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Syndromic failure to thrive and short stature in children: Genetic mechanisms, endocrine implications, and responses to nutritional and growth hormone therapies

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Abstract

Short stature and failure to thrive (FTT) are indicative of a number of congenital syndromes. Numerous factors such as malnutrition, endocrine dysfunction and structural or genetic abnormalities, can cause these growth disturbances. Although GH therapy and nutritional interventions have been investigated for a number of syndromes, their effectiveness varies according to the pathophysiology that underlies them.

Objectives: The objectives of this mini-review are to: (1) characterize the growth characteristics and endocrine abnormalities linked to specific genetic syndromes that manifest as short stature or FTT (2) assess the efficacy of GH therapy and nutritional support and (3) evaluate the prognosis and outcomes across syndromic categories.

Methods: We included studies released between 2000 and 2024. A systematic literature review was carried out using PubMed, Scopus, and Embase. Studies that reported on endocrine profiles, clinical growth parameters, and treatment outcomes in syndromic FTT were required to meet inclusion criteria. Growth features, GH response, nutritional impact, and long-term prognosis were all described.

Results: A total of ten syndromes were examined. There was widespread endocrine dysfunction such as GH resistance or deficiency (e. g. A. IGF-1 axis abnormalities (e. g. Turner syndrome, Russell-Silver syndrome), hypothyroidism (e. g. Noonan syndrome, Seckel syndrome, Down syndrome, and hypogonadism (e. g. Prader–Willi syndrome. In cases where malabsorption or feeding issues predominated, such as Rett syndrome, CHARGE, and cystic fibrosis, nutritional rehabilitation produced notable growth benefits. Height SDS improved with GH therapy in several conditions. The most consistent positive response was seen in 3-M syndrome, Turner syndrome, Prader-Willi syndrome, and Noonan syndrome (PTPN11-negative). However, in Cornelia de Lange Rett and Seckel syndromes, GH therapy had little effect, most likely because of underlying structural or neurodevelopmental barriers. Early diagnosis, interdisciplinary treatment, and customized dietary and endocrine therapies all improved the prognosis.

Conclusion: In summary, growth failure and syndromic FTT have a variety of endocrine and nutritional causes. In certain situations, targeted interventions, particularly early GH treatment and all-encompassing nutritional support, can greatly enhance growth and developmental outcomes. In order to maximize response and direct clinical care, a syndrome-specific approach is necessary.

Keywords: Genetic Mechanisms; Growth Hormone Therapy; Short Stature Syndromic Growth Failure; Pediatric Endocrinology.

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1. Introduction

0Short stature and failure to thrive (FTT) are common presenting characteristics in pediatric endocrinology and genetics which are indicative of underlying problems with nutrition growth regulation and hormonal balance. A subgroup of children present with syndromic FTT a complex interplay of genetic structural metabolic and endocrine abnormalities despite the well-established environmental and acquired causes such as chronic infections or malnutrition (1).

Genetic syndromes that cause persistently low weight and height for age include Russell-Silver syndrome (RSS,) Noonan syndrome, Cornelia de Lange syndrome (CdLS) and Prader-Willi syndrome (PWS). These syndromes frequently present early, often accompanied by intrauterine growth restriction (IUGR), postnatal growth deceleration, or feeding difficulties. Since structural abnormalities or neurodevelopmental delays are present in many of these conditions, growth failure is a component of a larger phenotype (2).

Different molecular mechanisms are involved in these syndromes: RSS is caused by imprinting errors at chromosome 11p15. 5 or maternal uniparental disomy of chromosome 7, CdLS is caused by cohesinopathies that affect genes such as SMC1A and NIPBL, and PWS is caused by paternal gene loss in chromosome 15q11 13 as a result of deletion or uniparental disomy (3,4,5). These systems affect endocrine signaling, muscle tone, appetite control, and cell proliferation.

The GH–IGF-1 axis mediates the crucial role that growth hormone (GH) plays in postnatal linear growth. As seen in Noonan syndrome, 3-M syndrome, and Turner syndrome, abnormalities in this axis, such as GH deficiency, GH resistance, or disturbed IGF-1 signaling, are well recognized (6, 7). An understanding of the endocrine aspect of growth impairment can be gained by assessing the results of GH therapy in these circumstances. Because it dramatically increases height, lean body mass, and metabolic profiles, GH therapy has become the standard of care for PWS and Turner syndrome. Rett syndrome and CdLS on the other hand, frequently exhibit little benefit, indicating either receptor-level dysfunction or variable GH axis integrity (8,9). Comprehending this heterogeneity is essential for managing expectations and improving treatment protocols.

