Original Research Article

Lactase Non-Persistence and General Patterns of Dairy Intake in Indigenous and Mestizo Chilean Populations

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Objectives: Lactase persistence (LP) is a genetic trait that has been studied among different countries and ethnic groups. In Latin America, the frequencies of this trait have been shown to vary according to the degree of admixture of the populations. The objective of this study is to better understand the relationship between this genetic trait and dairy intake in a multiethnic context through a synthesis of studies conducted in four regions of Chile.

Methods: Genotypes frequencies for the SNP LCT-13910C>T (rs4988235) and frequency of dairy consumption were obtained from four populations: Polynesians from Easter Island (Rapanui); Amerindians (Mapuche) and Mestizos from the Araucanía region; urban Mestizos from Santiago; and rural Mestizos from the Coquimbo region. Genetic differentiation and association between milk consumption and genotype frequencies were estimated.

Results: Genetic differentiation between Native and Mestizo populations was significant; the LP frequency in Mapuche and Rapanui was 10% and 25%, respectively, whereas among the Mestizos, LP frequency was near 40%. Dairy intake was below the nutritional recommendations for the four groups, and extremely below recommendations among the indigenous populations. Association between milk intake and LP was found in Santiago and Rapanui populations.

Conclusions: Although the frequency of LP varies among the populations according to their degree of admixture, dairy consumption was very low across the populations. Given that the association between milk consumption and expected phenotype was found only in two of the populations analyzed, it seems that lactase non-persistence (LNP) is not the only cause for dairy avoidance. Thus, it is suggested that SES and cultural preferences are likely affecting dairy consumption. Am. J. Hum. Biol. 28:213–219, 2016. © 2015 Wiley Periodicals, Inc.

INTRODUCTION

Humans have developed a world of symbols and cultural representations regarding food, which determine specific patterns, habits, and behaviors among different human groups, including particular food preferences and aversions (i.e., taboos). The wide diversity of cuisines observed between people of different religions and cultures within a region illustrate that ecological constraints are not the only barrier that the human diet has to overcome. Cultural preferences and aversions have also had an explicit impact on the biology of these populations. This is due to the selection of advantageous traits in specific historical and geo-ecological contexts (Harris, 1998; Simoons and Frederick, 1994). Thus, due to different mechanisms, cultural variations in diet are associated with genetic differences among populations.

Evidence of coevolution between food habits and genetics has been obtained from diverse food-models in human populations. The variability seen within genes associated with the metabolism of carbohydrates, proteins, lipids, ethanol, phosphates, toxins, etc., among human populations provides concrete examples of this relationship (Nabhan, 2006). Additionally, differential prevalence of metabolic diseases among human groups—and their circumscription to particular ethnic groups or geographic areas—is indicative of diverse historical processes that have occurred at a micro-evolutionary level in our species. One of the archetypal examples of gene–culture coevolution is the domestication and milking of cattle and the evolution of lactase persistence (LP) in some human populations (Arjamaa and Timo, 2010; Beja-Pereira et al., 2003).

LP is an exclusive human trait that allows the synthesis and expression of the lactase enzyme in adulthood. This enzyme is required to digest the lactose present in all dairy products into its constituent monosaccharides. LP is genetically determined by an autosomal dominant gene, and its carriers have the advantage of being able to digest the lactose beyond weaning. For most mammals, including almost all human populations, the synthesis of this enzyme ceases during childhood, resulting in a condition known as lactase non-persistence (LNP). In these individuals, dairy consumption may produce lactose malabsorption, which has physiological effects known as lactose intolerance (OMIM #223100). The common symptoms include abdominal pain and bloating, diarrhea, nausea and vomiting, among others (Vesa et al., 2000; Lomer et al., 2008).

