



Research article

Lactase persistence in the Jordanian population: Potential effects of the Arabian Peninsula and Sahara's aridification

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ABSTRACT

The single nucleotide polymorphism (SNP) $-13910\ C > T$ has proved a good predictor of the incidence of lactase persistence in Europe and South Asia. Yet, this is not the case in the Near East, although this region is a passageway between the two continents. Lactase persistence is associated with cattle breeding, which originated in the Fertile Crescent of the Near East and spread later during the Middle Neolithic throughout Europe. Here we analyzed five SNPs ($-13915\ T > G$ (rs41380347), $-13910\ C > T$ (rs4988235), $-13907\ C > G$ (rs41525747), $-14009\ T > G$ (rs869051967), and $-14010\ G > C$ (rs145946881)) in three Jordanian human groups, namely the Bedouins, Jordan valley farmers, and Jordanian urban people. The SNPs $-14009\ T > G$ and $-14010\ G > C$ were not detected in the sample, $-13907\ C > G$ was virtually non-existent, $-13910\ C > T$ showed low frequencies, and $-13915\ T > G$ exhibited salient frequencies. The estimated incidence of lactase persistence was lower in the urban population (16 %), intermediate in the Jordan Valley's farmer population (30 %), and higher among the Bedouins (62 %). In explaining our findings, we postulated climatic change brought about by the aridification episode of the Arabian Peninsula and the Sahara 4200 years ago. This climatic milestone caused the collapse of the Akkadian Empire and the Old Kingdom in Egypt. Also, it could have led to a drastic decline of cattle in the region, being replaced by the domestication of camels. Loss of traditional crops and increasing dependence on camel milk might have triggered local selective pressures, mainly associated with $-13915\ T > G$ and differentiated from the ones in Europe, associated with $-13910\ C > T$.

1. Introduction

Since the early Neolithic era, some 10,000 years ago, humans began to domesticate different animal species, including cows, sheep, and goats, which provided them with the capability to enrich their diet with milk [1]. Among other plausible benefits, the availability of this food resource meant an interesting nutritional supplement; at the same time, it represented a selective advantage in periods of shortage of other foodstuffs. When the crops failed because of any given circumstance, assimilating lactose from milk could have been essential for survival. Also, milk intake could be a crucial source of uncontaminated water and electrolytes in circumstances of extreme

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aridity [2,3]. Therefore, selection might have acted against the epigenetic inactivation of the lactase gene during infancy. Indeed, some authors report evidence of intensive selective pressure favoring lactase persistence [4–12]. It is most likely the cause for many populations throughout Europe, Asia, and Africa, showing a high frequency of lactase persistence.

The geographical distribution of these populations is very uneven and potentially related to the domestication events. Several mutations have proved to be associated with lactase persistence in Europe, South Asia, Southwest Asia, and Africa, suggesting the influence of distinctive selective pressures [1,5,13]. The oldest cattle domestication processes occurred in the Near East between 8000 and 10,000 years ago [14]. Some authors propose these pioneering processes as a potential source of origin of European cattle [15]. Domestication of *Bos taurus* also occurred in northeastern (NE) Africa. There, cattle further underwent repeated introgressions from the Near East and even mixed with *Bos indicus* [16,17]. Likewise, humans domesticated the camel (*Camelus dromedarius*) around the late second millennium (1100–1800) BCE in the Arabian Peninsula, which underwent consecutive introgressions of wild specimens [18, 19]. Further east, the Indus Valley was probably the region where the domestication of *Bos indicus* occurred about 7000 years ago [20]. About 50 % of the milk produced in India comes from the water buffalo (*Bubalus bubalis*), although the origin of its domestication remains unknown so far [8]. It has also been argued that some environmental changes could have conditioned the introduction and dispersal of cattle in Africa [21,22].

There is ample evidence that the SNP variants (–13915 T > G (rs41380347), –13910 C > T (rs4988235), –13907 C > G (rs41525747), –14009 T > G (rs869051967), and –14010 G > C (rs145946881)), located in a regulatory region upstream of the lactase gene LCT, are essential mutations for the persistence of lactase activity [23–29], although probably not the only ones [3]. There is a remarkable diversity among the mutations associated with lactase persistence, with a peculiar geographic distribution. Lactase persistence highly correlates with the SNP marker –13910 C > T in Europe [13], whereas SNP –13915 T > G is the most strongly associated in the Near East [23]. Similarly, some authors found an association with –14010 G > C, –13915 T > G, –13907 C > G, and –14009 T > G in East Africa [5,30], and with –13910 C > T in the Sahel [1,31]. On the other hand, –13910 C > T substantially explained lactase persistence in India, and the authors suggested that this mutation could be identical by descent to the European one [8]. According to the heterogeneous geographic distribution of mutations related to lactase persistence, scholars hypothesize different selective events affecting diverse SNPs and linked to different types of cattle. Indeed, numerous researchers claim that lactase persistence has evolved at least four times independently [1,5,13].

