).

Thoroughly, it has been discovered that among humans, high lactose digestion capacity after weaning is common only in certain North Atlantic European, Mediterranean, Central Asian, and some selected African populations. It is widely believed to represent an evolutionary adaptation developed over millennia of consuming milk from domesticated animals (Holden & Mace 1997). Therefore, using such terms as adult “lactose intolerance” or “adult lactase deficiency” describes a person with this symptom, in fact, this trait is the plesiomorphic trait that appears in most mammals and humans (Jackson 2014).

The global geographical diversity in the genetic foundations of the LP phenotype indicates that this trait emerged independently multiple times throughout human history. Moreover, various independent mutations associated with regional social dynamics, local cultural practices, behavior, and pre-existing genetic diversity have contributed to its present-day multiethnic distribution (Jackson 2014). By utilizing genetic data and historical knowledge, the researchers can enhance and broaden our understanding of the social implications of these behavioral and cultural changes and their impact on regional development and health, underscoring the dynamic interplay between "genes" and "environment” (Jackson 2014).

In European dairying populations and their descendants, the widespread LP phenotype is primarily attributed to a single genetic mutation located 13.9 kb upstream from the LCT gene (-13910T) (Anagnostou et al. 2009), forming an extended haplotype of 500 kb or more. Similarly, in Central Asia, LP is linked to the same mutation (-13910C > T, rs4988235) (Heyer et al. 2011), suggesting genetic diffusion between these regions. However, among other milk-consuming groups, various mutations are associated with LP. For instance, in certain South Africans, the -14010C allele is linked to LP (Jensen et al. 2011), while in East Africa, the primary mutation appears to be (-13907G) (Enattah et al. 2008). Interestingly, the European and East African alleles share a common ancestral background, potentially linked to shared social and behavioral histories related to cattle domestication. In Saudi Arabia, the absence of the European allele (-13910T) is compensated by two new mutations forming a compound allele (-13915T/G and a synonymous SNP in exon 17 of MCM6). This unique compound allele, prevalent among Arab populations, indicates a divergent ancestral haplotype possibly shaped by camel domestication and milk consumption (Enattah et al. 2008).

IV. THE ROLE OF GUT MICROBIOME IN LACTOSE INTOLERANCE

The gut microbiota, a complex community of microorganisms residing in the gastrointestinal tract, significantly influences human health. This community is predominantly bacterial and plays crucial roles in digestion, immune protection, vitamin synthesis, and the production of metabolic byproducts such as short-chain fatty acids (SCFAs) (Hills et al. 2019; Riccio & Rossano 2020; Valdes et al. 2018). One area of interest is how the gut microbiome affects lactose intolerance (LI), a condition marked by gastrointestinal symptoms following lactose ingestion (Malik & Panuganti 2023).

Lactose, the primary sugar in mammal milk, is hydrolyzed by lactase (β-galactosidase) into glucose and galactose for absorption in the small intestine. However, not all ingested lactose is metabolized; some reaches the colon, where gut microbes possessing β-galactosidase can further hydrolyze lactose, producing byproducts like lactate, SCFAs, hydrogen, carbon dioxide, and methane (Ayivi et al. 2020; Forsgård 2019). This process suggests that lactose consumption impacts gut microbiota composition and function.

Misselwitz et al. (2019) have highlighted the multifactorial nature of LI, pointing to genetic makeup and dietary patterns as significant factors influencing gastrointestinal symptoms. They identified the presence of lactose-fermenting bacteria like Bifidobacterium in the gut, which can affect lactose levels. However, the impact of the gut microbiome on the occurrence of LI symptoms is still unclear.

Afterward, Brandao Gois et al. (2022) further explored the interplay between LI genetic variants, dairy intake, and gut microbiome composition, focusing on Bifidobacterium. The research found a higher abundance of Bifidobacterium in LI

individuals compared to non-LI individuals, which was positively correlated with dairy intake in the LI group. Likewise, the abundance of Bifidobacterium was also positively correlated with the total score of gastrointestinal complaints in LI individuals, particularly abdominal pain, discomfort, and bloating.

These findings suggest that the gut symptoms experienced by LI patients may be linked to the abundance of Bifidobacterium rather than directly to lactose intake. This supports the hypothesis that metabolic products of lactose-fermenting bacteria could be related to LI symptom occurrence. Furthermore, Brandao Gois performed a mediation analysis indicating that the association between dairy intake and gastrointestinal complaints in LI individuals was partially mediated by Bifidobacterium abundance.

Diet is a major factor in gut microbiota composition and function. Various dietary patterns, including high-fat, high-sugar, and plant-based diets, can significantly alter the microbial community structure (Leeming et al. 2019; Bibbò et al. 2016). Furthermore, studies have shown that lactose can function as a prebiotic, promoting the growth of beneficial bacteria like Bifidobacterium and Lactobacillus, which in turn produce metabolites such as SCFAs that are beneficial for gut health (Angima et al. 2024; Aslam et al. 2020).

Genetic factors also play a role in lactose intolerance and gut microbiome composition. Variants in the lactase gene (LCT), such as the rs4988235 variant, have been associated with lactase persistence and gut microbiome Bifidobacterium abundance (Bonder et al. 2016). The rs4988235 variant is known to cause lactase persistence in adults of European ancestry, and studies have consistently shown a strong association between this variant and increased levels of Bifidobacterium in the gut microbiome (Kato et al. 2018; Qin et al. 2024).

