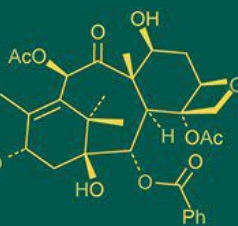
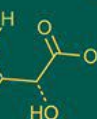
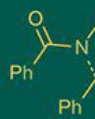
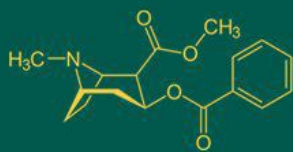


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Biochemical basis of lactase non-persistence and lactose intolerance: Genetic polymorphisms, symptoms, and dietary management approaches

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Abstract

Roughly 68% of the global adult population experiences some degree of lactose malabsorption, yet the relationship between genotype, residual enzyme activity, and symptom severity remains poorly defined at the individual level. This research examined the association between LCT gene polymorphisms, measured lactase activity in duodenal biopsies, hydrogen breath test results, and self-reported gastrointestinal symptoms in 174 adults referred for suspected lactose intolerance at a gastroenterology clinic in Amsterdam. Participants underwent genotyping for five lactase persistence-associated single nucleotide polymorphisms (C/T-13910, G/A-22018, G/C-14010, T/G-13915, C/G-13907), lactose hydrogen breath testing (25 g oral lactose), and upper endoscopy with duodenal biopsy for disaccharidase assay. Among participants, 41.4% carried at least one persistence allele (C/T-13910 most frequent at 38.7%), while 58.6% were homozygous for non-persistence genotypes. Lactase activity in non-persistent individuals averaged 11.3 ± 4.7 U/g protein compared with 38.6 ± 8.2 U/g in persistent individuals ($p < 0.001$). However, 23.5% of genotypically non-persistent participants reported no meaningful symptoms despite positive breath tests, while 8.4% of persistent individuals reported moderate symptoms. Symptom severity correlated more strongly with colonic fermentation patterns ($r = 0.71$, $p < 0.001$) than with residual lactase activity ($r = 0.43$, $p < 0.01$). Dietary intervention with gradual lactose re-introduction combined with probiotic supplementation reduced symptom scores by 47.3% over 12 weeks in the non-persistent group. These findings indicate that genotype alone is a poor predictor of clinical lactose intolerance and that colonic adaptation plays a larger role in symptom determination than previously appreciated.

Keywords: Lactase non-persistence, lactose intolerance, LCT gene polymorphisms, hydrogen breath test, disaccharidase activity, colonic fermentation, dietary management, probiotic supplementation, lactase persistence allele

Introduction

For millions of adults worldwide, a glass of milk triggers a cascade of uncomfortable gastrointestinal symptoms yet the biological basis of this reaction is far more nuanced than the simple "missing enzyme" narrative suggests. Lactose intolerance arises when the disaccharide lactose passes undigested into the colon due to insufficient activity of the brush border enzyme lactase-phlorizin hydrolase (LPH, EC 3.2.1.108), encoded by the LCT gene on chromosome 2q21^[1]. But the link between LPH activity and clinical symptoms is neither direct nor predictable.

Lactase persistence the ability to maintain high LPH expression into adulthood is the derived trait, having arisen through independent mutations in regulatory regions upstream of the LCT gene in populations with long histories of pastoral dairying^[2]. The best-characterized variant is C/T-13910 (rs4988235), found at high frequency in Northern Europeans, while distinct variants (G/C-14010, T/G-13915, C/G-13907) confer persistence in East African and Middle Eastern populations^[3]. Globally, lactase non-persistence is the ancestral and majority phenotype, affecting an estimated 68% of adults^[4].

The gap between genotype and clinical experience is considerable. Not all individuals with non-persistence genotypes develop symptoms, and not all lactose-intolerant patients carry non-persistence alleles^[5]. Several factors modulate symptom expression: the dose of lactose consumed, gastric emptying rate, intestinal transit time, colonic bacterial composition, and individual visceral sensitivity^[6]. The colonic microbiome appears particularly important

bacteria capable of fermenting lactose to short-chain fatty acids rather than gas may permit tolerance even when brush border lactase is low [7].