Jordan is situated at the crossroads between Africa, Asia, and Europe. Geographically, it belongs to the Near East, which is arguably the region where one of the main events of cattle domestication occurred. It is also near other relevant cattle domestication centers. Then, those mutations associated with lactase persistence are present at remarkable frequencies in surrounding populations. The Jordan population is rather heterogeneous, with a proportion of Bedouin contribution, a portion of farmers (located mainly in the Jordan Valley), and an urban component. The urban population mainly originated from migratory flows from neighboring lands and can be considered the general population of this Near Eastern area. The Jordan Valley population has secularly been engaged in agricultural and livestock activities with a sedentary character. Conversely, the Bedouins have traditionally been nomadic pastoralists. In the present work, we jointly analyzed the three main Jordan population groups by testing the SNPs (–13915 T > G (rs41380347), –13910 C > T (rs4988235), –13907 C > G (rs41525747), –14009 T > G (rs869051967), and –14010 G > C (rs145946881)). Our study aimed to examine if environmental factors might have affected the persistence of lactase activity in different communities of the Jordanian population.

2. Materials and methods

The total study sample consisted of 337 Jordanian people. We first recorded the participation agreement of all voluntary donors by obtaining an informed consent form signed by each person. Before the sampling process, the Institutional Review Board of Yarmouk University (Irbid, Jordan) approved the study protocols and the donor recruitment for our research (Ref: YU. IRB/2022/22).

According to ethnical and socioeconomic features, we classified all sampled individuals into three different communities or categories: the Bedouins, who are the Arab nomads living in the desert area (N = 98); the Jordan valley farmers, who are mainly engaged in agriculture and pastoralism (N = 35), around the Jordan river (Jordan rift valley). The third group consisted of Jordanian people living in the main cities and farmers from villages (N = 204). This group was called the general or urban population. Subjects were asked about their family roots, tracing all biographical information back three generations and excluding those individuals with ancestors belonging to two different sociocultural groups or communities.

DNA was extracted from the blood samples using a commercial kit (Vivantis GF-1 extraction kit, Malaysia), following the manufacturer's instructions. Five SNPs associated with lactose persistence SNPs (–13915 T > G (rs41380347), –13910 C > T (rs4988235), –13907 C > G (rs41525747), –14009 T > G (rs869051967), and –14010 G > C (rs145946881)) were examined by sequencing a 383 bp fragment of the intron 13 of the MCM6 gene. PCR amplifications were performed in a final volume of 30 µl, using 5X HOT FIREPol Blend Master Mix (Bento Bioworks Ltd., UK), and starting from 100 ng of genomic DNA and 1 µl of 20 ng of each primer [32] forward: 5'-GAATGCTCATACGACCATGGAA-3', and reverse: 5'-CTGCTTTGGTTGAAGCGAAG-3'. PCRs ran as follows: an initial denaturation step at 94 °C for 5 min, followed by 35 denaturation cycles (94 °C for 30 s each), annealing at 58 °C for 30 s, and elongation at 72 °C for 75 s. Finally, an extension step at 72 °C was performed for 10 min [32]. PCR products (383 bp fragment) were purified and sequenced (Sanger method, ABI PRISM® kit, Macrogen Company, Korea). We further edited and analyzed all chromatograms through FinchTV programs.

2.1. Statistical analysis

SNP allele frequencies in the three Jordan populations examined were assessed by the direct counting method. To test for Hardy–Weinberg equilibrium (HWE) expectations, a Fisher’s exact probability test was conducted to estimate *P*-values [33] using the Arlequin v.3.5 software [34].

SNP frequencies for –13910 C > T and –13915 T > G from previous studies were compiled to assess the genetic relationships of the three Jordanian groups in a broader geographical scope. A total of 26 Near Eastern populations previously typed for the targeted SNPs were included in further analyses. Populations considered, sample sizes, and the corresponding references can be consulted in [Supplementary Table S1](#). These SNP frequencies were then employed to assess genetic heterogeneity in the Near East, by determining the fraction of genetic variability attributable to differences within and among population groups through a hierarchical AMOVA [35,36]. AMOVA tests were performed with the Arlequin v.3.5, considering two Near Eastern population clusters according to geographic criteria.

