Rev Esp Endocrinol Pediatr 2026; Volumen 17 (Suppl 2)
10.3266/RevEspEndocrinolPediatr.pre2026.May.1084

An Update on New Genetic Causes of Short Stature

Actualización sobre nuevas causas genéticas de la talla baja

Alexander Augusto de Lima Jorge

Genetic Endocrinology Unit (LIM25), Endocrinology Division, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP), São Paulo, Brazil

Abstract

Short stature is a highly heritable trait and a frequent reason for referral in pediatric endocrinology. Although many acquired and endocrine disorders can impair growth, genetic factors account for a substantial proportion of children evaluated for growth failure. Advances in next-generation sequencing have profoundly transformed this field by enabling broad, hypothesis-free investigation through gene panels, exome sequencing, and genome sequencing. These approaches have markedly increased diagnostic yield, particularly in children with syndromic short stature, skeletal dysplasia, or defects of the GH–IGF axis, while also revealing monogenic causes in patients previously classified as having idiopathic isolated short stature. Recent years have seen a rapid expansion in the number of genes and molecular mechanisms associated with growth disorders, including both novel syndromes and the phenotypic expansion of known conditions. International guidance now supports the incorporation of genetic testing into the clinical evaluation of a substantial subset of children with short stature. Our group has contributed to the characterization of several new genetic causes of growth disorders, ranging from ultrarare syndromic conditions to more frequent monogenic causes of isolated short stature. Reanalysis of negative exome data and implementation of genome sequencing have further improved diagnostic success. Together, these advances are reshaping the clinical approach to short stature and refining our understanding of the genetic architecture of human growth.

Correspondencia:
Alexander Augusto de Lima Jorge
Avenida Dr. Arnaldo, 455, 5 andar, sala 5340, São Paulo, SP 01246-903, Brazil
E-mail: alexj@usp.br

Height as a highly heritable trait

Height follows a characteristic normal distribution, and by definition, short stature is usually defined as a height below -2 standard deviations for age and sex in a given population. A wide range of health conditions may underlie short stature, but genetic causes account for a substantial proportion of children with growth disorders evaluated in clinical practice[1]. This is expected, given that height is one of the most heritable human traits. Studies in large families and twins have estimated the heritability of adult height as ranging from 68% to 94%[2]. Individuals carrying combinations of genetic factors that reduce growth potential are therefore frequently encountered in clinical practice because of short stature.

Height determination results from the combined contribution of thousands of common variants, each exerting a very small effect on stature (typically <2 mm per allele), together with rare variants of moderate effect size, each capable of influencing height by several centimeters, thereby contributing to the polygenic architecture of height[3]. At the other end of the spectrum, ultrarare variants may exert large effects on stature and in isolation, cause what is recognized as monogenic short stature[4].

From classical evaluation to genomic diagnosis

Traditionally, the evaluation of a child with short stature has relied on a detailed clinical history and physical examination, complemented by laboratory and radiological investigations aimed at improving phenotypic characterization and identifying signs that may indicate a specific etiology for the growth disorder[1]. In addition to excluding a range of secondary causes of short stature, this approach allows patients to be broadly classified into four major categories[5]: disorders of the GH-IGF axis, skeletal

dysplasia, syndromic, and isolated short stature. All of these groups have a strong genetic component. Establishing a definitive diagnosis without genetic testing is possible in only a minority of cases, owing to the extreme rarity of many conditions, their phenotypic diversity and overlap, and the frequent absence of pathognomonic findings that would permit diagnosis on clinical grounds alone.

The development of medical genetics has historically been closely linked to the investigation of growth disorders. The introduction of karyotyping, the first genetic test widely available in clinical practice, elucidated the genetic basis of two syndromic conditions associated with short stature, Turner syndrome[6] and Down syndrome[7]. The longstanding recommendation to investigate Turner syndrome in every girl with otherwise unexplained short stature remains a clear proof of concept for the importance of incorporating genetic testing into the diagnostic work-up of children with growth disorders[8].