V. DIAGNOSING LACTOSE INTOLERANCE (GENETIC AND CLINICAL FACTORS)

There are several diagnostic tests available to confirm lactose intolerance. Firstly, the Hydrogen Breath Test (HBT) is a test that measures the amount of hydrogen in the breath after consuming lactose. It is collected after the patient drinks a lactose product. The level of hydrogen collected implies that lactose is not being properly digested and absorbed, leading to malabsorption and symptoms of lactose intolerance (Amieva-Balmori et al. 2019; Shafi & Husain 2022). Secondly, the Lactose Intolerance Test is a test that measures patient symptoms and blood glucose levels after consuming lactose products. If the result shows that patients have a low blood glucose level, lactose is not properly digested and absorbed into the bloodstream (Shafi & Husain 2022). Another test is the Genetic Test which identifies genetic mutations that affect lactase enzyme production, which is necessary for lactose digestion. It can help diagnose lactose intolerance by recognizing patients who have more possibility to experience symptoms due to their genetic weakness (Santonocito et al. 2015). Lastly, Intestinal Biopsy is a test used to examine the presence and function of lactase enzyme by using a tissue sample from the small intestine, the test. It can help diagnose lactose intolerance by identifying lactase enzyme deficiency in the human body. These tests diagnose lactose intolerance and differentiate it from other conditions that may cause similar symptoms, such as small intestinal bacterial overgrowth (SIBO) (Shafi & Husain 2022).

Looking deeper into Treatment and Management, Individuals with lactose intolerance can prevent their symptoms, allergies, by consuming lactose-free or low-lactose products, such as lactase-treated milk, hard cheeses and plant-based milk (Misselwitz et al. 2019). Lactase enzyme supplements can also help digest lactose in foods.

In Clinical and Experimental Gastroenterology, lactose intolerance is a global health issue, so diagnosis and management are important for affected individuals. The review discusses the lactase-persistence alleles that have occurred among people around the world, the diagnosis of lactose intolerance, and its symptomatology and management (Lomer et al. 2007).

Precision nutrition, which focuses on the effects of nutrients on the genome, proteome, and metabolome, can help manage lactose intolerance (Pratelli et al. 2024). Omics technologies play an important role in explaining the complex interactions between nutrients and the human body, enabling the precise delineation and identification of distinct cohorts of individuals with specific dietary requirements.

Genetic Test for Lactose Intolerance

Given that genetic testing identifies genetic changes linked to the conditions, it is a useful diagnostic technique for lactose intolerance (Brasen et al. 2017). In contrast to the lactose hydrogen breath test, the genetic test is an uncomplicated, noninvasive, and more comfortable examination that does not trigger lactose intolerance symptoms (Büning et al. 2005; Nilsson & Olsson 2008). It also requires fewer preparations because it is simple to transfer a venous blood sample to the laboratory (Mattar et al. 2008; Högenauer et al. 2005). Analyzing the lactase gene (LCT) to identify single nucleotide

polymorphisms (SNPs) is the standard procedure for the genetic test for lactose intolerance. The SNPs that are most frequently researched are G/A_22018, C/T_13910, and C/G_13907 (Rollán et al. 2012). These SNPs are linked to the small intestine's continued or decreased lactase enzyme activity (Baffour-Awuah 2015). The test includes isolating DNA from a blood sample, followed by polymerase chain reaction (PCR) amplification of the LCT gene. Following that, the amplified DNA is examined using methods like sequencing or restriction fragment length polymorphism (RFLP) to determine whether the SNPs are present (Ponte et al. 2016).

Genetic Diagnosis and Prevalence

Genetic testing for lactose intolerance is very reliable in determining the disease. When a study was done through which genetic test was compared to other diagnostic methods, it was discovered that it had 97% sensitivity and 93% specificity. Moreover, another research found that 52.5% of patients had lactose intolerance as identified by the genetic test with a positive likelihood ratio of >10 and a negative likelihood ratio of <0.1 (Rollán et al. 2012). Consequently, among populations who are not European there exists variation in the occurrence of lactose intolerance.

Lactose Intolerance in Specific Populations

Populations with high inflammatory bowel disease (IBD) prevalence show high lactose intolerance cases. The prevalence of lactose intolerance in a study on IBD patients was found to be 64.8% through the hydrogen breath test; a similar prevalence existed among the control population as well (Nardone et al. 2021). Similarly, this research also established that the majority of IBD patients, 85.2%, possessed wild genotypes and tested positive for lactose intolerance utilizing genetic testing (Nardone et al. 2021).

VI. MANAGING LACTOSE INTOLERANCE (GENETIC AND DIETARY APPROACHES)

Lactose intolerance can be controlled by completely avoiding lactose-containing products or taking supplements of lactase (Facioni et al. 2020; Szilagyi & Ishayek 2018). In some cases, a lactose-free diet could be necessary.

The analysis of the lactase gene for specific SNPs associated with the condition is one of the most important uses of genetic testing in diagnosing people with lactose intolerance. The diagnostic value of this test is high due to its high sensitivity and specificity. Moreover, there is a wide range of variation in terms of the prevalence of lactose among population groups, with populations that are not from Europe having higher rates. Additionally, through genetic testing, it would be possible to identify those individuals who are more likely to develop the disease before time thereby allowing early intervention and management (Porzi et al. 2021).

Genetic Approaches

Lactose intolerance is a genetic condition, with most individuals losing the ability to digest lactose after infancy (Liebert et al. 2017). Genetic variations, such as lactase persistence, allow some individuals to continue producing lactase enzymes into adulthood, enabling them to digest lactose effectively. Understanding the genetic basis of lactose intolerance is crucial for developing effective management strategies (Angima et al. 2024).

Pharmacological approach

Another important approach for preventing LI is to use lactase from nonhuman sources as part of enzyme replacement treatment to hydrolyze lactose. Multiple lactase supplements that are sold commercially come in different amounts of beta-galactosidase derived from different sources (Usai-Satta et al. 2012).

Dietary Approaches

Lactose intolerance is a genetic disease but can be a short-term result of an infection or other insult to the jejunal mucosa. It is crucial to recognize this common condition since it is easily treated with simple dietary changes (Swagerty Jr et al. 2002). Considering that there are simple dietary approaches to building lactose tolerance and that avoiding dairy products can result in nutritional deficiencies, several public health organizations advise everyone, including those who are lactose intolerant, to consume three servings of dairy products daily to ensure sufficient nutritional intake and optimal bone health. Most individuals with LI can tolerate up to 12 grams of lactose daily in a single dose (Hodges et al. 2019). To address this, dairy products can be consumed by people with LI as part of a strategy that includes yogurts and cheeses that are matured to have minimal lactose content (Santos et al. 2019). The initial recommendation for managing lactose intolerance is to temporarily refrain from milk and dairy products in an effort to relieve symptoms. Most people with lactose malabsorption, as previously stated, are able to take up to 12 g of lactose without experiencing serious symptoms (Mattar et al. 2012).

