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(CASE REPORT)

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Insight into Insulin-like Growth Factor-1 Receptor (IGF-1R) gene mutations: Implications for growth disorders and treatment: A review of the literature and case report

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Abstract

Background: Insulin-like Growth Factor -1 Receptor (IGF-1R) and its ligand, IGF-1, are crucial for human tissue growth and development. Mutations in IGF-1R and, to a lesser extent, IGF-1 genes lead to diverse growth disorders, characterized by intrauterine growth retardation and postnatal growth challenges.

Case report: We present a case of a 6-year-old girl with speech and mild cognitive delays, exhibiting normal motor skills, no neurological issues, and standard vital signs. Her growth parameters indicated significant retardation, with a height standard deviation score (Ht-SDS) of -2 and an IGF-1 level of +1.8 SDS, normal thyroid function and delayed bone age. Genetic analysis identified a 3335 mbp interstitial loss in 15q26.1, encompassing the IGF-1R gene, critical for growth and development.

Literature review: Analysis of 34 papers provided insight into the genetic complexities of IGF-1R and IGF-1 mutations. Studies ranged from familial cases to cohort studies, uncovering mutations including missense mutations, deletions, and copy number variations (CNVs), each associated with unique growth disorder phenotypes. Advances in diagnostic techniques like multiplex ligation-dependent probe amplification (MLPA) and whole exome sequencing (WES) have been pivotal in identifying these mutations, facilitating more targeted management approaches.

Conclusions: This case and review of literature underscore the importance of an integrated genetic, endocrine, and developmental approach in managing growth hormone deficiency (GHD) and IGF-1 resistance. The variability in growth disorders and response to therapy highlights the need for personalized treatment plans, informed by genetic insights, to optimize outcomes for patients with these complex conditions.

Keywords: IGF-1; IGF-1R; Mutation; Genotype; Phenotype; Growth; rhGH therapy.

1. Introduction

In the evolving landscape of pediatric endocrinology, the study of genetic factors contributing to growth disorders has become increasingly pivotal. Growth is a complex biological process governed by a myriad of factors, including genetic, hormonal, nutritional, and environmental influences (1). Among these, the insulin-like growth factor -1 (IGF-1) pathway plays a crucial role. The IGF-1 receptor (IGF-1R) and the IGF-1 gene, in particular, have emerged as significant

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determinants of growth and development (2). Mutations in these genes are increasingly recognized as key contributors to various growth disorders, ranging from intrauterine growth retardation to postnatal growth failure (3).

The rationale for focusing on IGF-1R and IGF-1 gene mutations stems from their critical roles in the growth regulation process. IGF-1, primarily produced in the liver, acts via the IGF-1R, influencing cellular growth, proliferation, and survival (4). Disruptions in this pathway, particularly mutations in the IGF-1R or IGF-1 gene, can lead to significant growth anomalies (5).

In recent years, advances in genetic testing and molecular biology have allowed for the identification of these mutations, providing new insights into the pathophysiology of growth disorders (6). However, the clinical presentation of these mutations varies widely, encompassing a spectrum from mild growth retardation to severe growth failure and associated comorbidities (7). This variability presents a challenge in clinical practice, necessitating a comprehensive understanding of the underlying genetics and their clinical implications.

Moreover, the response to conventional growth hormone (GH) therapy in patients with IGF-1R and IGF-1 mutations is notably variable (8). While some patients demonstrate a good growth response (8-10), others show little to no improvement (11,12). This variability highlights the need for personalized treatment approaches, tailored to the genetic makeup of the individual patient. Thus, a thorough review of the literature on IGF-1R and IGF-1 gene mutations is essential for informing clinical decision-making and optimizing treatment strategies.

A review that synthesizes current knowledge and recent advances is crucial for keeping clinicians and researchers abreast of the latest developments in this field.