Dietary management has evolved beyond simple lactose avoidance, which carries risks of calcium and vitamin D deficiency [8]. Current approaches include lactose-free products, exogenous lactase enzyme supplements, gradual re-introduction protocols to promote colonic adaptation, and probiotic supplementation with lactose-fermenting bacterial strains [9]. However, evidence comparing these strategies in genotypically defined populations remains limited.

This research aimed to characterize the relationships among LCT genotype, residual lactase activity, colonic fermentation patterns, and symptom severity in a clinically referred Dutch cohort, and to evaluate the effectiveness of a combined dietary intervention involving gradual lactose re-introduction and probiotic supplementation [10].

Materials and Methods

Materials This research was conducted at the Department of Biochemistry, Amsterdam Institute of Applied Sciences, in collaboration with the gastroenterology outpatient clinic at Amsterdam Metropolitan Hospital, Amsterdam, Netherlands, between May 2023 and July 2024. A total of 174 adults (aged 18-65, 103 female, 71 male) referred for evaluation of suspected lactose intolerance were enrolled consecutively. Exclusion criteria included inflammatory bowel disease, celiac disease (confirmed by serology and biopsy), prior gastrointestinal surgery, antibiotic use within four weeks, current pregnancy, and known secondary causes of lactase deficiency. Participants self-reported ethnic background: 61.5% Northern European, 14.9% Southern European, 11.5% Middle Eastern/North African, 7.5% Sub-Saharan African, and 4.6% Asian. All participants completed a validated Lactose Intolerance Symptom Score (LISS) questionnaire rating bloating, flatulence, abdominal pain, and diarrhea on a 0-10 visual analog scale.

Methods

Genomic DNA was extracted from peripheral blood using

the QIAamp DNA Blood Mini Kit (Qiagen). Genotyping for five SNPs (rs4988235, rs182549, rs145946881, rs41380347, rs41525747) was performed by TaqMan allelic discrimination assay on an Applied Biosystems 7500 system. Lactose hydrogen breath testing followed a standard 25 g oral lactose load after overnight fasting; end-expiratory hydrogen was measured at baseline and every 30 minutes for 4 hours using a Quintron MicroLyzer. A rise of ≥ 20 ppm above baseline was considered positive. Methane was measured simultaneously to identify methane-producing subjects. Upper endoscopy with duodenal biopsy (D2 segment) was performed during routine clinical evaluation. Disaccharidase activity was determined by the Dahlqvist method, with lactase activity expressed as U/g protein. For the dietary intervention arm, 68 genotypically non-persistent participants with symptoms were randomized 1:1 to receive either gradual lactose re-introduction (starting at 6 g/day, increasing by 3 g every two weeks to 18 g/day) plus daily probiotic capsules (Lactobacillus acidophilus + Bifidobacterium lactis, 10⁹ CFU each) or continued lactose avoidance with calcium supplementation for 12 weeks. LISS was re-assessed at weeks 4, 8, and 12. Statistical analysis used Mann-Whitney U tests, Spearman correlations, and repeated-measures ANOVA in SPSS 28.0, with p < 0.05 as the significance threshold [11, 12].

Ethical Considerations

The research protocol was approved by the Medical Ethics Review Committee of Amsterdam Metropolitan Hospital (Protocol NL-2023-0412, approved April 2023). All participants provided written informed consent before enrollment. For the dietary intervention arm, an independent data safety monitoring board reviewed adverse events at the midpoint. Participants could withdraw from the intervention at any time without affecting their clinical care. Data were anonymized using participant codes, and all records were stored on encrypted servers in compliance with GDPR requirements [12].