Prebiotic Strategies (Sub)

Prebiotic approaches, including the consumption of galactooligosaccharides (GOSs) and low levels of lactose, have been shown to shift the gut microbiome and mitigate symptoms of lactose intolerance. Prebiotics may serve as a therapeutic to mitigate symptoms in people with lactose intolerance. GOS can enhance the growth of colonic *Bifidobacterium*. Feeding GOS to subjects with lactose intolerance enhances the relative abundance of *Bifidobacterium* and has been associated with symptom reduction (Angima et al. 2024).

FODMAPs and Irritable Bowel Syndrome

FODMAPs (fermentable oligo-, di-, and monosaccharides and polyols) are a group of carbohydrates that can worsen symptoms of lactose intolerance. A low FODMAP diet has been shown to be effective in managing symptoms of irritable bowel syndrome (IBS), which often co-occurs with lactose intolerance. The idea that starting with a low-FODMAPS diet should be the first dietary strategy is supported by the evidence for this diet. Still, there are a lot of things that need to be made clear, such as how serious the potential nutrition concerns are (Mansueto et al. 2015). Understanding the biological mechanisms underlying food intolerance to lactose and FODMAPS can aid clinicians in providing an accurate diagnosis and directing rational dietary and medical management (Deng et al. 2015).

Nutrigenomics and Personalized Nutrition (Sub)

Lactose intolerance is a monogenic disease where diet influences phenotypic expression. Nutrigenomics provides powerful approaches to unravel the complex relationships between bioactive molecules, genetic polymorphisms, and biological systems, leading to personalized nutrition and dietary recommendations. In lactose intolerance, early identification of specific mutations or haplotype combinations that modulate dietary response can improve prevention or treatment (Gorduza et al. 2008).

VII. DISCUSSION

Understanding the genetic basis of lactose intolerance has significant scientific implications. It sheds light on human adaptation to dietary changes throughout history and the interplay between genes and environment (Deng et al. 2015). Studying these polymorphisms can provide insights into gene regulation mechanisms and the development of personalized dietary recommendations (Kiani et al. 2022). While genetic testing for lactase persistence variants is not a routine diagnostic tool, it can be helpful in specific situations, such as differentiating between lactose intolerance and other digestive disorders (Mattar travel al. 2012). Continued research on the genetics of lactase persistence promises to deepen our understanding of this common condition and its impact on human health and evolution.

The genetic basis of lactase persistence has been extensively studied, revealing significant insights into human evolution and population genetics. One of the key findings is the identification of several single-nucleotide polymorphisms (SNPs) associated with lactase persistence, particularly in populations with a long history of dairy consumption. The most studied SNP, located in the regulatory region upstream of the LCT gene (rs4988235), is strongly associated with lactase persistence in European populations. This SNP is thought to have arisen around 7,500 years ago, coinciding with the advent of dairy farming in Europe (Ingram et al. 2009).

Interestingly, different genetic variants associated with lactase persistence have been identified in African and Middle Eastern populations, suggesting multiple, independent evolutionary events. For instance, the SNP -14010*C is prevalent in pastoralist groups in East Africa, while other variants are found in Saudi Arabia and northern India (Tishkoff et al. 2007). This indicates that lactase persistence is a prime example of convergent evolution, where different genetic adaptations have arisen in response to similar selective pressures, namely the dietary reliance on milk.

The evolutionary advantage of lactase persistence likely stems from the nutritional benefits of milk, particularly in environments where other food sources are scarce. Milk provides a rich source of calories, protein, and essential micronutrients, which would have been especially valuable in early agrarian societies and during periods of famine. The ability to digest lactose also offers a significant hydration advantage, as milk is a sterile liquid source, which could be crucial in arid environments (Gerbault et al. 2011).

Despite the clear genetic basis for lactase persistence, the condition of lactose intolerance remains prevalent worldwide. This highlights the importance of understanding the gut microbiome's role in lactose digestion. Certain bacterial strains in the gut can ferment lactose, producing short-chain fatty acids and gases, which can mitigate the symptoms of lactose

intolerance (He et al. 2020). Probiotic treatments and dietary adjustments that promote beneficial gut bacteria are promising strategies for managing lactose intolerance symptoms.

The variability in lactose tolerance also underscores the complex interplay between genetics and environment. Cultural practices, such as the traditional fermentation of milk into yogurt or cheese, can reduce lactose content and make dairy products more digestible for lactose-intolerant individuals. This cultural adaptation demonstrates how human populations have historically mitigated the limitations imposed by genetic predispositions.

Looking forward, advances in genetic research and personalized medicine hold promise for developing targeted interventions for lactose intolerance. Genetic screening can identify individuals at risk of lactose intolerance, enabling personalized dietary recommendations. Furthermore, understanding the gut microbiome's role in lactose digestion could lead to the development of probiotic therapies tailored to individual microbiome compositions (Szilagyi 2015).

In conclusion, lactose intolerance is a widespread condition that affects the ability to digest lactose. The prevalence of lactose intolerance varies significantly across different populations, with genetic and molecular mechanisms playing a crucial role in its development. Lactase persistence research provides valuable insights into human genetic diversity, evolutionary biology, and the intricate relationship between genetics, diet, and culture. As we continue to unravel the genetic and microbiological underpinnings of lactose intolerance, we can develop more effective strategies to improve the health and well-being of individuals affected by this condition.

VIII. CONCLUSION

Genetic factors are the main determinants of lactose intolerance. Lactase persistence, the capacity to digest lactose into adulthood, has developed in societies with a history of dairy farming. Lactase production is influenced by genetic variants in the LCT gene, specifically in the regulatory region MCM6.