However, genetic investigations remained poorly accessible for many decades and were often confined to research groups. As a result, patients with rare syndromic causes of short stature or skeletal dysplasia frequently underwent prolonged diagnostic odysseys, with sequential investigations and specialist evaluations that still failed to provide a definitive diagnosis. In parallel, children with short stature and no other major associated findings came to be classified as having idiopathic short stature, a pseudo-diagnostic label that encompasses a highly heterogeneous group of conditions with a strong underlying genetic basis.

The advent of next-generation sequencing (NGS), also referred to as massively parallel sequencing, made it possible to analyze multiple genes simultaneously through targeted panels, all coding regions of the genome through exome sequencing, or even the entire genome. These technologies have transformed genetic investigation by increasing automation, reducing cost, and shortening turnaround time. In research, this has led to unprecedented progress in the identification of new genetic conditions, and particularly rare monogenic disorders (Figure 1)[9].

As genetic testing has become more accessible in clinical practice, exome and genome sequencing have shortened the diagnostic odyssey for a substantial proportion of patients[5]. A recent systematic review evaluating the diagnostic yield of genetic testing in children with short stature of previously unknown cause has quantified the impact of this new approach[10].

Determinants of diagnostic yield

First, the diagnostic yield is strongly influenced by the technique employed[10]. A targeted strategy remains preferable when a specific clinical diagnosis can guide genetic investigation. However, in many children with short stature, a clinical diagnosis cannot be established because of the absence of specific signs or because of the difficulty in recognising the large number of rare disorders associated with growth impairment. In the

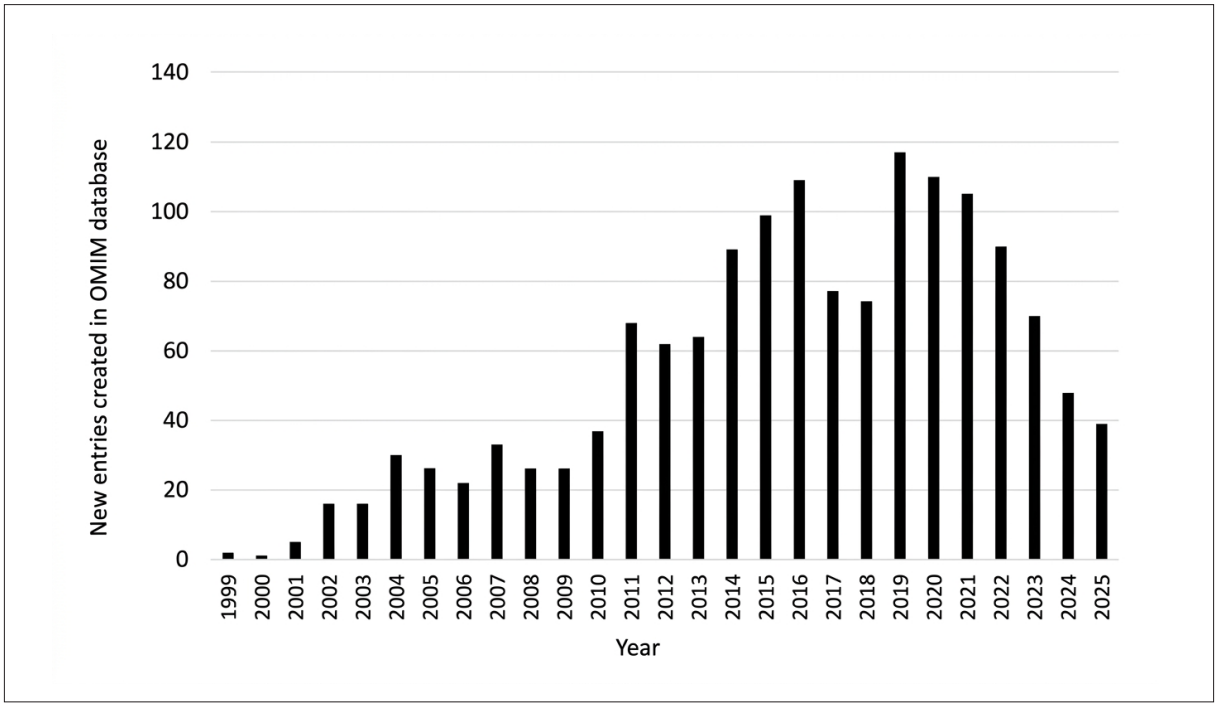


Figure 1. New entries (gene–phenotype correlations) created in the OMIM database per year related to short stature or growth impairment disorders.

investigation of unexplained short stature, studies limited to one or a few genes perform substantially worse than broad genomic approaches such as exome sequencing, which provide a comprehensive and hypothesis-free strategy (Table 1).