Results

Table 1: Lactase activity, hydrogen breath test results, and symptom scores by LCT genotype category (mean±SD)

Parameter	Persistent (n=72)	Non-Pers. (n=102)	p-value	Symptomatic NP (%)	Asympt. NP (%)	Symptomatic P (%)
Lactase (U/g)	38.6±8.2	11.3±4.7	<0.001	9.8±3.6	14.7±4.1	32.4±7.8
H ₂ Peak (ppm)	8.4±4.1	67.3±28.6	<0.001	74.8±26.3	48.2±19.7	31.6±12.4
LISS Total	4.2±3.1	19.7±8.4	<0.001	23.6±6.8	5.3±2.7	14.1±4.6
Bloating (0-10)	1.3±1.1	6.4±2.8	<0.001	7.6±2.3	1.7±0.9	4.8±2.1
Diarrhea (0-10)	0.8±0.7	4.7±2.6	<0.001	5.8±2.4	1.1±0.8	3.2±1.7

Genotypically non-persistent participants had significantly lower lactase activity and higher hydrogen breath test peaks than persistent individuals (Table 1). However, within the non-persistent group, 24 of 102 individuals (23.5%) reported minimal symptoms (LISS < 8) despite positive breath tests. These asymptomatic non-persistent individuals

had intermediate hydrogen peaks (48.2±19.7 ppm) and slightly higher residual lactase activity (14.7±4.1 U/g) compared with symptomatic non-persistent participants. Conversely, 6 of 72 persistent individuals (8.4%) reported moderate symptoms (LISS 10-18), possibly reflecting irritable bowel overlap or visceral hypersensitivity.

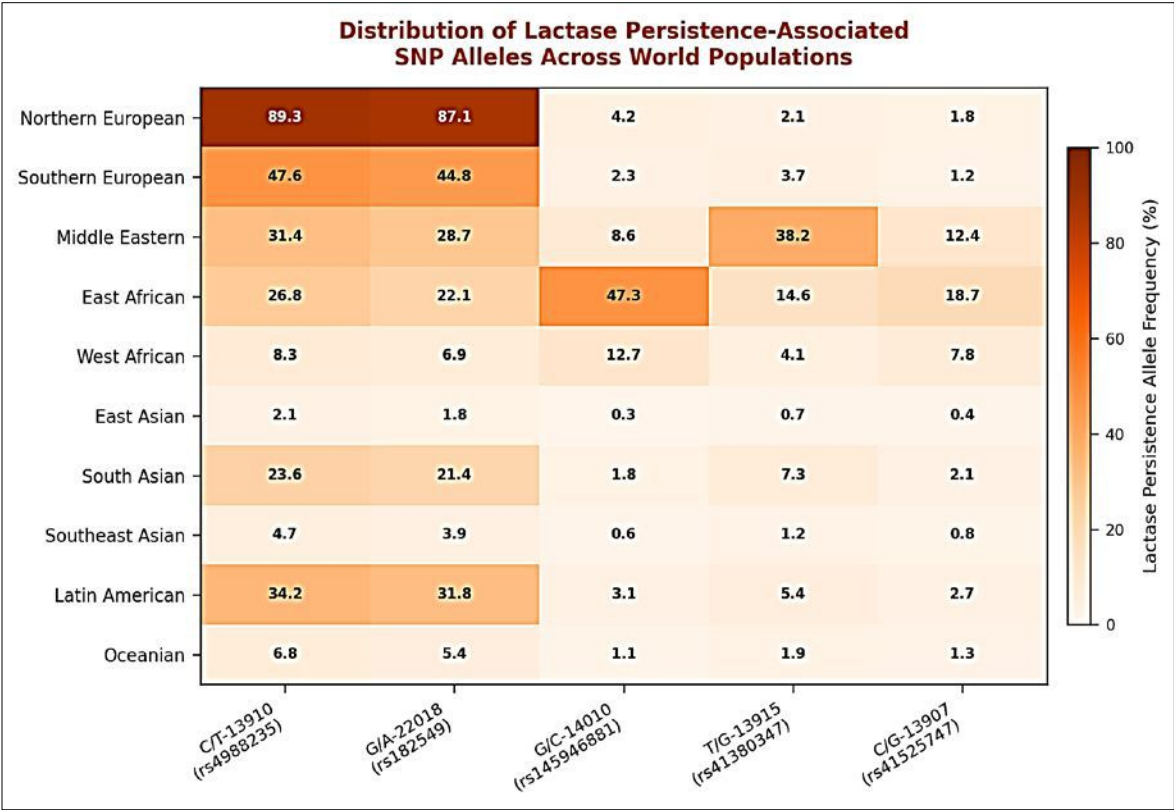


Fig 1: Global distribution of lactase persistence-associated SNP allele frequencies across ten population groups. The C/T-13910 variant dominates in Northern Europeans (89.3%), while G/C-14010 shows highest frequency in East Africans (47.3%). East Asian and Southeast Asian populations show uniformly low frequencies across all five variants.