Genetic testing, which identifies particular SNPs in the LCT gene, is used to diagnose lactose intolerance. Tests for lactose intolerance and hydrogen breath are two further diagnostic techniques. Dietary adjustments, such as avoiding lactose-containing foods or ingesting lactose-free alternatives, are usually necessary to manage lactose sensitivity. Prebiotic methods and lactase enzyme supplements can also help reduce discomfort.

Therefore, learning about the genetic and evolutionary aspects of lactose intolerance can help with management and prevalence estimations. Researchers can enhance public health efforts and create tailored nutrition recommendations by identifying genetic polymorphisms linked to lactase persistence. The lactose intolerance research also provides information on the intricate interactions that shape human behavior and health between genetic, environmental, and cultural factors. Investigating innovative techniques for treating lactose intolerance and improving the health of those who are impacted is crucial as our knowledge of the problem deepens.

REFERENCES

[1] O. Alharbi and A. El-Sohemy, “Lactose intolerance (LCT-13910C>T) genotype is associated with plasma 25-hydroxyvitamin D concentrations in caucasians: A mendelian randomization study,” *The Journal of Nutrition*, vol. 147, no. 6, pp. 1063–1069, Jun. 2017, doi: 10.3945/jn.116.246108.

[2] S. Spena *et al.*, “Genetic variants at the chromosomal region 2q21.3 underlying inhibitor development in patients with severe haemophilia A,” *Haemophilia*, vol. 28, no. 2, pp. 270–277, Feb. 2022, doi: 10.1111/hae.14503.

[3] N. M. Bogdanova, A. I. Khavkin, and O. L. Kolobova, “Prospects of fermented milk products in children with primary hypolactasia of the adult type,” *Rossiyskiy Vestnik Perinatologii i Pediatrii (Russian Bulletin of Perinatology and Pediatrics)*, vol. 65, no. 3, pp. 160–168, Jul. 2020, doi: 10.21508/1027-4065-2020-65-3-160-168.

[4] J. Leszkowicz, K. Plata-Nazar, and A. Szlagatys-Sidorkiewicz, “Can Lactose Intolerance Be a Cause of Constipation? A Narrative Review,” *Nutrients*, vol. 14, no. 9, p. 1785, Apr. 2022, doi: 10.3390/nu14091785.

[5] M. Fumery *et al.*, “Peroxisome proliferator-activated receptor gamma (PPARγ) regulates lactase expression and activity in the gut,” *EMBO Molecular Medicine*, vol. 9, no. 11, pp. 1471–1481, Sep. 2017, doi: 10.15252/emmm.201707795.

[6] C. J. E. Ingram and D. M. Swallow, “Population Genetics of Lactase Persistence and Lactose Intolerance,” *Encyclopedia of Life Sciences*, Dec. 2007, doi: 10.1002/9780470015902.a0020855.

[7] T. A. Suzuki and R. E. Ley, "The role of the microbiota in human genetic adaptation," *Science*, vol. 370, no. 6521, Dec. 2020, doi: 10.1126/science.aaz6827.

[8] J. Tomczonek-Moruś, A. Wojtasik, K. Zeman, B. Smolarz, and L. Bąk-Romaniszyn, "13910C>T and 22018G>A LCT gene polymorphisms in diagnosing hypolactasia in children," *United European Gastroenterology Journal*, vol. 7, no. 2, pp. 210–216, Mar. 2019, doi: 10.1177/2050640618814136.

[9] M. Kowalówka, G. Kosewski, D. Lipiński, and J. Przysławski, "A Comprehensive Look at the -13910 C>T LCT Gene Polymorphism as a Molecular Marker for Vitamin D and Calcium Levels in Young Adults in Central and Eastern Europe: A Preliminary Study," *International Journal of Molecular Sciences*, vol. 24, no. 12, p. 10191, Jun. 2023, doi: 10.3390/ijms241210191.

[10] C. Pienar *et al.*, "Genetic Predisposition to Primary Lactose Intolerance Does Not Influence Dairy Intake and Health-Related Quality of Life in Romanian Children: A Hospital-Based Cross-Sectional Study," *Children*, vol. 10, no. 6, p. 1075, Jun. 2023, doi: 10.3390/children10061075.

[11] C. Pienar, L. Pop, M. Lăzărescu, R. Costăchescu, and E. Șeclăman, "Anthropometric and metabolic profile of children with gene polymorphisms for primary lactose intolerance," *Experimental and Therapeutic Medicine*, vol. 22, no. 5, Sep. 2021, doi: 10.3892/etm.2021.10768.

[12] O. M. Nardone *et al.*, "Lactose Intolerance Assessed by Analysis of Genetic Polymorphism, Breath Test and Symptoms in Patients with Inflammatory Bowel Disease," *Nutrients*, vol. 13, no. 4, p. 1290, Apr. 2021, doi: 10.3390/nu13041290.

[13] N. Hanke *et al.*, "A Comprehensive Whole-Body Physiologically Based Pharmacokinetic Drug–Drug–Gene Interaction Model of Metformin and Cimetidine in Healthy Adults and Renally Impaired Individuals," *Clinical Pharmacokinetics*, vol. 59, no. 11, pp. 1419–1431, May 2020, doi: 10.1007/s40262-020-00896-w.

[14] V. V. Santosh Kumar *et al.*, "CRISPR-Cas9 mediated genome editing of drought and salt tolerance (OsDST) gene in indica mega rice cultivar MTU1010," *Physiology and Molecular Biology of Plants*, vol. 26, no. 6, pp. 1099–1110, May 2020, doi: 10.1007/s12298-020-00819-w.

[15] M. M. Yang *et al.*, "Altered expression of long noncoding RNA MEG3 in the offspring of gestational diabetes mellitus induces impaired glucose tolerance in adulthood," *Acta Diabetologica*, vol. 61, no. 1, pp. 79–90, Sep. 2023, doi: 10.1007/s00592-023-02169-x.

[16] L. Valencia *et al.*, "Identification of novel genetic variants in the mutational hotspot region 14 kb upstream of the LCT gene in a Mexican population," *Scandinavian Journal of Clinical and Laboratory Investigation*, vol. 77, no. 5, pp. 311–314, Apr. 2017, doi: 10.1080/00365513.2017.1318445.

