Lactose intolerance or ignorance?

An educational approach to the foundations of lactase persistence and non persistence

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Introduction

Lactose, the main carbohydrate in milk, is hydrolysed by the intestinal enzyme lactase (LPH). A total or partial deficiency of LPH can limit milk intake despite lactose-free products being available.

Several European countries have reported low compliance of the dairy intake recommendation. This evidence led us to the hypothesis that there is a lack of awareness regarding the fundaments of lactose maldigestion. This may lead to inadequate practises that could explain the low compliance. In order to test this and study this unawareness, we carried out a survey on Norwegian and Catalan university students.

The aim of this project was to carry out a survey to determine the level of awareness and to provide a solution. Therefore, we carried out an exhaustive review of the topic and elaborated an Informative Booklet.

Material and methods

- Computer-based **scientific literature review:**
  - Databases: MEDLINE, PubMed, PlosOne, ScienceDirect and Google Scholar
  - Main keywords: 'lactose intolerance'; 'lactase persistence'; '-13910'; 'adult-type hypolactasia'; 'LPH' and 'post-weaning downregulation' or a combination.
- Elaboration of an **Informative Booklet**
- Additional elaboration of an **online survey** (platform: Google Forms) targeted to Norwegian and Catalan university students (18-30yrs old).

1 Background

Lactose is a disaccharide hydrolysed by **lactase (LPH)** in the intestinal mucosa.

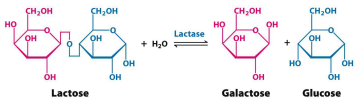


Figure 4. Diagram of lactose condensation and its hydrolysis by lactase.

A total or partial LPH deficiency leads to lactose maldigestion. When this causes gastrointestinal symptomatology we talk about **'lactose intolerance' (LI).**

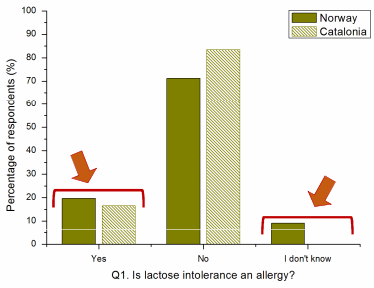


Figure 1. Correct ('No'), incorrect ('Yes') and dubious answers ('I don't know') in Norwegian and Catalan populations for Q1 of the survey evaluating the 'concept' of LI. Incorrect and dubious answers are indicators of 'unawareness'.

In our survey, respondents usually answered correctly. However, **a still non-negligible number of the responses were wrong**, suggesting a considerable unawareness (13-20% in Figure 1).

BIG IMPACT

Around **65-70%** of the global population suffer from lactose maldigestion.

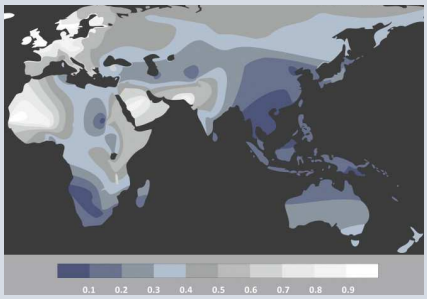


Figure 2 .LNP worldwide distribution. Source: Leonardi *et al*, 2012

2 LNP Post-weaning downregulation

LPH is encoded in ***LCT* gene** (2q21.3) and expressed in the apical membrane of the enterocytes.

The mature form has 2 enzymatic active sites:
- **'lactase active site'**
- 'Phlorizin hydrolase active site'

LPH is subject to different levels of regulation, among which **post-weaning down-regulation** implies a reduction in LPH expression after weaning. This leads to a '**lactase non persistence' (LNP) phenotype** or 'adult-type hypolactasia'.

It is due to a regulation at the ***transcriptional level*** and involves the synergistic action of the transcription factors(TFs):

HNF-1α, Cdx-2 and **GATA-5 and GATA-4.**

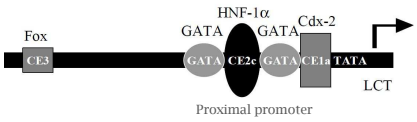


Figure 3. TF responsable for post-weaning down-regualtion.

Because lactose is the major sugar found in dairy, **LNP widely limits dairy consumption**

3 LP Genetic & Molecular Basis

Oppositely to LNP, some individuals keep LPH expression high during adulthood. They are referred as **'lactase persistent' (LP).**

LP associates with concrete alleles of **Single Nucleotide Polymorphisms (SNPs)** in cis-regulatory elements 5'-upstream of the *LCT* promoter. The SNP better associated to European and Northern African LP frequencies is the **C/T-13910 variant.** Its 2 alleles are: **-13910*T and -13910*C**

LPH expression increases with the -13910*T allele when compared with the -13910*C allele (Figure 5)

The -13910*T allele is associated to LP

Current models suggest **higher affinity** for the -13910*T allele of TF that have an enhancing synergistic effect:

Oct-1, HNF-1α and **GATA-6**

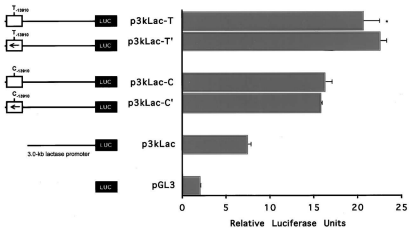


Figure 5. Luciferase activity (p3k) as function of the presence of the T (Lac-T) or C allele (Lac-C) of the C/T -13910 variant. Source: Olds *et al*, 2003

Other SNP variants have been suggested to explain South African LP frequencies with similar TF models, yet it is less well studied.

4 LP Origin and evolution of C/T -13910

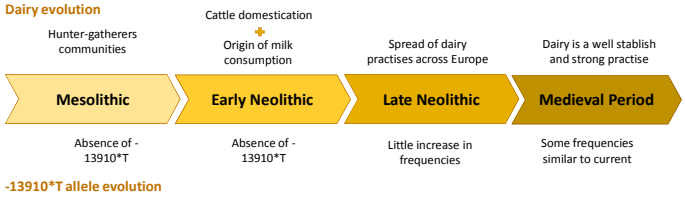
The origin of -13910*T allele is estimated to be:

Neolithic (180-18,600 BC or 5,500-10,300 BC)

Around that time, domestication of cattle and thus, milk consumption, started to spread around Europe.

The introduction of dairy as part of the 'Neolithic Package' has been suggested as a **positive selective pressure** placing a survival advantage on LP individuals. This is supported by the parallel evolution of -13910*T frequencies and dairy and known as:

'gene-culture co-evolutionary theory'



Conclusions

In summary:

- The **LNP phenotype** is a physiologic condition affecting 65-70% of the worldwide population that is caused by a post-weaning downregulation of *LCT* controlled at the *transcriptional level* by different TFs (e.g. Cdx-2, HNF-1α, GATA-4/-5/-6).
- The **LP phenotype** implies the maintenance of LPH expression through adulthood. It is regulated at the *transcriptional level* by cis-regulatory elements 5' upstream of the *LCT* promoter that contain SNPs. The ***C/T-13910 SNP variant*** is the best associated to European LP frequencies with its -13910*T allele showing higher affinity for TFs with an enhancing effect. According to the 'gene-culture co-evolutionary theory' a positive selection pressure exert by the introduction of dairy during Neolithic would have favoured LP.

Our data suggest unawareness regarding this knowledge supporting our hypothesis. Hence, we elaborated an Informative Booklet with an overview of the information here reviewed.