

Limited Public Health Utility of LCT Genotyping for Lactose Intolerance Screening in Adolescents: A Cross-Sectional Study from Türkiye

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ABSTRACT

Objective: Lactose intolerance (LI) is a common cause of gastrointestinal complaints in adolescents and young adults, often leading to unnecessary dietary restrictions and reduced calcium intake. Although lactase non-persistence (LNP) is genetically determined, its clinical expression varies considerably. Genetic variants associated with lactase persistence/non-persistence (LCT/MCM6 locus), particularly rs4988235 and rs3754686, are frequently used in genetic testing; however, their clinical utility remains uncertain, especially in populations with a high prevalence of LNP, such as Türkiye.

Materials and Methods: In this cross-sectional study, 209 individuals aged 12–25 years were evaluated. Lactose-related symptoms were assessed using a validated questionnaire (a score ≥ 7 defined symptomatic individuals). Consumption of raw milk and fermented dairy products was recorded using a standardized frequency scale. Genotyping of rs4988235 and rs3754686 was performed using TaqMan real-time PCR. Associations between genotype, symptom status, age at symptom onset, and dietary patterns were statistically analyzed.

Results: Among the participants, 116 (55.5%) were symptomatic and 93 (44.5%) were asymptomatic. Symptomatic individuals were significantly older ($p < 0.001$). The genotype distributions of rs4988235 and rs3754686 did not differ between symptomatic and asymptomatic individuals and were not associated with age at symptom onset. Dairy consumption patterns were not associated with symptom severity, although fermented dairy consumption was slightly higher among symptomatic individuals ($p = 0.046$).

Conclusion: Common LCT/MCM6 variants did not predict clinical LI in this adolescent and young adult population. Therefore, routine genetic testing appears unlikely to provide limited additional value in supporting the diagnosis of lactose intolerance, particularly in populations with a high prevalence of LNP. Symptom-based assessment and functional testing should remain central to diagnosis and management, and, supporting appropriate nutritional guidance and avoiding unnecessary dietary restriction.

Keywords: Adolescents, dairy consumption, lactose intolerance, LCT, MCM6.



INTRODUCTION

Lactose intolerance (LI) is a common clinical concern among adolescents and young adults and represents one of the most frequent causes of diet-related gastrointestinal symptoms worldwide. Primary lactase non-persistence (LNP), characterized by the genetically programmed decline in lactase-phlorizin hydrolase activity after childhood, is the predominant biological mechanism underlying lactose malabsorption.^{1–3} Although lactase activity is typically high during infancy, its expression progressively decreases during late childhood and adolescence, leading to the emergence of symptoms such as abdominal pain, bloating, diarrhea, and flatulence in susceptible individuals.^{4,5} Clinical recognition often occurs during adolescence, when the physiological decline in lactase activity coincides with greater autonomy in dietary choices.

The most extensively studied regulators of lactase expression are noncoding variants within the MCM6 gene, such as rs4988235 (–13910 C/T) and rs3754686 (–22018 G/A), which act as enhancer elements that modulate transcription of the adjacent LCT gene and thereby influence the persistence or downregulation of lactase activity into adulthood.^{6–8} In European and neighboring populations, the T allele of rs4988235 strongly correlates with lactase persistence, whereas the ancestral C allele is associated with LNP and adult-type hypolactasia.⁷ Türkiye is recognized as a population with a naturally high prevalence of genetically determined LNP, with previous phenotypic studies reporting low lactase activity in up to 70–80% of adults.^{9–11} Despite the high frequency of LNP genotypes, only a subset of individuals develop clinical intolerance, suggesting that symptom expression is influenced by multiple physiological, microbial, and environmental factors beyond genetic background.^{12–14}

Given the widespread availability of direct-to-consumer genetic testing and increasing clinician awareness of LCT polymorphisms, genotyping is sometimes requested as part of the diagnostic evaluation of LI. However, the clinical utility of genetic testing in populations with a high prevalence of LNP remains uncertain, particularly among adolescents, in whom symptom onset, dietary behavior, microbiota composition, and visceral sensitivity are highly variable.^{15–17} Furthermore, few studies have examined genotype–phenotype relationships specifically in adolescents or young adults, despite this being the developmental period during which symptoms most commonly manifest.

