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Galactose mutarotase deficiency as the galactosemia type IV

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Galactose, a monosaccharide, plays diverse biological roles in energy production, especially in the glycolysis and glycosylation of proteins and lipids. Galactose metabolism is mediated by the Leloir pathway, which comprises four key enzymes. Following lactose hydrolysis, galactose mutarotase (GALM) catalyzes the anomerization of β-D-galactose to α-D-galactose, providing a substrate for the downstream pathway. In 2019, GALM deficiency was defined as the fourth type of galactosemia. Affected individuals may develop cataracts similar to those observed in individuals with galactokinase deficiency, disrupting the subsequent steps in the Leloir pathway. However, cataracts generally occur less frequently and tend to be milder in patients with GALM deficiency, likely because of the partial compensation provided by spontaneous galactose mutarotation in aqueous solutions. Because lactose, the primary dietary source of galactose, is the predominant carbohydrate consumed until weaning, the timely initiation of lactose restriction can prevent or even reverse cataract formation. To date, other complications or adverse events, including those in heterozygous carriers of *GALM* variants, have not been clearly demonstrated. This review aims to synthesize current knowledge and findings of GALM deficiency on molecular mechanisms, clinical presentation, diagnostic approaches, carrier risk, and dietary management, with particular emphasis on cataract prevention and reversibility through early lactose restriction. By consolidating available evidence, we propose future research directions, with broader implications for newborn screening programs, clinical decision-making, and a deeper understanding of galactose metabolism.

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INTRODUCTION

The word *galactose* is derived from the Ancient Greek word *galaktos*, meaning milk and the chemical suffix for sugars *-ose* [1]. The etymology indicates that milk and dairy products are rich in lactose, a disaccharide composed of galactose and glucose, and a major carbohydrate [2–4]. In humans, lactose is hydrolyzed into β-D-glucose and β-D-galactose by β-galactosidase, which is found on the intestinal villi [5, 6]. β-D-galactose is subsequently converted to α-D-galactose and then enters the glycolysis and glycosylation pathways, among others [1]. When one of the four components of the galactose metabolic pathway, also known as the Leloir pathway, is disrupted by a genetic defect, the pathophysiology of galactosemia can result (Fig. 1) [7, 8]. For consistency, "galactosemia" is defined as elevated blood galactose levels resulting from enzyme deficiencies in the Leloir pathway, whereas "hypergalactosemia" denotes elevated blood galactose levels irrespective of etiology. We identified galactose mutarotase (GALM) deficiency in 2019 through the study of cases with unexplained hypergalactosemia [9, 10]; since then, the concept of galactosemia has continued to evolve [1, 11–14]. This review provides a historical overview of galactosemia, with a focus on GALM deficiency, summarizing current knowledge, including the discovery of GALM, carrier risk, and future perspectives.

BRIEF HISTORY OF GALACTOSEMIA

Historical observations and subsequent research have contributed to the current understanding of galactosemia. In 1908, Von Ruess, an Austrian ophthalmologist, reported the first case of galactosemia [15]. His description introduced the concept of an inborn error in galactose metabolism, as lactation cessation improved the abnormal characteristics of galactosuria. In 1917, Göppert et al. provided evidence of a genetic basis for galactosemia through dietary experiments with cottage cheese [16]. In 1956, Isselbacher et al. identified a precise enzyme defect in galactose-1-phosphate uridylyltransferase (GALT, EC2.7.7.12) [17], defining the classical form of galactosemia as GALT deficiency (MIM# 230400) [18, 19]. Affected neonates typically present within the first week of life with poor feeding, vomiting, diarrhea, failure to thrive, jaundice, liver failure, renal tubular dysfunction, hypotonia, cataracts, and severe bacterial infections, especially sepsis or meningitis caused by *Escherichia coli* [20, 21]. Early lactose restriction is lifesaving [21], and there are now newborn screening systems for galactosemia worldwide, which have saved the lives of many children [22–24]. Nevertheless, long-term complications, including cognitive disability, speech and language difficulties, neuropsychiatric manifestations, ovarian insufficiency, and impaired bone health, remain prognostic challenges despite continuous lactose restriction, although they are generally non-progressive [25–27]. There are currently three recognized types of GALT deficiency: classic galactosemia, which is the severe form described above; clinical variant galactosemia, which presents with a severe neonatal phenotype similar to classic galactosemia but is not typically associated with long-term complications; and biochemical variant