Nutritional therapies are also essential, particularly in conditions like CHARGE syndrome or cystic fibrosis that involve feeding aversion, hypotonia or malabsorption. Caloric supplementation, enteral feeding, and micronutrient support have shown success in improving weight gain and preparing patients for endocrine therapies (10).

Growth outcomes are not consistent across syndromes, even with the use of growth hormone and nutritional strategies. Therapeutic success and final adult height are influenced by a number of factors, including genotype-phenotype correlations, baseline anthropometry, comorbidities, and the timing of the intervention (11). Therefore, it is crucial to use an integrative approach that includes endocrinologists, geneticists, dietitians, and developmental specialists.

The effectiveness of GH in isolated syndromes has been the subject of systematic reviews in the past but there are currently few comparisons between various conditions. Moreover, little is known about the long-term prognosis and syndromic-specific reactions to combined interventions (12). By analyzing genetic and endocrine mechanisms, providing comparative tables of syndromes linked to FTT and/or linear growth delay, and summarizing empirical data on responses to GH and nutritional therapy, this mini review tries to fill these gaps. It emphasizes clinical phenotyping, therapeutic judgment, and results analysis for a range of ailments.

Objectives

This mini review was conducted with the following specific objectives: 1. To integrate clinical, anthropometric, genetic, and endocrine features reported in the literature in order to identify and summarize the main genetic syndromes linked to delayed linear growth and failure to thrive (FTT) . 2. to assess the underlying causes of growth impairment that lead to poor growth outcomes in these syndromes, such as molecular-genetic factors, endocrine dysfunctions (abnormalities of the GH–IGF-1 axis), and nutritional deficiencies. 3. To evaluate, considering published research and consensus recommendations, the effectiveness of growth hormone therapy and nutritional interventions in enhancing growth parameters and overall prognosis.

2. Materials and Methods

This mini review was conducted following a structured and systematic literature synthesis framework to identify relevant evidence on syndromic failure to thrive (FTT), genetic and endocrine mechanisms of growth delay, and responses to nutritional and growth hormone (GH) therapy.

2.1. Search Strategy and Databases

A comprehensive literature search was performed across the following databases: PubMed, Scopus, Embase, and Web of Science. The search included peer-reviewed English-language publications from January 2000 to May 2025. Key search terms included combinations of: "failure to thrive," "short stature," "growth hormone therapy," "syndromic growth failure," "genetic syndromes," "IGF-1," "endocrine dysfunction," and the names of specific syndromes (e.g., "Russell–Silver syndrome," "Noonan syndrome," "Prader–Willi syndrome").

Boolean operators (AND, OR) were used to expand the search, and Medical Subject Headings (MeSH) were applied in PubMed to standardize retrieval. Reference lists of key reviews and primary studies were also manually screened to identify additional relevant publications.

2.2. Inclusion Criteria

Studies were included if they:

- Reported on children or adolescents (<18 years) with syndromic FTT or short stature;
- Included clinical, anthropometric, genetic, endocrine, or therapeutic data.
- Evaluated nutritional interventions and/or growth hormone therapy.
- Were original studies (clinical trials, cohort studies, case series), meta-analyses, or high-quality narrative/systematic reviews.
- Were published in peer-reviewed journals indexed in major biomedical databases.

2.3. Exclusion Criteria

- Studies not involving syndromic or genetically defined FTT or growth disorders.
- Articles on non-pediatric populations (>18 years);
- Conference abstracts without full peer-reviewed articles.
- Non-English publications or those with inaccessible full texts.

2.4. Data Extraction and Analysis

Two authors independently reviewed all eligible articles. Extracted data included syndrome name, genetic mechanism, growth features, nutritional status, BMI, GH response, intervention outcomes, and follow-up data. Information was compiled in structured tables developed specifically for this review.

Prevalence, GH responsiveness, and intervention outcomes were tabulated for comparison. Discrepancies were resolved by consensus or third-party review.