The present study aimed to evaluate the relationship among LI symptoms, dairy consumption patterns, and the two major LCT regulatory variants (rs4988235 and rs3754686)

KEY MESSAGES

- In populations with a high prevalence of lactase non-persistence, such as Türkiye, *LCT/MCM6* variants (rs4988235 and rs3754686) provide limited diagnostic value for clinical lactose intolerance.
- Genetic testing to support the diagnosis of lactase non-persistence offers minimal additional clinical benefit and should not be part of routine practice.
- Clinical evaluation based on symptoms is more informative than genotype. When necessary, functional testing should complement clinical assessment to ensure an accurate diagnosis and prevent unnecessary dietary restriction.

in a cohort of adolescents and young adults in Türkiye. By assessing genotype distributions, symptom severity, and dietary behavior in symptomatic and asymptomatic individuals, we sought to clarify whether these variants have diagnostic value in a population with a high baseline prevalence of LNP. Understanding this relationship is essential for guiding clinicians regarding the appropriate role of genetic testing and improving diagnostic pathways in routine practice.

MATERIALS AND METHODS

Study Design and Participants

This cross-sectional study included adolescents and young adults aged 12–25 years who presented to the Adolescent Health Clinic and the General Pediatrics Outpatient Clinic of Ankara University Faculty of Medicine, Ankara Children's Hospital, either with lactose-related gastrointestinal complaints or without such symptoms. Participants were recruited consecutively during routine outpatient visits and were eligible for inclusion if they were within the specified age range and able to complete the study questionnaires. Exclusion criteria included any documented chronic gastrointestinal disease, including celiac disease and inflammatory bowel disease, chronic use of medications that could affect gastrointestinal motility, and a history of abdominal surgery. Demographic characteristics, medical history, and dietary habits were obtained using structured questionnaires administered by trained researchers. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (Approval Number: İ09-671-24, Date: 10.10.2024). Written informed consent was obtained from all participants and from the parents or legal guardians of minors.

This was an exploratory cross-sectional study. Because reliable local data regarding the expected effect size of the association between LCT/MCM6 genotypes and clinical symptoms of LI were unavailable, a formal a priori sample size calculation was not performed. A total of 209 adolescents and young adults who met the eligibility criteria were enrolled during the study period.

Symptom Assessment

LI symptoms were evaluated using a validated symptom questionnaire assessing abdominal pain, bloating, diarrhea, flatulence, nausea, and urgency occurring within 30 minutes to 2 hours after consumption of milk or dairy products.¹⁸ Participants with scores ≥ 7 were classified as symptomatic, whereas those with scores < 7 were classified as asymptomatic.

Dairy Consumption Assessment

All participants completed a detailed frequency questionnaire assessing the consumption of raw milk and fermented dairy products (pasteurized yogurt, ayran, and kefir). Each item was scored on a 0–4 Likert scale, with higher scores indicating more frequent intake (0=never, 1=very rarely, 2=a few times per month, 3=a few times per week, and 4=every day). Raw milk and fermented dairy product consumption scores were analyzed separately.

Genotyping Procedures

Peripheral venous blood (minimum, 5 mL) was collected from all participants after informed consent was obtained. Genomic DNA was extracted using the QIAamp DNA Blood Mini Kit (Qiagen, Germany) according to the manufacturer's instructions.

Genotyping of the rs4988235 (–13910 C/T) and rs3754686 (–22018 G/A) variants was performed using TaqMan® real-time PCR assays (Thermo Fisher Scientific).