The second major determinant of diagnostic yield is the phenotype accompanying short stature[10]. In this context, patients can be classified into four main groups after careful clinical and laboratory evaluation. The first group includes children with syndromic short stature, in whom growth impairment is associated with significant dysmorphism, major congenital anomalies, or neurodevelopmental abnormalities. The second comprises children with skeletal dysplasia, suggested by bone deformities, body disproportion, or characteristic radiological abnormalities. The third includes disorders of the GH-IGF axis, in which endocrine evaluation is central to distinguishing between growth hormone deficiency, GH insensitivity, defects in the formation or metabolism of the ternary complex, and IGF insensitivity. Finally, there are otherwise healthy children with short stature and few or no additional findings, corresponding to isolated short stature[11]. These groups differ markedly not only in the proportion of cases in which genetic testing establishes a diagnosis, but also in the most appropriate investigative strategy.

Overall, children in syndromic, skeletal, and GH-IGF axis categories have a high diagnostic yield, generally exceeding 40%, when broad gene panels or exome/genome sequencing are applied[10]. An important exception is isolated GH deficiency, in which the diagnostic yield is often low when patients have no associated structural abnormalities on imaging and are evaluated outside the setting of consanguinity. Whenever possible, genetic testing should be guided by clinical findings that point to genes related to the working diagnostic hypothesis. However, this is not feasible in many patients because of the rarity and heterogeneity of the many conditions associated with growth disorders.

The Online Mendelian Inheritance in Man (OMIM) database currently lists thousands of phenotypes with an established monogenic basis, involving several thousand genes. An increasing number of genes are associated with more than one phenotype, and conversely, similar clinical presentations may result from defects in different genes. This substantially increases diagnostic complexity and limits the effectiveness of highly focused single-gene approaches. A search in OMIM using terms related to short stature in the Clinical Synopsis section illustrates how descriptions of growth-related conditions with an established molecular basis have steadily increased since 2011. Around 30% of the conditions listed in OMIM include short stature and/or growth restriction among the features summarized in the Clinical Synopsis.

This multiplicity of rare and distinct disorders, many of which have only recently been described and still incompletely characterized, often leads patients to experience a prolonged diagnostic odyssey, involving multiple specialist assessments and sometimes incorrect diagnoses[12]. The implementation of broad genetic testing strategies, particularly exome or genome sequencing, has helped to shorten this process and in many cases spared unnecessary investigations and costs. Importantly, these approaches have also enabled the characterization of a large number of new genetic causes of short stature in recent years.

Against this background, the recently published International guideline on genetic testing of children with short stature provides the first structured framework to guide the use of genetic testing in clinical practice[5]. The guideline also outlines the benefits that justify incorporating genetic testing into the evaluation of a substantial proportion of children with short stature (Box 1).

Many of these recommendations are well aligned with the experience of our group and with the data we have generated over the past decades.

Illustrative discoveries by our group

Our group has directly contributed to associating 11 genes with clinical conditions involving short stature, in addition to proposing novel candidate genes that still await confirmation of their relationship

Table 1. Diagnostic yield of genetic testing in children with short stature of unknown cause.

Methodology	Number of studies	Diagnostic yield (%)	95% CI
Single gene	79	4.4	3.3-5.7
Few genes (2 - 10)	8	4.4	1.8-7.8
Gene panel (> 10)	15	21.6	15.1-28.9
CMA	8	16.3	8.1-26.4
Exome sequencing	39	**33.3**	26.4-40.6

Data derived from the publication by Scalco et al.[10]; CMA = Chromosomal Microarray Analysis.

Box 1. Potential benefits of genetic testing applied to children with short stature.