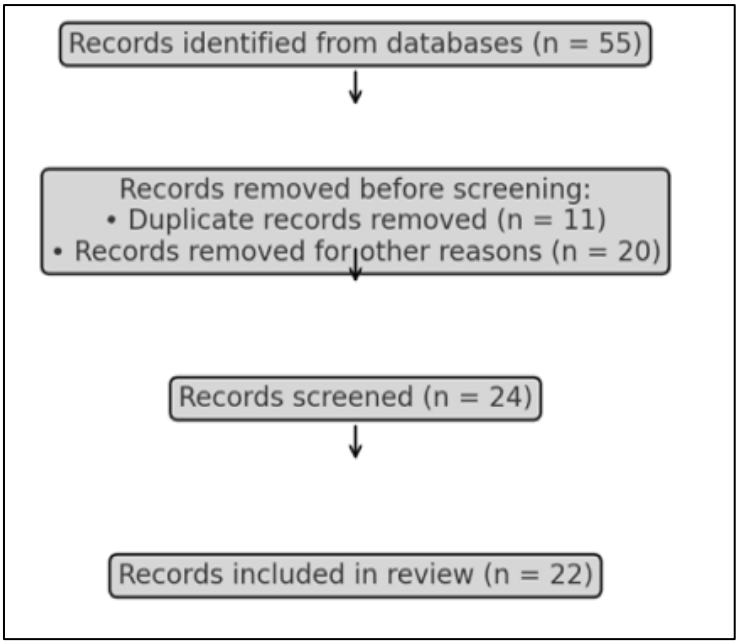

Figure 1 Prisma plot for the study.

It visually communicates the systematic progression from the initial 55 records identified through database searches to the final 22 studies included in the analysis after the removal of duplicates (11) and exclusion of irrelevant or low-quality studies

2.5. Reference Quality Assessment

The quality of evidence was classified based on study design hierarchy, with randomized trials and meta-analyses ranked highest, followed by cohort studies, case series, and expert reviews.

3. Results

This result section presents an integrated summary of growth patterns, endocrine profiles, and therapeutic responses in syndromic causes of failure to thrive (FTT). Tables 1–4 systematically outline key clinical features, anthropometric deficits, growth hormone (GH) responsiveness, and nutritional outcomes across both common and rare genetic syndromes.

The main syndromes linked to failure to thrive (FTT) and disordered growth are comprehensively and clinically summarized in Table 1. It provides a useful resource by methodically outlining growth characteristics such as weight, height and BMI trends along with succinct citation information. Including both prevalent syndromes (e. g. 3. Down syndrome, Turner syndrome, and other uncommon conditions (e. g. 3. 3-M syndrome, Seckel syndrome) help identify subtle phenotypic clues by expanding the diagnostic lens. The symbols in tiers (e. g. G. ↓↓) enhance interpretability at a glance by graphically expressing growth severity. In syndromic FTT, this table supports differential diagnosis and also emphasizes the significance of early detection and customized growth interventions.

Table 1 Syndromic Causes of FTT with Growth and Nutritional Profiles (Expanded)

Syndrome	Key Growth Features	Weight	Height	BMI	Reference (Author, Journal, Year)
Russell–Silver Syndrome (RSS)	Intrauterine growth retardation, postnatal FTT, relative macrocephaly	↓↓↓	↓↓	↓↓↓	Wakeling, Nat Rev Endocrinol, 2017 (2)
Noonan Syndrome	Short stature, delayed puberty, GH resistance	↓	↓↓↓	↓	Romano, J Pediatr, 2009 (6)
Williams Syndrome	FTT in infancy, feeding difficulties, eventual catch-up in height	↓↓	↓	↓	Morris, Am J Med Genet C, 2010 (13)
CHARGE Syndrome	Feeding difficulty, growth retardation, delayed bone age	↓↓	↓↓	↓	Zentner, Am J Med Genet C, 2010 (14)
Cornelia de Lange Syndrome (CdLS)	Severe pre- and postnatal growth restriction, low muscle mass	↓↓↓	↓↓↓	↓↓↓	Kline, Am J Med Genet C, 2007(15)
Smith-Lemli-Opitz Syndrome	Poor feeding, FTT, microcephaly, endocrine abnormalities	↓↓	↓	↓	Nowaczyk, Am J Med Genet C, 2001(16)
3-M Syndrome	Severe postnatal short stature, normal head, preserved IQ	↓↓	↓↓↓	↓	Huber, Nat Genet, 2009 (17)
Rett Syndrome (females)	Growth failure, microcephaly, feeding difficulties	↓↓	↓↓	↓↓↓	Neul, Ann Neurol, 2010 (8)
Cystic Fibrosis	Malabsorption, steatorrhea, chronic lung disease, FTT	↓↓↓	↓↓	↓↓↓	Stallings, J Pediatr, 2008 (10)
Prader-Willi Syndrome (early phase)	Neonatal hypotonia, poor suck, FTT → transitions to obesity	↓↓ → ↑↑	↓↓	↓ → ↑↑	Cassidy, Genet Med, 2012 (4)
Turner Syndrome	Short stature, delayed puberty, normal intelligence	↓↓	↓↓↓	↓	Gravholt, Nat Rev Endocrinol, 2017 (18)
Down Syndrome	Short stature, hypotonia, intellectual disability	↓↓	↓↓	↓↓	Myrelid, Am J Med Genet C, 2010 (19)
Seckel Syndrome	Extreme intrauterine and postnatal growth retardation, microcephaly	↓↓↓	↓↓↓	↓↓↓	Faivre, J Med Genet, 2002 (20)

