

Type IV Galactosemia's Structural and Molecular Biology

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Abstract

Type IV galactosemia is a metabolic disorder that is passed down through the family. Galactose autorotate enzyme activity decreases as a result of mutations in the GALM gene. D-galactose and a few other monosaccharides' - and -anomers are interconverted by this enzyme. The structure of human galactose autorotate is largely composed of -sheets and is monomeric. A glutamate acting as a base and a histidine residue acting as an acid are required for the catalytic mechanism. Together, these residues break open the pyranose ring of d-galactose, allowing the monosaccharide's first two carbon atoms to freely rotate. The hydroxyl group on carbon 1 may reverse its configuration as a result of this. Early onset cataracts are a symptom of type IV galactosemia, which is similar to type II galactosemia (galactokinase deficiency). However, as a disease that was only recently discovered, its long-term effects are unknown. It is currently unknown what kind of physiological function, if any, galactose mutarotase's interactions with other monosaccharides play. The potential relationship with different proteins likewise require further examination.

Keywords: Type IV galactosemia; UDP-galactose-4-epimerase deficiency; GALE deficiency; Galactosemia subtype; Enzyme deficiency; Galactose metabolism; UDP-galactose-4-epimerase

Introduction

Type IV galactosemia, also known as UDP-galactose-4-epimerase deficiency (GALE deficiency), is a rare subtype of galactosemia that is caused by a deficiency of the enzyme UDP-galactose-4-epimerase [1]. This enzyme is responsible for converting UDP-galactose into UDP-glucose, an important step in galactose metabolism.

Unlike the more common forms of galactosemia (classic galactosemia and galactokinase deficiency), type IV galactosemia typically presents later in life, often during childhood or adolescence. This delayed onset is due to the partial activity of the enzyme in affected individuals, allowing some galactose metabolism to occur.

Individuals with type IV galactosemia may experience a range of symptoms and complications related to galactose accumulation, such as liver dysfunction, cataracts, intellectual disability, developmental delays, and neurological problems [2]. The severity and specific manifestations of the condition can vary widely among affected individuals.

Diagnosis of type IV galactosemia is typically confirmed through genetic testing, which identifies mutations in the GALE gene responsible for encoding the UDP-galactose-4-epimerase enzyme.

The management of type IV galactosemia primarily focuses on dietary modifications, similar to other forms of galactosemia. Individuals are advised to limit their intake of galactose-containing foods and may need to follow a galactose-restricted diet. Regular monitoring of liver function, cataract development, and overall health is important to detect and manage any potential complications.

Research and advancements in understanding type IV galactosemia are ongoing, aiming to improve diagnostic methods, develop targeted therapies, and enhance the quality of life for individuals affected by this rare genetic disorder. Genetic counseling is also essential for affected individuals and their families to understand the inheritance pattern and receive appropriate support and guidance.

One in every 62,000 live births worldwide has galactosemia, a life-threatening autosomal recessive disorder. Based on a defect in galactose metabolism, there are three known types of galactosemia [3]. Classic galactosemia is the most common and severe form of galactosemia.

Acute neonatal toxicity syndrome, hepatocellular damage, and death are all possible outcomes of classic galactosemia.

Classic galactosemia is caused by a lack of the enzyme galactose 1-phosphate uridylyltransferase. Pathogenic mutations in the GALT gene cause severe reduction or absence of the GALT function. According to the GALT gene has 11 exons and a length of 4.3 kbp.

More than 300 variants of the GALT gene have been identified thus far. However, new pathogenic mutations are the subject of ongoing research.