We finally explored the spatial trend of the SNP frequency distributions in a system of rotating coordinates, intending to detect potential allele frequency clines. This analysis was performed by calculating the linear regression of SNP frequencies on the geographic coordinates of the populations considered, using the GenoCline v.1.5 program [37]. The same cited software was also employed to perform spatial autocorrelation analysis, using SNP allele frequencies and the distances between populations.

3. Results

SNP frequencies in the three Jordanian population groups examined are shown in [Table 1](#). All of them met Hardy–Weinberg equilibrium expectations for the SNPs analyzed. Among the variants responsible for the persistence of lactase activity, the –14009 T > G and –14010 G > C alleles were not found, and the –13907 C > G allele was virtually absent. Allele –13910 C > T appeared at polymorphic frequencies, although very low, being significantly more frequent among the Bedouin than in the urban population (Fisher exact test, $P = 0.0043$). Finally, allele –13915 T > G showed a more heterogeneous distribution, with significantly higher value in Bedouins than in the Jordan Valley (Fisher exact test, $P = 4.59 \times 10^{-6}$) or the urban group (Fisher exact test, $P = 1 \times 10^{-6}$), and slightly higher in the Jordan Valley than in the urban group (Fisher exact test, $P = 0.0131$). Based on these frequencies, the estimated incidence of lactase persistence was found to be lowest in the urban population (16 %), intermediate in the Jordan Valley farming population (30 %), and highest among the Bedouin (62 %).

To widen the geographical scope of our study, we compiled SNP frequencies for –13910 C > T and –13915 T > G in different Near Eastern populations from earlier studies. Based on this database, we explored the existence of genetic clines through the GenoCline v.1.5 version [37]. Since –13907 C > G, –14009 T > G and –14010 G > C are virtually non-existent both in the Jordanian groups and the other Near Eastern collections, they were not included in further analysis. Both –13910 C > T and –13915 T > G disclosed significant allele frequency clines with markedly different orientations ([Fig. 1](#)). Thus, –13910 C > T tended to show higher frequencies towards the north, while –13915 T > G showed increasing frequencies from north to south.

Regarding geographical distribution, –13910 C > T allele frequencies presented values over the Near East area ranging from 0 to 0.054 ([Fig. 2](#)), lower than in neighboring regions such as Western Europe or the eastern zone of South Asia [38]. The lowest values were obtained in Saudi Arabia, Kuwait, and some Jordanian and Palestinian populations. Conversely, the highest values were detected for some subpopulations of Jordanians, together with Lebanese, Palestinians, Assyrians, Druze, Bedouin, and Turks. Overall, these are populations located in the north of the Near East. The genetic gradient obtained significantly correlated with the geographic coordinates of the samples involved ($P < 0.01$).

SNP allele –13915 T > G had frequency values between 0 and 0.724, with the lowest figures observed in the north among Jordanians, Lebanese, Palestinians, and Druze ([Fig. 3](#)). The only exception within this geographic area was the Bedouins of Jordan, which featured average values. On the other hand, Saudi Arabia and Yemen collections showed the highest frequencies, especially the Dhofari Arabs of Southern Oman, which peaked at 0.724 [39]. Once again, the frequency gradient obtained for this SNP marker significantly correlated with the geographic location of the samples involved ($P < 0.0001$).

The combined spatial autocorrelation analysis for the SNPs –13910 C > T and –13915 T > G showed a consistent trend of decreasing Moran index with increasing geographic distance. This phenomenon showed some variability at shorter distances, most likely due to the existence of contact zones and gene flow between subpopulations and, therefore, the lack of complete isolation between neighboring groups ([Supplementary Fig. S2](#)).

Table 1

Allele frequencies (\pm standard error) for three SNP markers associated with lactase persistence in three Jordanian population groups.

SNP allele	Bedouin (N = 196)	Jordan Valley (N = 70)	General Population (N = 408)
–13907*G	0.000 \pm 0.000	0.000 \pm 0.000	0.005 \pm 0.003
–13910*T	0.036 \pm 0.013	0.029 \pm 0.020	0.010 \pm 0.005
–13915*G	0.327 \pm 0.033	0.129 \pm 0.040	0.066 \pm 0.012
–14009*G	0.000 \pm 0.000	0.000 \pm 0.000	0.000 \pm 0.000
–14010*C	0.000 \pm 0.000	0.000 \pm 0.000	0.000 \pm 0.000

N: sample size as chromosome number.

