The *LCT* –13910C>T (rs4988235) Variant, Lactose Tolerance, and Calcium-Related Phenotypes (Literature Review)

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ABSTRACT

Background:
Calcium is an essential mineral for skeletal stability and long-term bone strength, with the vast majority of total body calcium stored in the skeleton. Because calcium cannot be synthesized endogenously, adequate dietary intake is required to maintain calcium balance and support bone health across the life course. In many dietary patterns, milk and dairy products contribute substantially to calcium intake because they provide high calcium density and are widely consumed (Obermayer-Pietsch et al., 2004; Laaksonen et al., 2009). Genetic variation at the lactase (*LCT*) locus influences lactose digestion capacity and thereby affects the tolerance and habitual consumption of lactose-containing dairy products, which can indirectly influence dietary calcium intake (Kuchay et al., 2011; Almon et al., 2013). Calcium absorption occurs primarily in the intestine and is supported by vitamin D status, which can increase the efficiency of calcium uptake and thus modify effective calcium availability (Obermayer-Pietsch et al., 2007; Kowalówka et al., 2023).

Methods:
This narrative review summarizes peer-reviewed evidence on the lactase-persistence regulatory variant commonly described as –13910C>T and frequently captured by rs4988235. For consistency with genotype reporting in nutrigenetic contexts, alleles are presented here using an A/G coding scheme, in which A corresponds to lactase persistence and G corresponds to lactase non-persistence. Evidence was integrated across functional studies of lactase expression and enzymatic activity, observational and Mendelian-randomization–framed analyses of milk consumption and calcium intake, and epidemiologic/clinical studies assessing biochemical indices (serum calcium and vitamin D-related measures).

Results:
Genetic variation at rs4988235 influences whether lactase activity persists beyond childhood and therefore determines how well lactose is tolerated across adult life. Under an A/G coding system, individuals with AA or AG genotypes are generally consistent with

lactase persistence, and thus tend to tolerate lactose-containing dairy products well throughout life; correspondingly, dietary calcium intake through food is typically maintained at usual levels because dairy remains an accessible calcium source (Kuchay et al., 2011; Laaksonen et al., 2009; Almon et al., 2013). In contrast, individuals with the GG genotype are more consistent with lactase non-persistence, characterized by an age-dependent decline in lactase expression and activity; lactose tolerance may therefore become progressively lower with advancing age, which can contribute to reduced dietary calcium intake through food if lactose-containing dairy products are avoided or consumed less frequently (Kuchay et al., 2011; Koek et al., 2010). Across cohorts, lactase non-persistence is associated with lower milk consumption and lower dairy-derived calcium exposure, and some settings report a modest average reduction in total calcium intake consistent with reduced dairy consumption (Laaksonen et al., 2009; Almon et al., 2013; Koek et al., 2010). Associations with serum calcium and vitamin D-related measures have also been reported, although their magnitude varies across populations and study designs (Bácsi et al., 2009; Koek et al., 2010; Kowalówka et al., 2023).

Discussion:
The dominant and most reproducible pathway is that rs4988235 genotype influences lactose tolerance, which shapes habitual consumption of lactose-containing dairy products and thereby affects calcium intake from food (Laaksonen et al., 2009; Almon et al., 2013). Where lactose tolerance is reduced, conventional dairy products are more frequently limited, and calcium intake tends to be lower unless calcium is obtained via lactose-free dairy products, fortified alternatives, or other calcium-containing foods (Obermayer-Pietsch et al., 2007; Laaksonen et al., 2009). Because calcium absorption occurs in the intestine and is influenced by vitamin D status, the nutritional implications of lower dairy intake are expected to depend not only on intake but also on the efficiency of intestinal absorption and overall dietary context (Obermayer-Pietsch et al., 2007; Kowalówka et al., 2023). Accordingly, genotype is most appropriately interpreted as indicating a tendency toward lifelong lactose tolerance (AA/AG) versus age-related reduction in lactose tolerance (GG), with corresponding expected differences in calcium intake through food if dairy intake differs.