2. Case Report

A 6-year-old Nigerian girl with a history of speech delay and mild global developmental delay (GDD), presented with isolated speech delay, mild cognitive delay, and normal motor development. The past history did not report seizures, encephalopathy, sleep, or social disorders. Vital signs were within normal limits, and physical examination showed no motor difficulties, normal coordination, and gait. The heart examination was normal. Growth parameters indicated a height standard deviation score (Ht-SDS) of -2, with a slow linear growth velocity (GV- SDS) of -1 SD for the past three years and a body mass index (BMI) of -1SD. Endocrine evaluation revealed an IGF-1 level of +1.8 SD with normal thyroid function, bone age delayed by one year relative to chronological age, and no signs of early puberty (Table 1).

Genetic analysis identified a 3335 mbp interstitial loss in 15q26.1, encompassing the IGF-1R gene, critical for growth and development. Literature suggests that haploinsufficiency of the IGF-1R gene correlates with growth deficiencies observed in patients with distal deletions of 15q25-26. Our patient's phenotype, including pre- and postnatal growth retardation, aligns with reported cases, supporting a role for IGF-1R in her clinical presentation.

Table 1 Anthropometric and lab data of our case

Investigation	Results	Reference values/Comments
Age at first evaluation	6 years	
Height Standard Deviation Score (Ht-SDS)	-2	Significant deviation from mean expected for age
Growth Velocity Standard Deviation Score (GV- SDS)	-1 SD	Slow growth velocity over the past 3 years
Body Mass Index (BMI -SDS)	-1 SD	Below average, indicating undernutrition or a growth related issue
Insulin-like Growth Factor 1 (IGF-1 SDS)	+1.8 SD	Elevated; may indicate IGF-1 resistance
Thyroid Function Tests	Normal	Normal thyroid function excludes hypothyroidism as a cause of short stature
Bone age (Greulich and Pyle assessment)	5 years	Delayed by 1 year relative to chronological age

Serum creatinine	Normal	Normal kidney function
Alanine aminotransferase (ALT)	Normal	Normal liver function
Complete blood count (CBC)	Normal	Normal hematologic status
Genetic microarray	3335 mbp loss at 15q26.1	Includes critical genes like IGF-1R
Tanner pubertal stage	Breast 1 and Pubic hair 1	No signs of pubertal development

2.1. Revision of literature

We conducted a comprehensive literature search across various electronic databases, including PubMed, MEDLINE, EMBASE, and Google Scholar from January 2000 to December 2023. We utilized a combination of keywords and phrases, including "IGF-1 receptor mutations," "IGF1 gene mutations," "growth disorders," "growth hormone therapy," and "short stature." Studies were selected based on their relevance to IGF-1R and IGF-1 gene mutations, along with their implications for growth disorders and treatment. Human and in vitro studies were included to ensure a broad range of data. Non-English articles, abstracts without full texts, and studies not directly related to the topic were excluded. Two independent reviewers screened the titles and abstracts for relevant data including study design, sample size, type of mutation, clinical outcomes, and response to therapy. The quality of the studies was assessed using standardized tools, such as the Newcastle-Ottawa Scale for observational studies (Table 2). We adopted a narrative approach to synthesize findings from the selected studies, given the heterogeneity in study designs and outcomes. Key themes, such as types of mutations, clinical presentation, response to growth hormone therapy, and implications for management, were identified and discussed

A comprehensive analysis of 34 research papers was conducted to understand the intricacies of growth disorders, particularly focusing on IGF-1 resistance and its genetic underpinnings (Figure 1 and Table 2).

