

Role of Pregnancy-Associated Plasma Proteins (PAPP A and PAPP A2) and Insulin-Like Growth Factor-Binding Proteins in Children with Idiopathic Short Stature

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Abstract

Background: Idiopathic short stature (ISS) is a poorly understood growth disorder in children who have normal growth hormone secretion but remain significantly shorter than their peers. This review synthesises current evidence on the roles of pregnancy-associated plasma proteins (PAPP-A and PAPP-A2) and insulin-like growth factor-binding proteins (IGFBPs) in the pathophysiology of ISS, and evaluates their potential as diagnostic biomarkers and therapeutic targets.

Main Body: We performed a narrative review of peer-reviewed literature published up to 2024, focusing on the biochemical regulation of the growth hormone–insulin-like growth factor (GH–IGF) axis, with special emphasis on PAPP-A, PAPP-A2, and IGFBPs. Genetic, diagnostic, and treatment studies in children with ISS were also examined.

PAPP-A and PAPP-A2 are metalloproteinases that cleave IGFBP-3 and IGFBP-5, thereby increasing free IGF-1 bioavailability and promoting chondrocyte proliferation and linear bone growth. Disrupted activity of these proteins leads to relative IGF-1 resistance and impaired growth. Several genetic variants in the GH–IGF axis (GHR, IGFALS) and in growth-plate regulators (SHOX, NPR2, FGFR3, ACAN) have been identified in ISS children, although routine testing for PAPP-A/A2 is not yet standard. GH therapy remains the only FDA-approved treatment for ISS, but its efficacy is variable and long-term safety data are limited.

Conclusion: PAPP-A, PAPP-A2, and IGFBPs are key modulators of IGF bioavailability. Their measurement may improve diagnostic accuracy in ISS and open avenues for targeted therapy. Future research should focus on standardised assays and clinical trials of PAPP-A/A2 modulators.

Keywords: Idiopathic short stature, PAPP-A, PAPP-A2, Insulin-like growth factor binding proteins, Growth hormone

Plain English Summary

Idiopathic short stature (ISS) is a condition where children are much shorter than average, but doctors cannot find a clear medical reason after routine tests. This review looks at two proteins called PAPP-A and PAPP-A2, and a family of proteins called IGFBPs, which control how the body uses growth hormones. In healthy children, PAPP-A and PAPP-A2 act like molecular scissors – they cut IGFBPs to release growth factors that help bones grow longer. In children with ISS, this system may not work properly, so growth factors are trapped and cannot do their job. Understanding these proteins could help doctors diagnose ISS more accurately and develop new treatments. This article explains the

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science behind ISS, how doctors currently diagnose it (using growth charts, bone X-rays, and blood tests), and what treatments are available, including growth hormone injections. We also discuss new genetic discoveries that may explain why some children are short. The goal is to give patients, families, and doctors a clearer picture of what ISS is and how future research might lead to better care.

Background

Idiopathic short stature (ISS) remains one of the most challenging paediatric growth disorders because it is defined not by a specific cause, but by the absence of identifiable pathology. According to the Paediatric Endocrine Society, ISS is diagnosed when a child's height standard deviation score is ≤ -2.25 (below the 1.2nd percentile) despite normal growth hormone (GH) secretion, normal birth weight, and no evidence of systemic, endocrine, nutritional, or chromosomal abnormalities (1, 2). Although GH therapy has been approved for ISS in several countries, its modest efficacy and high cost have fuelled a search for better diagnostic markers and more targeted treatments.

The GH–insulin-like growth factor (IGF) axis is central to linear growth. GH stimulates the liver and other tissues to produce IGF-1, which then acts on the growth plate to promote chondrocyte proliferation and bone elongation (3). However, most circulating IGF-1 is bound to IGF-binding proteins (IGFBPs), particularly IGFBP-3 and IGFBP-5, which prolong its half-life but also restrict its access to receptors (4). The bioavailability of free IGF-1 is therefore tightly controlled by proteolytic cleavage of IGFBPs – a process largely mediated by pregnancy-associated plasma proteins A and A2 (PAPP-A and PAPP-A2) (5).

