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Epigenetics and Epidemiology of Lactase Persistence

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ABSTRACT: In adult mammals, the inability to digest lactose due to lactase non-persistence or adult-type hypolactasia, is relatively common after the weaning stage. However, there is a fraction of the adult population who continue to exhibit lactase persistence, sparking the interest of many scientists. The epigenetics of lactase persistence and non-persistence differ greatly, as well as the factors affecting the genotype and phenotype. Other studies used genome editing technology, genomic DNA isolation, genomic DNA methylation analysis and more to investigate the factors determining the LCT gene expression. Here, analyzed field data highlighted these significant findings together to discuss the epigenetics of lactase non-persistence. This paper will review the epigenetics of lactase non-persistence and lactase persistence and the factors influencing expression and modification on a molecular level. Findings regarding nutritional and environmental factors, as well as differences in frequencies in various continents will also be displayed. The aim of this article is to deepen the understanding of the epigenetic mechanisms revolving around lactase non-persistence, factors like mutations in the -13910 allele, and analyze past and recent articles to inform on epigenetic targets and implications as future treatments.

KEYWORDS: Biomedical and Health Sciences; Genetics and Molecular Biology of Disease; Epigenetics; Lactase Persistence; Single Nucleotide Polymorphism.

Introduction

From infancy to adulthood, the genetic evolution of lactase production shapes the capacity of a human to digest lactose. Interestingly, a large amount of the human population develops lactase non-persistence (LNP), or adult-type hypolactasia.

In the small intestine, there is a critical enzyme called lactase responsible for splitting and hydrolyzing lactose. The resulting monosaccharides, glucose and galactose, are essential for babies, as their primary source of nourishment and nutrition is milk from their mother, which contains an abundance of lactose, the major carbohydrate component.[1] As aging continues in some humans, physiological decrease of the lactase (LCT) gene occurs, leading them to be unable to break down lactose.[2] This is known widely as LNP.[3] In fact, 65% of humans around the world have LNP, as this trait is the ancestral state of lactase regulation.[1,4] However, it was discovered that LCT mRNA, and thus LCT activity, remained high in exceptional populations who continue to exhibit lactase persistence (LP), an autosomal dominant trait, throughout adult life.[4] Generally, LP is more frequent throughout Europe, compared to other populations.[5] DNA sequence variations situated upstream of LCT have currently been noted among human adults to cause variations within individuals. Within intron 13 of the minichromosome maintenance complex component 6 (*MCM6*) gene, specifically, *in vitro* studies proved that there is a single nucleotide polymorphism (SNP) located 13,910 bp upstream the LCT gene, emerging as a crucial factor associated with LP or LNP in European populations, where the T-13910 allele represents LP.[6,7] *MCM6* codes for proteins in the crypts of the intestines, where expression and DNA replication occurs, but is not limited to, the small intestine.[8] The *MCM6* exon 13-intron 13 site has been identified as an important modulator influencing the LCT transcriptional gradient, particularly its establishment and sustenance.[9] Other polymorphisms nearby have also been found to be determinants of LCT production. However, in Africa, this SNP is not associated with LP or LNP.[10]

This article will review the epigenetics of LP and LNP, modifications, and influencing factors. This review will enhance the biological and molecular understanding of LP and LNP, inform with old and recent studies, and possibly inspire development of new treatments involving this disorder. As opposed to current articles, which specify only a few factors and modifications, this paper will compile all existing key information into this comprehensive article by investigating the differences of SNPs in those with LNP, exploring several genetic modifications involved, discussing all major detected variations within different countries, and explaining possible nutritional and environmental factors previously discovered.

Genetic Association with LP:

LNP is a very common condition within the human population, also widely known as lactose intolerance. As an autosomal recessive trait, it is characterized by a reduction in lactase activity in the intestinal lumen following the weaning stage.[12] These subjects are unable to hydrolyze a large amount of the lactose consumed into glucose and galactose, resulting in an osmotic load within the small intestine. This triggers an influx of water into the intestinal lumen, accelerating the movement of contents within the digestive tract, as shown in Figure 1. It is genetically determined whether lactase production would slowly down-regulate as one ages. Essentially, LNP is the ancient phenotype since it also occurs in other mammals, like rabbits and rats.[13] LNP causes primary lactose malabsorption,[14] but

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there are other cases where secondary lactose malabsorption is caused because the reasons are not genetically determined LNP. For example, celiac disease, microbial infections, and conditions that affect the intestinal villi can cause LNP.[15] In Northern Europe, the genetic combination for LNP would be homozygous CC.