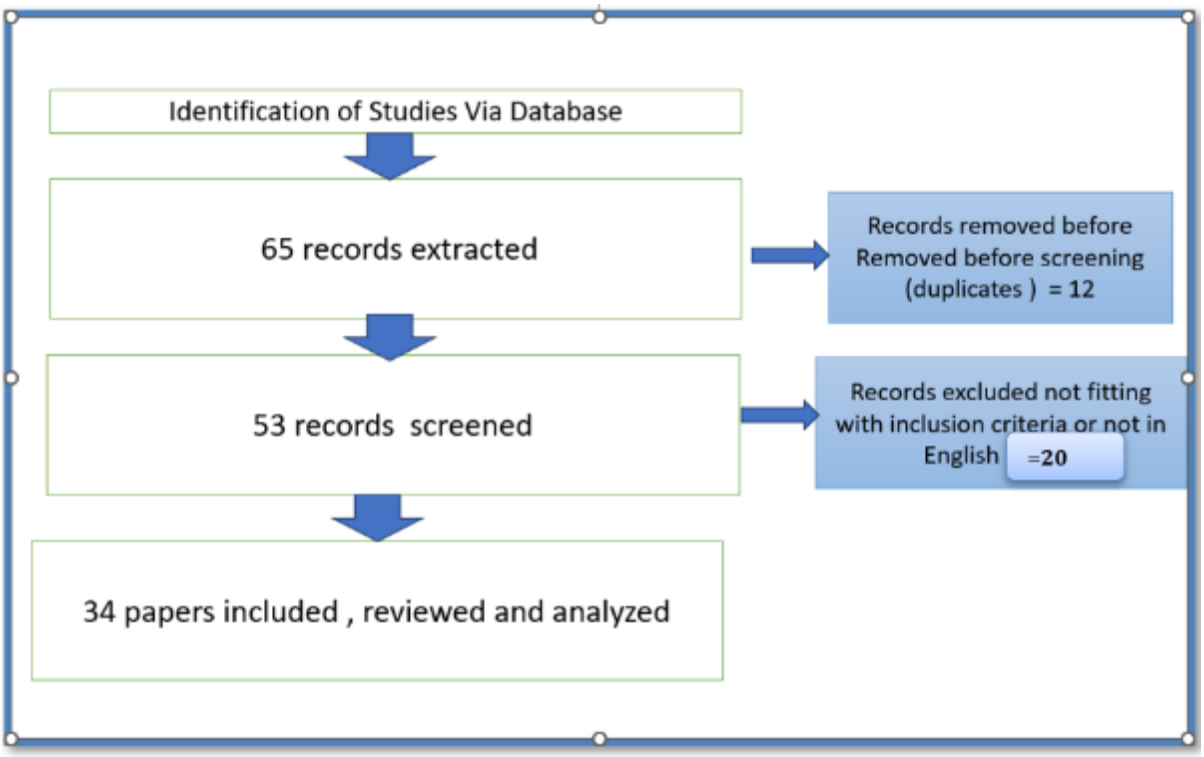

Figure 1 PRISMA flow diagram used for studies selection.

Table 2 A comprehensive analysis of 34 research papers on growth disorders, particularly focusing on IGF-1 resistance (IGF-1R) and its genetic underpinnings.

Category	Key Findings
Growth delay and IGF-1R	Growth delays associated with IGF-1 resistance are linked to genetic anomalies (e.g., ring chromosome 15, mutations in IGF-1R gene). Management is complex (13-15).
Heterozygous IGF-1R mutations	Impaired growth due to heterozygous IGF-1R mutations affecting downstream signaling. Critical role in regulating growth across different family histories (7,12,16,17).
Phenotypic diversity and clinical scoring	Over 30 pathogenic IGF-1R variants were identified. rhGH treatment leads to height gains and high serum IGF-1 levels, highlighting the need for refined clinical scoring (8, 18-22).
Intrauterine twin discordancy and IGF-1R mutation	Case study of partial postnatal growth recovery in a girl with IGF-1R mutation following intrauterine growth retardation (19).
Postnatal growth Retardation and IGF-1R mutations	10-14% of SGA children without spontaneous growth catch-up may have IGF-1R gene defects, indicating genetic factors in unexplained growth failure (5, 23-25).
Novel mutations and familial short stature	Novel IGF-1R mutations linked to familial short stature and severe prenatal growth retardation, affecting IGF-1R gene activity (26-31).
IGF-1R and Intracellular Trafficking	IGF-1R mutations leading to protein retention within the endoplasmic reticulum shed light on molecular mechanisms of associated growth disorders (12, 32,33).
Growth and rhGH Therapy Response Analysis	Distinct growth response patterns to rhGH therapy among individuals with IGF-1R mutations compared to typical SGA cases (8, 34,35).
Proposed clinical score for diagnosis	A clinical scoring system proposed to enhance diagnosis of IGF-1R defects and classification of variants of unknown significance (35, 36).
IGF-1 mutations and insulin resistance	IGF-1 gene mutations in individuals with short stature and insulin resistance, suggesting a role in metabolic disorders (37-40).
Wider implications of IGF-1R and IGF-1 mutations	IGF-1R and IGF-1 mutations potentially affect metabolic pathways, insulin resistance, and related disorders (17, 41-45).
Advancements in genetic diagnostics	Use of MLPA in detecting IGF-1R gene copy number variations emphasize advanced diagnostics in identifying genetic variations related to growth disorders (35, 46, 47).

