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EDITORIAL

Exploring the genetic basis of childhood monogenic diabetes

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Abstract

Monogenic diabetes is caused by one or even more genetic variations, which may be uncommon yet have a significant influence and cause diabetes at an early age. Monogenic diabetes affects 1% to 5% of children, and early detection and genetically focused treatment of neonatal diabetes and maturity-onset diabetes of the young can significantly improve long-term health and well-being. The etiology of monogenic diabetes in childhood is primarily attributed to genetic variations affecting the regulatory genes responsible for beta-cell activity. In rare instances, mutations leading to severe insulin resistance can also result in the development of diabetes. Individuals diagnosed with specific types of monogenic diabetes, which are commonly found, can transition from insulin therapy to sulfonylureas, provided they maintain consistent regulation of their blood glucose levels. Scientists have successfully devised materials and methodologies to distinguish individuals with type 1 or 2 diabetes from those more prone to monogenic diabetes. Genetic screening with appropriate findings and interpretations is essential to establish a prognosis and to guide the choice of therapies and management of these interrelated ailments. This review aims to design a comprehensive literature summarizing genetic insights into monogenetic diabetes in children and adolescents as well as summarizing their diagnosis and management.

Key Words: Monogenic diabetes; Genetic mutation; Insulin resistance; Beta-cell function; Diabetes mellitus

Core Tip: Monogenic diabetes, a rare yet impactful condition in childhood, results from genetic variations, causing early-onset diabetes. Affecting 1%-5% of children, early detection and tailored genetic treatments can enhance long-term health. Culprits include genetic variations in beta-cell regulatory genes and severe insulin resistance. Identifying specific types allows transitioning to sulfonylureas while maintaining glucose control. Tools to differentiate diabetes types underscore genetic screening's importance for prognosis and treatment guidance. This review delves into genetic insights into childhood monogenic diabetes, offering diagnosis and management guidance for affected youth's better health.

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INTRODUCTION

In the ever-evolving landscape of pediatric healthcare, the intricate interplay between genetics and clinical outcomes becomes a central focus of research and treatment strategies. This review article by Sun and Lin[1] delves into the complex world of childhood monogenic diabetes, seamlessly connecting genetic mutations, clinical manifestations, and innovative management approaches. This comprehensive review serves as a beacon, illuminating the path toward improved understanding and personalized care for young patients grappling with this condition.

GENETICS OF CHILDHOOD MONOGENIC DIABETES

Diabetes mellitus (DM) is a metabolic disorder associated with increased blood glucose levels and its associated symptoms which significantly impact an individual's health, life expectancy, and public health. The lifetime risk of DM is one in three for individuals born in the United States[2]. This multifaceted condition includes autoimmune-mediated type 1 diabetes, injury-induced diabetes, genetically influenced diabetes, and the prevalent type 2 diabetes[3,4]. This article focuses on monogenic diabetes, a less common but genetically distinct form, accounting for about 1% to 5% of cases in pediatric and young populations[5-7].

Monogenic diabetes arises from mutations in a single gene, representing a distinct subset that lends itself to more targeted therapies. There are several forms of monogenic diabetes including maternally inherited diabetes and deafness, gestational diabetes due to the *glucokinase* (*GCK*) gene and maturity-onset diabetes of the young (MODY)[8-10]. Despite its lower prevalence (1%-5% in pediatric and young populations), accurate diagnosis remains a challenge, with approximately 80% of cases undetected[7].

Sun and Lin[1] explore the variation in genes linked to childhood diabetes, particularly focusing on ATP-sensitive potassium channels. These genes, like *KCNJ11* and *ABCC8*, play a crucial role in forming KATP channels. The article discusses how these gene variations impact insulin release and the importance of catching them early, opening up possibilities for moving away from insulin reliance to oral medications.

Monogenic diabetes offers a unique window into diabetes pathophysiology, with genetic variations serving as key players. While comprising a small percentage of overall diabetes cases, the well-defined genetic basis allows for precise prognostic and treatment procedures. However, due to its clinical and genetic heterogeneity, diagnosing monogenic diabetes, especially in pediatric patients, remains challenging[11].

The review unfolds the hidden mechanism within the INS and GCK genes, revealing their role in causing permanent neonatal diabetes. By focusing on disruptions caused by INS mutations and the contribution of GCK mutations to familial hyperglycemia, Sun and Lin stress the need for early diagnosis, especially in couples with close family ties. This decoding sets the stage for more effective treatments and understanding familial risks.

The narrative extends to rare genetic origins and variations in childhood diabetes. Sun and Lin[1] shed light on clinical landscapes, underlining the importance of accurate diagnoses in conditions like Wolfram syndrome. This review emphasizes the diversity within childhood diabetes, urging doctors to be vigilant in how they diagnose.

Recent progress in genetic testing, particularly through next-generation sequencing (NGS) technologies, has significantly enhanced the identification of specific genetic mutations linked to monogenic diabetes. NGS enables a more thorough genetic analysis, unveiling rare mutations that traditional methods might overlook. Machine learning algorithms are also emerging to assist in interpreting genetic data, streamlining the diagnostic process[12-14]. Therapeutically, the article talks about personalized treatment plans, especially using sulfonylureas for specific gene mutations like HNF1A-MODY3, showing how genetic insights can guide more effective treatment choices. The review provides valuable insights, but its relevance might vary due to regional genetic differences, and some recent advancements or lesser-known mutations may not be fully addressed, affecting how it can be applied and accessed equitably.

Tailoring treatment for monogenic diabetes is evolving, guided by a deeper understanding of the genetic basis. Gene-based therapies, including CRISPR-Cas9 gene editing, show promise in correcting genetic mutations responsible for monogenic diabetes subtypes. Initiatives including international collaborations and data-sharing could further enhance treatment strategies and outcomes[15-17].

CONCLUSION

The collaborative work of Sun and Lin[1] navigates a genetic exploration in pediatric diabetes. Their comprehensive review not only enhances our understanding of the intricate genetic tapestry but also paves the way for a future where personalized care becomes the cornerstone of pediatric diabetes management.

FOOTNOTES

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