Most human populations (~65%–70%) have low frequencies of LP; however, there are remarkable exceptions in northern Europe, where the highest frequencies are found in Scandinavia and it decreases slowly toward the south. In addition, high LP frequencies have been found

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in some populations of eastern Africa and the Middle East (Itan et al., 2010). In both areas, the high level of LP frequencies seems to be related to the habit of drinking milk of other mammals. This was a cultural practice developed by a few groups of shepherds during the Neolithic period, but absent in most human populations until recently. Thus, LP is common only in populations that have historically depended on milk and dairy products as nutritional resources (Simoons, 1978). This indicates that LP is a genetic mechanism by means of which some populations have managed to biologically adapt within the circumstances of this emergent cultural practice.

Different hypotheses have been proposed to explain the geographic and ethnic distribution of LP (Holden and Mace, 1997). All of them consider an important natural selection pressure favoring the LP trait in those herding groups that began milking early. The first studies proposed three main hypotheses: the historical–cultural hypothesis (Simoons, 1970), the solar radiation hypothesis (Flatz and Rotthauwe, 1973) and the hypothesis of dry environments (Cook and Torki, 1975). A fourth theoretical approach, based on the historical–cultural hypothesis, suggests a theoretical framework of gene–culture coevolution of LP and milking, considering both traits as heritable (Aoki, 1986; Aoki, 2001).

Until now, several genetic variants in the region of DNA flanking the lactase gene (LCT) have been identified that control the expression of this enzyme in the small intestine. Although only one variant (LCT-13910*T) is highly associated with LP in European populations (Enattah et al., 2002), it has been shown that this is not the cause of high levels of LP outside of Europe. At least four other variants (LCT-13907*G, LCT-13915*G, LCT-14010*C, and LCT-14009*G) are highly associated with LP in populations in Africa and the Middle East (Enattah et al., 2008; Imtiaz et al., 2007; Ingram et al., 2007; Jones et al. 2013; Tishkoff et al., 2007). Recent studies have indicated that LP is highly associated with the European variant LCT-13910*T in the Americas (Bulhões et al., 2007; Friedrich et al. 2012a; Morales et al., 2011), but there are still no conclusive studies that allow the identification of emergent variants in the Americas.

Although the assessment of all loci involved in the LP regulation have not yet been performed for South American populations, recent studies have shown that the LCT-13910C>T polymorphism is not correlated with the LP/LNP condition in some populations of Colombia (Mendoza et al., 2012) and Brazil (Friedrich et al., 2012a). In these areas the African component has been shown to be high, suggesting that other mutations could also be correlated with LP. However, in the majority of South American Mestizo and indigenous populations, it has been demonstrated that the LCT-13910*T allele is associated with LP (Morales et al., 2011; Montalva, 2014).

The patterns of admixture observed in South American populations have resulted in high variability in the frequency of LP. The South American indigenous groups of each country are those that exhibit the lowest proportion of individuals with LP. LP frequency in populations with very little admixture, such as the Xavante of Brazil and the Guahibo of Colombia, is close to zero, while in the more admixed populations of these countries the frequencies vary between 30%–55% and 20%–45%, respectively (Ángel et al., 2005; Escoboza et al., 2004; Friedrich et al., 2012a; Mattar et al., 2009; Mendoza et al., 2012; Osier et al., 2002). In Chile, a recent study reported that the prevalence of LP estimated by the frequency of LCT-13910C>T in the native Mapuche population is close to 10%, while in the admixed population of the capital (Santiago) it is close to 40% (Morales et al., 2011). This is consistent with the European origin of colonists, the low African component in the region (Arcos-Burgos et al., 2004) and the absence of longstanding milking practices in the country. An exception to this is represented by the agricultural communities in the semi-arid region in North Central Chile, where the base-subsistence relied almost exclusively on nomadic goat herding from the 17th century until the end of the 20th century (Alexander, 2008; Gallardo, 2002).

Fig. 1. Geographic regions of Chile sampled in this study.