Legend= rhGH: recombinant human growth hormone; **MLPA:** multiplex ligation-dependent probe amplification.

2.2. A comprehensive analysis in 12 steps of 34 research papers on growth disorders, particularly focusing on IGF-1 resistance (IGF-1R) and its genetic underpinnings is reported, as follows:

2.2.1. Growth delay and IGF-1 resistance (IGF-1R)

IGF-1R is marked by growth delays both before and after birth, frequently coupled with intellectual challenges and distinct physical features. This condition is linked to various genetic anomalies such as ring chromosome 15, and deletions or mutations in the IGF-1R gene, showcasing the diverse genetic landscape contributing to this condition. Management of IGF-1 resistance is multifaceted, reflecting the complexity of addressing these growth delays (13-15).

2.2.2. Heterozygous IGF-1R mutations

Research consistently indicates that heterozygous mutations in the IGF-1R gene are associated with impaired growth. These mutations disrupt the gene's downstream signaling pathways, emphasizing its crucial role in regulating growth across different family histories (7,12,16,17).

2.2.3. Phenotypic diversity and clinical scoring

Studies of patients with heterozygous IGF-1R mutations have identified over 30 pathogenic variants, all associated with short stature. A detailed examination of genetic and clinical data, along with responses to GH therapy in 11 patients, revealed a spectrum of phenotypes, often indistinguishable from more common forms of short stature at diagnosis. Notably, a significant number of these patients presented with thin upper lips, and GH treatment in five patients led to considerable height gains and exceptionally high serum IGF-1 levels, underlining the need for a refined clinical scoring system to detect IGF-1R mutations more effectively (8, 18-22).

2.2.4. Intrauterine twin discordancy and IGF-1R mutation

A case study shed light on a girl with an IGF-1R mutation, highlighting the potential for partial postnatal growth recovery following intrauterine growth retardation (19).

2.2.5. Postnatal growth retardation and IGF-1R mutations

Approximately 10-14% of children born small for gestational age (SGA) without spontaneous postnatal growth catch-up may possess IGF-1R gene defects, underscoring the need to consider genetic factors in cases of unexplained growth failure (5, 23-25).

2.2.6. Novel mutations and familial short stature

Research links novel IGF-1R mutations with familial short stature and severe prenatal growth retardation, illustrating the mutations' varied impact on IGF-1R gene activity and the resulting disruption to IGF-1 signaling. This is evidenced by the diverse clinical manifestations and the severe outcomes observed in mice lacking functional IGF-1R (26-31).

2.2.7. IGF-1R and intracellular trafficking

Mutations in IGF-1R that lead to the protein's retention within the endoplasmic reticulum offer new insights into the molecular mechanisms underlying growth disorders associated with IGF-1R (12, 32,33).

2.2.8. Growth and recombinant human growth hormone (rhGH) therapy response analysis

Comparative studies between individuals with IGF-1R mutations and SGA children without these mutations reveal distinct growth response patterns to rhGH therapy. Despite early initiation and higher dosing of GH therapy suggesting potential benefits, responses vary widely. A study encompassing two patient groups highlighted significant growth with GH treatment, albeit less than in typical SGA cases, suggesting a nuanced response to GH therapy among those with IGF-1R defects (8, 34,35).

2.2.9. Proposed clinical score for diagnosis

New research proposes a clinical scoring system designed to enhance the diagnosis of IGF-1R defects and the classification of variants of unknown significance, contributing valuable insights into the complex genetics of growth disorders (35, 36).