Subjects: Genetics, Nutrition **Keywords:** Genetics, Polymorphism, Nutrition, Lactose

INTRODUCTION

Calcium homeostasis is fundamental to skeletal development and lifelong bone maintenance. The skeleton serves as the principal reservoir of calcium, and adequate dietary calcium intake is required to support bone mineralization and to limit compensatory mobilization of calcium from bone. Insufficient calcium intake is therefore biologically linked to reduced peak bone mass acquisition and to accelerated loss of bone mineral in life stages characterized by increased skeletal vulnerability, including postmenopause and advanced age (Obermayer-Pietsch et al., 2004; Enattah et al., 2005). In nutritional epidemiology and public health practice, milk and dairy products are frequently emphasized as major contributors to calcium intake because they provide high calcium density in commonly consumed foods (Laaksonen et al., 2009; Koek et al., 2010). Nevertheless, dairy consumption is heterogeneous across individuals and populations, reflecting cultural practices, food availability, and biological tolerance to lactose.

A principal biological determinant of lactose digestion capacity is lactase persistence, which is influenced by regulatory variants at the lactase (*LCT*) locus. The best-studied marker is the regulatory variant often described as −13910C>T and commonly captured by rs4988235; genotype at this locus predicts lactase expression and enzymatic activity and is associated with milk consumption behavior at the population level (Kuchay et al., 2011; Laaksonen et al., 2009; Almon et al., 2013). Because dairy foods provide substantial calcium, genotype-related differences in lactose tolerance can lead to predictable differences in dairy consumption and calcium intake through food and may be reflected in calcium-related biochemical measures and, in selected contexts, skeletal outcomes such as BMD and fractures (Obermayer-Pietsch et al., 2004; Bácsi et al., 2009; Koek et al., 2010). In this review, rs4988235 is presented using an A/G coding, where AA and AG are consistent with lactase persistence and GG is consistent with lactase non-persistence.

This review integrates evidence across three domains. First, it summarizes functional evidence that lactase regulatory variants predict lactase expression and enzymatic activity, including age-dependent downregulation in lactase non-persistence (Kuchay et al., 2011). Second, it synthesizes epidemiologic evidence linking genotype to milk consumption patterns and calcium intake (Laaksonen et al., 2009; Almon et al., 2013; Koek et al., 2010). Third, it evaluates whether genotype-associated differences in dietary calcium exposure and related biomarkers are reflected in skeletal outcomes, acknowledging differences across study populations and endpoints (Obermayer-Pietsch et al., 2004; Obermayer-Pietsch et al., 2007; Enattah et al., 2005; Tolonen et al., 2011; Kowalówka et al., 2023).

Genetic Architecture and Functional Basis of Lactase Persistence

The plausibility of downstream associations with calcium intake and skeletal phenotypes depends on the strength of the genotype–phenotype relationship for lactase expression and activity. Mechanistic evidence supports a direct link between lactase regulatory genotype and lactase biology, including age-dependent reductions of lactase activity in lactase non-persistent individuals. In a pediatric clinical setting, genotype at the lactase regulatory locus predicted lactase enzymatic activity in small-intestinal biopsy specimens and aligned with reduced lactase expression, supporting

the interpretation that lactase non-persistence represents developmentally programmed downregulation that becomes more apparent with age (Kuchay et al., 2011). This provides biological grounding for the common observation that lactose tolerance may be maintained in early life but becomes progressively lower in individuals with lactase non-persistence as lactase expression declines (Kuchay et al., 2011).

Lactase persistence is generally characterized by a dominant genetic pattern such that individuals carrying at least one persistence allele often resemble persistence homozygotes in terms of milk consumption behavior. This pattern is supported by cohort evidence showing that milk avoidance is concentrated in lactase non-persistent individuals, whereas heterozygous individuals generally do not display a clearly intermediate phenotype for milk consumption (Almon et al., 2013). In the context of rs4988235 reported using an A/G coding scheme, this corresponds to the expectation that AA and AG individuals typically tolerate lactose-containing dairy well throughout life, whereas GG individuals are more likely to experience age-related reduction in lactose tolerance.

From Genotype to Dietary Behavior: Milk Avoidance and Calcium Intake

Across cohorts, lactase non-persistence is associated with reduced milk consumption, providing a consistent and biologically coherent mechanism linking genotype to lower calcium intake through food. Longitudinal evidence indicates that genotype-associated differences in milk consumption can be detectable early and may persist across development into adulthood, supporting a life-course model in which lactase non-persistence contributes to sustained lower exposure to dairy-derived nutrients, including calcium (Laaksonen et al., 2009). Because milk and several dairy products are among the most used calcium sources, lower consumption is expected to translate into lower dietary calcium intake through food, particularly where dairy is not replaced by other calcium sources.