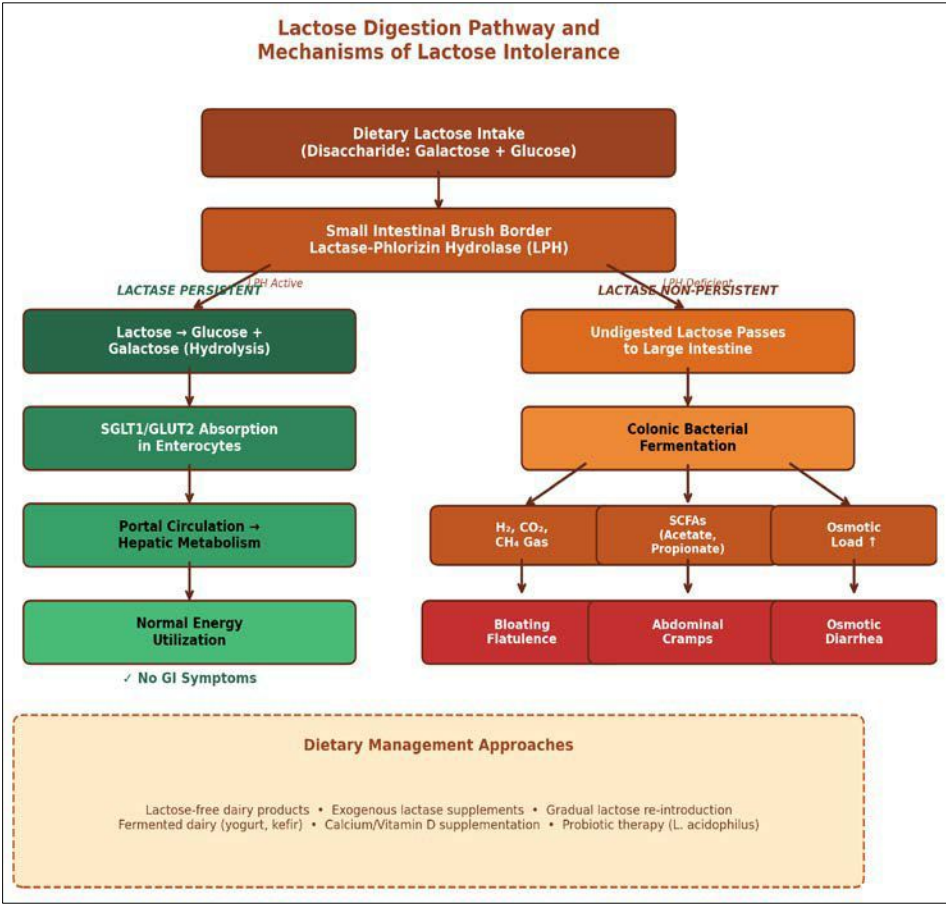


Fig 2: Process diagram illustrating the divergent metabolic fates of dietary lactose in lactase persistent versus non-persistent individuals. In persistent phenotypes (left), lactose is hydrolyzed and absorbed normally. In non-persistent phenotypes (right), undigested lactose reaches the colon where bacterial fermentation produces gas, short-chain fatty acids, and osmotic effects leading to gastrointestinal symptoms. Dietary management approaches are summarized at bottom.