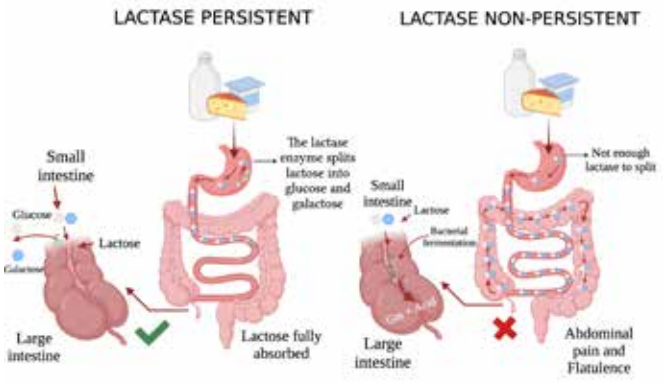

Figure 1: Diagram of LP digestive system compared with LNP digestive system. Lactose is fully absorbed in persistent individuals, while there is not enough lactase to absorb lactose in non-persistent individuals. Created with BioRender.com.

LNP has many symptoms that might not occur in every subject with this condition. Reported symptoms include bloating, flatulence, diarrhea and abdominal pain after a relatively high amount of lactose-containing dairy product is consumed. Since individuals carrying this inability have low enzymatic levels,[2] LNP is optimally diagnosed using enzymatic measurement of the subject using intestinal biopsies. However, it is quite invasive, and inefficient considering the large percent of the human population with LNP. Instead, blood glucose tests or hydrogen breath tests are used to diagnose LNP.[1,16] These lactose tolerance tests begin with the subject consuming large amounts of lactose after an overnight fast. Then, blood glucose levels or hydrogen levels are taken in certain time intervals after consuming. If blood glucose increases, it suggests that lactose is being digested and absorbed properly, as the lactase enzyme hydrolyzes lactose into glucose and galactose. If blood glucose does not change, it suggests probably LNP. Meanwhile, an increase in hydrogen in one's breath indicates and reflects fermentation of lactose in the colon, meaning the individual carries LNP. However, these tolerance tests are not always accurate, though the hydrogen test has proven to be more effective.[1,16]

As one ages, LNP becomes more apparent if the subject carries it, and certain SNPs have been discovered to have significant association with it. Though, it is different depending on the ethnicity and ancestry of the individual. SNPs associated with LP enhance LCT transcription compared to LNP, at sites like the Oct-1 and HNF1a binding sites (refer to Figure 2). They are commonly seen and involved in LP enhancers, which will be explained in greater detail below where different specific SNPs are mentioned.[8]

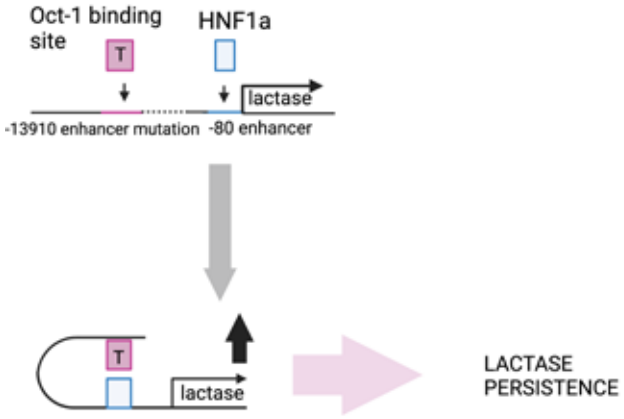

Figure 2: LP enhancer diagram displaying -13910*T creating a binding site for the transcription factor Oct-1, forming a complex with HNF1α. It bends the DNA and helps greatly to initiate transcription. Modified from Ajna S. Rivera and Colwin Yee, University of the Pacific. Created with BioRender.com.