Recent evidence suggests that subtle dysregulation of the PAPP-A/A2–IGFBP axis may underlie some cases of ISS that are otherwise indistinguishable from healthy short children (6). Moreover, advances in molecular genetics have uncovered mutations in genes beyond the classical GH–IGF axis – such as *SHOX*, *NPR2*, *FGFR3*, and *ACAN* – that can present as ISS without syndromic features (7). These discoveries have transformed ISS from a single diagnostic label into a heterogeneous group of growth-limiting conditions.

In this review, we summarise the current understanding of how PAPP-A, PAPP-A2 and IGFBPs regulate the IGF system, and we explore their diagnostic and therapeutic potential in ISS. We also briefly discuss other genetic causes, diagnostic algorithms, and treatment options to provide a comprehensive overview for clinicians and researchers.

Methods

This is a narrative review of the scientific literature on the role of PAPP-A, PAPP-A2, and IGFBPs in children with idiopathic short stature.

We searched PubMed, Scopus, and Google Scholar for articles published in English between January 1990 and December 2024. The search strategy combined the following keywords (using Boolean operators): “idiopathic short stature” OR “ISS” AND “PAPP-A” OR “PAPP-A2” OR “pregnancy-associated plasma protein” AND “IGFBP” OR “insulin-like growth factor binding protein” AND “growth hormone” OR “IGF-1”. Additional searches were performed for genetic markers (*SHOX*, *NPR2*, *FGFR3*, *ACAN*), diagnostic methods (bone age, growth charts), and treatments (GH therapy, IGF-1 therapy).

We included original research articles, systematic reviews, meta-analyses, and clinical guidelines. Case reports and conference abstracts were excluded. After removing duplicates, two authors (RWS and SA) screened titles and abstracts, then read full texts of potentially relevant articles. Reference lists of included articles were hand-searched for additional studies. A total of 43 articles were initially identified; after applying inclusion/exclusion criteria and prioritising those most relevant to the biochemical regulation of IGF bioavailability, we selected 30 key references for this review.

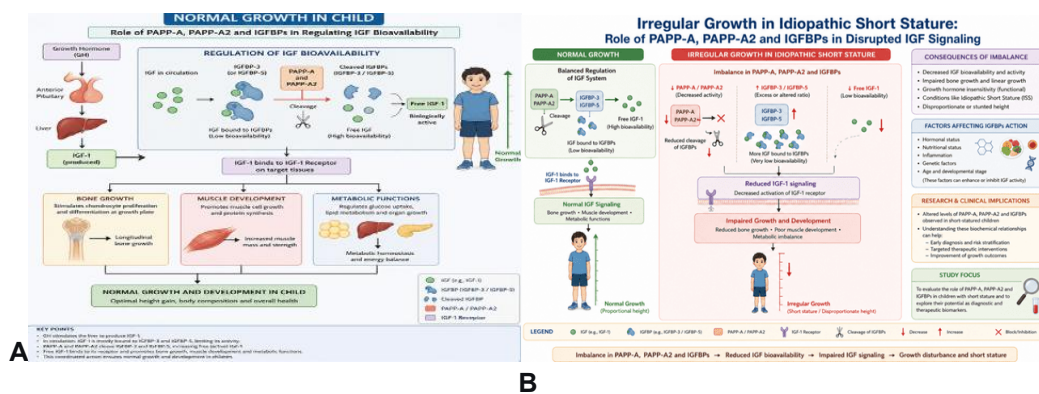
Because this is a narrative review of published data, no ethical approval or patient consent was required.

The GH–IGF Axis and the Role of PAPP-A and PAPP-A2

Normal linear growth depends on a finely tuned balance between GH, IGF-1, and their binding proteins. GH is secreted by the anterior pituitary and acts on the liver to induce IGF-1 synthesis. Over 75% of circulating IGF-1 is bound in a ternary complex with IGFBP-3 and the acid-labile subunit (ALS), which prevents IGF-1 from crossing the capillary endothelium and prolongs its plasma half-life to about 12–15 hours (3, 4). Only a small fraction of “free” IGF-1 can bind to the IGF-1 receptor on chondrocytes and stimulate cell proliferation.