- Provides a clear genetic diagnosis.
- Enables accurate genetic counseling and recurrence-risk prediction.
- Reduces need for further extensive / invasive diagnostic tests (including GH stimulation test).
- Allows earlier diagnosis before full phenotype.
- Guides treatment choices (when to use, avoid or adjust growth-stimulating therapies).
- Flags comorbidities that require targeted screening and specialist referral.
- Supports testing of relatives and detection of actionable secondary variants for prevention.

with growth disorders. These discoveries have ranged from phenotypic expansion of known gene-related conditions to the delineation of entirely new syndromes. Many resulted from decades of follow-up of emblematic patients, or from the systematic study of carefully phenotyped cohorts.

The challenges involved in establishing a diagnosis in unique patients are illustrated particularly well in two cases. When our clinic for growth disorders of unknown cause was established in 1997, two patients drew our attention because they presented with severe prenatal-onset short stature associated with microcephaly but without significant neurodevelopmental impairment (Figure 2). One of them had consanguineous parents (first cousins), suggesting a recessive disorder, although both individuals were otherwise isolated cases within their families. Clinically, they fell within the heterogeneous group of microcephalic primordial dwarfism, which includes defects in genes involved in cell proliferation, genome stability, DNA replication, and mitosis[13]. Over the years, both were investigated using all the technologies that successively became available, including karyotyping, conventional Sanger sequencing of multiple candidate genes[14], and chromosomal microarray analysis[15], all without diagnostic success.

They were the first patients in our group to undergo exome sequencing, in 2012. However, the analytical framework was still limited at that time, and no known cause of microcephalic primordial dwarfism was identified[16]. These patients grew into adulthood without a definitive diagnosis. As our group gained experience in the interpretation of exome data, particularly in the search for novel disease genes through a multidimensional strategy integrating multiple layers of biological evidence, including expression data, population frequency, variant characteristics, animal models, signaling pathways, and human genetic data, it became possible to identify strong candidate genes in both cases.

The candidate genes identified in these patients were highly compelling. One patient harbored a homozygous variant in *CDK4* leading to aberrant splicing and loss of the transcript that would normally generate the wild-type protein[17]. *CDK4* encodes a cell-cycle kinase



Patient	1	2
Consanguinity	Yes	No
Born SGA	Yes	Yes
Height SDS	-2.5	-6.5
Head circumference SDS	-3.7	-2.6
BMI SDS	-0.1	-3.9
Sitting height : total height SDS	1.0	+
Neurodevelopmental disorder	No	No
Additional clinical finding	Shawl scrotum, epilepsy during childhood; normocytic, elevated TSH with normal FT4, elevated LH with normal testosterone, small testicles in adulthood	Congenital hip dislocation, triangular face, high-pitched voice, retrognathia

Figure 2. Summary of clinical findings in two patients with microcephalic primordial dwarfism.

with a central role in cell-cycle regulation. Somatic gain-of-function variants in *CDK4* were already known to be associated with melanoma[18], whereas loss-of-function variants in *CDK6*, a gene with partially redundant functions in relation to *CDK4*, had been associated with a phenotype of microcephalic primordial dwarfism[19]. The second patient carried compound heterozygous splice-altering variants in *WDHD1*, a gene encoding a protein essential for DNA replication and maintenance of genomic stability[20]. However, identifying a strong candidate gene is only the first step. Establishing causality requires the identification of additional patients in whom genotype and phenotype are concordant[21].

In this regard, platforms such as GeneMatcher have become essential tools for connecting clinicians and researchers caring for patients with similar genetic and clinical findings[22]. In general, only a small minority of the candidate genes identified in our cohort are robust enough to justify submission to public matchmaking platforms. Many candidates are excluded after segregation analysis, identification of internal patients with incompatible phenotypes, or additional functional studies conducted by our group. Many of the genes we have submitted to GeneMatcher were ultimately discarded because the phenotypes observed in matching cases were not compatible with those in our patients., However, there was strong phenotypic concordance across multiple independent cases in a small subset. This was the case for the two patients described above. Both were ultimately shown to have ultrarare disorders caused by genes involved in cell-cycle regulation, leading to the delineation of two new genetic syndromes within the spectrum of microcephalic primordial dwarfism.