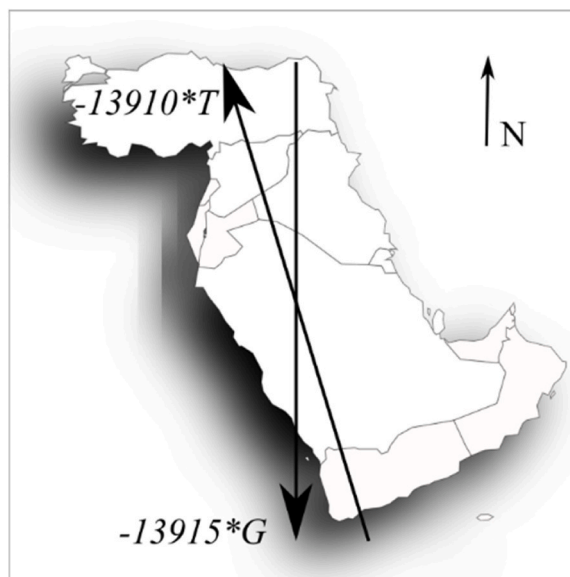


Fig. 1. Orientation of the clines identified for lactase persistence variants in the Near East. The SNP allele -13910^*T displays increasing frequencies toward the north, with an azimuth of 344° . Likewise, the frequency of allele -13915^*G increases toward the south (azimuth of 180°).

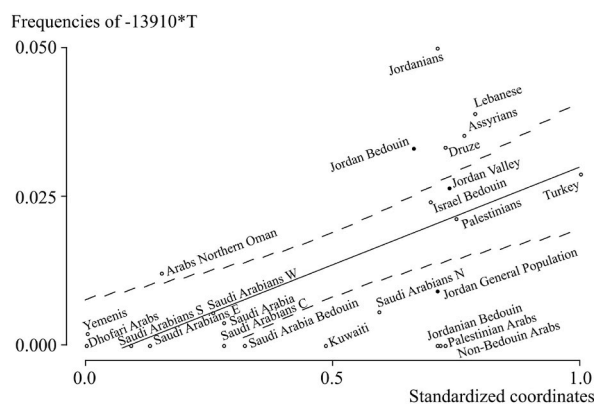


Fig. 2. Linear regression of $-13910 C > T$ allele frequencies in Near East populations against a rotating coordinate axis. Parameter values match the function $y = a + b \cdot x$, where $a = 0.0036$, and $b = 0.0358$. The axis is rotated 344° relative to the North. Dashed lines are 95 % confidence limits. $R: 0.61$; $d.f: 23$; $P < 0.01$.

For a refined resolution of the two genetic clines obtained, we ran AMOVA analyses based on the frequency distribution of $-13910 C > T$ and $-13915 T > G$ (Table 2). We established two groups in both cases, one comprising the samples of the northern half of the Near East and the other including the populations of the southern half of the region. Results revealed statistically significant F_{CT} values, which support a spatial pattern of interregional genetic diversity. We further found a higher statistical significance of among-groups heterogeneity for $-13915 T > G$ ($P < 0.00001$) than for $-13910 C > T$ ($P < 0.01$).

4. Discussion

According to the findings of our study, Jordanian subpopulations showed differentiated frequencies among them in the SNP alleles responsible for lactase persistence. Thus, Bedouins exhibited the highest values for both $-13910 C > T$ and $-13915 T > G$. The general population, urban for the most part, showed the lowest values, while farmers from the Jordan Valley featured intermediate values for both alleles. As expected, a stronger association with livestock practices might have triggered selective pressures, thereby favoring the acquisition of lactase persistence [40].

As a crossing zone between three continents, this region shows a substantial frequency of two mutations with a markedly differentiated geographic origin. On the one hand, the $-13910 C > T$ allele is predominant in Europe [4,13], and in South Asia [4,8]. In the case of Europe, some researchers argue that milk consumption would be associated with the arrival, during the Middle Neolithic, of the

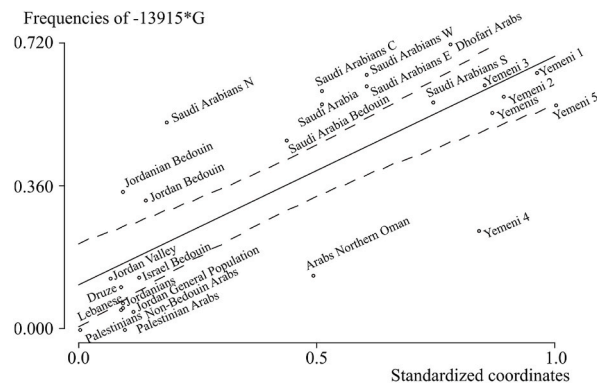


Fig. 3. Linear regression of $-13915 T > G$ allele frequencies in Near East populations against a rotating coordinate axis. Parameter values match the function $y = a + b \cdot x$, where $a = 0.1096$, and $b = 0.5786$. The axis is rotated 180° relative to the North. Dashed lines are 95 % confidence limits. R: 0.79; d.f. 25; $P < 0.0001$.

