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Review Article

Comprehensive Review of Galactosemia: Genotype-Phenotype Correlations, Molecular Pathophysiology, and Clinical Spectrum

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ABSTRACT

Galactosemia is a hereditary disorder of carbohydrate metabolism with autosomal recessive inheritance, resulting from a defect in an enzyme in the Leloir pathway. The most common and severe form is classical galactosemia (Type I), caused by a deficiency of the enzyme Galactose-1-Phosphate Uridyltransferase (GALT). Despite early diagnosis through newborn screening and strict dietary restriction, patients with classical galactosemia continue to face debilitating long-term complications, including cognitive impairment, speech apraxia, and premature ovarian insufficiency (POI).

This review article provides a detailed examination of the molecular genetics of the GALT gene, genotype-phenotype correlation analysis in common variants (p.Q188R, p.S135L, Duarte), and specific mutations in the Iranian population. Furthermore, cellular mechanisms of injury, including endoplasmic reticulum (ER) stress, oxidative stress, and protein glycosylation defects, are discussed as primary factors for the occurrence of complications despite treatment. The main clinical take-home message is that genotype strongly predicts long-term outcomes, and dietary restriction alone does not prevent neurological or ovarian complications; therefore, early genetic diagnosis and personalized monitoring are essential.

Keywords: Classical galactosemia, GALT gene, Genotype-phenotype correlation, Premature ovarian insufficiency, Glycosylation defect

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INTRODUCTION

Galactosemia refers to a group of metabolic anomalies that impair the body's ability to metabolize galactose (the main sugar in milk). The main pathway for galactose metabolism is the Leloir Pathway. A defect in any of the three main enzymes in this pathway leads to different phenotypes:

1. Classical galactosemia (Type I): Deficiency in the GALT enzyme, which is the most common and severe form.
2. Galactokinase deficiency (Type II): Deficiency in the GALK1 enzyme.
3. Epimerase deficiency (Type III): Deficiency in the GALE enzyme (1).

The prevalence of classical galactosemia varies globally between 1:40,000 and 1:60,000 live births. However, in societies with high rates of consanguineous marriages, such as Iran, the prevalence may be higher. The main paradox in galactosemia is that eliminating galactose (milk and dairy) from the diet prevents neonatal death and acute liver failure, but it is unable to completely prevent long-term neuropsychiatric and endocrine complications (2).

Biochemistry and Molecular Pathophysiology

Understanding the correlation between genotype and phenotype requires knowledge of cellular injury mechanisms. In classical galactosemia, the absence of the GALT enzyme leads to precursor accumulation.

Regarding metabolite toxicity in galactosemia, intracellular accumulation of galactose-1-phosphate depletes inorganic phosphate (Pi) and reduces cellular ATP levels, a phenomenon known as the "Phosphate Trap." Additionally, excess galactose is reduced to galactitol by the enzyme aldose reductase. Galactitol is an osmolar sugar alcohol that does not cross the cell membrane; its accumulation causes water absorption, cellular swelling, and cataracts (3).

Novel Cellular Injury Mechanisms (Beyond Toxin Accumulation)

Recent studies show that damage is not solely due to acute toxicity but involves epigenetic and cellular processes, including:

Glycosylation defects: The GALT enzyme is necessary for the production of UDP-Galactose, the primary galactose donor for synthesizing glycoproteins and glycolipids. UDP-Gal deficiency prevents membrane and secretory proteins (such as FSH hormone and neural adhesion molecules) from being synthesized correctly. This phenomenon is termed "Secondary Congenital Disorder of Glycosylation" (CDG), a condition in which impaired glycosylation of proteins and lipids leads to multi-systemic manifestations, including neurodevelopmental delay and endocrine dysfunction (4).

Endoplasmic reticulum (ER) stress: The accumulation of Gal-1-P and misfolded proteins triggers the Unfolded Protein Response (UPR) pathway in the ER. Chronic activation of these pathways leads to apoptosis (cell death), particularly in non-regenerative tissues like the ovaries and brain (5).

Recent advances (2019-2023): Registry-based studies from the GalNet consortium have confirmed that even with early dietary intervention, long-term complications persist, underscoring the need for therapies targeting these cellular mechanisms (6).

Genetics and Genotype-Phenotype Correlation

The GALT gene is located on chromosome 9p13, and more than 300 mutations have been identified. The type of mutation strongly determines residual enzyme activity and, consequently, disease severity.

