Original Research Paper

Volume-9 | Issue-12 | December - 2019 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Medicine

THE GENETIC AND EPIGENETIC BASIS OF LACTOSE INTOLERANCE IN THE ADULTHOOD

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ABSTRACT The *LCT* gene encodes the synthesis of lactase; gene expression and lactase activity are high in newborns, but after ablation they become depressed; thus, the adult has lactose intolerance due to little or no lactase activity. The *MCM6* gene contains an enhancer region with profound effects on *LCT* expression. A SNP (C>T) located upstream from the start site of the transcription of the *LCT* gene at position -13910 is the main responsible of lactase persistence in some people because the T-allele is not subject of methylation, which is the main mechanism of silencing of the *LCT* gene. Knowledge about whether lactose intolerance has this origin is important to guide alimentary interventions.

KEYWORDS : Lactose, Lactase, Lactase Persistence, *LCT Gene, MCM6 Gene*

Lactose is a disaccharide formed by galactose and glucose, linked by a β1-4 glycosidic bond, constituting the main sugar in milk. Lactose is enzymatically hydrolyzed to free glucose and galactose in order to be absorbed by the intestinal microvilli; the enzyme lactase, produced by the brush border cells of the microvilli of the small intestine, is responsible for this hydrolytic process. The *LCT* gene encodes the synthesis of lactase; gene expression and lactase activity are high in newborns, but after ablation they become depressed, declining to a 0-10% of the child levels in the adulthood. Thus, the adult has the so-called adult-type hypolactasia and lactose intolerance due to little or no lactase activity. When milk and dairy products are consumed, gastrointestinal symptomatology such as bloating, flatulence, vomiting and diarrhea arises due to lactose malabsorption and fermentation by gut microbiota, as well as fluid shifts caused by formation of an osmotic gradient.

However, in a large number of people the expression of the *LCT* gene is not depressed after childhood and lactase activity continues to exist in adulthood, a state known as persistence of lactase; this phenotype appeared about 8,000 years ago and gave rise to selective advantage in milk-consuming pastoralist communities in northern Europe and in nomadic groups in Africa and the Middle East; this phenotype is inherited as a dominant trait.

MOLECULAR MECHANISM OF LACTASE PERSISTENCE

The persistence of lactase is genetically determined. The human *LCT* gene is located in the q21 region of chromosome 2. *MCM6* is a gene located upstream of *LCT*; it contains an amplifying sequence which, through interaction with the *LCT* promoter region, acts as a positive regulator inducing a high rate of transcription. In this way, this enhancer in *MCM6* is the main responsible for the persistence of lactase [1]. *MCM6* gene contains several single nucleotide polymorphisms (SNPs), one of which, named (rs4988235), has profound effects on *LCT* expression.This SNP consists in the change of the C by the T allele, which originates the homozygous genotypes CC, TT and the CT heterozygous genotype. This SNP is located upstream at position -13910 from the start site of the transcription of the *LCT* gene. As a dominant trait, homozygous TT and heterozygous CT individuals present lactase persistence. The global prevalence the T allele carriers is of 25%, according to data from the 1000 Genomes consortium, the most detailed basis of genetic variability (www.internatio nalgenome.org/). However, the prevalence of this allele is highly variable in the different population groups around the world: the highest frequency of the T allele is found in European populations with values of 72% in Great Britain and 59% in Finland. On the other hand, is practically absent in most of Japanese Chinese and African populations. In South Asia, Punjabi people of Lahore frequency is 27%, and in Latin América Colombians and Peruvians have frequencies of 31 and 21% respectively. In Gujarati Indians residing in Houston, Tx., the value is 14%.

In the adult people, the T allele is responsible for the persistence of lactase. The silencing of the *LCT* gene after ablactation is epigenetic in nature and involves the methylation of cytosines in both the *MCM6* and *LCT* genes. As cytosine is the only base in DNA susceptible of this epigenetic modification, the foregoing determines that the amplifying region responsible for the high expression of the *LCT* gene, when methylated (which occurs by the time of the ablactation), loses its correct interaction with the promoter region of *LCT*, which results in a weak promoter and poor *LCT* expression; on the contrary, the carriers of the T instead of the C allele in the -13910 site are not susceptible to this epigenetic suppression, since T is not modifiable by the addition of methyl groups. Consequently, carriers of one or two T alleles have strong promoters and maintain high expression of *LCT* [1-3] (Figure 1).

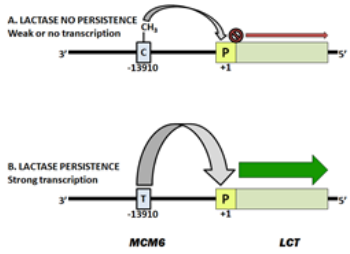

Figure 1. Epigenetic mechanism of silencing of the LCT gene.