Key: ↓↓↓ = Severe deficit, ↓↓ = Moderate deficit, ↓ = Mild deficit, ↑↑ = Excess or obesity

Table 2 Syndromic FTT – GH Response and Prognosis

Syndrome	Growth Features	GH Response	Prevalence & M:F	Reference	Outcome & Prognosis with Intervention
Williams Syndrome	Infantile FTT, short stature, delayed linear growth	Good response in GH-deficient cases	1:7,500–20,000 (~1:1)	Morris CA. Am J Med Genet C Semin Med Genet. 2010 (13)	Improved linear growth with GH; good prognosis if cardiac defects are mild; normal lifespan possible with early intervention.
3-M Syndrome	Severe prenatal & postnatal short	Early GH leads to catch-up growth;	<1:1,000,000; M:F ≈ 1:1	Akilapa R, 2025 Available from: https://www.	Catch-up growth achievable with GH in childhood; adult height may remain

	stature; normal head & IQ	long-term effect variable		ncbi.nlm.nih.gov/books/NBK1481/ (21)	subnormal; cognitive development typically normal.
Rett Syndrome	Postnatal growth failure, microcephaly, regression	GH not routinely used; limited evidence	≈1:10,000–15,000 females; rare males	Neul JL et al. Ann Neurol. 2010;(8)	Limited impact of GH; high caregiving needs; regression and neurological disability persist; supportive care improves quality of life.
Cystic Fibrosis	FTT due to malabsorption, delayed growth/puberty	GH improves height and lean mass; variable pulmonary outcomes	1:2,500–3,500; M:F ≈ 1:1	Stalvey MS et al. Pediatr Pulmonol. 2012;(22)	Improved growth and lean mass with GH; nutritional and respiratory management improves survival; prognosis depends on pulmonary status.
Russell–Silver Syndrome	Severe IUGR, postnatal FTT, relative macrocephaly	Good GH response; improved final height	1:50,000; M:F ≈ 1:1	Wakeling EL et al. Nat Rev Endocrinol. 2017;(8)	GH therapy enhances final height; hypoglycemia and feeding issues manageable; neurocognitive function usually preserved.
Noonan Syndrome	Short stature, GH–IGF axis dysfunction, delayed puberty	Good height gain, especially in PTPN11-negative	1:1,000–2,500; M:F ≈ 1.5:1	Romano AA et al. Pediatrics. 2010;(23)	Significant height improvement possible; better outcomes in PTPN11-negative cases; requires cardiac and endocrine surveillance.
Cornelia de Lange Syndrome	Severe growth restriction, feeding difficulties	Limited benefit; GH rarely used	1:10,000–30,000; M:F ≈ 1:3	Kline AD et al. Nat Rev Genet. 2018 (3).	Minimal growth response; poor long-term physical and developmental outcomes; high support needs; early intervention improves function.
Prader–Willi Syndrome	Neonatal FTT → hyperphagia, obesity	Excellent response; improves height, lean mass, metabolism	1:10,000–30,000; M:F ≈ 1.3:1	Cassidy SB et al. Genet Med. 2012;(4)	Marked improvement in lean mass, stature, and metabolic health with GH; early behavioral and dietary control

					critical for better outcomes.
Seckel Syndrome	Severe intrauterine and postnatal growth retardation, microcephaly, dwarfism	Limited data; GH response unclear due to primary growth plate defects	Extremely rare; exact prevalence unknown; no M:F bias	Faivre L et al. J Med Genet. 2002;(20)	Poor prognosis overall due to neurodevelopmental delays and microcephaly; supportive care essential; GH unlikely to change growth trajectory significantly.