Fluorogenic allele-specific probes were labeled with FAM for the minor allele and HEX for the major allele, with Black Hole Quencher™ 1 (BHQ1) at the 3' end. The primer concentration in each reaction was 36 μ M, and the probe concentration was 20 μ M. PCR reactions were performed using a LightCycler® 480 Real-Time PCR System (Roche Diagnostics). Genotypes were automatically assigned by the LightCycler software and manually confirmed. Any ambiguous or low-quality curves were classified as uninterpretable and excluded.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics (version XX; IBM Corp., Armonk, NY, USA). The normality of continuous variables was evaluated using the Shapiro–Wilk test and visual inspection of histograms. Continuous

variables are presented as mean $\pm$ standard deviation (SD) or median (Q1–Q3), depending on their distribution, and categorical variables as frequencies and percentages. Group comparisons were performed using independent-samples t-tests or Mann–Whitney U tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. Correlations between symptom scores and dairy consumption were assessed using Spearman's rank correlation coefficients, and a two-sided p value < 0.05 was considered statistically significant.

RESULTS

Participant Characteristics

A total of 209 participants aged 12–25 years were enrolled. The mean age of the cohort was 17.9 ± 4.2 years, and 65.1% ($n=136$) were female. Based on the LI symptom score, 116 individuals (55.5%) were classified as symptomatic (score ≥ 7), and 93 (44.5%) were classified as asymptomatic (score < 7).

The symptomatic group was significantly older than the asymptomatic group (19.25 ± 4.26 vs. 16.31 ± 3.49 years, $p < 0.001$). Mean symptom scores were 20.34 ± 8.85 (range, 8–41) in symptomatic individuals and 1.69 ± 1.98 in the asymptomatic group.

Among the 105 symptomatic participants who reported the age at symptom onset, symptoms began at a mean age of 14.2 ± 4.7 years (range, 2–23 years).

Genotype Distributions

The rs4988235 (–13910 C/T) genotype distribution was similar between symptomatic and asymptomatic participants (Table 1). There was no significant difference between the groups ($p=0.842$). Similarly, rs3754686 (–22018 G/A) genotype frequencies did not differ between the groups. Furthermore, when rs4988235 and rs3754686 were considered jointly, 16 of 209 participants (7.7%) were homozygous for both non-persistence-associated genotypes (CC at rs4988235 and GG at rs3754686), whereas the remaining 193 (92.3%) carried at least one persistence-associated or heterozygous genotype.

Genotype and Symptom Onset

Neither rs4988235 nor rs3754686 genotype was associated with age at symptom onset. For rs4988235, both C/C and C/T genotypes showed symptom onset at approximately 13–14 years, with no significant difference. For rs3754686, ages at symptom onset were similar across T/T, T/C, and C/C genotypes (mean, 14.7–14.9 years), with no statistically significant differences. These results indicate that genetic variation did not influence the timing of symptom onset.

Table 1. Genotype distributions of rs4988235 (–13910 C/T) and rs3754686 (–22018 G/A) in symptomatic and asymptomatic groups, with estimated frequencies reported for the Turkish population

Variant/genotype	Symptomatic (%)	Asymptomatic (%)	Estimated frequency in Türkiye* (%)	p
rs4988235 (–13910 C/T)				0.842
C/C (G/G)	85.3	86.0	80–90	
C/T (G/A)	12.9	12.9	10–20	
T/T (A/A)	0.9	0.0	0–2	
rs3754686 (–22018 G/A)				0.596
T/T (A/A equivalent)	44.8	48.4	40–60	
T/C (A/G equivalent)	43.1	36.6	30–40	
C/C (G/G equivalent)	12.1	15.1	5–10	

*: Precise population-wide frequencies of these SNPs are not available for Türkiye; the available data represent estimates and ranges derived from the literature. References: Flatz et al.,¹ 1986; Özden et al.,² 1992; Enattah et al.,¹³ 2002; Itan et al.,³ 2010.