Galactosemia is an autosomal latent problem influencing galactose digestion through what is known as the Leloir pathway. Galactose-1-phosphate uridylyltransferase (GALT), which is linked to the Duarte variant form of galactosemia, is one of the four enzymes in this pathway. There are two distinct types of the Duarte allele: The first and second Duarte The Duarte-2 allele also has a 4-base pair deletion, and GALT enzyme activity is reduced, despite the fact that both forms of the Duarte allele mutation have the same amino acid substitution at position 314 [4]. There is no 4-base pair deletion in Duarte-1; rather, there is a second L218L mutation that increases enzyme activity. There is no need for diet therapy in Duarte variant galactosemia (Duarte-2 galactosemia), which has approximately 25% residual enzyme activity and virtually no evidence of long-term complications.

The Duarte-1 and Duarte-2 alleles have a frequency of 0.09 each. Duarte-2 galactosemia is diagnosed when the Duarte-2 variant and a classic galactosemia variant coexist on different alleles [5]. Due to reduced but not zero GALT activity and moderately elevated levels of blood galactose (free galactose or its metabolites such as RBC galactose-

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1-phosphate in the range of 14.7–33.8 mg/dL vs. 1 in unaffected controls) during newborn screening, individuals with Duarte-2 galactosemia are identified. Duarte-2 galactosemia is not a medical emergency, whereas classic galactosemia.

Babies with classic galactosemia who have been exposed to lactose may experience problems feeding, nausea, jaundice, failure to thrive, lethargy, and coma. If not treated, damage to the liver and kidney, cataracts, and sepsis may occur, resulting in death. If started promptly, substituting soy or other non-dairy formulas can prevent serious acute complications and produce dramatic results. Long haul treatment comprises of evasion of most dairy items, the essential wellspring of galactose. The majority of people with classic galactosemia experience developmental delays, speech impairments, issues with fine motor function, and slow growth despite treatment. Scholarly capacities are for the most part sub optimal, with impressive inconstancy among patient associates. Females with exemplary galactosemia are likewise at a more serious gamble for hypogonadotropic hypogonadism or essential ovarian inadequacy.

Materials and Method

The methods and materials used in the management and diagnosis of type IV galactosemia (UDP-galactose-4-epimerase deficiency) involve a combination of clinical evaluations, laboratory testing, genetic analysis, and dietary interventions [6]. Here are the key components:

Clinical evaluation

Patient history: Gathering detailed information about the patient's medical history, including any symptoms or complications related to galactosemia.

Physical examination: A comprehensive physical examination is conducted to assess the overall health status of the individual, including liver function, growth, and neurological development.

Laboratory testing

Blood tests: Blood samples are analyzed to measure levels of galactose, galactose metabolites, and liver function markers. This helps in assessing the extent of galactose accumulation and evaluating liver health.

Biochemical assays: Enzymatic assays may be performed to measure the activity of UDP-galactose-4-epimerase enzyme in red blood cells or other tissues.

Metabolic profiling: Metabolomic analysis may be conducted to identify specific metabolic abnormalities associated with type IV galactosemia.

Genetic analysis

Genetic testing: DNA analysis is performed to identify mutations in the GALE gene, which encodes the UDP-galactose-4-epimerase enzyme [7]. This confirms the diagnosis of type IV galactosemia.

Gene sequencing: Techniques such as Sanger sequencing or next-generation sequencing are used to identify specific mutations or variants in the GALE gene.

Dietary interventions

Galactose-restricted diet: Similar to other forms of galactosemia, individuals with type IV galactosemia may be advised to limit their intake of galactose-containing foods and follow a galactose-restricted diet.

Nutritional guidance: Consultation with a registered dietitian is often recommended to ensure adequate nutrition while avoiding galactose-rich foods.

Medical monitoring

Regular follow-up: Individuals with type IV galactosemia require periodic medical evaluations and monitoring to assess liver function, growth, and development.

Ophthalmologic assessments: Regular eye examinations are conducted to monitor the development of cataracts, a potential complication of type IV galactosemia.

It's important to note that the specific methods and materials used may vary based on the clinical practice and available resources. Consulting with healthcare professionals experienced in managing type IV galactosemia is crucial for personalized treatment plans and accurate diagnosis.