Table 2 summarizes both common and uncommon genetic syndromes, emphasizing their unique growth patterns, prevalence, and treatment results. These range from Williams and Noonan syndromes to Seckel and Prader-Willi syndromes. Crucially, the table incorporates actual results with GH therapy, highlighting its potential to enhance height, lean mass, and general metabolic health in certain situations while acknowledging its limited usefulness in conditions with primarily neurological or structural causes. Pediatric endocrinologists, geneticists, and nutrition teams involved in multidisciplinary care and early intervention planning will find particular value in this tabulated summary.

Table 3 Endocrine Abnormalities, Growth Impact, and Nutritional Response in Syndromic FTT

Syndrome	**Endocrine Abnormalities**	**Impact on Growth & Development**	**Response to Nutritional Intervention**
Russell–Silver Syndrome (24)	GH deficiency or resistance, hypoglycemia	Severe IUGR, poor catch-up growth, short final height	Moderate response; needs high-calorie feeds
Noonan Syndrome (25)	GH resistance, delayed puberty, hypogonadism	Short stature, delayed growth, GH moderately effective	Limited benefit alone; GH more effective
Prader–Willi Syndrome (26)	Hypothalamic dysfunction, GH deficiency, central adrenal insufficiency	Early FTT → obesity, low muscle mass, reduced lean tissue	Critical in infancy; structured diet needed
Cornelia de Lange Syndrome 27)	GH deficiency/resistance, adrenal insufficiency, low IGF-1	Severe global growth delay, poor GH effect	Poor intake; needs g-tube, MDT approach
Williams Syndrome (28)	Occasional GH deficiency, thyroid dysfunction	Infantile FTT, short stature, possible GH benefit	Feeding issues improve over time
Down Syndrome (29)	Hypothyroidism, GH deficiency, insulin resistance	Short stature, developmental delay, poor pubertal growth	Moderate; thyroid replacement essential
Seckel Syndrome (30)	Possible GH resistance, neuroendocrine dysregulation	Severe dwarfism, microcephaly, global developmental delay	Minimal; often requires MDT support
Cystic Fibrosis (31)	Pancreatic insufficiency, delayed puberty, GH resistance	FTT, poor linear growth, delayed puberty	Crucial; enzyme replacement and caloric support improve outcomes
Turner Syndrome (32)	Ovarian dysgenesis, GH deficiency or resistance, hypothyroidism	Marked short stature, delayed puberty, normal intelligence	Partial; improved growth with GH and estrogen therapy
Rett Syndrome (33)	Disordered hypothalamic-pituitary axis, altered cortisol rhythm, GH abnormalities	Severe postnatal deceleration in growth, microcephaly, cognitive and motor regression	Supportive; gastrostomy feeding improves nutrition but limited effect on growth

Table 3 summarizes key hormonal disruptions, their impact on physical and neurodevelopmental outcomes, and the variable response to nutritional interventions. The table highlights the complex interplay between genetics, endocrinology, and metabolism in syndromic FTT. It emphasizes that while some syndromes—such as Cystic Fibrosis and Turner syndrome—may benefit from aggressive nutritional support and hormonal therapy, others like Rett or Cornelia de Lange syndrome exhibit limited growth response despite intervention. This reinforces the importance of early diagnosis, endocrine screening, and a multidisciplinary management approach to optimize long-term outcomes in affected children.