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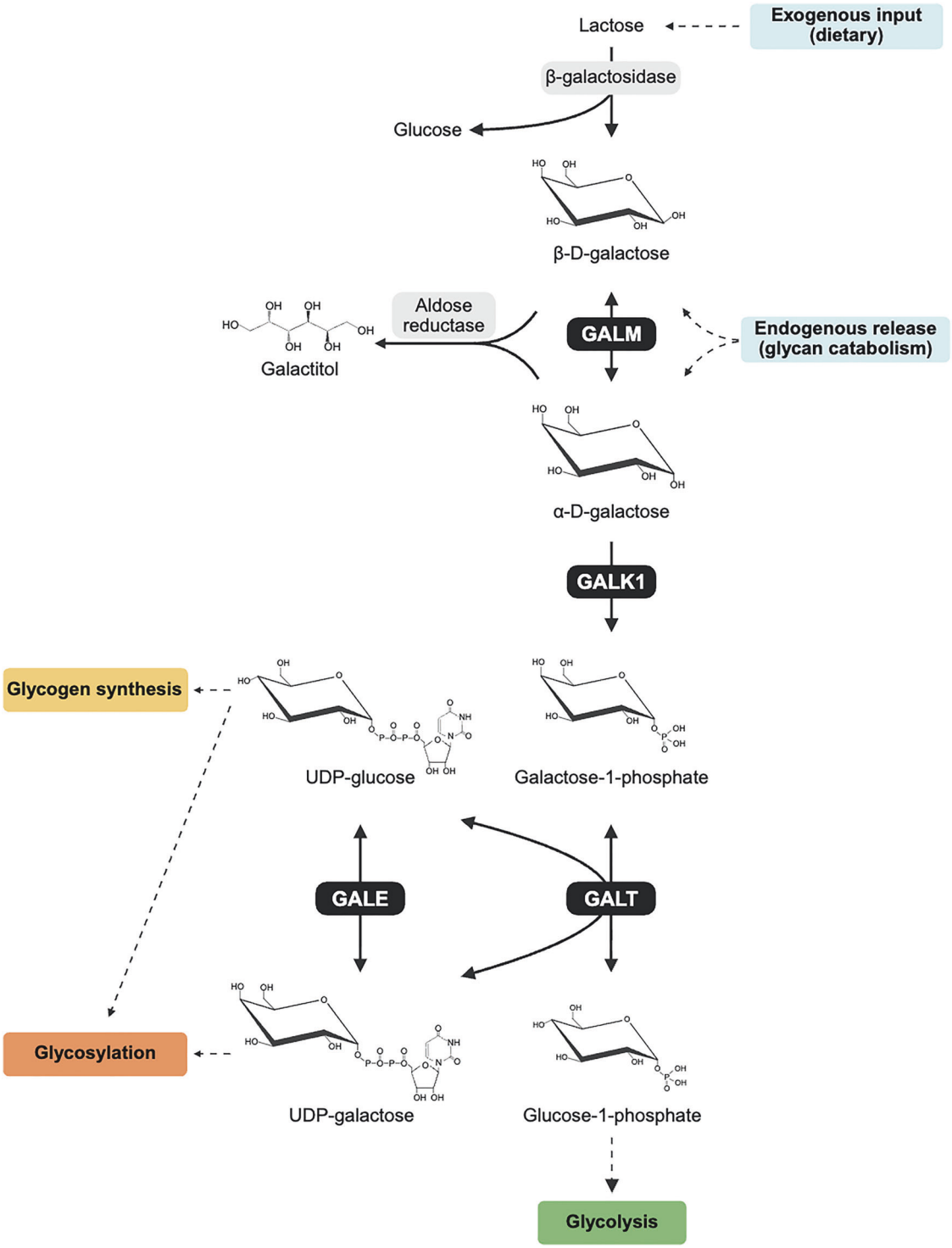

Fig. 1 The Leloir pathway of galactose metabolism. Schematic overview of endogenous or exogenous galactose metabolism via the Leloir pathway. GALM galactose mutarotase, GALK1 galactokinase, GALE UDP-galactose-4-prime-epimerase, GALT galactose-1-phosphate uridylyltransferase

galactosemia, exemplified by the Duarte variant, which is usually asymptomatic [18, 28–30].

Clarification of the causal link between GALT deficiency and its clinical phenotype was achieved through the stepwise elucidation of the galactose metabolic pathway, primarily accomplished by Luis Federico Leloir et al. [17, 31]. Their sustained and pioneering efforts not only clarified the biochemical basis of galactosemia but also earned Leloir the Nobel Prize; the pathway is now referred to as the "Leloir pathway" (Fig. 1) [32–34]. In addition to milestones in biochemical discovery, the development of newborn screening is another cornerstone for the modern understanding of galactosemia. Beutler contributed to the development of the first practical spot test for GALT activity, and Guthrie pioneered its implementation in population-wide screening [22, 35]. The recognition that early detection and dietary intervention could prevent life-threatening neonatal complications led to the introduction of

newborn screening for GALT deficiency in 1964, representing one of the earliest examples of preventive genetics [23].