Epidemiology

SNPs Associated with LP in Europe:

In Europe, most adults are able to consume dairy products without discomfort. In north-western Europe, LP is at highest frequency at more than 95%, decreasing to the south and east.[1,6] Notably, the SNP 13,910 base pairs upstream of the LCT gene are strongly linked with LP. The SNP involves a single C to T transition in intron 13 of the MCM6 gene that encodes proteins in the intestinal tract. This particular site has been identified as an important modulator influencing the LCT transcriptional gradient,[9] binded to the Oct-1 site where it has an enhancer effect. Oct-1 expression only stimulates gene expression from the C/T-13910 variant and lactase-phlorizin hydrolase (LPH) promoter constructs when it is in the presence of co-expressed HNF1a.[7] In a previous article, functional analysis of the -13910 enhancer region and LPH promoter region was done, where co-expression of Oct-1 and HNF1a proved to significantly increase the -13910*T enhancer activity to about 133-fold compared to the proximal promoter alone, Figure 2 showing the process.

The prevalence of the -13910*T allele exhibits regional differences among Europe. In eastern and southern Europe, the frequency ranges from 6% to 36%, while in central and western Europe, it ranges from 56% to 67%.[17] Moreover, in Scandinavia and the British Isles, the frequency is even higher, ranging from 73% to 95%.[11,17] Meanwhile, LP frequency exhibits a similar trend; with rates of 15% to 54% in eastern and southern Europe, 62% to 86% in central and western Europe, and 89% to 96% in the Scandinavia and the British Isles, thus making the -13910*T variant, a very reliable predictor of LP in the European population. Additionally, identification of this variant in the Finnish population was also made. In a past experiment, after genotyping 1902 Finnish individuals, 18% were homozygous CC, 47% were heterozygous CT, and 35% were homozygous TT.18 The -22018 position was also discovered to be associated significantly in Finland through sequence analysis.[6] This SNP, situated approximately 22 kb upstream of the LCT gene, is located in intron 9 of the MCM6 gene,

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and exhibits complete co-segregation with the LP trait. The genotype associated with LP is -22018*A. The -13910*T and -22018*A alleles were found to be associated with LP at rates of 100% and 97%, respectively.[6,19]

Estimates regarding the age of the -13910*T variants are consistent with the proposed timeline for the emergence of dairying practices. The age profiles of slaughtering practices in sheep, goats, and cattle hint at the presence of dairying in the early stages of the Neolithic period in southeastern Europe.[20] Additionally, allelic age estimates prove that the -13910*T variant was rare or absent among early farming populations, aligning with observations supporting that LP only became increasingly frequent after the emergence of dairying, opposing the "reverse-cause" hypothesis which states that dairying occurred after LP evolved.[21,22] In general, Europe displays a reduced amount of variants contributing to LP, with the common -13910*C/T and -22018*G/A variants having tight associations with LP.[6]

SNPs Associated with LP in Africa:

In the continent of Europe, it was proved that a CT polymorphism 13.9kb upstream of the LCT gene was strongly linked with LP in a group of Finnish subjects.[6] However, Mulcare and colleagues were not able to discover a trend between the T allele and African populations after typing the SNP in an abundance of individuals in seven different African countries and 20 cultural groups.[16] In fact, it was relatively rare, even though >25% of the population display the LP phenotype. Consequently, comparisons of the genotype and phenotype frequencies repeatedly show that the -13910*T allele cannot explain LP in Africa. However, past studies have explained and revealed several other SNP variants nearby to this allele, which have been proven to be connected to LP in separate regions in East Africa.

The first notable SNP to be associated with LP is the -14010G>C variant. It was shown that the -14010 allele position is also located in an Oct-1 binding site similar to the -13910 position, indicating that Oct-1 is a valuable factor in LP phenotypes.[8] Oct 1 can form a complex with HNF1a, a transcription factor with a binding site just upstream of the LCT coding region. Gel shift assays revealed that the -14010*C variant exhibits a notably higher binding affinity to the Oct-1 site compared to -14010*G, the G>C nucleotide, increasing the binding. Furthermore, it was also proved using deletion analysis that -14010*C was a significantly stronger enhancer of the LCT promoter, thus being associated with LP, unlike the -14010*G, which is the ancestral allele. It was even suggested to be a causal mutation causing LP in Africans. The -14010*C variant was only identified in eastern and southern Africa, highly prevalent among Afroasiatic-speaking (42.1%), Nilo-Saharan-speaking (38.3%), and Niger-Kordofanian-speaking (25%) groups.[10]