In contrast to these emblematic single-patient discoveries, other conditions were characterized through the analysis of larger cohorts followed in our center. This was the case for heterozygous variants in Indian hedgehog (*IHH*) associated with isolated short stature. *IHH* is a key regulator of endochondral growth[23]. Biallelic variants had long been recognized as a cause of severe skeletal dysplasia, acrocapitofemoral dysplasia[24], whereas heterozygous variants had been associated with brachydactyly type A1[25], an autosomal dominant disorder characterized by shortening or absence of the middle phalanges in all digits.

In 2016, we began an exome sequencing project in families with unexplained short stature and clear autosomal dominant inheritance. In an initial set of 17 families, we identified deleterious *IHH* variants segregating with short stature in three, with or without subtle skeletal abnormalities, particularly affecting the middle phalanges, most notably the second and fifth digits[26]. Importantly, however, the families we investigated did not display the classic brachydactyly phenotype and in routine clinical practice, were frequently classified as having idiopathic short stature[27]. This finding strongly suggested relevant phenotypic expansion.

Motivated by these results, we expanded the analysis to our own cohort, comprising approximately 130 individuals or families, and in collaboration with Karen Heath's group, included a Spanish cohort of patients with short stature and radiological suspicion of non-specific skeletal abnormalities. In both cohorts, we confirmed the presence of deleterious *IHH* variants, with familial segregation whenever possible, and demonstrated enrichment of these variants relative to population databases, thereby strengthening the evidence for causality[26].

This project was the first to establish *IHH* as a relevant cause of short stature in individuals previously labelled as having idiopathic short stature, and to systematically describe the associated clinical spectrum and response to growth hormone treatment. Together with previous work by our group on *SHOX*[28] and *NPR2*[29], this study helped consolidate our experience in elucidating the genetic basis of phenotypes initially considered idiopathic, precisely at a time when pediatric endocrinology was definitively entering the genomic era.

These findings were later recognized and expanded by additional studies, including international collaborative projects that further refined the phenotype associated with heterozygous *IHH* variants[30], as well as more recent evidence suggesting that this defect may be among the more frequent monogenic causes within the spectrum of short stature initially classified as idiopathic[10, 31]. Finally, the translational trajectory of this discovery has extended to therapeutic outcomes. In a recent publication, we reported that prolonged growth hormone therapy in children heterozygous for *IHH* variants was associated with improved adult height[32].

Current directions and future perspectives

At present, our group is working on the reanalysis of exome sequencing data and on the application of genome sequencing as an additional strategy in patients with syndromic growth disorders or skeletal dysplasia whose initial exome analysis was inconclusive. In parallel, we are performing burden analyses and validating polygenic risk scores to better understand the contribution of rare and common variants to common growth-related phenotypes.

We have observed a high rate of positive findings on reanalysis of previously negative exome data, particularly in tests performed before 2015, largely because copy number variant analysis is now incorporated into exome pipelines[33] and because

many additional gene-phenotype associations have been established in recent years[9]. In addition, for persistently negative cases, genome sequencing has allowed the identification of structural variants and pathogenic variants in regions not adequately captured by exome sequencing, including non-coding regions and the 5'UTR and 3'UTR[34], providing an additional diagnostic gain up to 10%.

Taken together, our overall experience using a stepwise approach to establish the etiology of syndromic short stature, beginning with careful clinical evaluation and hypothesis-driven molecular investigation whenever possible, followed by broad exome sequencing, systematic reanalysis of negative cases, and the implementation of genome sequencing, has yielded a diagnostic success rate of approximately 80%. This would have been almost unimaginable less than a decade ago.

In conclusion, the number of monogenic causes of short stature continues to grow rapidly. We should expect the description of new syndromes, expansion of recognized phenotypic spectra, and identification of novel genetic mechanisms of disease. In the near future, integration of rare high-impact variants with the contribution of common variants through polygenic risk scores will improve our understanding of the genetic architecture of height and of the clinical variability observed even within established genetic conditions, which is one of the major unresolved challenges in the field.

Conflict of interest: A.A.L.J. has received consulting fees from Novo Nordisk and Bridgebio and an independent research grant from BioMarin.

Funding: A.A.L.J. is funded by grant 303294/2020-5 from the National Council for Scientific and Technological Development (CNPq).