Considering the multiethnic and multicultural context of Chile, its marriage patterns, and the high social–demographic segregation, a heterogeneous distribution of both the LP variants and the frequency of dairy consumption is to be expected. Using published (Fernández and Flores, 2014) and unpublished data obtained from four parallel studies, the aim of this article is to synthesize the genotypic frequencies data obtained for the European LP variant (LCT-13910C>T) in four regions of Chile and to assess how they relate to dairy consumption. In addition, we attempt to distinguish common patterns across populations and specific patterns in each of the areas analyzed.

SUBJECTS AND METHODOLOGY

As part of four independent studies, four regions or localities of Chile were sampled (Fig. 1): (a) a Polynesian population from Easter Island (Rapanui); (b) one Amerindian (Mapuche) and one Mestizo population from the Araucanía region (IX region; Fernández and Flores, 2014); (c) a Mestizo urban population from Santiago, and (d) Mestizo herders from the Coquimbo region (IV region).

TABLE 1. Allele, genotype and phenotype frequency for each zone and its populations

Locality/region	Sample	*N*	Genotype frequency			Allele frequency	LNP (%)
			CC	CT	TT	T	
IX region	Temuco	115	0.7	0.25	0.05	0.175	70
	Mapuche	29	0.9	0.1	0	0.05	90
	TOTAL	**144**	**0.74**	**0.22**	**0.04**	**0.15**	**74**
Easter island	**TOTAL**	**86**	**0.75**	**0.24**	**0.01**	**0.13**	**75**
Santiago	**TOTAL**	**116**	**0.603**	**0.336**	**0.06**	**0.228**	**60**
IV region	Elqui	13	0.77	0.15	0.08	0.15	77
	Limarí	223	0.61	0.33	0.06	0.23	61
	Choapa	201	0.64	0.32	0.04	0.2	64
	TOTAL	**437**	**0.62**	**0.32**	**0.06**	**0.22**	**62**

The data obtained were integrated here to report an overview of the genetics of LP and dairy consumption in Chile.

These four studies comprised a sample size of 783 individuals. The Santiago sample was composed of 116 university students from three universities in the city. The Easter Island sample consisted of 86 adults who currently live on the island. The sample of the IX region included two groups: 115 individuals from rural localities near the city of Temuco and 29 from Mapuche indigenous communities of Freire and Pitrufquén. Data from this sample were originally published in Fernández and Flores (2014) and they were used here to be compared with other Chilean populations. Finally, the sample of the IV region ($n = 437$) came from different agricultural communities: Elqui Valley ($n = 13$), Limarí Valley ($n = 223$), and Choapa Valley ($n = 201$).

All individuals sampled were at least 18 years old and participated voluntarily by signing a written informed consent document, which was approved by the Social Sciences Research Ethics Committee (CEDEA, University of Chile) for each of the four studies. Additionally, ethical approval for the IV region samples was obtained from the University College of London Research Ethics Committee, as part of the study in the IV region. Participants were asked to give a biological sample consisting of 2 ml of saliva for the samples of Easter Island, IX region and Santiago, and a buccal swab for the samples of the IV region. Additionally, to evaluate the relationship of LNP with other variables, individuals answered a questionnaire about their eating habits and self-perceived symptoms associated with dairy intake. Estimations of dairy consumption frequency were obtained using a food frequency questionnaire.

Except for the IV region samples, DNA extraction from the saliva was performed using the protocol of Quinque et al. (2006). Purified DNA was amplified by PCR for the region containing the LCT-13910C>T polymorphism, using the primers described by Bulhões et al. (2007). The amplified fragments (210 bp) were genotyped using the BsmFI restriction enzyme (Fermentas). Digestion products were separated by electrophoresis on agar gels, obtaining patterns that allowed identification of the genotype of each individual.

Most of the samples of the IV region were processed and analyzed in a different laboratory (UCL, UK), therefore, DNA extraction from these samples was performed using both the protocols of Freeman et al. (2003) with modifications and Quinque et al. (2006). Both DNA extraction methods have been shown to provide enough DNA concentration for the assays performed in this study (Freeman et al., 2003; Quinque et al., 2006). In addition, due to differences in aims and funding of the study at the IV region, genotyping was done through sequencing. Purified DNA was amplified for a 706 bp region using the primers described by Ingram et al. (2007). Genotypes were determined by sequencing the enhancer region of the lactase gene (MCM6). This method enables the detection of the LCT-13910C>T mutation, while discarding the presence of other variants.