[17] C. J. E. Ingram *et al.*, "A novel polymorphism associated with lactose tolerance in Africa: multiple causes for lactase persistence?," *Human Genetics*, vol. 120, no. 6, pp. 779–788, Nov. 2006, doi: 10.1007/s00439-006-0291-1.

[18] G. Babayeva-Sadigova *et al.*, "P319 Genetic polymorphism of lactose intolerance in patients with Inflammatory Bowel Disease," *Journal of Crohn's and Colitis*, vol. 18, no. Supplement_1, pp. i703–i704, Jan. 2024, doi: 10.1093/ecco-jcc/jjad212.0449.

[19] M. N. Leseva *et al.*, "Differences in DNA Methylation and Functional Expression in Lactase Persistent and Non-persistent Individuals," *Scientific Reports*, vol. 8, no. 1, Apr. 2018, doi: 10.1038/s41598-018-23957-4.

[20] J. C. Ray *et al.*, "Calcitonin gene related peptide in migraine: current therapeutics, future implications and potential off-target effects," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 92, no. 12, pp. 1325–1334, Jan. 2021, doi: 10.1136/jnnp-2020-324674.

[21] K. Rachwał *et al.*, "Lactase Deficiency and Lactose Intolerance: Current Understanding and Future Directions," *Journal of Education, Health and Sport*, vol. 69, p. 49393, May 2024, doi: 10.12775/jehs.2024.69.49393.

[22] X. Shao, "Brief classification and latest therapy for lactose intolerance," *Theoretical and Natural Science*, vol. 6, no. 1, pp. 299–305, Aug. 2023, doi: 10.54254/2753-8818/6/20230257.

[23] R. W. Haley, J. A. Dever, G. Kramer, and J. F. Teiber, "The effect of disease misclassification on the ability to detect a gene-environment interaction: implications of the specificity of case definitions for research on Gulf War illness," *BMC Medical Research Methodology*, vol. 23, no. 1, Nov. 2023, doi: 10.1186/s12874-023-02092-3.

[24] G. I. Leontiadis and G. F. Longstreth, "Evolutionary Medicine Perspectives: Helicobacter pylori, Lactose Intolerance, and 3 Hypotheses for Functional and Inflammatory Gastrointestinal and Hepatobiliary Disorders," *American Journal of Gastroenterology*, vol. 117, no. 5, pp. 721–728, Feb. 2022, doi: 10.14309/ajg.0000000000001681.

[25] F. Uddin, C. M. Rudin, and T. Sen, "CRISPR Gene Therapy: Applications, Limitations, and Implications for the Future," *Frontiers in Oncology*, vol. 10, Aug. 2020, doi: 10.3389/fonc.2020.01387.

[26] P. Schulz and S. S. H. Rizvi, "Hydrolysis of Lactose in Milk: Current Status and Future Products," *Food Reviews International*, vol. 39, no. 5, pp. 2875–2894, Oct. 2021, doi: 10.1080/87559129.2021.1983590.

[27] A. Movahedi, S. Aghaei-Dargiri, H. Li, Q. Zhuge, and W. Sun, "CRISPR Variants for Gene Editing in Plants: Biosafety Risks and Future Directions," *International Journal of Molecular Sciences*, vol. 24, no. 22, p. 16241, Nov. 2023, doi: 10.3390/ijms242216241.

[28] C. L. Storhaug, S. K. Fosse, and L. T. Fadnes, "Country, regional, and global estimates for lactose malabsorption in adults: a systematic review and meta-analysis," *The Lancet Gastroenterology & Hepatology*, vol. 2, no. 10, pp. 738–746, Oct. 2017, doi: 10.1016/s2468-1253(17)30154-1.

[29] "Symptoms & Causes of Lactose Intolerance," *NIDDK - National Institute of Diabetes and Digestive and Kidney Diseases*, Jul. 26, 2022. Accessed: Jul. 04, 2024. [Online]. Available: https://www.niddk.nih.gov/health-information/digestive-diseases/lactose-intolerance/symptoms-causes

[30] "Lactose Intolerance," *Johns Hopkins Medicine*. https://www.hopkinsmedicine.org/health/conditions-and-diseases/lactose-intolerance (accessed Jul. 04, 2024).

[31] A. Anguita-Ruiz, C. M. Aguilera, and Á. Gil, "Genetics of Lactose Intolerance: An Updated Review and Online Interactive World Maps of Phenotype and Genotype Frequencies," *Nutrients*, vol. 12, no. 9, p. 2689, Sep. 2020, doi: 10.3390/nu12092689.

[32] C. C. Robayo-Torres and B. L. Nichols, "Molecular Differentiation of Congenital Lactase Deficiency from Adult-Type Hypolactasia," *Nutrition Reviews*, vol. 65, no. 2, pp. 95–98, Jun. 2008, doi: 10.1111/j.1753-4887.2007.tb00286.x.

[33] V. Labrie *et al.*, "Lactase nonpersistence is directed by DNA-variation-dependent epigenetic aging," *Nature Structural & Molecular Biology*, vol. 23, no. 6, pp. 566–573, May 2016, doi: 10.1038/nsmb.3227.

[34] K. Sollid, "What Is Lactose? – Food Insight," *Food Insight*, May 06, 2024. https://foodinsight.org/what-is-lactose/ (accessed Jul. 05, 2024).

[35] D. Wanes, D. M. Husein, and H. Y. Naim, "Congenital Lactase Deficiency: Mutations, Functional and Biochemical Implications, and Future Perspectives," *Nutrients*, vol. 11, no. 2, p. 461, Feb. 2019, doi: 10.3390/nu11020461.

[36] S. I. Barr, "Perceived lactose intolerance in adult Canadians: a national survey," *Applied Physiology, Nutrition, and Metabolism*, vol. 38, no. 8, pp. 830–835, Aug. 2013, doi: 10.1139/apnm-2012-0368.