PAPP-A (pregnancy-associated plasma protein A) and its homologue PAPP-A2 are zinc-dependent metalloproteinases that specifically cleave IGFBP-4 (PAPP-A) and IGFBP-3 and IGFBP-5 (PAPP-A2) (5). By cleaving these binding proteins, PAPP-A and PAPP-A2 increase the concentration of free IGF-1, thereby amplifying IGF-1 signalling (Figure 1). In the growth plate, this leads to

increased chondrocyte proliferation, matrix synthesis, and ultimately bone lengthening (6).



Studies in children with ISS have shown that serum levels of PAPP-A2 may be lower than in age-matched controls, and that free IGF-1 levels are often disproportionately reduced relative to total IGF-1 (8). This pattern suggests a “functional IGF-1 deficiency” caused by impaired proteolysis of IGFBPs, rather than an absolute lack of IGF-1 production. Banaszak-Ziemska et al. (8) recently measured PAPP-A2, free IGF-1, IGFBP-5, and ALS in 22 children with ISS and found significantly lower free IGF-1 concentrations compared with healthy peers, despite normal total IGF-1. This finding supports the concept that ISS may result from a relative resistance to IGF-1 due to excessive binding protein activity (9).

Genetic Variations Affecting the PAPP-A/A2–IGFBP Axis

Although mutations in the *PAPPA2* gene are rare, polymorphisms that reduce PAPP-A2 activity have been associated with short stature in population-based studies (10). In one family with autosomal dominant short stature, a heterozygous *PAPPA2* mutation led to increased IGFBP-3 and IGFBP-5 levels, low free IGF-1, and a poor response to GH therapy (11). These observations highlight the potential of *PAPPA2* as a candidate gene in ISS. Beyond PAPP-A2, other genetic abnormalities within the GH–IGF axis can mimic ISS. For example, partial GH insensitivity due to heterozygous *GHR* mutations may present with normal or borderline GH stimulation tests but low IGF-1 and IGFBP-3 (12). Similarly, mutations in *IGFALS* (encoding the acid-labile subunit) reduce the formation of the ternary complex, leading to accelerated IGF-1 clearance and modest growth failure (13). Children with these

conditions often meet the clinical criteria for ISS unless specialised testing (e.g., GH binding protein, ALS concentration) is performed.

Other Genetic Causes of ISS (Beyond the GH–IGF Axis)

Growing evidence indicates that many children labelled as ISS actually have unsuspected mutations in genes that regulate the growth plate directly. The most well-characterised among these are *SHOX*, *NPR2*, *FGFR3*, and *ACAN* (7, 14).

SHOX

The short stature homeobox gene is essential for chondrocyte differentiation in the distal limbs. Heterozygous *SHOX* mutations cause Léri-Weill dyschondrosteosis, but milder variants can present as non-syndromic short stature with normal body proportions (15). Approximately 2–5% of ISS children carry *SHOX* defects.

NPR2

This gene encodes the receptor for C-type natriuretic peptide (CNP), a positive regulator of growth plate chondrogenesis. Heterozygous *NPR2* mutations account for 2–6% of familial ISS cases and often cause disproportionate short stature with mesomelia (16).

FGFR3

Activating mutations in *FGFR3* cause achondroplasia and hypochondroplasia, but milder variants have been reported in children with proportionate short stature and no skeletal dysplasia (17).

ACAN

Mutations in the aggrecan gene lead to defective extracellular matrix in cartilage. Heterozygous *ACAN* mutations cause autosomal dominant short stature with advanced bone age and early growth cessation (18).

Prevalence estimates range from 1.4% to 2.5% in non-syndromic short stature cohorts. Figure 2 summarises the key growth-plate signalling pathways affected by these genes (Figure 2 – insert here).