Table 1. Classification of Genotypes and Clinical Prognosis

Prognosis	Blood Gal-1-P Level	Enzyme Activity (GALT)	Example Mutations (Alleles)	Genotype Class
Poor (Long-term): High risk of intellectual disability, severe speech problems, 90% risk of ovarian insufficiency (POI).	Very High:> 30-50 mg/dL (without treatment)	Absent / Near Zero (< 1%)	p.Q188R / p.Q188R p. K285N / p.K285N	Severe Classical
Moderate to Good: Acute neonatal toxicity exists, but cognitive and ovarian complications are much lower than the classical form.	High (but normalizes faster)	< 1% (RBCs) ~10% (Liver/Intestine)	p.S135L / p.S135L p. S135L / p.Q188R	Clinical Variant
Excellent: Usually asymptomatic. Normal neurological growth. Often do not require treatment.	Mildly High	~25%	p.N314D (D2) / G (Duarte Variant)	Biochemical Variant
Asymptomatic	Normal	~50%	G / Normal	Carriers

Abbreviations: Gal-1-P = Galactose-1-Phosphate; RBCs = Red Blood Cells; POI = Premature Ovarian Insufficiency; G = normal GALT allele; Duarte variant = p.N314D polymorphism with reduced activity. Blood Gal-1-P levels refer to values on an unrestricted diet (before treatment initiation)

Analysis of Common Mutations

Mutation p.Q188R (c.563A>G):

This is the most common mutation in Indo-European populations and Iran. It is a "Missense" change occurring near the enzyme's catalytic site, completely destroying its activity. Phenotypically, Q188R homozygotes represent the most classical and severe form of the disease. Studies have shown that these patients' IQ is not inversely related to the age at treatment onset (meaning IQ decline is possible even with early treatment) (7).

Mutation p.S135L (c.404C>T):

This mutation was first identified in African-American populations but is also seen in the Middle East. The protein resulting from this mutation is unstable, but in tissues with high protein turnover (like the liver), some enzymatic activity is preserved. Phenotypically, S135L patients are generally spared from ovarian insufficiency and have better cognitive outcomes (8).

Mutation p.K285N (c.855G>T):

This mutation is common in Central and Eastern Europe as well as Iran. It is a "Null" mutation associated with a complete lack of enzymes, and its clinical severity is reported to be similar to or even more severe than Q188R (9).

Galactosemia Genetics in Iran

Studies in Iran (including Mirzajani et al. and Dastgheib et al.) show that the genetic profile of Iranian patients is highly diverse. The study by Mirzajani et al. (2006) included 32 unrelated Iranian families with classical galactosemia, while Dastgheib et al. (2016) reported data from 15 patients from a single center in Shiraz, southern Iran. These studies together suggest that the p.Q188R mutation accounts for approximately 55-60% of mutant alleles nationally, but regional differences may exist (e.g., higher prevalence of p.K285N in Northern provinces). The p.Q188R mutation accounts for about 55% to 60% of mutant alleles. The second most common mutation is p.K285N, accounting for about 8-10%. Rare and specific mutations such as p.A320T, p.L54F, and p.Q259R have also been reported in Iran. Identifying these mutations is vital for prenatal diagnosis (PND) in high-risk families (10).

Clinical Manifestations

Affected newborns appear normal at birth, but symptoms appear within a few days after consuming milk (containing lactose). These symptoms include:

Failure to thrive, hepatomegaly, and jaundice due to hepatic toxicity of Gal-1-P, coagulation disorders, prolonged PT and PTT.

Sepsis with E. coli: Inhibition of leukocyte glycosylation weakens the innate immune system and increases the risk of gram-negative infections. Death due to sepsis is the most common cause of death prior to diagnosis (11).

Furthermore, even with dietary adherence, the following complications are common, especially in homozygotes (Q188R):

A) Neurological and Cognitive Deficits:

The average IQ of patients is between 70 and 85. Executive function deficits, slow processing speed, and short-term memory problems are common. Cerebellar ataxia and tremors usually appear in adolescence.

B) Speech Disorders:

"Childhood Apraxia of Speech (CAS)" is a hallmark sign of this disease, seen in about 60% of patients. This disorder results from a problem in motor planning of speech muscles and is distinct from simple speech delay (12).