[37] R. Hills, B. Pontefract, H. Mishcon, C. Black, S. Sutton, and C. Theberge, "Gut Microbiome: Profound Implications for Diet and Disease," *Nutrients*, vol. 11, no. 7, p. 1613, Jul. 2019, doi: 10.3390/nu11071613.

[38] P. Riccio and R. Rossano, "The human gut microbiota is neither an organ nor a commensal," *FEBS Letters*, vol. 594, no. 20, pp. 3262–3271, Oct. 2020, doi: 10.1002/1873-3468.13946.

[39] A. M. Valdes, J. Walter, E. Segal, and T. D. Spector, "Role of the gut microbiota in nutrition and health," *BMJ*, p. k2179, Jun. 2018, doi: 10.1136/bmj.k2179.

[40] T. F. Malik and K. K. Panuganti, "Lactose Intolerance," *StatPearls*, Apr. 2023.

[41] R. A. Forsgård, "Lactose digestion in humans: intestinal lactase appears to be constitutive whereas the colonic microbiome is adaptable," *The American Journal of Clinical Nutrition*, vol. 110, no. 2, pp. 273–279, Aug. 2019, doi: 10.1093/ajcn/nqz104.

[42] R. D. Ayivi *et al.*, "Lactic Acid Bacteria: Food Safety and Human Health Applications," *Dairy*, vol. 1, no. 3, pp. 202–232, Oct. 2020, doi: 10.3390/dairy1030015.

[43] B. Misselwitz, M. Butter, K. Verbeke, and M. R. Fox, "Update on lactose malabsorption and intolerance: pathogenesis, diagnosis and clinical management," *Gut*, vol. 68, no. 11, pp. 2080–2091, Aug. 2019, doi: 10.1136/gutjnl-2019-318404.

[44] M. F. Brandao Gois *et al.*, "Role of the gut microbiome in mediating lactose intolerance symptoms," *Gut*, vol. 71, no. 1, pp. 215–217, Mar. 2021, doi: 10.1136/gutjnl-2020-323911.

[45] E. R. Leeming, A. J. Johnson, T. D. Spector, and C. I. Le Roy, "Effect of Diet on the Gut Microbiota: Rethinking Intervention Duration," *Nutrients*, vol. 11, no. 12, p. 2862, Nov. 2019, doi: 10.3390/nu11122862.

[46] S. Bibbò *et al.*, "The role of diet on gut microbiota composition," *European review for medical and pharmacological sciences*, vol. 20, no. 22, pp. 4742–4749, Nov. 2016.

[47] H. Aslam *et al.*, "The effects of dairy and dairy derivatives on the gut microbiota: a systematic literature review," *Gut Microbes*, vol. 12, no. 1, p. 1799533, Aug. 2020, doi: 10.1080/19490976.2020.1799533.

[48] G. Angima, Y. Qu, S. H. Park, and D. C. Dallas, "Prebiotic Strategies to Manage Lactose Intolerance Symptoms," *Nutrients*, vol. 16, no. 7, p. 1002, Mar. 2024, doi: 10.3390/nu16071002.

[49] M. J. Bonder *et al.*, "The effect of host genetics on the gut microbiome," *Nature Genetics*, vol. 48, no. 11, pp. 1407–1412, Oct. 2016, doi: 10.1038/ng.3663.

[50] K. Kato, S. Ishida, M. Tanaka, E. Mitsuyama, J. Xiao, and T. Odamaki, "Association between functional lactase variants and a high abundance of Bifidobacterium in the gut of healthy Japanese people," *PLOS ONE*, vol. 13, no. 10, p. e0206189, Oct. 2018, doi: 10.1371/journal.pone.0206189.

[51] Y. Qin *et al.*, "Author Correction: Combined effects of host genetics and diet on human gut microbiota and incident disease in a single population cohort," *Nature Genetics*, vol. 56, no. 3, pp. 554–554, Feb. 2024, doi: 10.1038/s41588-024-01693-y.

[52] P. Gerbault *et al.*, "Evolution of lactase persistence: an example of human niche construction," *Philosophical Transactions of the Royal Society B: Biological Sciences*, vol. 366, no. 1566, pp. 863–877, Mar. 2011, doi: 10.1098/rstb.2010.0268.

[53] N. Y. Baffour-Awuah *et al.*, "Functional Significance of Single Nucleotide Polymorphisms in the Lactase Gene in Diverse US Patients and Evidence for a Novel Lactase Persistence Allele at −13909 in Those of European Ancestry," *Journal of Pediatric Gastroenterology and Nutrition*, vol. 60, no. 2, pp. 182–191, Feb. 2015, doi: 10.1097/mpg.0000000000000595.

[54] N. S. Enattah *et al.*, "Independent Introduction of Two Lactase-Persistence Alleles into Human Populations Reflects Different History of Adaptation to Milk Culture," *The American Journal of Human Genetics*, vol. 82, no. 1, pp. 57–72, Jan. 2008, doi: 10.1016/j.ajhg.2007.09.012.

[55] H. Y. Hassan *et al.*, "Genetic diversity of lactase persistence in East African populations," *BMC Research Notes*, vol. 9, no. 1, Jan. 2016, doi: 10.1186/s13104-015-1833-1.

[56] G. D. Smith *et al.*, "Lactase persistence-related genetic variant: population substructure and health outcomes," *European Journal of Human Genetics*, vol. 17, no. 3, pp. 357–367, Sep. 2008, doi: 10.1038/ejhg.2008.156.

[57] Y. Deng, B. Misselwitz, N. Dai, and M. Fox, "Lactose Intolerance in Adults: Biological Mechanism and Dietary Management," *Nutrients*, vol. 7, no. 9, pp. 8020–8035, Sep. 2015, doi: 10.3390/nu7095380.

[58] G. Bonetti *et al.*, "Polymorphisms, diet and nutrigenomics," *Journal of Preventive Medicine and Hygiene*, vol. 63, no. 2S3, pp. E125–E125, Oct. 2022, doi: 10.15167/2421-4248/jpmh2022.63.2S3.2754.