The subsequent identification of additional enzymatic defects further expanded the spectrum of galactosemia. Galactokinase (GALK1; EC 2.7.1.6) was discovered in 1965 as the causative enzyme of galactosemia type II. Clinically, GALK1 deficiency is distinguished by cataracts; however, it may also involve transaminitis, cognitive complications, and pseudotumor cerebri [36–39]. Galactosemia type III UDP-galactose-4-prime-epimerase (GALE, EC 5.1.3.2) deficiency was first reported in 1972, and it ranges from an asymptomatic peripheral form to a generalized form closely resembling classical galactosemia [40–42]. Recent studies have described intermediate phenotypes with broader manifestations such as thrombocytopenia, thereby expanding the clinical spectrum [43–47]. By the mid-1970s, the classification of type I, type II, and type III galactosemia established a framework of inborn errors in the metabolism of galactose. However, galactose mutarotase (GALM, EC 5.1.3.3), an enzyme that accelerates galactose anomerization in the Leloir pathway [34, 48], has remained an intriguing but unconfirmed candidate for several decades [49].

GALACTOSE MUTAROTASE

Galactose mutarotase was first discovered by researchers investigating notatin, an old antibiotic isolated from *Penicillium notatum* [50]. Although notatin oxidases β-D-glucose rather than α-D-glucose, one kind of notatin showed greater activity toward α-D-glucose than the others. The high oxidation rate was due to accelerated anomerization in the simultaneously contained material, which is highly conserved in plants, bacteria, fungi, and animals [11, 51]. In humans, GALM is monomeric and prefers galactose over glucose as a substrate [49, 52]. The *GALM* gene (NCBI reference sequence: NM_138801.3 as the MANE Select Transcript and NP_620156.1) in 2p22.1 contains seven exons and encodes aldose 1-epimerase with 342 amino acids. Structural and fundamental insights have been summarized in other studies [11]. Spontaneous isomerization of galactose in the aqueous phase can hinder dynamic monitoring between β-D-galactose and α-D-galactose in vivo. In contrast, the intracellular environment slows the conversion, allowing GALM to supply α-D-galactose to the downstream steps in the Leloir pathway [53–55].

GALACTOSE MUTAROTASE DEFICIENCY

Identification

Clinicians have identified individuals who exhibit non-transient but reproducible hypergalactosemia without an identifiable etiology [56]. In Japan, the prevalence of previously unclassified hypergalactosemia was ~1 in 60,000 births, which is notably higher than that of galactosemia types I, II, and III (~1 in 1,000,000, 1 in 500,000, and 1 in 160,000 births, respectively) [57, 58]. We encountered a neonate with hypergalactosemia during a screening test. Blood galactose and galactose-1-phosphate levels exhibited a similar pattern to galactosemia type II, characterized by high galactose levels but low galactose-1-phosphate levels. In addition, hypergalactosemia due to lactose loading was reproducible. Cataracts were observed at 7 months of age. However, genetic panel testing did not reveal any mutations or variants of unknown significance in *GALK1*. Around the same time, another patient diagnosed with GALK1 deficiency was referred to our hospital. Again, genetic testing did not reveal any significant variants, as was the case with the previous patient. This prompted us to perform whole-exome sequencing in the two families, leading to the identification of the *GALM* gene as a candidate for the previously unknown hypergalactosemia. Interestingly, suspicious *GALM* variants have been detected in all individuals with similar episodes in Japan. An in vitro assay employing individually derived lymphocytes demonstrated decreased enzyme activity and instability of the mutant protein, supporting its classification as the fourth type of galactosemia, GALM deficiency (MIM# 618881) [9, 59]. After ~40 years, galactosemia type IV was confirmed due to biallelic pathogenic variants in the *GALM* gene as a novel type of galactosemia.