2.2.10. IGF-1 mutations and insulin resistance

The discovery of IGF-1 gene mutations in individuals with severe short stature and insulin resistance broadens the clinical spectrum of these mutations, highlighting their potential role in metabolic disorders (37-40).

2.2.11. Wider implications of IGF-1R and IGF-1 mutations

The broader impact of IGF-1R and IGF-1 mutations extends to metabolic pathways, possibly affecting insulin resistance and related metabolic and endocrine disorders. This suggests the need for a broader perspective on the health implications of these genetic mutations (17, 41-45).

2.2.12. Advancements in genetic diagnostics

The use of Multiplex Ligation-dependent Probe Amplification (MLPA) in detecting IGF-1R gene copy number variations signifies the importance of advanced genetic diagnostics in identifying subtle genetic variations that contribute to growth disorders (35, 46, 47).

3. Discussion

This case report and review of literature, particularly focusing on IGF-1R, sheds light on the intricate relationship between genetic factors and growth anomalies. The clinical presentation of our patient, characterized by isolated speech delay, mild cognitive delay, and notably pre- and postnatal growth retardation, is emblematic of the phenotypes associated with alterations in the IGF-1R gene. The identification of a 3335 mbp loss at 15q26.1, involving the IGF-1R gene, aligns with the literature that associates IGF-1R haploinsufficiency with growth deficiencies.

Variability in growth patterns and the degree of growth retardation associated with mutations in the IGF-1R gene are illustrated by studies showing a spectrum of growth impairments, from intrauterine growth retardation to postnatal growth challenges (14, 17). These findings highlight the phenotypic heterogeneity resulting from IGF-1R mutations, complicating the prediction of growth outcomes based solely on genetic alterations.

The clinical and functional characteristics of novel heterozygous mutations of the IGF-1R gene further emphasize the broad spectrum of phenotypic manifestations associated with these genetic alterations (16, 22). This diversity within IGF-1R haploinsufficiency's necessitates individualized approaches to diagnosis and treatment.

Additionally, the essential roles of insulin and IGF-1 receptors in embryonic development and their systemic roles suggest implications for overall health and disease beyond growth regulation (15, 30). This broadens our understanding of the systemic importance of these pathways.

The role of IGF-1 in various physiological systems beyond growth and development is underscored by the study on its implications in hearing physiopathology (13), suggesting a far-reaching impact of IGF-1 signaling.

Advancements in genetic diagnostics, particularly the use of Multiplex Ligation-dependent Probe Amplification (MLPA) to detect IGF-1R gene copy number variations, highlight the importance of precise genetic diagnostics in informing treatment plans and understanding the genetic basis of growth disorders more fully (46, 47).

4. conclusion

In conclusion, our case report and the present review of related literature underscore the critical importance of understanding the genetic underpinnings of growth disorders. This knowledge not only facilitates precise diagnoses and personalized treatment plans but also contributes to our broader comprehension of the genetic determinants of growth and development. The findings advocate for a holistic management strategy that considers the genetic, endocrine, and developmental dimensions of growth disorders, reinforcing the need for continued research and innovation in the field of pediatric endocrinology and genetics.

Compliance with ethical standards

Disclosure of conflict of interest

Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Conceptualization

ATS; Data collection, screening, and data analysis: All authors; Writing original draft preparation: ATS; Writing review and editing for important intellectual content: VDS provided expert editing and review; Case report writing: FA, NA, and NH contributed to writing the case report. Final approval of the version to be published: All authors have read and agreed to the published version of the manuscript, ensuring that questions related to the accuracy and integrity of any part of the work were appropriately analyzed and resolved.

Statement of informed consent

This review article adheres strictly to ethical standards, ensuring accurate representation of sourced literature, maintaining transparency, and upholding intellectual property rights. It encompasses a comprehensive and impartial synthesis of existing research, devoid of any conflicts of interest. This review article synthesizes published literature on IGF-1 and its receptor; therefore, no informed consent was necessary as it does not involve primary data collection or direct interaction with human or animal subjects.

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