Table 2. Comparison of raw milk and fermented dairy product consumption between symptomatic and asymptomatic participants

Dairy product category	Symptomatic group (n=116), mean±SD	Asymptomatic group (n=93), mean±SD	Asymptomatic group, median (Q1–Q3)	Effect size (r)	p
Raw milk consumption	2.67±1.04	2.65±1.27	3.0 (2.0–4.0)	0.03	0.868
Fermented dairy product consumption	2.12±0.72	1.88±0.94	2.0 (1.3–2.3)	0.11	0.046

Higher scores indicate more frequent consumption on a 0–4 Likert-type scale (0=never, 4=every day). Values are presented as mean±standard deviation (SD) and median (Q1–Q3); p values and effect sizes (r) refer to between-group comparisons.

Dairy Consumption Patterns

Raw milk consumption was similar between symptomatic and asymptomatic participants (2.67 vs. 2.64, $p=0.868$, $r=0.03$). In contrast, fermented dairy product consumption was higher in the symptomatic group (2.12 vs. 1.88, $p=0.046$, $r=0.11$) (Table 2). Despite their generally better tolerance, fermented products were still consumed less frequently than raw milk in both groups.

When raw milk and fermented dairy product intake were analyzed within each genotype category (rs4988235 and rs3754686), no consistent or statistically significant patterns were identified. Consumption frequency did not vary meaningfully across genotypes.

Relationship Between Dairy Intake and Symptom Severity

In the symptomatic group ($n=116$), dairy consumption scores showed no significant linear correlation with symptom severity (Table 3). Although the correlation between kefir consumption and symptom severity was positive ($r=0.160$, $p=0.086$), its magnitude was very weak and did not reach statistical significance. Overall, increased fermented dairy product consumption did not reduce symptom scores, and higher milk intake did not predict greater symptom

Table 3. Spearman correlation coefficients between dairy product consumption scores and symptom severity among symptomatic participants ($n=116$)

Dairy product	Correlation coefficient (r)	p
Raw milk	-0.129	0.167
Ayran	-0.080	0.392
Yogurt	0.131	0.160
Kefir	0.160	0.086

severity (all $|r|<0.20$). These relationships are illustrated in the scatterplot matrix shown in Figure 1.

DISCUSSION

In this cross-sectional study of adolescents and young adults, more than half of the participants reported LI-related symptoms, with a mean age at symptom onset of approximately 14 years. This pattern is consistent with the physiological decline in lactase activity that begins in late childhood and becomes clinically apparent during adolescence.^{5,10} The age distribution of our cohort (12–25 years) was intentionally selected to reflect this