Prevalence and distribution

As an unexpected prompt process from identification to finding the eight family degrees, curiosity raised the idea that a considerable number of individuals with GALM deficiency may have been missed. To estimate the prevalence of GALM deficiency, we performed a comprehensive study in which in vitro pathogenic evaluation of reported variants in a public genome database yielded an estimated frequency of 1:228,411 in all populations and 1:80,747 in Japan [60]. The relatively high frequency of GALM deficiency, both in comparison with other types of galactosemia within Japan and across populations worldwide, may explain why this entity was first confirmed in Japan [10, 60]. However, nationwide surveillance in Japan showed that the prevalence of GALM deficiency is 1:181,835 [13]. The discrepancy in the prevalence between the estimated and real-world data indicates that approximately half of the individuals with GALM deficiency remain unrecognized. Numerous factors might interfere, including the cutoff threshold in newborn screening, galactose profile variance, and sensitivity to galactose or total galactose and among others. Since the current newborn screening system is not proposed for GALM deficiency, a suitable protocol would be required if GALM deficiency is included in the conditions for newborn screening. Multidisciplinary discussions and additional research are required to confirm this hypothesis. The magnitude can be relatively considered due to its low prevalence and, as stated below, mild severity. Although GALM deficiency exists as a disease entity in areas other than Japan [12, 14, 61, 62], the exact situation remains uncertain. Our results indicate that the frequency was higher in certain populations than in Japan, such as Africans (1:10, 388 Africans and 1:47,228 in Finns, compared to that in Japan [60]. Further comprehensive studies are required to determine the overall state.

Biochemical characteristics and diagnosis

Blood galactose, galactose-1-phosphate, and total galactose patterns provide crucial insights into the metabolic disturbances associated with galactosemia, including GALM deficiency. A galactose-dominant elevation, defined as a galactose-1-phosphate to galactose ratio of less than one, together with only mildly elevated galactose-1-phosphate levels, is commonly observed and is consistent with impairment of the Leloir pathway [9, 13]. However, galactose-1-phosphate levels are often detectable during early infancy, possibly because of secondary accumulation related to the increased red cell mass from physiological neonatal polycythemia and/or a relatively low GALT-to-GALK1 activity ratio in neonates [63, 64]. Urinary galactitol levels are mildly elevated in individuals with GALM deficiency [65]. To date, there is no evidence supporting the use of these biochemical parameters as reliable indicators for stratifying cataract risk. Moreover, although blood galactose measurements play a role in newborn screening and subsequent monitoring, appropriate thresholds for screening or follow-up must be determined.

These biochemical findings may raise the suspicion of GALM deficiency, and a definitive diagnosis should rely on condition-specific approaches, such as enzyme activity and genetic analysis, as is the case for other types of galactosemia [66, 67]. A coupled assay with β-galactose dehydrogenase has been developed to measure GALM enzymatic activity; however, the rapid and spontaneous mutarotation of galactose has hindered its routine clinical use [9, 60]. Genetic testing for *GALM* is currently the most

practical and reliable diagnostic method. Given the phenotypic and biochemical similarities between GALM and GALK1 deficiencies, comprehensive sequencing approaches, including gene panel testing, whole-exome sequencing, and whole-genome sequencing, are desirable for an accurate diagnosis. Although genotype–phenotype correlations have not been firmly established, it is noteworthy that transaminitis has been reported exclusively in individuals with the c.424G>A variant [13]. Hepatocytes harboring the c.424G>A variant may be vulnerable to galactose or galactitol accumulation through unknown mechanisms. Functional studies using cellular and animal models are crucial for addressing these questions.

Pathophysiology, clinical manifestations, and natural history

The accumulation of galactose and galactitol, as demonstrated in individuals with GALM deficiency, contributes to disease pathogenesis. Cataract formation, the primary clinical manifestation of GALM deficiency, is biologically plausible because excessive galactitol increases osmolarity and oxidative stress, particularly in lens fiber cells, leading to cataract development, a well-known feature of galactosemia [68, 69]. The severity and frequency of cataracts in patients with GALM deficiency appear to be milder compared with those in patients with GALK1 deficiency; however, delayed initiation of lactose restriction results in irreversible cataracts, even in individuals with GALM deficiency [13, 61]. Persistent galactose ingestion might allow progressive galactitol accumulation, potentially causing central nervous system disturbances. Yet, to the best of our knowledge, no reports to date have suggested this association [70]. Transaminitis is also associated with GALM deficiency; however, additional symptoms have not been described [13]. Moreover, emerging evidence suggests that seemingly unrelated biological pathways intersect with GALM-related metabolism or phenotypes [71, 72]. Since the lifelong natural history of GALM deficiency has not been fully elucidated, continued clinical observation remains important. Nevertheless, the identification of healthy adults with GALM deficiency harboring biallelic *GALM* mutations supports the notion that GALM deficiency is unlikely to result in severe acute complications or long-term outcomes, as observed in classical GALT deficiency or generalized GALE deficiency [13].