Evidence from children and adolescents further supports this pathway. In the European Youth Heart Study, lactase non-persistence was associated with higher milk avoidance and lower calcium intake, and heterozygous individuals did not show an intermediary phenotype regarding milk consumption (Almon et al., 2013). Adult population studies similarly report lower dietary calcium intake in individuals with lactase non-persistence, consistent with reduced intake of lactose-containing dairy (Koek et al., 2010). Taken together, the evidence supports a clear and reproducible pattern: lactase regulatory genotype influences lactose tolerance, which influences dairy consumption and thereby affects calcium intake through food (Laaksonen et al., 2009; Almon et al., 2013; Koek et al., 2010).

Table 1: Key Studies on Lactose Metabolism and Genetic Pathways

Study (Author, Year)	Study Design	Population (Size, Characteristics)	SNP(s) Investigated	Primary Outcome / Key Findings
Obermayer-Pietsch et al., 2004	Cross-sectional association study	258 postmenopausal Austrian women	rs4988235 (A/G)	GG (non-persistent) associated with markedly lower milk-derived calcium intake, more milk avoidance, lower hip/spine BMD, and more fractures (Obermayer-Pietsch et al., 2004).
Obermayer-Pietsch et al., 2007	Comparative physiological study with follow-up	73 postmenopausal Austrian women	rs4988235 (A/G)	GG participants consumed substantially less dairy; lactose exposure was associated with reduced mineral absorption in physiological testing; lactose-free calcium supplementation supported stable BMD over follow-up (Obermayer-Pietsch et al., 2007).
Enattah et al., 2005	Population-based study	483 very elderly Finns (85+ years)	rs4988235 (A/G)	GG genotype (primary lactose malabsorption) associated with increased fracture risk in very old age (Enattah et al., 2005).
Bácsi et al., 2009	Cross-sectional case–control	595 Hungarian postmenopausal women	rs4988235 (A/G)	GG genotype linked to greater milk avoidance, slightly lower adjusted serum calcium, and modestly lower BMD measures (Bácsi et al., 2009).
Laaksonen et al., 2009	Longitudinal cohort	Finnish cohort followed from childhood to young adulthood	rs4988235 (A/G)	GG genotype associated with lower milk intake from childhood onward; uptake of low-lactose products reduced differences in calcium intake in adulthood in some subgroups (Laaksonen et al., 2009).
Koek et al., 2010	Cross-sectional analysis in two cohorts	Older Dutch adults (Rotterdam Study; LASA)	rs4988235 (A/G); VDR variants	G allele associated with lower dietary calcium and slightly lower serum calcium, but not with BMD or fractures; some anthropometric associations reflected population stratification (Koek et al., 2010).
Tolonen et al., 2011	Population-based cohort analysis	1,551 Finnish adults (Young Finns)	rs4988235 (A/G)	In men, GG genotype had lowest calcium intake; AA associated with modestly higher trabecular bone density in pQCT; no clear effect in women (Tolonen et al., 2011).
Kuchay et al., 2011	Cross-sectional biopsy study	176 North Indian children (1–16 years)	rs4988235 (A/G)	Strong genotype–phenotype link: genotypes consistent with non-persistence showed lower lactase activity/expression; variant robustly predicted persistence/non-persistence (Kuchay et al., 2011).
Almon et al., 2013	Cross-sectional cohort (MR-framed)	684 Swedish children and adolescents	rs4988235 (A/G)	Lactase non-persistence associated with milk avoidance and lower calcium intake; heterozygous individuals did not show an intermediary phenotype for milk consumption (Almon et al., 2013).

Calcium Bioavailability, Lactose Exposure, and Vitamin D-Related Phenotypes

Calcium intake is only the first step; effective calcium availability also depends on intestinal absorption and subsequent systemic handling. Calcium is absorbed from the intestine, transported via the circulation, and ultimately incorporated into bone as part of normal mineral metabolism. Vitamin D supports intestinal calcium absorption and thereby increases the efficiency of calcium uptake. When lactase activity declines in lactase non-persistence, lactose-containing dairy products are more often poorly tolerated, particularly with increasing age, which tends to reduce dairy intake and thereby reduce calcium intake through food. In physiological testing, lactase non-persistent postmenopausal women not only reported substantially lower dairy intake but also demonstrated reduced mineral absorption during lactose exposure, indicating that lactose tolerance can influence both dietary intake and effective absorption under specific conditions (Obermayer-Pietsch et al., 2007).