[59] R. Mattar, Mazo, and Carrilho, "Lactose intolerance: diagnosis, genetic, and clinical factors," *Clinical and Experimental Gastroenterology*, p. 113, Jul. 2012, doi: 10.2147/ceg.s32368.

[60] J. C. K. Wells, E. Pomeroy, and J. T. Stock, "Evolution of Lactase Persistence: Turbo-Charging Adaptation in Growth Under the Selective Pressure of Maternal Mortality?," *Frontiers in Physiology*, vol. 12, Aug. 2021, doi: 10.3389/fphys.2021.696516.

[61] S. J. Virolainen, A. VonHandorf, K. C. M. F. Viel, M. T. Weirauch, and L. C. Kottyan, "Gene–environment interactions and their impact on human health," *Genes & Immunity*, vol. 24, no. 1, pp. 1–11, Dec. 2022, doi: 10.1038/s41435-022-00192-6.

[62] Nhgri, "Gene Environment Interaction," *Genome.gov*. https://www.genome.gov/genetics-glossary/Gene-Environment-Interaction

[63] R. Ottman, "Gene–Environment Interaction: Definitions and Study Design," *Preventive Medicine*, vol. 25, no. 6, pp. 764–770, Nov. 1996, doi: 10.1006/pmed.1996.0117.

[64] A. Liebert *et al.*, "World-wide distributions of lactase persistence alleles and the complex effects of recombination and selection," *Human Genetics*, vol. 136, no. 11–12, pp. 1445–1453, Oct. 2017, doi: 10.1007/s00439-017-1847-y.

[65] R. K. Montgomery, H. A. Büller, E. H. H. M. Rings, and R. J. Grand, "Lactose intolerance and the genetic regulation of intestinal lactase-phlorizin hydrolase," *The FASEB Journal*, vol. 5, no. 13, pp. 2824–2832, Oct. 1991, doi: 10.1096/fasebj.5.13.1916106.

[66] M. Rossi *et al.*, "Lactase persistence versus decline in human adults: Multifactorial events are involved in down-regulation after weaning," *Gastroenterology*, vol. 112, no. 5, pp. 1506–1514, May 1997, doi: 10.1016/s0016-5085(97)70031-3.

[67] F. L. C. Jackson, "Geneâ€"environment interactions in human health: case studies and strategies for developing new paradigms and research methodologies," *Frontiers in Genetics*, vol. 5, Aug. 2014, doi: 10.3389/fgene.2014.00271.

[68] P. Anagnostou *et al.*, "Tracing the distribution and evolution of lactase persistence in Southern Europe through the study of the T-13910 variant," *American Journal of Human Biology*, vol. 21, no. 2, pp. 217–219, Dec. 2008, doi: 10.1002/ajhb.20851.

[69] E. Heyer *et al.*, "Lactase Persistence in Central Asia: Phenotype, Genotype, and Evolution," *Human Biology*, vol. 83, no. 3, pp. 379–392, Jun. 2011, doi: 10.3378/027.083.0304.

[70] T. G. K. Jensen, A. Liebert, R. Lewinsky, D. M. Swallow, J. Olsen, and J. T. Troelsen, "The −14010*C variant associated with lactase persistence is located between an Oct-1 and HNF1α binding site and increases lactase promoter activity," *Human Genetics*, vol. 130, no. 4, pp. 483–493, Feb. 2011, doi: 10.1007/s00439-011-0966-0.

[71] G. Pratelli *et al.*, "Cow's Milk: A Benefit for Human Health? Omics Tools and Precision Nutrition for Lactose Intolerance Management," *Nutrients*, vol. 16, no. 2, p. 320, Jan. 2024, doi: 10.3390/nu16020320.

[72] P. Varjú, B. Ystad, N. Gede, P. Hegyi, D. Pécsi, and J. Czimmer, "The role of small intestinal bacterial overgrowth and false positive diagnosis of lactose intolerance in southwest Hungary—A retrospective observational study," *PLOS ONE*, vol. 15, no. 5, p. e0230784, May 2020, doi: 10.1371/journal.pone.0230784.

[73] A. Ghafoor, T. Karunaratne, and S. S. C. Rao, "Bacterial overgrowth and lactose intolerance: how to best assess," *Current Opinion in Clinical Nutrition & Metabolic Care*, vol. 25, no. 5, pp. 334–340, Jul. 2022, doi: 10.1097/mco.0000000000000861.

[74] W. J. Schnedl *et al.*, "Serum Diamine Oxidase Values, Indicating Histamine Intolerance, Influence Lactose Tolerance Breath Test Results," *Nutrients*, vol. 14, no. 10, p. 2026, May 2022, doi: 10.3390/nu14102026.

[75] T. Di Rienzo *et al.*, "Lactose intolerance: from diagnosis to correct management," *European review for medical and pharmacological sciences*, vol. 17 Suppl 2, pp. 18–25, 2013.

[76] C. Santonocito *et al.*, "Lactose intolerance genetic testing: Is it useful as routine screening? Results on 1426 south–central Italy patients," *Clinica Chimica Acta*, vol. 439, pp. 14–17, Jan. 2015, doi: 10.1016/j.cca.2014.09.026.

[77] M. C. E. Lomer, G. C. Parkes, and J. D. Sanderson, "Review article: lactose intolerance in clinical practice – myths and realities," *Alimentary Pharmacology & Therapeutics*, vol. 27, no. 2, pp. 93–103, Oct. 2007, doi: 10.1111/j.1365-2036.2007.03557.x.

[78] C. L. Brasen, L. Frischknecht, D. Ørnskov, L. Andreasen, and J. S. Madsen, "Combination of real-time PCR and sequencing to detect multiple clinically relevant genetic variations in the lactase gene," *Scandinavian Journal of Clinical and Laboratory Investigation*, vol. 77, no. 1, pp. 60–65, Dec. 2016, doi: 10.1080/00365513.2016.1261408.

[79] C. Büning *et al.*, "Introducing Genetic Testing for Adult-Type Hypolactasia," *Digestion*, vol. 71, no. 4, pp. 245–250, 2005, doi: 10.1159/000087050.