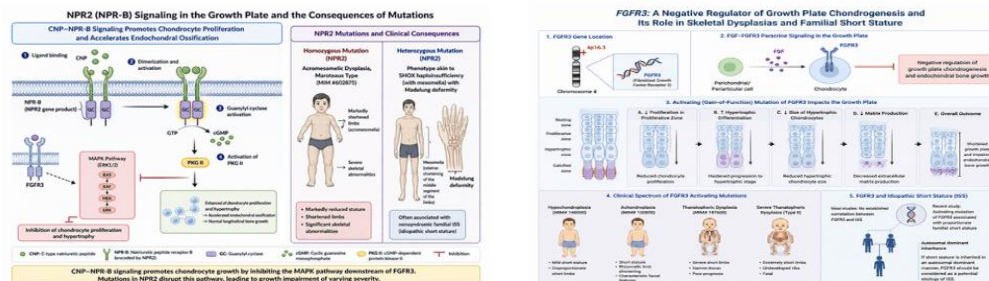


Figure 2: Paracrine signalling pathways in the growth plate

Chondrocyte proliferation is positively regulated by CNP binding to NPR-B (encoded by NPR2), which increases cGMP and inhibits the MAPK pathway. Conversely, FGF binding to FGFR3 activates MAPK signalling, which negatively regulates growth plate chondrogenesis. Gain-of-function FGFR3 mutations and loss-of-function NPR2 mutations both result in short stature, highlighting the balance between these pathways

Clinical Diagnosis of ISS: Current Algorithm

ISS remains a diagnosis of exclusion. The diagnostic work-up includes the following steps (1, 2, 19):

Anthropometry: Height below -2.25 SDS for age and sex, using standardised growth charts (e.g., WHO or CDC).

Growth rate

Usually normal or slightly reduced; a falling growth velocity warrants further investigation.

Bone age X-ray (left hand and wrist): In ISS, bone age is typically not delayed; if delayed, constitutional delay of growth and puberty (CDGP) is more likely.

GH stimulation tests

Peak GH >10 ng/mL rules out GH deficiency.

Laboratory screening

Complete blood count, inflammatory markers, celiac serology, thyroid function, and renal function to exclude systemic illness.

Genetic testing

For girls, karyotype to exclude Turner syndrome; selective testing for *SHOX*, *NPR2*, *ACAN*, and *FGFR3* in familial or disproportionate cases. Figure 3 presents a diagnostic algorithm for children with short stature

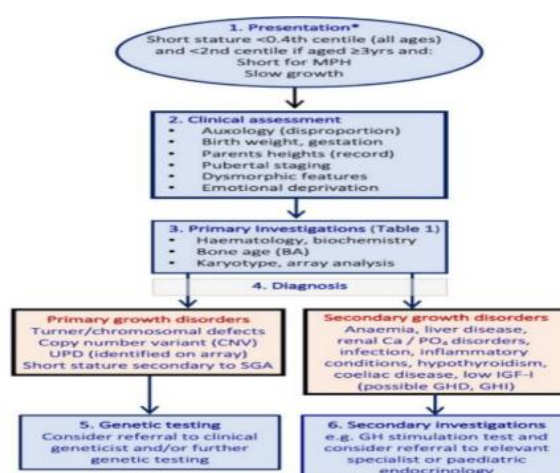


Figure 3: Diagnostic algorithm for a child with suspected idiopathic short stature

Evaluation begins with accurate height measurement and plotting on a growth chart. If height is below -2.25 SDS, bone age X-ray, GH stimulation test, and baseline laboratory screening are performed. After ruling out GH deficiency, Turner syndrome (karyotype in girls), systemic diseases, and skeletal dysplasias, a diagnosis of ISS is made. In selected cases (familial, disproportionate, or poor GH response), genetic testing for *SHOX*, *NPR2*, *ACAN*, *FGFR3*, and *PAPPA2* may be considered

Treatment Options for ISS

The only pharmacological treatment approved by the U.S. Food and Drug Administration for ISS is recombinant human GH (rhGH) (20). Typical doses range from 0.24 to 0.47 mg/kg/week, given as daily subcutaneous injections. A recent large observational study reported that rhGH treatment increases adult height by approximately 3.5–7.5 cm compared with untreated controls (21). However, the response is highly variable: younger children have a more delayed bone age, have lower baseline IGF-1 levels, and tend to gain more height.

Potential adverse effects of rhGH include benign intracranial hypertension, slipped capital femoral epiphysis, arthralgias, and glucose intolerance. Long-term safety (e.g., cancer risk) remains under surveillance, but current evidence does not show a significant increase (21).

Alternative or adjunctive treatments include: IGF-1 therapy (mecasermin) for children with severe primary IGF-1 deficiency, but it is not approved for ISS.

C-type natriuretic peptide (CNP) analogues (e.g., vosoritide), which are approved for achondroplasia and are being explored for ISS with *NPR2* mutations (22).