In Africa, the -13915*G variant, another noteworthy allele also situated within the Oct-1 motif, is associated with LP as well, positioned a mere 5 base pairs from the European LP variant C/T-13910.[23] The -13915*G variant was detected in populations in northern Africa (9.4% frequency), central Africa (<1%), and eastern Africa (3.9%), excluding Tanzania where it was not observed. To add on, it was identified in the Arabian Peninsula (4.0%) but was absent in populations from western and southern Africa.[10] Interestingly, another variant C/G–13907, 3 bp downstream from the C/T–13910 was identified, however it was only discovered in a mere 2 individuals out of 124 samples.[23] The highest frequencies of this allele occur in Ethiopia and Sudan (refer to Table 1).[1,23] Moreover, the -13907*G variant exhibited a highly restricted geographic distribution, being only exclusive to northern and eastern Africa, except Tanzania, with no occurrences being observed outside of Africa.[10]

Though there have been no reports of frequency of the -13910*T allele in Africa, it is important to note the interbreeding leading to genetic admixture between Europeans and Africans in the past, which is believed to have affected evolution and the results concluded today because of several previously isolated profiles being mixed together. There are lots of variations in LP frequency in Africa and complex distributions that could possibly be influenced by this, but more research needs to be conducted to prove it.[16]

SNPs Associated with LP in Countries in Asia:

In the continent of Asia, there are several different SNPs affiliated with LP and its phenotype. It generally has a low LP frequency, with East Asia near 0%, but there are various countries in Asia that are exceptions, displaying certain SNPs.

In Saudi Arabia, the -13915*G SNP, where T>G, was the most frequent variant associated with LP. In fact, it is the geographic location of the highest observed frequency of this allele (refer to Table 1 for more information on this SNP). In an experiment by Imtiaz and colleagues, of the 432 neonatal samples taken across 5 different districts, 332 (76.9%) had the hypothetical LP –13915*G allele.[24] The –13915*G variant was found at a high frequency ranging from 72% to 88% among Saudis and correlated well with the reported frequency of LP in these populations,[23] proving it to be closely associated with and a good predictor of LP. Recent and past data about the distribution of the 13915*G variants in African and Arab populations may suggest that LP could have likely been brought from Africa to the Arabian Peninsula.[24,25]

In Iran, the frequency of LP is especially low, averaging 9.5%, being much lower than populations in Central Asia (14%), Pakistan (38%), Afghanistan (19%), Turkey (30%), Saudi Arabia (81%), as well as Jordan (76%).[26-28] The most recent genetic screening in Iran identified three LP variants: -22018*A, –13915*G, in addition to –13910*T at a rate of 10%.[23] It was additionally noted that all three variants were carried only in heterozygotes and no homozygotes were detected.[26] This is most likely because ancestrally, LP was very rare in Asia, but homozygotes carrying the LP trait created heterozygotes, and natural selection took part in the process. The most frequent variant in the Iranian population was the –22018*A allele, as 11.25% of the population carried it. This allele was found in the Arab population, with 19.23% of the population carrying it.[26] However, the Lur population had a low amount of this variant detected at 4.16%. Excluding the Gilaks, the –13910*T variant was discovered in most populations, ranging from 4.16% to 7.69%. The –13915*G allele was

only found in one single individual, each from the Persians (n = 78, 1.28%) as well as the Arabs (n = 26, 3.84%), respectively, in a past experiment.[26] The co-occurrence of – 13910*T and – 22018*A was observed in all of the populations, with the exceptions of the Lurs and Gilaks, where these two variants are proven to be greatly associated with LP.[26]

In the Indian subcontinent, the -13910*T allele was observed to be common, similar to European populations. Not only was it the most frequent, it also had the widest distribution in India. The frequency ranges from 0.8% among the Tibeto-Burman speakers to 18.4% among Indo-European speakers, west India showing the highest frequency of -13910*T with an average countrywide frequency of 10.3%.[29]

Overall, Asia has a diversity of variants being causal of LP and LNP; -22018*A, -13910*T, -13915*, and possibly even more that are too rare to be mentioned.

Table 1: Details of various SNPs associated with LP. Note that there are many other alleles associated with LP that are relatively rarer within the 130 bp region where research is still ongoing. Modified from "Lactose Digestion and the Evolutionary Genetics of Lactase Persistence" by Catherine J.E. Ingram and colleagues. Created with BioRender.com.