ANALYSES

The observed allele and genotype frequencies were estimated and compared with the expected frequencies under the conditions of the Hardy–Weinberg equilibrium. Considering that the T allele determines LP, expected phenotypic frequencies for the trait in each population were also estimated. The F_{ST} index of Wright (1978) was used to evaluate the genetic differentiation among the four sampled populations using the software Arlequin version 3.5.1.3 (Excoffier and Lischer, 2010). Because of the potential for an individual's LP/LNP state to affect food habits, association between milk consumption and genotype frequencies for the samples from the IV region, Santiago, and Easter Island were estimated using chi-square, Kruskal Wallis, and Wilcoxon Mann–Whitney tests, respectively.

Allelic frequencies of −13,910*T reported from Latin American, Asian, and European populations in HapMap (The International HapMap 3 Consortium, 2010) and 1,000 Genomes (The 1000 Genomes Project Consortium, 2012) were examined to put this data in context. The reported frequencies were analyzed using multidimensional scaling based on between-populations pairwise F_{ST} to offer a graphical representation of the relationship between the analyzed Chilean groups and other world populations.

RESULTS

A total of 783 samples were amplified and genotyped for the locus LCT-13910C>T. The most frequent genotype was CC, thus LNP was predominant in all of the populations, although there were important differences between populations. The highest frequency of non-persistence was found in the Mapuche population of the IX region (90%), while the lowest frequency was found in Santiago (60%). Highly similar values were obtained between Santiago and the IV region (Table 1).

The expected gene and genotype frequencies did not differ significantly ($P > 0.05$) from the frequencies observed in all studied groups, thus the populations are apparently in Hardy–Weinberg equilibrium for this polymorphism.

TABLE 2. F_{ST} values among populations using 95% confidence intervals

	Temuco (IX)	Easter Island	Santiago	IV region
Easter island	0.002			
Santiago	0.003	0.024 (*)		
IV region	0.001	0.017 (*)	0.002	
Mapuche (IX)	0.049	0.022	0.084 (*)	0.068 (*)

* Significant values ($P < 0.05$).

The genetic differentiation among the populations in the four zones studied was estimated using the F_{ST} statistic. The highest values were observed in the Mapuche sample (IX region) when compared with the Santiago and the IV region samples. Intermediate values were observed when comparing the IX region samples to each other (Mapuche vs. Temuco), and also when comparing Easter Island with Santiago. The lowest differentiation was found in the comparison of the IV region with the other three zones (Table 2).

The examination of this data in comparison with the frequencies of −13,910*T reported in HapMap (The International HapMap 3 Consortium, 2010) and 1,000 Genomes (The 1000 Genomes Project Consortium, 2012) for other admixed populations from the Americas showed values similar to the two mestizo populations reported here: Colombians from Medellin, Colombia: CLM = 0.33, Mexican Ancestry from Los Angeles USA: MEX-MXL = 0.25, and Puerto Ricans from Puerto Rico: PUR = 0.2. Similarly, Asian and European groups were examined due to their proximity to the Amerindian and Spanish parental populations. The frequencies of −13,910*T for Han Chinese in Beijing, China: CHB-HCB = 0, Iberian Population in Spain: IBS = 0.57, and Utah Residents with Northern and Western European Ancestry: CEU = 0.71, are in agreement with the Amerindian–European admixture model characteristic of Chile (Eyheramendy et al., 2015) (Fig. 2).

A total of 659 individuals answered the food frequency questionnaire related to the consumption of dairy products and other associated variables. Of these, 431 were from the IV region, 116 from Santiago, 83 from Easter Island, and 29 from the Mapuche communities of the IX region.