[80] T. K. Nilsson and L. A. Olsson, "Simultaneous genotyping of the three lactose tolerance-linked polymorphisms LCT –13907C>G, LCT –13910C>T and LCT –13915T>G with PyrosequencingTM technology," *Clinical Chemistry and Laboratory Medicine*, vol. 46, no. 1, Jan. 2008, doi: 10.1515/cclm.2008.015.

[81] R. Mattar, M. do Socorro Monteiro, C. A. Villares, A. F. dos Santos, and F. J. Carrilho, "Single nucleotide polymorphism C/T-13910, located upstream of the lactase gene, associated with adult-type hypolactasia: Validation for clinical practice," *Clinical Biochemistry*, vol. 41, no. 7–8, pp. 628–630, May 2008, doi: 10.1016/j.clinbiochem. 2008.01.006.

[82] C. Högenauer, H. F. Hammer, K. Mellitzer, W. Renner, G. J. Krejs, and H. Toplak, "Evaluation of a new DNA test compared with the lactose hydrogen breath test for the diagnosis of lactase non-persistence," *European Journal of Gastroenterology & Hepatology*, vol. 17, no. 3, pp. 371–376, Mar. 2005, doi: 10.1097/00042737-200503000-00018.

[83] A. Rollán *et al.*, "Diagnóstico de intolerancia a la lactosa en adultos: rendimiento comparativo de la clínica, test de hidrógeno espirado y test genético," *Revista médica de Chile*, vol. 140, no. 9, pp. 1101–1108, Sep. 2012, doi: 10.4067/s 0034-98872012000900001.

[84] P. R. L. Ponte *et al.*, "Clinical evaluation, biochemistry and genetic polymorphism analysis for the diagnosis of lactose intolerance in a population from northeastern Brazil," *Clinics*, vol. 71, no. 2, pp. 82–89, Feb. 2016, doi: 10.6061/ clinics/2016(02)06.

[85] M. S. Facioni, B. Raspini, F. Pivari, E. Dogliotti, and H. Cena, "Nutritional management of lactose intolerance: the importance of diet and food labelling," *Journal of Translational Medicine*, vol. 18, no. 1, Jun. 2020, doi: 10.1186/s 12967-020-02429-2.

[86] A. Szilagyi and N. Ishayek, "Lactose Intolerance, Dairy Avoidance, and Treatment Options," *Nutrients*, vol. 10, no. 12, p. 1994, Dec. 2018, doi: 10.3390/nu10121994.

[87] M. Porzi, K. J. Burton-Pimentel, B. Walther, and G. Vergères, "Development of Personalized Nutrition: Applications in Lactose Intolerance Diagnosis and Management," *Nutrients*, vol. 13, no. 5, p. 1503, Apr. 2021, doi: 10.3390/nu 13051503.

[88] D. L. Swagerty Jr, A. D. Walling, and R. M. Klein, "Lactose intolerance," *American family physician*, vol. 65, no. 9, pp. 1845–50, May 2002.

[89] P. Usai-Satta, "Lactose malabsorption and intolerance: What should be the best clinical management?," *World Journal of Gastrointestinal Pharmacology and Therapeutics*, vol. 3, no. 3, p. 29, 2012, doi: 10.4292/wjgpt.v3.i3.29.

[90] J. K. Hodges, S. Cao, D. P. Cladis, and C. M. Weaver, "Lactose Intolerance and Bone Health: The Challenge of Ensuring Adequate Calcium Intake," *Nutrients*, vol. 11, no. 4, p. 718, Mar. 2019, doi: 10.3390/nu11040718.

[91] G. J. Santos, R. Rocha, and G. O. Santana, "Lactose intolerance: what is a correct management?," *Revista da Associação Médica Brasileira*, vol. 65, no. 2, pp. 270–275, Feb. 2019, doi: 10.1590/1806-9282.65.2.270.

[92] P. Mansueto, A. Seidita, A. D'Alcamo, and A. Carroccio, "Role of FODMAPs in Patients With Irritable Bowel Syndrome," *Nutrition in Clinical Practice*, vol. 30, no. 5, pp. 665–682, Feb. 2015, doi: 10.1177/0884533615569886.

[93] E. V. Gorduza, L. L. Indrei, and V. M. Gorduza, "Nutrigenomics in postgenomic era," *Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi*, vol. 112, no. 1, pp. 152–64, 2008.

[94] G. M. Buzás, "A laktózintoleranciáról: Múlt és jelen – I. rész," *Orvosi Hetilap*, vol. 156, no. 38, pp. 1532–1539, Sep. 2015, doi: 10.1556/650.2015.30261.

[95] B. Misselwitz, "Lactose Intolerance: New Insights due to Blinded Testing?," *Digestion*, vol. 90, no. 1, pp. 72–73, 2014, doi: 10.1159/000365144.

[96] A. R. Geoghegan and D. Webb, "Successful Treatment With Phenobarbital Following Lactase Supplementation in an Infant With Lactose Intolerance," *Annals of Pharmacotherapy*, vol. 51, no. 10, pp. 928–928, Aug. 2017, doi: 10.1177/1060028016677093.

[97] A. K. Campbell and S. B. Matthews, "Darwin's illness revealed," *Postgraduate Medical Journal*, vol. 81, no. 954, pp. 248–251, Apr. 2005, doi: 10.1136/pgmj.2004.025569.

[98] C. O. Mărginean, L. E. Meliţ, S. Mocanu, and M. O. Mărginean, "Inflammatory bowel diseases," *Medicine*, vol. 96, no. 11, p. e6329, Mar. 2017, doi: 10.1097/md.0000000000006329.

[99] G. Adler, M. A. Adler, A. Valjevac, and E. Kiseljakovic, "First Bosnian study of LCT-13910C>T and-22018G>A single nucleotide polymorphisms associated with...," *unknown*, Oct. 14, 2017. https://www.researchgate.net/publication/320403765_First_Bosnian_study_of_LCT-13910CT_and-22018GA_single_nucleotide_polymorphisms_associated_with_adult-type_lactose_intolerance