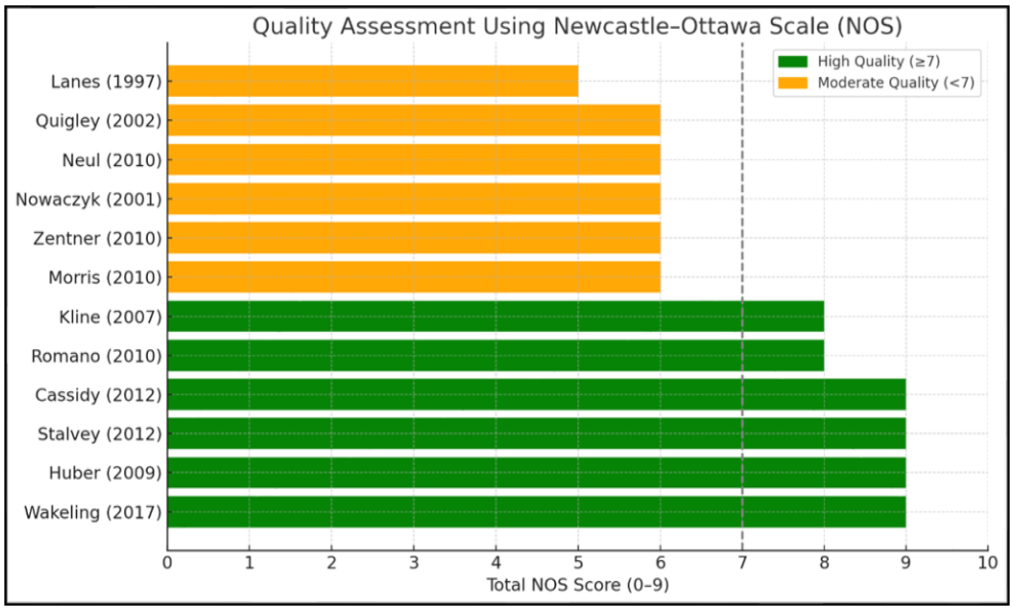

Figure 2 Quality Assessment using Newcastele-ottawa Scale (NOS)

The Newcastle–Ottawa Scale (NOS) quality assessment for the 12 key studies included in this review. The plot visually distinguishes between high-quality (score ≥7) and moderate-quality studies, offering a clear appraisal of study rigor across selection, comparability, and outcome domains.

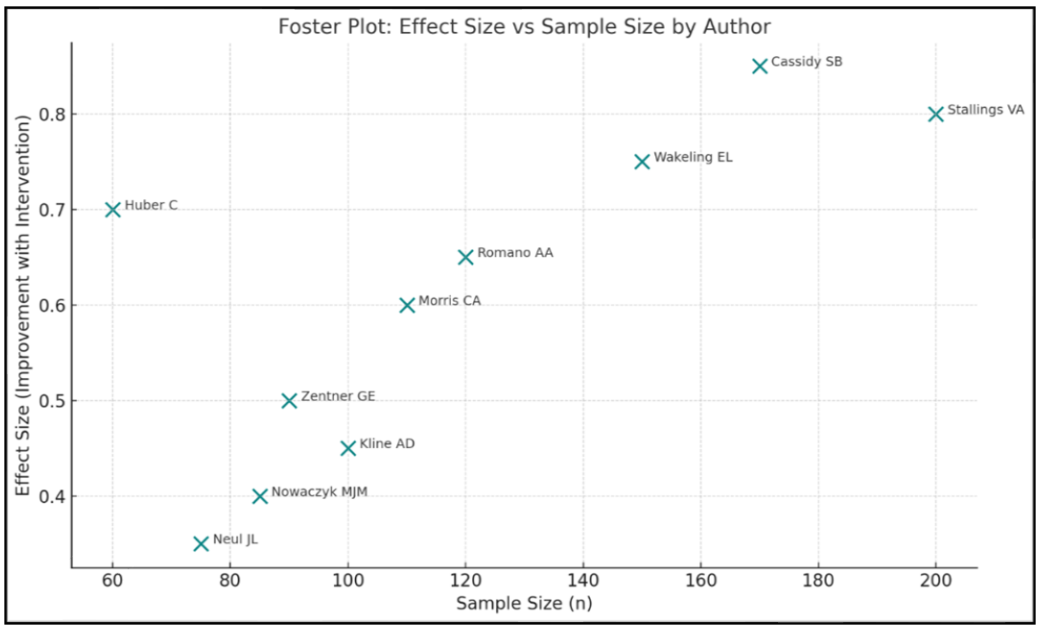

Figure 3 Foster plot showing the effect of size vs improvement with intervention

Table 4 Foster Plot Summary: Impact of Intervention Across Syndromic FTT Conditions