Position of SNP (bps upstream of LCT)	Substitution (ancestral allele first)	rs Number	Haplotype	Geographic location of highest observed frequency
13,910	C > T	rs4988235	A	Europe
14,010	G > C	Not included in dbSNP	B	Kenya/ Tanzania
13,915	T > G	rs41380347	C	Saudi Arabia
13,907	C > G	rs41525747	A	Ethiopia/ Sudan
22,018	G > A	rs182549	B	Europe

Nutritional and Environmental Factors Possibly Affecting LP in Specific Areas:

Generally, it was discovered that prevalence of lactase non-persistence was higher in populations with more extreme environmental conditions, where livestock was impossible to raise due to higher occurrence of endemic cattle diseases.[30] Moreover, it was noticed that the evolution of LP necessitates the prior domestication of dairy animals.[1,30] However, this does not apply to all pastoral groups. Rather, LP rates are specifically expected to be high in contexts where milk is not entirely processed into low-lactose products and/or in populations experiencing significant dietary stress.[31] In relation to this, it was also demonstrated that LP exhibits a stronger correlation with the quantity of fresh milk consumed, instead of the proportion of pastoralism in the population, although reliable data on such variables may not be consistently available for all places. For example, certain African ethnic groups proved to be exceptions from the typical LP distribution, exhibiting elevated frequencies. These groups successfully navigated challenging environmental conditions by adopting a pastoralist lifestyle, where milk was consumed in lieu of water when it was scarce.[28,32]

There also could have been major differences in diet among different populations during the Neolithic, where some European agro pastoral groups endured food shortages when they transitioned to agriculture. The previous explanation accounts for the notable intermediate LP frequency observed in populations situated near the Mediterranean in addition to the northern Middle East (39%).[33] Though dairying animals were initially domesticated in these areas, these populations typically consume about 102 liters of fresh milk per person annually and convert a significant amount of milk into cheese (averaging 38%), aligning with the observed LP frequency.[28] In contrast, Northern and Central Europeans display significantly higher fresh milk consumption per year (489 L per person), as well as a lower transformation rate into cheese (18%), and consequently, a notably greater LP frequency (91%).[28,31] However, if all populations had access to milk processing techniques, it raises intriguing questions on why certain populations, despite several ongoing intestinal discomforts and symptoms, continue to favor fresh milk when cultural adaptation of milk processing existed, which contained more cost-effective vitamins and minerals.

Additionally, archeological evidence tells us that cattle domestication originated not only in the south of Egypt approximately 7,700 to as late as 9,000 years ago but also in the Middle East around 7,000 to 8,000 years ago. This data consistently aligns with the estimated age of -13910*T allele found in Europeans, which is about 8,000-9,000 years. Recently, the estimated age range of 2,700 to 6,800 years for the -14010*C allele in African populations corresponds with previous archeological data suggesting that the spread of pastoralism did not occur south of the Sahara and reach northern Kenya until approximately 4,500 years ago nor did it spread into southern Kenya or northern Tanzania until around 3,300 years ago,[19] so pastoralism must be a major influencing factor.

From these pieces of data, it can be inferred that nutritional and environmental factors are very significant in LP frequencies in different places, especially pastoralism and cultural adaptations.

■ Conclusion and Perspective

In conclusion, LP has been studied greatly so far, and is a leading example of natural selection in humans. It is also a significant example of SNPs being regulatory elements, affecting the genotype and phenotype of individuals.

There have been many trends within ethnic populations involving which SNP is causal of lactase non-persistence, the most common one being the -13910T>C allele. However, recent research concluded that there were several SNPs important to LP in different areas around the world, like the -14010 position, which is frequently seen in Africa. There are also several reasons like pastoralism explaining why some areas

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like East Asia have LP frequency near 0%, while Northern Europe has LP frequency of nearly 100%. These topics still require further research, however it is intriguing to many, especially with new findings and important information. In the present, there are not many treatments in medicine targeting lactase non-persistence as it is very common, genetic, and the ancient phenotype. However, future treatment plans can be aided with this comprehensive article, as potential treatment targets can be manipulated for investigation and trials. Moreover, the mentioned SNPs can be utilized for early diagnoses, and even create possible genetic therapies targeting certain ethnic groups and populations. In addition, possible genetic therapies could be able to target the SNP that the subject carries. However, these treatments still need lots of research. The nutritional and environmental factors mentioned can be useful in future research and understanding the LP frequencies of countries.

This area still requires further research, and more SNPs associated with LP could exist. Though it is genetic and so far has no cure, families could benefit from knowing all the different modifications to be better equipped for diagnoses of LNP. Moreover, diseases that cause secondary LNP could potentially help us learn more about this common disorder.

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