GnRH agonists or aromatase inhibitors to delay puberty and extend the growth period, although efficacy and safety are not established for routine use.

Discussion

This review synthesises the current understanding of how PAPP-A, PAPP-A2 and IGFBPs regulate the GH–IGF axis and how their dysregulation may contribute to idiopathic short stature. The main finding is that many children with ISS have a functional impairment of IGF-1 bioavailability that is not captured by standard total IGF-1 or GH stimulation tests. Instead, measuring free IGF-1, IGFBP-3, IGFBP-5, and PAPP-A2 could identify a subset of ISS children who have a “proteolysis-resistant” state and who might benefit from different therapeutic strategies.

Our results align with recent studies showing that lower PAPP-A2 activity correlates with reduced free IGF-1 and shorter stature (8, 9). Importantly, the same mechanism may explain why some ISS children respond poorly to GH therapy: if IGFBPs are not adequately cleaved, even supraphysiological doses of GH may not increase free IGF-1 sufficiently to drive growth. This has direct clinical implications. For instance, a child with low free IGF-1 but normal total IGF-1 could be considered for IGF-1-based treatment rather than high-dose GH.

The expanding list of genetic causes of ISS – from *GHR* to *ACAN* – reinforces the notion that ISS is a diagnostic umbrella rather than a single disease entity. In practice, this means that a child labelled as ISS today may, after genetic testing, be reclassified as having a specific growth-plate disorder tomorrow. The challenge for clinicians is to decide when to order such tests. Based on current evidence, we suggest that genetic testing should be offered to children with: (a) a family history of short stature in an autosomal dominant pattern; (b) disproportionate body proportions (sitting height/height ratio >2 SDS); (c) advanced bone age with early growth cessation (suggestive of *ACAN*); or (d) failure to respond to GH therapy after 12–18 months.

Study Limitations

This review has several limitations. First, it is a narrative rather than a systematic review, so we cannot rule out publication bias. Second, the evidence for PAPP-A/A2 in ISS is still limited to small cross-sectional studies; no longitudinal or interventional trials have been performed. Third, we did not have access to individual patient data, so we could not perform quantitative synthesis (e.g., meta-analysis) of free IGF-1 or PAPP-A2 levels. Fourth, most of the studies cited were conducted in Caucasian or Middle Eastern populations; generalisability to other ethnic groups is uncertain. Finally, the optimal cut-offs for free IGF-1 or PAPP-A2 in diagnosing ISS have not been established.

Future Directions

Future research should focus on: Standardising assays for free IGF-1 and PAPP-A2 across laboratories. Conducting prospective cohort studies to determine whether low PAPP-A2 activity at diagnosis predicts poor response to GH. Randomised controlled trials of recombinant IGF-1 or CNP analogues in ISS children with documented IGFBP-related abnormalities. Integrating whole-exome sequencing into the diagnostic algorithm for ISS to identify rare but actionable genetic variants.

Conclusion

Idiopathic short stature is a heterogeneous condition with a complex molecular basis that extends well beyond the classical GH-IGF axis. Pregnancy-associated plasma proteins A and A2, together with IGFBPs, play a critical role in determining the bioavailability of free IGF-1 to the growth plate. Children with ISS often exhibit a functional deficit in IGF-1 bioavailability that is not detected by routine hormone tests, suggesting that measurement of free IGF-1 and PAPP-A2

could improve diagnostic precision and guide treatment choices. While GH therapy remains the mainstay of treatment, novel agents such as CNP analogues and personalised approaches based on genetic profiling hold promise for the future. Clinicians should maintain a high index of suspicion for underlying genetic causes, especially in familial or treatment-resistant cases.

List of Abbreviations

ALS: Acid-labile subunit
BHI: Bone health index
CDGP: Constitutional delay of growth and puberty
CNP: C-type natriuretic peptide
FDA: U.S. Food and Drug Administration
GH: Growth hormone
GHR: Growth hormone receptor
IGF: Insulin-like growth factor
IGF 1: Insulin-like growth factor 1
IGFALS: Insulin-like growth factor acid-labile subunit gene
IGFBP: Insulin-like growth factor binding protein
ISS: Idiopathic short stature
PAPP A: Pregnancy-associated plasma protein A
PAPP A2: Pregnancy-associated plasma protein A2
rhGH: Recombinant human growth hormone
SDS: Standard deviation score
SGA: Small for gestational age
SHOX: Short stature homeobox-containing gene

Declarations

Ethics Approval and Consent to Participate

Not applicable. This is a narrative review of published literature; no human or animal subjects were involved.