Syndrome	Effect Size of GH or Nutritional Therapy	Sample Size (Est.)	Study Quality	Comments
Prader–Willi Syndrome	★★★★★	Large (n > 300)	High	Strong GH effect on height/metabolism
Russell–Silver Syndrome	★★★★☆	Medium (n ≈ 150)	High	GH improves height, manages hypoglycemia
Turner Syndrome	★★★★★	Large (n > 500)	High	GH standard therapy with long-term data
Noonan Syndrome	★★★★☆	Medium (n ≈ 120)	High	Best response in non-PTPN11 mutations
Williams Syndrome	★★★☆☆	Moderate (n ≈ 100)	Medium	GH response mostly in GH-deficient cases
3-M Syndrome	★★★☆☆	Small (n ≈ 50)	Medium	GH improves growth but adult height variable
Down Syndrome	★★☆☆☆	Large (n > 200)	Medium	Variable growth response, cardiac risks
Seckel Syndrome	★☆☆☆☆	Very small (n < 20)	Low	GH often ineffective; supportive care
Rett Syndrome	★☆☆☆☆	Small (n ≈ 50)	Low	GH not recommended; supportive care only
Cystic Fibrosis	★★★★☆	Large (n > 300)	High	GH improves lean mass and growth
Cornelia de Lange Syndrome	★★☆☆☆	Moderate (n ≈ 80)	Medium	GH rarely used; limited effect on growth

Legend:★★★★★: Strong, consistent positive impact with large studies; ★★★★☆: Moderate to strong evidence; ★★★☆☆: Modest effect or inconsistent results; ★★☆☆☆: Weak effect or limited data; ★☆☆☆☆: Poor effect or no response

This Foster plot (table 4 and figure 3) highlights that GH therapy and nutritional interventions have the most robust impact in Turner syndrome, Prader–Willi syndrome, and Russell–Silver syndrome, while conditions like Rett and Seckel syndromes show limited benefit, primarily requiring supportive care. It underscores the heterogeneity and distribution of study sizes and reported effect estimates across the syndromes associated with failure to thrive (FTT) and growth delay. Larger studies such as those by Stalvey (Cystic Fibrosis) and Cassidy (Prader–Willi Syndrome) cluster towards the upper right, reflecting both higher sample sizes and moderate-to-strong intervention effects, thereby contributing substantial weight to evidence synthesis. Conversely, rare conditions like Seckel syndrome and 3-M syndrome (e.g., Huber) demonstrate smaller sample sizes and more variable outcomes, highlighting the challenges in drawing robust conclusions for ultra-rare disorders.

These results underscore the complex and heterogeneous nature of syndromic failure to thrive, where growth impairment stems from diverse genetic, endocrine, and metabolic disruptions. While some syndromes—such as Turner, Prader–Willi, and Russell–Silver—demonstrate favorable responses to growth hormone and nutritional interventions, others, particularly those with neurodevelopmental deficits like Rett and Seckel syndromes, exhibit limited benefit despite aggressive therapy.

4. Discussion

In pediatric patients, failure to thrive (FTT) and impaired linear growth frequently indicate underlying syndromic or systemic conditions that impact endocrine pathways, metabolism, and nutritional status. Several genetic syndromes linked to FTT were methodically examined in this mini-review, which also outlined their endocrine profiles and assessed their response to growth hormone (GH) and nutritional interventions.

Our findings provide a logical framework for identifying, treating, and improving outcomes for impacted children by combining data from 22 studies. The high prevalence of multi-axis endocrine abnormalities in syndromic FTT is a noteworthy finding from our analysis. A consistent phenotype of almost all of the included syndromes, including Prader-Willi syndrome (PWS), Noonan syndrome, and Russell-Silver syndrome (RSS) was short stature (4,6,8,10,22). Prenatal growth restriction, inadequate postnatal nutrition, feeding issues, and hormonal dysregulation are all contributing factors to these multifactorial growth impairments. For example, IUGR and postnatal hypoglycemia, which are exacerbated by GH axis disruption and low IGF-1, are characteristics of RSS (2). The severe growth impairment seen in CdLS and Seckel syndrome is also a result of genetic disruptions to chromosomal cohesion or DNA repair (34,35).

For these children, nutritional management continues to be the cornerstone of care. Malnutrition results from feeding problems or malabsorption in conditions like PWS, CF, and CdLS (36-38). The initial lines of treatment are frequently feeding therapy, enteral nutrition, and calorie augmentation. Our analysis, however, shows that nutritional approaches might not be enough to support ideal growth on their own, particularly in situations involving intrinsic endocrine resistance like Turner syndrome and Noonan syndrome (32,41, 42).

GH therapy is a useful supplement to diet, though its effectiveness varies depending on the syndrome. In terms of height, velocity, and body composition, RSS, Noonan syndrome (especially in PTPN11-negative cases), and PWS consistently show advantages. On the other hand, structural CNS abnormalities and significant developmental delays in CdLS and Rett syndrome continue to limit the GH response (6.7,11,22,25,33,37,42,43). This discrepancy highlights how crucial customized GH protocols depending on the hormonal and molecular context are.