References

1. Collett-Solberg PF, Ambler G, Backeljauw PF, Bidlingmaier M, Biller BMK, Boguszewski MCS, et al. Diagnosis, Genetics, and Therapy of Short Stature in Children: A Growth Hormone Research Society International Perspective. Horm Res Paediatr. 2019;92(1):1–14.

2. Jelenkovic A, Sund R, Hur YM, Yokoyama Y, Hjelmborg JV, Moller S, et al. Genetic and environmental influences on height from infancy to early adulthood: An individual-based pooled analysis of 45 twin cohorts. Sci Rep. 2016;6:28496.

3. Bicknell LS, Hirschhorn JN, Savarirayan R. The genetic basis of human height. Nat Rev Genet. 2025.

4. Baron J, Savendahl L, De Luca F, Dauber A, Phillip M, Wit JM, et al. Short and tall stature: a new paradigm emerges. Nat Rev Endocrinol. 2015;11(12):735–46.

5. Dauber A, Jorge AAL, Nilsson O, Dekkers OM, Argente J, Netchine I, et al. International guideline on genetic testing of children with short stature. Eur J Endocrinol. 2026.

6. Ford CE, Jones KW, Polani PE, De Almeida JC, Briggs JH. A sex-chromosome anomaly in a case of gonadal dysgenesis (Turner's syndrome). Lancet. 1959;1(7075):711–3.

7. Lejeune J, Gautier M, Turpin R. [Study of somatic chromosomes from 9 mongoloid children]. C R Hebd Seances Acad Sci. 1959;248(11):1721–2.

8. Gravholt CH, Andersen NH, Christin-Maitre S, Davis SM, Duijnhouwer A, Gawlik A, et al. Clinical practice guidelines for the care of girls and women with Turner syndrome. Eur J Endocrinol. 2024;190(6):G53–G151.

9. Bamshad MJ, Nickerson DA, Chong JX. Mendelian Gene Discovery: Fast and Furious with No End in Sight. Am J Hum Genet. 2019;105(3):448–55.

10. Scalco RC, Schoones JW, Galetaki D, Santillan-Vasconez AM, Kim GJ, Cellin LP, et al. Diagnostic Yield of Genetic Testing in Children with Short Stature: a Systematic Review. Eur J Endocrinol. 2026.

11. Vasques GA, Andrade NLM, Jorge AAL. Genetic causes of isolated short stature. Arch Endocrinol Metab. 2019;63(1):70–8.

12. Knight AW, Senior TP. The common problem of rare disease in general practice. Med J Aust. 2006;185(2):82–3.

13. Khetarpal P, Das S, Panigrahi I, Munshi A. Primordial dwarfism: overview of clinical and genetic aspects. Mol Genet Genomics. 2016;291(1):1–15.

14. Leal AC, Montenegro LR, Saito RF, Ribeiro TC, Coutinho DC, Mendonca BB, et al. Analysis of the insulin-like growth factor 1 receptor gene in children born small for gestational age: in vitro characterization of a novel mutation (p.Arg511Trp). Clin Endocrinol (Oxf). 2013;78(4):558–63.

15. Canton AP, Costa SS, Rodrigues TC, Bertola DR, Malaquias AC, Correa FA, et al. Genome-wide screening of copy number variants in children born small for gestational age reveals several candidate genes involved in growth pathways. Eur J Endocrinol. 2014;171(2):253–62.

16. Homma TK, Freire BL, Honjo Kawahira RS, Dauber A, Funari MFA, Lerario AM, et al. Genetic Disorders in Prenatal Onset Syndromic Short Stature Identified by Exome Sequencing. J Pediatr. 2019;215:192–8.

17. Verdu Schlie A, Leitch A, Arismendi MI, Stok C, Castro Leal A, Parry DA, et al. CDK4 loss-of-function mutations cause microcephaly and short stature. Genes Dev. 2025;39(9-10):634–51.

18. Wolfel T, Hauer M, Schneider J, Serrano M, Wolfel C, Klehmann-Hieb E, et al. A p16INK4a-insensitive CDK4 mutant targeted by cytolytic T lymphocytes in a human melanoma. Science. 1995;269(5228):1281–4.