Lactase persistence is associated to the T allele in *MCM6.*

The gene silencing of *LCT* is also dependent on the epigenetic state of the chromatin, which is responsible in the early childhood of its lack of expression in sites other than intestinal mucosa. In this way, strong epigenetic tags corresponding to gene silencing such as H3K27me3 are localized throughout the *LCT* gene in most tissues and, on the contrary, expression associated tags, such as H3K36me3 are found with low intensity or absent (Figure 2).

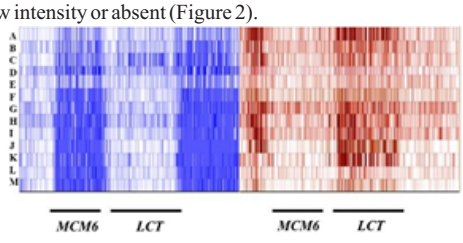

Figure 2. Epigenetic marks in the *LCT* and *MCM6* genes.

The trimethylation of lysine 36 of histone 3 (H3K36me3, blue panel) is

found in active chromatin, whereas trimethylation of lysine 27 of histone 3 (H3K27me3, red panel) is found in silenced chromatin. The intensity of the color corresponds to the intensity of the mark. In the *LCT* gene both marks correspond to gene silencing. Tissues from A through M are: small intestine, colonic mucosa, duodenal mucosa, esophagic mucosa, pancreas, monocytes, amnios, prefrontal cortex, gastric mucosa, adipose tissue, fetal adrenals, fetal brain, mamary tissue. (Figure created with the Roadmap Epigenome Browser v1.19, of the Washington University at St. Louis, Mo. (http://epigenome gateway.wustl.edu).

Consolidated epigenomes from the Roadmap Epigenomics Project show that the *LCT* expresión is only active in fetal tissues, notwithstand *MCM6* is also in the active state (Figure 3).

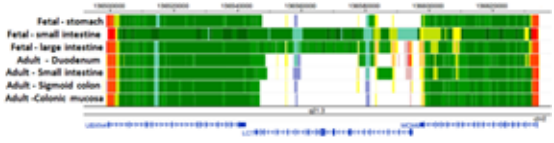

Figure 3. *LCT* expression according to data of consolidated epigenomes in the Roadmap Epigenomics Project.

While the *MCM6* gene is actively transcribed in fetal and adult stomach and intestine (green), the *LCT* gene is only expressed in fetal and newborn tissues but not in the adulthood. *UBXN4* gene is included only for reference. Red color corresponds to active promoters, yellow color to enhancers, and purple color to signals heterochromatine zones. The arrow lines at the bottom show the position and strand of the genes flanking *LCT* (http://egg2.wustl.edu/ roadmap/).

Other SNPs with impact on lactase persistence in European people are the -22018 G>A [1-4], and the -13909C>A [4], In pastoralist people of WestAfrica, other SNPs 14010G>C, 13915T>G, and 13907C>G have been unveiled [5-6].

To guide alimentary interventions, it is important to know if lactose intolerance has this origin.

REFERENCES:

1. Enattah NS, Sahi T, Savilahti E, Terwilliger JD, Peltonen L, Järvelä I. Identification of a variant associated with adult-type hypolactasia. Nat Genet.2002;30:233-7.
2. Labrie V, Buske OJ, Oh E, Jeremian R, Ptak C, Gasiūnas G, et al. Lactase nonpersistence is directed by DNA-variation-dependent epigenetic aging. NatStruct Mol Biol. 2016 Jun;23(6):566-73.
3. Swallow DM, Troelsen JT. Escape from epigenetic silencing of lactaseexpression is triggered by a single-nucleotide change. Nat Struct Mol Biol. 2016;23:505-7.
4. Baffour-Awuah NY, Fleet S, Montgomery RK, Baker SS, Butler JL, Campbell C, et al. Functional significance of single nucleotide polymorphisms in the lactase gene in diverse US patients and evidence for a novel lactase persistence allele. J Pediatr Gastroenterol Nutr. 2015;60(:182-91
5. Tishkoff SA, Reed FA, Ranciaro A, Voight BF, Babbitt CC, Silverman JS, et al. Convergent adaptation of humanlactase persistence in Africa and Europe. Nat Genet. 2007;39:31-40.
6. Torniainen S, Parker MI, Holmberg V, Lahtela E, Dandara C, Jarvela I. Screening of variants for lactase persistence/non-persistence in populations fromSouth Africa and Ghana. BMC Genet. 2009 Jul 5;10:31.