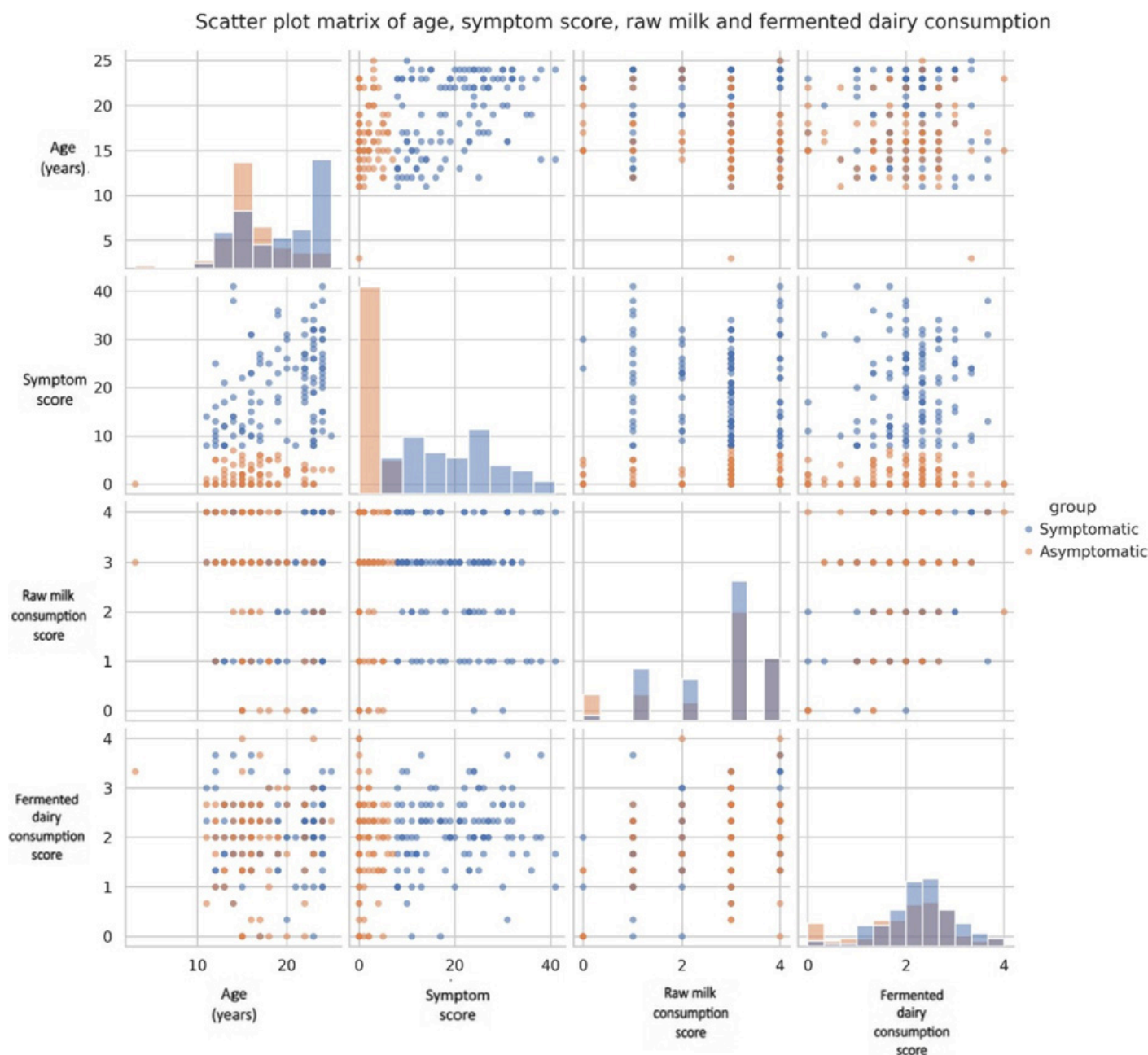


Figure 1. Scatterplot matrix of age, symptom severity, and dairy consumption scores in symptomatic and asymptomatic participants.

developmental period. According to both WHO definitions and the Lancet Adolescent Health Commission, adolescence extends up to age 24 because of prolonged neurobiological and psychosocial maturation. Including participants up to 25 years of age therefore allowed us to capture the full clinical spectrum of LI from late adolescence to young adulthood, the age range during which symptoms most commonly emerge.^{5,6}

A central finding of our study was the absence of a genotype–phenotype association for the two major LCT/MCM6 regulatory variants, rs4988235 (–13910 C/T) and rs3754686 (–22018 G/A). Genotype frequencies were nearly identical between symptomatic and asymptomatic individuals. These results are consistent with historical Turkish population studies demonstrating that the lactase non-persistence (LNP) phenotype and ancestral genotypes are highly prevalent,

with frequencies ranging from 70% to 90%.^{1,2} Our observed genotype rates (approximately 85% C/C for –13910 C/T) closely match the estimated frequencies for Türkiye and reflect expected population genetics rather than disease-specific biology.

These findings are biologically plausible because genetically determined lactase non-persistence does not universally translate into clinical LI. Many individuals with non-persistence-associated genotypes remain asymptomatic or report only mild symptoms, indicating that symptom expression is influenced by additional modifying factors beyond the LCT/MCM6 locus.^{5,7,9,16} In particular, gut microbiota composition, colonic fermentation capacity, habitual lactose exposure, variability in lactose tolerance thresholds, visceral hypersensitivity, and coexisting functional gastrointestinal disorders such as IBS are all likely to influence whether genetically predisposed individuals develop symptoms.^{5,9,16} Our results are consistent with this multifactorial model: LNP genotypes were frequent in the cohort, but their distribution did not differ between symptomatic and asymptomatic participants, and dairy consumption scores showed only very weak, nonsignificant correlations with symptom severity. Together, these observations support the view that LI in adolescents cannot be reliably predicted by LCT genotyping alone, particularly in populations in which LNP alleles are common.