19. Hussain MS, Baig SM, Neumann S, Peche VS, Szczepanski S, Nurnberg G, et al. CDK6 associates with the centrosome during mitosis and is mutated in a large Pakistani family with primary microcephaly. Hum Mol Genet. 2013;22(25):5199–214.

20. Tibbe D, Vogt MR, Holling T, Schlieben LD, Kortum F, Shoukier M, et al. Bi-allelic WDHD1 variants cause microcephalic primordial dwarfism. Am J Hum Genet. 2026.

21. Strande NT, Riggs ER, Buchanan AH, Ceyhan-Birsoy O, DiStefano M, Dwight SS, et al. Evaluating the Clinical Validity of Gene-Disease Associations: An Evidence-Based Framework Developed by the Clinical Genome Resource. Am J Hum Genet. 2017;100(6):895–906.

22. Sobreira N, Schiettecatte F, Valle D, Hamosh A. GeneMatcher: a matching tool for connecting investigators with an interest in the same gene. Hum Mutat. 2015;36(10):928–30.

23. Long F, Chung UI, Ohba S, McMahon J, Kronenberg HM, McMahon AP. Ihh signaling is directly required for the osteoblast lineage in the endochondral skeleton. Development. 2004;131(6):1309–18.

24. Hellemans J, Coucke PJ, Giedion A, De Paepe A, Kramer P, Beemer F, et al. Homozygous mutations in IHH cause acrocapitofemoral dysplasia, an autosomal recessive disorder with cone-shaped epiphyses in hands and hips. Am J Hum Genet. 2003;72(4):1040–6.

25. Gao B, Guo J, She C, Shu A, Yang M, Tan Z, et al. Mutations in IHH, encoding Indian hedgehog, cause brachydactyly type A-1. Nat Genet. 2001;28(4):386–8.

26. Vasques GA, Funari MFA, Ferreira FM, Aza-Carmona M, Sentchordi-Montane L, Barraza-Garcia J, et al. IHH Gene Mutations Causing Short Stature With Nonspecific Skeletal Abnormalities and Response to Growth Hormone Therapy. J Clin Endocrinol Metab. 2018;103(2):604–14.

27. Cohen P, Rogol AD, Deal CL, Saenger P, Reiter EO, Ross JL, et al. 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. J Clin Endocrinol Metab. 2008;93(11):4210–7.

28. Jorge AA, Souza SC, Nishi MY, Billerbeck AE, Liborio DC, Kim CA, et al. SHOX mutations in idiopathic short stature and Leri-Weill dyschondrosteosis: frequency and phenotypic variability. Clin Endocrinol (Oxf). 2007;66(1):130–5.

29. Vasques GA, Amano N, Docko AJ, Funari MF, Quedas EP, Nishi MY, et al. Heterozygous mutations in natriuretic peptide receptor-B (NPR2) gene as a cause of short stature in patients initially classified as idiopathic short stature. J Clin Endocrinol Metab. 2013;98(10):E1636–44.

30. Sentchordi-Montane L, Benito-Sanz S, Aza-Carmona M, Pereda A, Parron-Pajares M, de la Torre C, et al. Clinical and Molecular Description of 16 Families With Heterozygous IHH Variants. J Clin Endocrinol Metab. 2020;105(8).

31. Andrade NLM, Funari MFA, Malaquias AC, Collett-Solberg PF, Gomes N, Scalco R, et al. Diagnostic yield of a multigene sequencing approach in children classified as idiopathic short stature. Endocr Connect. 2022;11(12).

32. Cavalcante JM, Cellin LP, Damiao ALS, Funari MFA, Malaquias AC, Digilio Vieira da Silva L, et al. Long-Term Growth Hormone Therapy Improves Adult Height in Children with Indian Hedgehog-Related Short Stature. Horm Res Paediatr. 2026:1–9.

33. Raca G, Astbury C, Behlmann A, De Castro MJ, Hickey SE, Karaca E, et al. Points to consider in the detection of germline structural variants using next-generation sequencing: A statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2023;25(2):100316.

34. Clark MM, Stark Z, Farnaes L, Tan TY, White SM, Dimmock D, et al. Meta-analysis of the diagnostic and clinical utility of genome and exome sequencing and chromosomal microarray in children with suspected genetic diseases. NPJ Genom Med. 2018;3:16.