Consent for Publication

All the authors gave consent for the publication of this work under the Creative Commons Attribution Non-Commercial 4.0 license.

Data Availability

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Author Contributions

SRW: Conceptualisation, Writing - original draft, Visualisation (figures).

AS: Methodology, Investigation, Data curation, Writing - review & editing.

AYH: Validation, Formal analysis, Writing - review & editing, Supervision.

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References

1. Wilson TA, Rose SR, Cohen P, Rogol AD, Backeljauw P, Brown R, Hardin DS, Kemp SF, Lawson M, Radovick S, Rosenthal SM. Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. The Journal of Pediatrics. 2003 Oct 1;143(4):415-21. [https://doi.org/10.1067/S0022-3476\(03\)00246-4](https://doi.org/10.1067/S0022-3476(03)00246-4)
2. Cohen P, Rogol AD, Deal CL, Saenger P, Reiter EO, Ross JL, Chernauek SD, Savage MO, Wit JM, 2007 ISS Consensus Workshop participants. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. The Journal of Clinical Endocrinology & Metabolism. 2008 Nov 1;93(11):4210-7. <https://doi.org/10.1210/jc.2008-0509>
3. Cirillo F, Lazzeroni P, Sartori C, Street ME. Inflammatory diseases and growth: effects on the GH-IGF axis and on growth plate. International Journal of Molecular Sciences. 2017 Aug 31;18(9):1878. <https://doi.org/10.3390/ijms18091878>
4. Steffensen LB, Conover CA, Oxvig C. PAPP-A and the IGF system in atherosclerosis: what's up, what's down?. American Journal of Physiology-Heart and Circulatory Physiology. 2019 Nov 1;317(5):H1039-49. <https://doi.org/10.1152/ajpheart.00395.2019>
5. Andrew M, Liao L, Fujimoto M, Khoury J, Hwa V, Dauber A. PAPP2 as a therapeutic modulator of IGF-I bioavailability: in vivo and in vitro evidence. Journal of the Endocrine Society. 2018 Jul;2(7):646-56. <https://doi.org/10.1210/js.2018-00106>
6. Upners EN, Ljubicic ML, Busch AS, Fischer MB, Almstrup K, Petersen JH, Jensen RB, Hagen CP, Juul A. Dynamic changes in serum IGF-I and growth during infancy: associations to body fat, target height, and PAPP2 genotype. The Journal of Clinical