Furthermore, asymptomatic adolescents with non-persistence genotypes may still develop intolerance later in life as lactase activity declines further, dietary habits change, or the intestinal environment shifts.^{5,16} Longitudinal data suggest that lactose tolerance can improve or worsen over time depending on continued lactose exposure, microbial adaptation, and the development of other gastrointestinal conditions, underscoring that clinically relevant LI represents a dynamic rather than a fixed genetic state.^{5,15} Our cross-sectional design cannot resolve these trajectories, but the coexistence of symptomatic and asymptomatic LNP carriers in our cohort highlights the need for individualized, symptom-guided counseling instead of lifelong dairy restriction based solely on genotype.

We also examined dairy consumption behaviors. Although fermented dairy intake was modestly higher among symptomatic individuals, raw milk consumption was similar between the groups, and raw milk remained the most frequently consumed dairy product overall. This suggests that cultural preferences and habitual consumption patterns may outweigh symptom-driven dietary modifications. Importantly, none of the dairy intake measures, including raw milk, yogurt, ayran, or kefir, showed significant correlations with symptom severity. This finding supports previous studies indicating that lactose

dose alone does not fully determine symptom generation and that sensitivity thresholds vary widely among individuals.^{17–19}

These findings have practical implications for clinical care. In regions such as Türkiye, where LNP genotypes are the norm rather than the exception, LCT genotyping has limited discriminatory value and cannot differentiate symptomatic from asymptomatic individuals. Routine genetic testing may therefore contribute to unnecessary costs without improving diagnostic accuracy. Current best-practice guidelines emphasize symptom-based clinical assessment and, when needed, hydrogen or methane breath testing as the diagnostic standards.^{5,19} Our study strongly supports the view that LI should remain a clinically driven diagnosis rather than a genetically defined one in populations with a high prevalence of LNP.

Limitations

Symptom assessment relied on self-reported questionnaires, which may introduce recall bias. Dairy intake scores were based on consumption frequency rather than precise lactose content, limiting dose–response interpretation. The sample size of 209 participants was primarily determined by feasibility within the study period rather than by a formal a priori power calculation for small genotype effects.¹² Given the high background prevalence of lactase non-persistence in Türkiye, the study was sufficiently powered to detect moderate-to-large differences in genotype distributions between symptomatic and asymptomatic groups but may have been underpowered to detect small effect sizes. As a result, subtle genotype–phenotype associations cannot be definitively excluded. Direct biochemical testing (breath hydrogen or enzyme assays) was not performed, preventing assessment of concordance among genetic, biochemical, and clinical measures.

CONCLUSION

In this cohort of adolescents and young adults, LI symptoms were common, yet the distribution of the major LCT/MCM6 variants (rs4988235 and rs3754686) was nearly identical between symptomatic and asymptomatic individuals. These findings indicate that genetically determined lactase non-persistence, although highly prevalent in Türkiye, does not reliably predict clinical intolerance. Symptom expression appears to be influenced more by physiological, microbial, and behavioral factors than by genotype alone.

Dairy consumption patterns and symptom severity showed no meaningful association, further supporting the concept that LI in this age group is multifactorial rather than genetically defined. Importantly, our results demonstrate that LCT genotyping provides limited diagnostic value in populations with a high prevalence of LNP and should not be routinely used to evaluate adolescents with suspected LI.

Clinical diagnosis should continue to rely primarily on symptom-based assessment, dietary history, and hydrogen–methane breath testing when needed. Recognizing the limited role of genetics in this context may help guide more cost-effective, accurate, and patient-centered diagnostic pathways in routine practice.

Ethics Committee Approval: Ethics committee approval was obtained from Ankara University Faculty of Medicine Human Research Ethics Committee (Approval Number: İ09-671-24, Date: 10.10.2024).

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