Table 2

Fixation indices (F_{ST} , F_{SC} , and F_{CT}) generated by hierarchical AMOVA based on -13910^*T and -13915^*G allele frequencies. AMOVA included three Jordanian subpopulations and other 26 Near Eastern collections, separated into two geographical clusters (North vs South).

Variance component	-13910^*T	-13915^*G
Among groups (F_{CT})	0.0129 ^a	0.3228 ^b
Among populations within groups (F_{SC})	0.0033	0.0959**
Within populations (F_{ST})	0.0161*	0.3877**

Northern cluster includes populations from Turkey, Siria, Lebanon, Israel, Palestina, Jordan, and north of Saudi Arabia; Southern cluster includes populations from Oman, Yemen, Kuwait, and Saudi Arabia (except Northern Saudi Arabians).

^a Statistical significance of the fixation index at $P < 0.01$.

^b Statistical significance of the fixation index at $P < 0.00001$.

cattle culture that originated in the Near East by the domestication of taurine cattle, *Bos taurus* [15]. In South Asia, milk consumption might have started with the domestication of zebu cattle (*Bos indicus*) in the Indus Valley about 7000 years ago [8,20]. Yet, some authors refer that short- and long-range haplotype data strongly suggest a single shared origin of the $-13910 C > T$ mutation in Europe, India, and the Sahel region [8,41]. The $-13915 T > G$ allele proved to be particularly prevalent in Saudi Arabia, although it was also present in some African regions [1,5,23,42]. Hypotheses on the allele origins place it in the Arabian Peninsula, most likely associated with the domestication of the Arabian camel, *Camelus dromedarius* [1].

It has been widely accepted by scientists that the Near East is the geographic region where *Bos taurus* was probably first domesticated. Furthermore, the oldest evidence of extensive dairy processing also comes from this area, specifically Anatolia, between 8000 and 8500 years ago [43]. From such evidence, it is somewhat unexpected that the Near East would stand out for very low or even zero frequencies for the bovine cattle-associated lactase persistence mutation ($-13910 C > T$). Indeed, the maximum levels of lactase persistence predicted in Jordanian people by this mutation would only reach 7 % in Bedouins.

A plausible scenario to explain such results would be the scarce practice of bovine cattle farming throughout the Near East. At present, cattle numbers are low in Jordan and across the Near East. The dramatic fall in the amount of bovine livestock in this region would have occurred 4200 years ago, coinciding with the dramatic aridification of the climate over a broad area involving the Arabian Peninsula and the Sahara. This climate episode brought about catastrophic consequences such as the collapse of the Akkadian empire [44] and the Old Kingdom in Egypt [45]. This date roughly coincides with the end of the African Humid Period [46]. Probably, this aridification would have drastically decreased the cattle population size across the Near East from then on, thus blurring the benefits of milk intake in case of food crises.

Based on the frequencies estimated for the $-13915 T > G$ allele, one might predict a lactase persistence frequency of 55 % in the Jordan Bedouin subpopulation. This mutation is postulated to be associated with camel domestication [1]. In this way, allele frequencies in Jordan and the Arabian Peninsula might be attributable to a certain dependence on camel milk, which would have replaced bovine cattle during the aridification process that affected the region. Interestingly, the estimated age for the most recent common ancestor (TMRCA) of the $-13915 T > G$ allele is 4095 (± 2045) years, supporting the “camel breeding” hypothesis [1].

To summarize, the frequency of mutations associated with lactase persistence in Jordan seems to reflect the effect of specific selective pressures in the Near East, owing to the aridification of the region about 4200 years ago. Such a natural phenomenon would have resulted in the loss of agriculture-based food and, consequently, the replacement of cows with camels as a source of milk for human consumption.

Data availability statement

Data associated with this study has not been deposited into a publicly available repository. Data will be made available on request.

CRedit authorship contribution statement

Almuthanna K. Alkaraki: Writing – original draft, Supervision, Resources, Project administration, Methodology, Funding acquisition. **Miguel A. Alfonso-Sánchez:** Writing – review & editing, Writing – original draft, Validation, Formal analysis, Data curation. **Jose A. Peña:** Writing – review & editing, Writing – original draft, Validation, Investigation, Formal analysis, Conceptualization. **Alanoud I. Abuelezz:** Writing – original draft, Investigation, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.heliyon.2024.e33455>.

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