Management

Consistent with other types of galactosemia, the fundamental therapeutic approach for GALM deficiency is lactose restriction. However, an optimal regimen and duration of lactose restriction have not yet been established. In clinical practice, we recommend introducing and continuing a lactose-free formula until weaning, after which intermittent consumption of lactose-containing foods may be permitted. Given the high lactose content of breast milk and standard infant formula, as well as the frequent feeding patterns during infancy, lactose restriction appears to be a reasonable approach. The quantity of lactose intake per body and the frequency of consumption typically decrease after weaning. However, excessive or sustained dairy consumption should be avoided to prevent the accumulation of galactose and galactitol because GALM enzyme activity remains unchanged with age. Therefore, management can be reframed as permitting intermittent dairy intake rather than strict lifelong avoidance. In practice, dietary tolerance may be assessed by measuring blood galactose levels 1.5–2 h after the ingestion of lactose-containing foods. Supplementation with β-galactosidase lowers blood galactose levels and may help increase dietary tolerance in some individuals [65].

Carrier risk of the GALM mutation

The biochemical and phenotypic similarity between GALM deficiency and GALK1 deficiency has raised concern about a potential cataract risk in heterozygous carriers of *GALM* variants, particularly because the "Osaka" variant (p.Ala198Val) in *GALK1* is associated with age-related cataracts [73]. To explore the relationship between cataracts and carrier status, we analyzed the allele frequencies of known hypergalactosemia-related genes in a cohort of individuals with cataracts (Supplementary Table 1) [74]. No significant mutation enrichment, including the Osaka variant, was observed in *GALT, GALK1, GALM*, or other relevant genes. In line with previous reports, heterozygosity for *GALT* variants did not appear to increase the risk of cataracts [75]. Moreover, because the Duarte variant, a mild biochemical form of GALT deficiency, is not associated with cataracts, our findings are consistent with the expectation that heterozygous carriers with higher residual GALT activity than Duarte homozygotes would not manifest cataracts [76]. However, our results do not entirely exclude a possible association between *GALM* heterozygosity or the *GALK1* Osaka variant and age-related cataracts, as the age distribution of our cohort may have limited our ability to detect such a relationship [73]. Indeed, previous studies have implicated other genes, such as aldose reductase, as risk factors for cataract, suggesting that larger and more age-stratified studies are required to clarify potential associations [77–80].

FUTURE PERSPECTIVES AND CONCLUSION

Our understanding of GALM deficiency, the fourth most recognized type of galactosemia, is continually increasing. However, several key questions remain unresolved. First, the natural history of the disorder across an individual's lifespan must be clarified in diverse populations. Although cataracts are a hallmark of GALM deficiency, there is no established critical period for their development, nor are there reliable surrogate biomarkers. Urinary galactitol may prove helpful in this regard; however, additional clinical data, particularly from adults, are required.

Further discussion is warranted regarding the inclusion of GALM deficiency in newborn screening programs. The current platform for GALT and GALK1 deficiency could detect GALM deficiency by adjusting the blood galactose cutoff value. Yet, lowering the threshold may increase the rate of false positives, and precise management criteria have not been established. Robust evidence regarding the efficacy of screening is necessary to assess its feasibility and balance its potential benefits against its harms. Genome-based screening, as well as other emerging approaches, may offer more precise solutions. Finally, optimal management strategies must be defined. Prompt and sustained lactose restriction during infancy, followed by gradual relaxation to allow the intermittent consumption of lactose-containing foods, appears to be a reasonable approach. Improved risk stratification for cataract development may help refine individual management strategies. Given the partial efficacy of β-galactosidase supplementation in reducing galactose levels [65], variability in endogenous villous β-galactosidase activity may contribute to individual differences in galactose tolerance.

GALM deficiency is a rare condition, as is the case for most inborn errors of metabolism, underscoring the need for international collaboration, such as through GalNet, to collect comprehensive data, delineate its full clinical spectrum and phenotypic diversity, and improve care and management for individuals with GALM deficiency and their families [81].

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request. Supplementary information is available at the Journal of Human Genetics' website.

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AUTHOR CONTRIBUTIONS

Data acquisition and curation: YA, TS, RF, and OO; visualization: YW and YM-S; writing–original draft: YW; writing–review and editing: all authors.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL

The Ethics Committee of the Faculty of Medicine at Tohoku University (Miyagi, Japan) approved the study investigating the relationship between cataract occurrence and genetic background (approval number: 2019-1-012). During the preparation of this study, YW utilized ChatGPT5 to enhance readability and language clarity. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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