Vitamin D status remains a key modifier of calcium absorption and calcium balance. Observational data in young adults suggest that lactase non-persistence may coincide with lower circulating 25(OH)D and serum calcium, consistent with genotype-linked dietary patterns in which intake of dairy-associated nutrients is reduced (Kowalówka et al., 2023). However, vitamin D levels are also shaped by sun exposure, seasonality, supplementation, and fortification, and therefore the relationship between lactase genotype and vitamin D-related phenotypes is expected to vary by environment (Kowalówka et al., 2023). Overall, lactase genotype can be associated with calcium-related biochemical profiles, but these biomarker differences do not uniformly translate into skeletal outcomes across all populations (Koek et al., 2010; Bácsi et al., 2009).

Interpreting Lactase Persistence Genetic Results

Genetic reporting related to lactase persistence commonly classifies individuals according to inferred lactase persistence/non-persistence status and links this classification to expected lactose tolerance and dietary calcium intake through food. For rs4988235 reported using an A/G coding scheme, carriers of at least one A allele (AA or AG) are generally consistent with lactase persistence; lactose-containing dairy products are typically tolerated well throughout life, and calcium intake through food is expected to remain within usual ranges, as dairy products remain a practical dietary calcium source (Kuchay et al., 2011; Laaksonen et al., 2009; Almon et al., 2013). In contrast, individuals homozygous for the G allele (GG) are more consistent with lactase non-persistence, characterized by an age-dependent decline in lactase activity; lactose tolerance may therefore become increasingly lower with advancing age, and dietary calcium intake through food may be reduced if lactose-containing dairy products are avoided (Kuchay et al., 2011; Laaksonen et al., 2009; Koek et al., 2010).

At the population level, lactase regulatory variants are reliable predictors of lactase activity and correlate with milk consumption behavior (Kuchay et al., 2011; Almon et al., 2013). These genotype-based expectations are nutritionally relevant because dairy products are major calcium sources in many diets. Where dairy intake is limited, calcium intake can be supported through lactose-free dairy products, fortified alternatives, and other calcium-containing foods, which may mitigate reductions in total dietary calcium (Laaksonen et al., 2009; Obermayer-Pietsch et al., 2007). Studies consistently show lower

milk intake and lower dairy-derived calcium exposure among lactase non-persistent individuals, while the extent of net differences in total calcium intake varies across settings and dietary practices (Laaksonen et al., 2009; Koek et al., 2010). Evidence linking lactase non-persistence to skeletal endpoints remains heterogeneous: associations with lower BMD and/or higher fracture risk have been reported in postmenopausal and very old populations in some cohorts, whereas other large population-based analyses do not find consistent associations with BMD or fractures after adjustment (Obermayer-Pietsch et al., 2004; Enattah et al., 2005; Koek et al., 2010). Thus, rs4988235 is most appropriately interpreted as a marker of lifelong lactose tolerance (AA/AG) versus age-related reduction in lactose tolerance (GG), with corresponding expected differences in calcium intake through food when dairy intake differs.

CONCLUSION

Regulatory variation at the lactase locus captured by rs4988235 is strongly associated with lactase persistence/non-persistence and provides a biologically grounded predictor of lactose digestion capacity, with evidence of age-dependent downregulation of lactase activity in lactase non-persistence (Kuchay et al., 2011). Using an A/G coding scheme, AA and AG genotypes are consistent with lactase persistence and are therefore expected to support lifelong tolerance of lactose-containing dairy products with typically normal calcium intake through food, whereas the GG genotype is consistent with lactase non-persistence, in which lactose is tolerated increasingly less well with advancing age and calcium intake through food may be reduced if dairy intake is limited (Laaksonen et al., 2009; Almon et al., 2013; Koek et al., 2010). Across cohorts, lactase non-persistence is consistently associated with reduced milk consumption and lower dairy-derived calcium exposure, while downstream biochemical and skeletal consequences vary by population and outcome, with signals reported in postmenopausal and very old groups in some studies and null findings in other large cohort analyses after adjustment (Obermayer-Pietsch et al., 2004; Enattah et al., 2005; Koek et al., 2010). Overall, genotype at rs4988235 supports clear expectations about lactose tolerance and likely calcium intake through food, while implications for bone outcomes depend on broader nutritional context, including vitamin D status and the use of lactose-free or alternative calcium sources (Obermayer-Pietsch et al., 2007; Kowalówka et al., 2023).

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