Results and Discussion

The results and discussion of type IV galactosemia (UDP-galactose-4-epimerase deficiency) typically revolve around the findings from clinical evaluations, genetic analysis [8], dietary interventions, and the impact on the individual's health and well-being. Here are some key points that may be addressed in the results and discussion of type IV galactosemia:

Clinical findings

Symptomatology: The discussion may include a description of the presenting symptoms and complications observed in individuals with type IV galactosemia, such as liver dysfunction, cataracts, intellectual disability, developmental delays, and neurological problems.

Variation in symptom severity: The variability in the severity and specific manifestations of the condition may be explored, as individuals with type IV galactosemia can exhibit a wide range of clinical presentations [9].

Genetic analysis

Mutation identification: The results may describe the specific mutations identified in the GALE gene through genetic testing, confirming the diagnosis of type IV galactosemia.

Genotype-phenotype correlations: The discussion may address any observed relationships between the identified mutations and the clinical manifestations or severity of the disorder.

Dietary interventions

Impact of galactose-restricted diet: The results may evaluate the effectiveness of dietary interventions, including a galactose-restricted diet, in managing symptoms and preventing complications associated with type IV galactosemia.

Challenges and compliance: The discussion may highlight the challenges faced by individuals and families in adhering to the dietary restrictions and the impact on their quality of life.

Long-term outcomes

Health and developmental outcomes: The results may discuss the long-term health and developmental outcomes of individuals with type IV galactosemia, including the progression or stabilization of symptoms, impact on growth, and intellectual functioning.

Quality of life: The discussion may address the overall impact of type IV galactosemia on the individual's quality of life, considering factors such as educational attainment, social interactions, and psychological well-being.

Research and future directions

Advancements in understanding: The discussion may highlight any recent research findings or advancements in understanding the pathophysiology of type IV galactosemia, potential treatment approaches, or novel therapeutic targets.

Unmet needs: The results may emphasize the gaps in knowledge, challenges, and areas for further investigation in order to improve the management and outcomes of individuals with type IV galactosemia.

It's important to note that the results and discussion section can vary based on the specific research study, clinical observations, or case reports being conducted [10]. Incorporating findings from relevant literature and previous studies may also contribute to the discussion.

Conclusion

In conclusion, type IV galactosemia, also known as UDP-galactose-4-epimerase deficiency or GALE deficiency, is a rare subtype of galactosemia caused by a deficiency of the UDP-galactose-4-epimerase enzyme. It typically presents with delayed onset during childhood or adolescence due to partial enzyme activity.

The diagnosis of type IV galactosemia involves clinical evaluations, laboratory testing, and genetic analysis to confirm the presence of GALE gene mutations. Dietary interventions, including a galactose-restricted diet, are recommended to manage symptoms and prevent complications associated with galactose accumulation.

The results of clinical evaluations and genetic analysis help characterize the symptomatology and genotype-phenotype correlations of type IV galactosemia. Dietary interventions play a crucial role in minimizing the impact of the disorder and improving the overall health and well-being of affected individuals.

Long-term outcomes of type IV galactosemia vary, with a range of symptoms and severity observed among individuals. Regular medical monitoring and follow-up are important to assess liver function, growth, and developmental progress. The challenges faced by individuals and families in adhering to the dietary restrictions should be acknowledged, along with efforts to provide support and guidance.

Further research is needed to enhance the understanding of type IV galactosemia, identify potential treatment approaches beyond dietary modifications, and address the unmet needs in the management of the condition. Genetic counseling remains crucial to provide comprehensive care, support family planning decisions, and ensure appropriate follow-up for affected individuals.

Although type IV galactosemia presents unique challenges, early diagnosis, proper management, and ongoing medical care can help individuals live fulfilling lives, minimizing the impact of the condition and optimizing their overall health and well-being.

Acknowledgement

None

Conflict of Interest

None

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