The average monthly consumption of milk in the IV region was approximately 17 cups (SD = 22), and the number of days that individuals consumed at least one dairy product was on average 13 per month (SD = 10.5). There was no association between genotype and avoidance of dairy products (χ^2 test; $P = 0.4$), nor between the presence of the LP allele (T; expected phenotype LP), and milk consumption (Fisher's exact test; $P = 0.82$) or other dairy products (Fisher's exact test; $P = 0.4$).

In Santiago, mean consumption of dairy products was on average 84 servings per month (SD = 50.6) and only four individuals declared they never consumed dairy products. Among dairy products, milk was the most frequently consumed. Mean consumption of milk was different between expected phenotype LNP and LP individuals ($P = 0.03$), indicating a higher consumption in the latter group; nevertheless, no significant differences between groups were found for the other dairy products ($P > 0.05$).

On average, a low dairy intake was found in Easter Island. Among the dairy products, milk was the most frequently consumed; 31% of individuals indicated consumption of milk one or more times per day, whereas only 14% and 17% indicated consumption of cheese and yogurt, respectively, on a daily basis. The comparison of the frequency of milk consumption between the LNP and LP expected phenotypes showed a significant difference between the groups ($P = 0.04$). This difference indicates greater milk consumption by individuals whose expected phenotype is LP. No significant differences between expected phenotypes were found when the frequencies of other dairy products were analyzed.

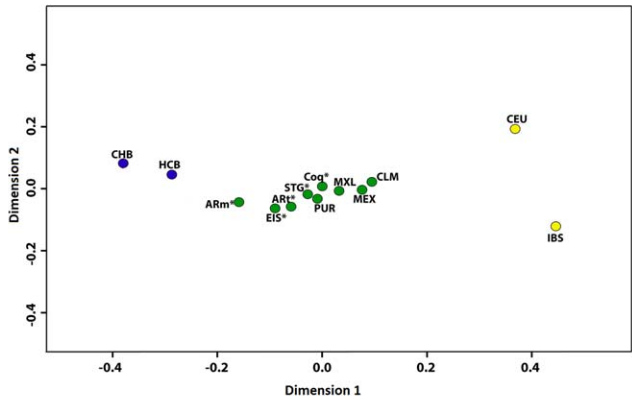

Fig. 2. Multidimensional scaling (MDS) analysis using a F_{ST} matrix of the LCT-13910 locus in some European, Asian and Latin American samples. Data were obtained from HapMap (The International HapMap 3 Consortium, 2010), 1,000 Genomes (The 1000 Genomes Project Consortium, 2012) and this study (Coq, Coquimbo; STG, Santiago; EIS, Easter Island; ARt, Temuco subsample of Araucanía; and ARm, Mapuche subsample of Araucanía).

The frequency of dairy consumption in the Mapuche communities of the IX region was estimated to be 28 servings per month (SD = 24.9), slightly less than one portion per day. As in the other samples, cow's milk was the most frequent dairy product; however, nearly 50% of the individuals reported never drinking milk. Among them, individuals showed a preference for cow's milk cheese than any other dairy product, although the mean consumption was only 5 servings monthly. Production and consumption of dairy products from other milking animals was almost nonexistent, represented by only one case in the entire sample. Due to the low number of individuals carrying the persistence allele ($n = 3$) statistical analysis of the relationship of LP and dairy consumption was not performed.