C) Premature Ovarian Insufficiency (POI):

More than 80% of women with classical galactosemia suffer from POI. Symptoms include primary or secondary amenorrhea and high FSH levels. The mechanism is direct galactose toxicity to ovarian follicles during the fetal and neonatal periods. Spontaneous pregnancy is very rare in these patients (13).

D) Reduced Bone Density:

Osteopenia and osteoporosis occur due to restricted dairy (calcium) intake as well as intrinsic defects in the bone matrix.

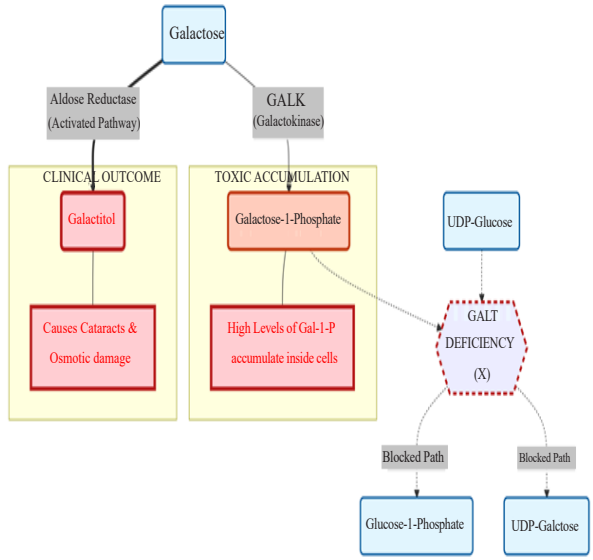


Figure 1. The Leloir pathway and metabolic blocks in classic galactosemia. Galactose is normally converted to glucose-1-phosphate via three enzymatic steps: GALK (galactokinase), GALT (galactose-1-phosphate uridyltransferase), and GALE (UDP-galactose-4-epimerase). In GALT deficiency (red cross), galactose-1-phosphate accumulates, leading to cellular toxicity. Aldose reductase also converts galactose to galactitol, causing osmotic damage and cataracts.

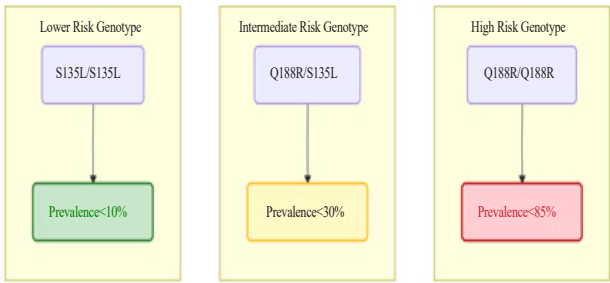


Figure 2. Genotype-phenotype correlation for premature ovarian insufficiency (POI) in classic galactosemia. Severe mutations (e.g., p.Q188R/p.Q188R) are associated with >80% risk of POI, with onset typically in adolescence. Mild variants (e.g., p.S135L/p.S135L or Duarte variants) show significantly lower risk (<20%). Heterozygous carriers have normal ovarian function. Data compiled from longitudinal cohort studies (13, 14).

Management and Treatment

Based on the international guidelines of the Galactosemia Network (GalNet 2017), management and treatment include:

Diet: Complete elimination of lactose and galactose sources (breast milk, cow's milk, goat's milk, etc.). Use of soy-based or elemental formulas (2).

Monitoring: Measuring red blood cell (RBC) Galactose-1-Phosphate (Gal-1-P) levels with the goal of keeping levels below 3-5 mg/dL. Urine galactitol levels are also monitored (2).

Screening for Complications:

- Speech evaluation at 18 months (12).
- Annual measurement of calcium and vitamin D, and DEXA scan in adolescence (2).
- Measurement of FSH/LH in girls starting at age 10 for early detection of POI (13, 14).

CONCLUSION

Classical galactosemia is a prime example of a genetic disease where the "phenotype" extends beyond a simple metabolic defect. There is a strong correlation between genotype (especially the Q188R mutation) and the severity of neurological and ovarian complications. Identifying specific mutations in patients (especially in the Iranian population with its specific allelic diversity) is essential for predicting disease progression and providing accurate genetic counseling. Future therapies must focus on correcting glycosylation defects and reducing cellular stress, as diet alone is insufficient to prevent long-term complications. Recent studies from 2019-2023 have reinforced that genotype-directed monitoring and early intervention are the cornerstones of care (6, 15, 16).

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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