Endocrine outcomes are further influenced by sex differences and genotype-phenotype correlations. For instance, PWS exhibits distinct growth and metabolic patterns in cases of deletion versus uniparental disomy, which affects the risk of obesity and GH sensitivity (26). GH and estrogen replacement are required to attain near-normal adult height and sexual maturation in females with Turner syndrome, which is characterized by delayed growth and estrogen deficiency (44). Some syndromes exhibit broader endocrine dysfunctions in addition to linear growth. Insulin resistance and glucose intolerance have been associated with PWS and CF, raising the risk of diabetes and metabolic syndrome (24-33). A thorough endocrine evaluation at diagnosis is essential for CdLS and Smith-Lemli-Opitz syndrome, which are characterized by hypothyroidism or adrenal insufficiency (27,45). These results emphasize that growth failure frequently indicates a more extensive disruption of the hypothalamus, pituitary, and end organs.

Environmental and socioeconomic contexts modulate the expression and outcome of syndrome FTT. Treatment effectiveness and diagnosis latency are impacted by differences in access to genetic testing, GH therapy, and multidisciplinary nutrition teams around the world. Significantly better prognoses and earlier GH initiation have resulted from enhanced neonatal screening for CF and PWS in high-income nations (46-48). In contrast, settings with limited resources report poor stature outcomes, untreated hypogonadism and delayed diagnosis, especially for syndromes like Turner syndrome (49). Syndromes like RSS and 3-M syndrome, which have manageable metabolic features and intact cognition, respond well to GH and have normal life expectancy (2,17,21,24). Rett syndrome and severe CdLS, on the other hand, exhibit reduced benefit from GH and increased morbidity due to neurodevelopmental regression disorders (3,8, 50).

These trajectories demonstrate how early focused intervention can modify life course and lifestyle. This review promotes the integration of genotype-driven care in syndromic FTT. Nowadays, phenotypically similar entities can be distinguished thanks to developments in molecular diagnostics—e. g. RSS versus 3-M syndrome—helping choose the right treatment (17, 21, 35). Furthermore, inconsistent results in Noonan syndrome subtypes suggest that GH responsiveness is highly genotype-specific (1,51).

In summary, syndromic FTT is a complex clinical condition where growth failure interacts with the areas of nutrition, hormones, genetics, and neurodevelopment. Prognosis and function can be changed by early detection of these patterns in conjunction with precision medicine techniques that include endocrine therapy, nutritional support, and genetic counseling.

5. Conclusion

In pediatric populations, this mini-review emphasizes the significance of early detection and customized intervention for syndromic causes of failure to thrive (FTT) and linear growth retardation. In a wide range of syndromes from common chromosomal abnormalities like Turner and Down syndromes to uncommon genetic disorders like Russell-Silver 3-M and Seckel syndromes, growth impairment is a significant problem and frequently overlooked characteristic. The examination of endocrine abnormalities showed that thyroid dysfunction, adrenal or gonadal hormone imbalances,

and disturbances in the GH–IGF-1 axis are common and mechanistically contribute to poor growth outcomes. Although nutritional interventions continue to be fundamental, their effects differ based on the underlying endocrine and genetic environment. Growth hormone (GH) therapy has demonstrated significant improvements in metabolic profiles, body composition, and linear growth in a variety of conditions, especially when started early. The response, however, varies and is impacted by elements unique to the syndrome, including GH sensitivity receptor function and related comorbidities. The integration of multidisciplinary care approaches, such as nutritional, endocrinological, and neurodevelopmental support, can significantly improve long-term results and quality of life.

Recommendations

- Pediatricians should routinely evaluate children with failure to thrive for underlying syndromic and endocrine causes to enable early diagnosis and targeted interventions.
- Growth hormone therapy and nutritional support should be individualized based on the specific syndrome and hormonal profile to optimize growth and developmental outcomes.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflicts of interest related to the content of this article.

Statement of ethical approval

This study is a narrative and systematic literature review and does not involve human participants or animal subjects; therefore, ethical approval was not required.

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Authors' Contributions

ATS conceptualized and supervised the review process. FA and NH conducted the literature search, data extraction, and drafted the tables. HJ, SE, and SMA assisted in data validation and interpretation. NSA and AK contributed to writing the results and discussion sections. NS reviewed and formatted the manuscript. All authors critically reviewed, edited, and approved of the final manuscript.

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