- Endocrinology & Metabolism. 2022 Jan 1;107(1):219-29.
<https://doi.org/10.1210/clinem/dgab653>
7. Kang MJ. Novel genetic cause of idiopathic short stature. *Annals of Pediatric Endocrinology & metabolism*. 2017 Sep 28;22(3):153-7.
<https://doi.org/10.6065/apem.2017.22.3.153>
8. Banaszak-Ziemska M, Rojek A, Niedziela M. Genetic analysis of the PAPP-A2 gene and evaluation of free IGF-1, IGFBP-5, and ALS concentrations in a group of 22 patients with idiopathic short stature. *Endokrynologia Polska*. 2024;75(4):428-37.
<https://doi.org/10.5603/ep.100030>
9. Dauber A, Muñoz-Calvo MT, Barrios V, Domené HM, Klopperpris S, Serra-Juhé C, Desikan V, Pozo J, Muzumdar R, Martos-Moreno GÁ, Hawkins F. Mutations in pregnancy-associated plasma protein A2 cause short stature due to low IGF-I availability. *EMBO Molecular Medicine*. 2016 Apr 1;8(4):363-74.
<https://doi.org/10.15252/emmm.201506106>
10. Andrew M, Liao L, Fujimoto M, Khoury J, Hwa V, Dauber A. PAPP2 as a Therapeutic Modulator of IGF-I Bioavailability: *in Vivo* and *in Vitro* Evidence. *J Endocr Soc*. 2018 May 28;2(7):646-656.
<https://doi.org/10.1210/js.2018-00106>
11. Rosenfeld RG, Rosenbloom AL, Guevara-Aguirre J. Growth hormone (GH) insensitivity due to primary GH receptor deficiency. *Endocrine Reviews*. 1994 Jun 1;15(3):369-90. <https://doi.org/10.1210/edrv-15-3-369>
12. Hwa V, Haeusler G, Pratt KL, Little BM, Frisch H, Koller D, Rosenfeld RG. Total absence of functional acid labile subunit, resulting in severe insulin-like growth factor deficiency and moderate growth failure. *The Journal of Clinical Endocrinology & Metabolism*. 2006 May 1;91(5):1826-31.
<https://doi.org/10.1210/jc.2005-2842>
13. Baron J, Säwendahl L, De Luca F, Dauber A, Phillip M, Wit JM, Nilsson O. Short and tall stature: a new paradigm emerges. *Nature Reviews Endocrinology*. 2015 Dec;11(12):735-46.
<https://doi.org/10.1038/nrendo.2015.165>
14. Wit JM, Oostdijk W, Losekoot M, van Duyvenvoorde HA, Ruivenkamp CA, Kant SG. Mechanisms in endocrinology: novel genetic causes of short stature. *European Journal of Endocrinology*. 2016 Apr;174(4):R145-73.
<https://doi.org/10.1530/EJE-15-0937>
15. Vasques GA, Arnhold IJ, Jorge AA. Role of the natriuretic peptide system in normal growth and growth disorders. *Hormone Research in Paediatrics*. 2014 Sep 3;82(4):222-9.
<https://doi.org/10.1159/000365049>
16. Hisado-Oliva A, Garre-Vázquez AI, Santaolalla-Caballero F, Belinchón A, Barreda-Bonis AC, Vasques GA, Ramirez J, Luzuriaga C, Carlone G, González-Casado I, Benito-Sanz S. Heterozygous NPR2 mutations cause disproportionate short stature, similar to Léri-Weill dyschondrosteosis. *The Journal of Clinical Endocrinology & Metabolism*. 2015 Aug 1;100(8):E1133-42.
<https://doi.org/10.1210/jc.2015-1612>
17. Mamada M, Yorifuji T, Kurokawa K, Kawai M, Momoi T, Nakahata T. Prevalence of mutations in the FGFR3 gene in individuals with idiopathic short stature. *Clinical Pediatric Endocrinology*. 2006;15(2):61-4.
<https://doi.org/10.1297/cpe.15.61>
18. Dateki S, Nakatomi A, Watanabe S, Shimizu H, Inoue Y, Baba H, Yoshiura KI, Moriuchi H. Identification of a novel heterozygous mutation of the AggreCan gene in a family with idiopathic short stature and multiple intervertebral disc herniation. *Journal of Human Genetics*. 2017 Jul;62(7):717-21.
<https://doi.org/10.1038/jhg.2017.33>
19. Yau M, Lu J, Rapaport R. Idiopathic short stature and growth failure of unknown etiology. *Endotext* [Internet]. 2023 Oct 24.
20. Linglart A, Dauber A, de Lima Jorge A, Luo X, Ogata T, Säwendahl L. Efficacy, safety, and outcomes of growth hormone treatment in children with idiopathic short stature. *Growth Hormone & IGF Research*. 2025 Aug 9;101661.
<https://doi.org/10.1016/j.ghir.2025.101661>
21. Child CJ, Quigley CA, Cutler, Jr GB, Moore WV, Wintergerst KA, Ross JL, Rosenfeld RG, Blum WF. Height gain and safety outcomes in growth hormone-treated children with idiopathic short stature: experience from a prospective observational study. *Hormone Research in Paediatrics*. 2019 Jun 1;91(4):241-51.
<https://doi.org/10.1159/000500087>
22. Savarirayan R, Irving M, Bacino CA, Bostwick B, Charrow J, Cormier-Daire V, Le Quan Sang KH, Dickson P, Harmatz P, Phillips J, Owen N. C-type natriuretic peptide analogue therapy in children with achondroplasia. *New England Journal of Medicine*. 2019 Jul 4;381(1):25-35.
<https://doi.org/10.1056/NEJMoa1813446>