Several studies have concluded that LNP individuals can consume at least one glass of milk (240 ml) without experiencing physiological adverse symptoms (Suarez et al., 1995, 1997; Vesa and Korpela, 1996). For this reason, it is likely that consuming two or more glasses is a good predictor of the relationship between LNP and milk avoidance. Considering two or more glasses of milk as the quantity that would be exceeded for experiencing symptoms and probably the avoidance of milk consumption, data on milk intake among the four populations analyzed was grouped in three categories: "none or less than one glass of milk per day", "one glass of milk per day" and "two or more glasses of milk per day" (Supporting Information 1). When data was grouped using these categories, it is

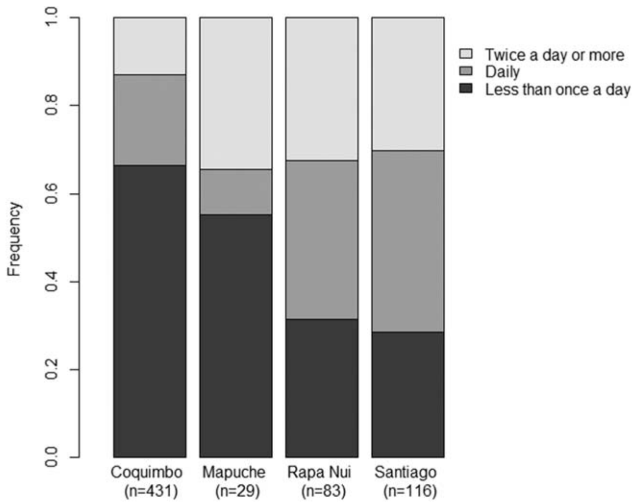

Fig. 3. Frequency of the three consumption categories in each population.

evident that Mapuche and Coquimbo samples have the lowest milk intake, and that Rapanui and Santiago exhibit very similar frequencies in the three categories (Fig. 3).

The association between milk consumption and expected phenotype was statistically significant only in the Rapanui population (χ^2 test; $P = 0.031$). Since an association between milk consumption and LP was not found in Santiago using this classification (χ^2 test; $P = 0.28$), this discrepancy suggest that these categories cannot distinguish a recognizable trend when milk consumption data was disaggregated into the exact number of servings referred by each individual.

DISCUSSION

This study is the first synthesis of the research performed in Chile on the genetic LP trait and its relationship to consumption of dairy products. The synthesis proposed here also brings to light important questions concerning the biological, cultural and biocultural variability in Chilean populations, which is of interest to such diverse disciplines as anthropology, nutrition, archaeology, population genetics, history and public health, among others.

The prevalence of LNP among the populations followed the expected pattern. The highest frequencies were observed in the indigenous Mapuche and Rapanui populations, reaching 90% and 75%, respectively. Percentages close to 60% were observed in the Mestizo populations of Santiago and the IV region. Evaluating the genetic differentiation among the populations, the highest values were found when comparing the indigenous populations (Mapuche and Rapanui) to the samples in the regions with greater admixture and European component (Santiago and the IV region).

The results of this study concur with those obtained in Brazil and Colombia, in which the Amerindian populations (Xavante and Guahibo, respectively) exhibit LNP values close to 100% (Friedrich et al., 2012b; Osier et al., 2002), while in the Mestizo populations of urban areas the frequency of LNP ranges between 45% and 70% in Brazil and between 55% and 80% in Colombia (Ángel et al., 2005; Escoboza et al., 2004; Friedrich et al., 2012a; Mattar et al., 2009; Mendoza et al., 2012). This correspondence reflects noteworthy biological variability and heterogeneity within and between the populations of South America. As has been indicated, ancestry, marriage patterns and other cultural practices could explain the observed allele frequencies and the differentiation between indigenous and Mestizo populations.

Since the ancestral populations of both Amerindians and Rapanui are believed to have come from Asia (Friedlaender et al., 2008; Salzano and Bortolini, 2002; Wang, 1984), they are likely to have provided only LNP alleles. By contrast, the allele that explains LP in the Chilean population is likely to be the European mutation LCT-13910C>T, which shows very high association (≈100%) with lactose digestion in the studies by Morales et al. (2011), Latorre et al. (2014), and Montalva (2014). Thus, the presence of the T allele that determines LP in the Chilean population stems mainly from the Spanish migrants who arrived in South America during and after colonization.

In addition, the pattern of differentiation between indigenous and Mestizo populations reflects the persistence of cultural and geographic barriers, resulting in individuals continuously reproducing mostly within their own communities or regions.