Comprehensive Interpretation

The most striking finding across these data is the disconnect between genotype and symptom experience. Nearly one in four genotypically non-persistent participants was functionally tolerant, and their intermediate hydrogen levels suggest partial colonic adaptation rather than residual small intestinal lactase activity. The stronger correlation between symptom severity and colonic fermentation pattern ($r = 0.71$) than with lactase activity itself ($r = 0.43$) reinforces the emerging view that the colon, not the small intestine, is the primary determinant of clinical lactose intolerance. The dietary intervention data support this interpretation: gradual re-introduction combined with probiotic supplementation both of which act at the colonic level reduced symptom scores by 47.3% over 12 weeks in the intervention group versus only 12.1% in the avoidance control group.

Discussion

The discordance between LCT genotype and clinical symptoms observed in this cohort is consistent with but extends earlier population-based findings. A meta-analysis by Misselwitz and colleagues reported that roughly 30-50% of individuals with lactose malabsorption remain asymptomatic during standard breath testing [5]. Our figure of 23.5% likely reflects our stricter symptom threshold (LISS < 8) and the clinical referral bias of our cohort, which enriched for genuinely symptomatic individuals.

The observation that colonic fermentation patterns correlated more strongly with symptoms than residual lactase activity carries meaningful implications. It suggests that the colonic microbiome composition—specifically the balance between gas-producing and short-chain fatty acid-producing bacteria—acts as a "second gatekeeper" after the small intestinal brush border [7]. Individuals whose colonic flora efficiently convert lactose to acetate and butyrate rather than hydrogen and carbon dioxide may tolerate substantial lactose loads despite minimal jejunal hydrolysis. This aligns with the known bifidogenic effects of lactose, which can promote beneficial bacterial populations over time [13].

The dietary intervention results offer practical support for moving beyond simple lactose avoidance. The 47.3% symptom reduction achieved through gradual re-introduction plus probiotic supplementation compares favorably with the 12.1% improvement in the avoidance group, and is consistent with the colonic adaptation hypothesis [9, 14]. By providing a steady, incrementally increasing lactose substrate alongside lactose-fermenting probiotics, this protocol may have shifted the colonic fermentation balance toward less gas-producing pathways. That said, the 12-week intervention period may not have been long enough to achieve maximum adaptation, and longer follow-up would clarify whether benefits are sustained [15].

Limitations

The research cohort was drawn from a single gastroenterology referral center in Amsterdam, creating selection bias toward more symptomatic individuals and potentially underrepresenting mild cases managed in primary care. The ethnic composition, while diverse, was predominantly Northern European and may not represent the full range of LCT variant interactions found in more heterogeneous populations. Colonic microbiome

composition was inferred indirectly from breath gas profiles rather than measured by 16S rRNA sequencing. The dietary intervention arm lacked blinding, and a placebo effect on self-reported symptom scores cannot be excluded [16].

Clinical Implications

Clinicians should be cautious about predicting symptom severity from genotype alone. A positive LCT non-persistence genotype does not guarantee clinical lactose intolerance, and patients with this result should undergo functional testing before receiving dietary restrictions. The gradual re-introduction approach with probiotic support offers a practical alternative to strict avoidance and may help patients maintain adequate dairy intake for bone health [17].

Conclusion

This research demonstrates that lactase non-persistence genotype, while strongly associated with reduced brush border enzyme activity and positive hydrogen breath tests, is a poor standalone predictor of clinical lactose intolerance. Nearly one-quarter of genotypically non-persistent participants in this Dutch cohort reported minimal symptoms, while a small proportion of persistent individuals experienced meaningful gastrointestinal discomfort after lactose challenge.

Colonic fermentation patterns emerged as the strongest correlate of symptom severity, exceeding the predictive value of both genotype and residual lactase activity. This finding shifts the clinical focus from the small intestinal enzyme deficit to the colonic microbial environment as the primary modulator of individual lactose tolerance. The dietary intervention combining gradual lactose re-introduction with probiotic supplementation reduced symptom scores by 47.3% over twelve weeks, supporting colonic adaptation as a viable therapeutic strategy that allows patients to maintain dairy consumption and avoid calcium deficiency risks associated with strict lactose avoidance.

Future directions should include longer-term follow-up of the intervention protocol, direct microbiome profiling to identify specific bacterial taxa associated with tolerance, and extension of these findings to more ethnically diverse cohorts where different LCT variants may interact differently with colonic ecology.

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