Until the arrival of Spanish colonizers, milking animals (cattle, sheep, and goats) as well as milking practices were unknown to the inhabitants of the Americas. Also, no other domesticated animals in this region could have been used for these purposes in pre-Hispanic times (Stahl, 2008); thus, dairy products were certainly not part of the diet until colonization was well established. Due to the absence of a selective pressure for the use of dairy products in this context, along with the ancestral condition of LNP, a LP genotype would not have represented an advantage in terms of survival.

The consumption of dairy products is very low in the four Chilean populations analyzed, and on average, remarkably lower in the Mapuche and IV region samples relative to the Santiago sample. Interestingly, this pattern is more accentuated when milk consumptions is analyzed separately. This difference may be due to the absence of dairy products in the traditional diets of these populations, along with an impaired access to dairy products due economic and geographic barriers (Fernández, 2013; Arias, 2011; Ferrari et al., 2004).

The association between expected phenotype and milk consumption was evaluated in Santiago, Rapanui, and IV region samples. Although a statistically significant association between LP and higher milk consumption was found in the Rapanui and Santiago populations, this trend was not observed in the IV region sample. Therefore, considering the very low dairy consumption across the populations analyzed, it is unclear whether dairy avoidance is a consequence of the LNP condition, or whether other biological, socioeconomic, and cultural factors are affecting dairy consumption patterns among Chilean populations. Further investigations should examine the specific determinants of this pattern in each cultural context.

The frequent relationship between LNP and low consumption of dairy products has been widely studied in different populations (Byers and Savaiano, 2005; Gugatschka et al., 2005; Jackson and Savaiano, 2001). In many cases it has been associated with impaired bone mineralization and greater prevalence of osteopenia and osteoporosis (Jackson and Savaiano, 2001; Obermayer-Pietsch et al., 2004). However, as mentioned above, dairy products did not represent a source of calcium or other nutrients for American populations until probably centuries after European colonization began. In this context, a diachronic approach to study the health status and dietary shifts among these populations would allow a direct estimation of the assumptions behind this relationship. In particular, a paleo-pathological analysis of bone mineral density and bone micro-architecture of pre-Hispanic osteological remains, along with a deeper understanding of diet in pre-Hispanic populations (e.g., stable-isotope studies, phytoliths, and domestic contexts) could provide valuable information regarding the prevalence of metabolic pathologies and their relationship with ecological and socioeconomic variables in the past.

The marked differentiation observed for this genetic trait between indigenous and Mestizo populations in the regions analyzed indicates longstanding reproductive barriers among these populations, suggesting that the process of admixture among Chilean populations has had significant consequences for the genetic structure and the food habits of these populations, both of which overlap largely with socio-demographic factors. Furthermore, patterns of dairy intake show a bias toward higher dairy consumption in populations with higher admixture. It is uncertain whether this phenomenon is explained by biological or cultural factors, or both.

On the other hand, ecological conditions and means of production adopted by the populations in relation to food production and consumption, purchasing power, and symbolic value associated with different foods have been demonstrated to affect food consumption behavior (Contreras and Gracia, 2005). In the specific cases of the Mapuche and Rapanui populations, several socioeconomic and cultural factors would explain the pattern of dairy consumption observed in this study. Among these are the recent adoption of animal husbandry, very restricted purchasing power, very low level of education (i.e., reduced access to information and government assistance programs (Cerda, 2006) and a food tradition that does not include dairy products as part of the diet (Comisión Verdad Histórica y Nuevo Trato, 2003).

The implementation of food policies by the Chilean government have been fundamentally focused on providing dairy products to economically disadvantaged citizens, encouraging a minimum intake of calories and milligrams of calcium through the consumption of provisioned dairy products. However, these programs fail to consider the ecological and cultural contexts in which they have been implemented. Based on the results obtained by the studies summarized in this synthesis, a critical review of the public policies on food and nutrition in Chile is needed.

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