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CRECIMIENTO Y PUBERTAD

A practical approach in genetic investigation of children with isolated short stature

Un enfoque práctico en la investigación genética de niños con talla baja aislada

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Short stature is defined by height more than 2 standard deviation scores below the mean observed in age and sex reference population (height SDS <-2) and, by definition, affects 2.3% of children. The majority of children with short stature are healthy and do not present any alteration in clinical or laboratory exam that could elucidate the cause of their growth impairment [1]. These children are classified according to their birth weight and length as having idiopathic short stature (ISS) or born small for gestational age (SGA), which can also be called as non-syndromic or isolated short stature.

Human height is a high heritable trait [2]. Several common variants (with a minor allele frequency greater than 5%) located throughout the genome explain around 25% oh height variability in general population [3]. Each of these frequent variants has an impact of 1-2 mm on height. Additionally, rare variants (with frequency less than 1%) may exert an effect of 10 to 20 times greater [4-6]. Although short stature can be caused by a combination of common genetic variants with a small impact on growth in a polygenic inheritance, especially in mild and isolated cases, several monogenic defects have been appointed as cause of the growth impairment in children with ISS or born SGA [7]. Multiple studies have applied multigene sequencing analysis [whole exome sequencing (WES) or targeted gene panel] to investigated children with isolated short stature. A recurrent observation of these studies is that approximately 1.5% of children with isolated short stature are the mildest clinical presentation of Noonan syndrome or neurofibromatosis type 1 [8-10]. Additionally, defects in several genes were associated with short stature and unspecific or absence of additional clinical symptoms and/or signals.

Defects located in genes related to somatotropic axis, as intuitively expected, were identified in several children classified as ISS or born SGA. The growth hormone (GH) and insulin-like growth factor 1 (IGF-1) are the key components of the somatotropic axis, which is recognized as the main endocrine regulator of longitudinal growth. For this reason, defects in genes that participate in the GH/IGF-1 pathway have always been the target of researches looking for genetic causes of short stature. These gene defects (summarized in Table 1) can disrupt from the synthesis of GH to the action of IGF-1. Although typical alterations in laboratory tests may indicate a candidate gene, some affected individuals have subtle findings of GH/IGF-1 deficiency or resistance and are classified as having ISS or SGA.

Longitudinal bone growth occurs due to endochondral ossification process that takes place in the growth cartilage. Proliferation and differentiation of the chondrocytes are part of that process, as well as the synthesis of extracellular matrix. Endochondral ossification is regulated by endocrine, paracrine and autocrine factors. Defects in genes that encode or regulate the expression of these factors have been recognized as cause of several skeletal dysplasias. More recently, it has increased the number of genes related to growth plate which are also associated with ISS or SGA (summarized in Table 1). Some affected individuals may have mild disproportionate short stature and/or nonspecific skeletal abnormalities.

Defects in the most genes described in Table 1 were firstly associated with extreme phenotypes and/or syndromic forms of growth disorders. Over the past years, with the greater availability of next-generation sequencing (NGS) techniques, it has become possible to identify an increasing number of genetic causes of short stature in children with the mildest spectrum of the diseases.

As a rule, the diagnoses of genetic conditions associated with short stature are realized based on clinical and

Table 1. Genes associated with isolated short stature.

Gene	Additional features	Year of first association with ISS	Ref
	Genes related to the GH/IGFs axis		
GHR	Laboratory evaluation suggests partial GH insensitivity	1995	(11)
GH1	Low growth velocity and delayed bone age	2003	(12)
IGF1R	Children usually were born small for gestational age, have microcephaly and have high levels of IGF-1 (basal and/or during GH therapy)	2003	(13)
IGFALS	Very low levels of IGF-1 and IGFBP-3 with mild short stature	2004	(14)
GHSR	ISS and DGH phenotype within the same family; delay in puberty in some children	2006	(15)
IGF1	Birth weight and birth length in the lower limit of the normal range	2012	(16
PAPPA2	High levels of IGF-1 and IGFBP-3	2016	(17)
STAT5B	Laboratory evaluation suggests partial GH insensitivity; elevated IgE and eczema	2018	(18)
	Genes related to the growth plate		
SHOX	Abnormal body proportion; presence of Madelung deformity in relatives	1997	(19)
NPR2	Nonspecific skeletal abnormalities; some children have abnormal body proportion	2013	(20)
ACAN	Advanced bone age, poor pubertal spurt and early-onset osteoarthritis	2014	(21)
FGFR3	Normal body proportion was described in only one family	2015	(22)
NPPC	Small hands; only six affected individuals from two families were described	2018	(23)
IHH	Abnormal body proportion in most cases; shortening of the middle phalanx of the 5th finger	2018	(24)
COL2A1, COL11A1/2	Abnormal body proportions and nonspecific skeletal abnormalities	2021	(25)

laboratory findings. In these cases, where the diagnosis was made based on the patient's phenotype, genetic testing is generally targeted for a particular gene or genetic defect, a candidate gene approach. This strategy mainly serves to confirm the diagnosis and subcategorization. In this scenario, genetic tests become especially important in mild or atypical cases where the clinical diagnosis is difficult. However, this candidate gene approach is not feasible when there are no specific findings to guide the recommendation of the specific genetic test, it is the case of most children with ISS or SGA.

In the absence of a particular phenotype that helps in the indication of a specific genetic testing, a broad evaluation of the genome is the logical choice to conduct a genetic investigation. In the Figure 1 there is a suggestion on how to proceed to genetic evaluation of a child with isolated short stature. The candidate gene approach may be useful if there is a characteristic finding, but a multiple-gene testing approach is generally preferable. The option of using a targeted gene panel or WES is dependent on availability, but with the gradual reduction in cost, it is likely that WES will soon be the most used methodology, and the analysis will be guided by knowledge of the genes capable of generating phenotype of isolated short stature.

Identifying the genetic etiology of short stature has important consequences:

1. Enables accurate genetic counseling

2. Allows the identification of other affected members of the family fast and at a lower cost

3. Provides information that should guide patient follow-up and treatment

The proportion of ISS and SGA children with an identified monogenic defect is relatively small (approximately 15%) and information on specific approaches is still

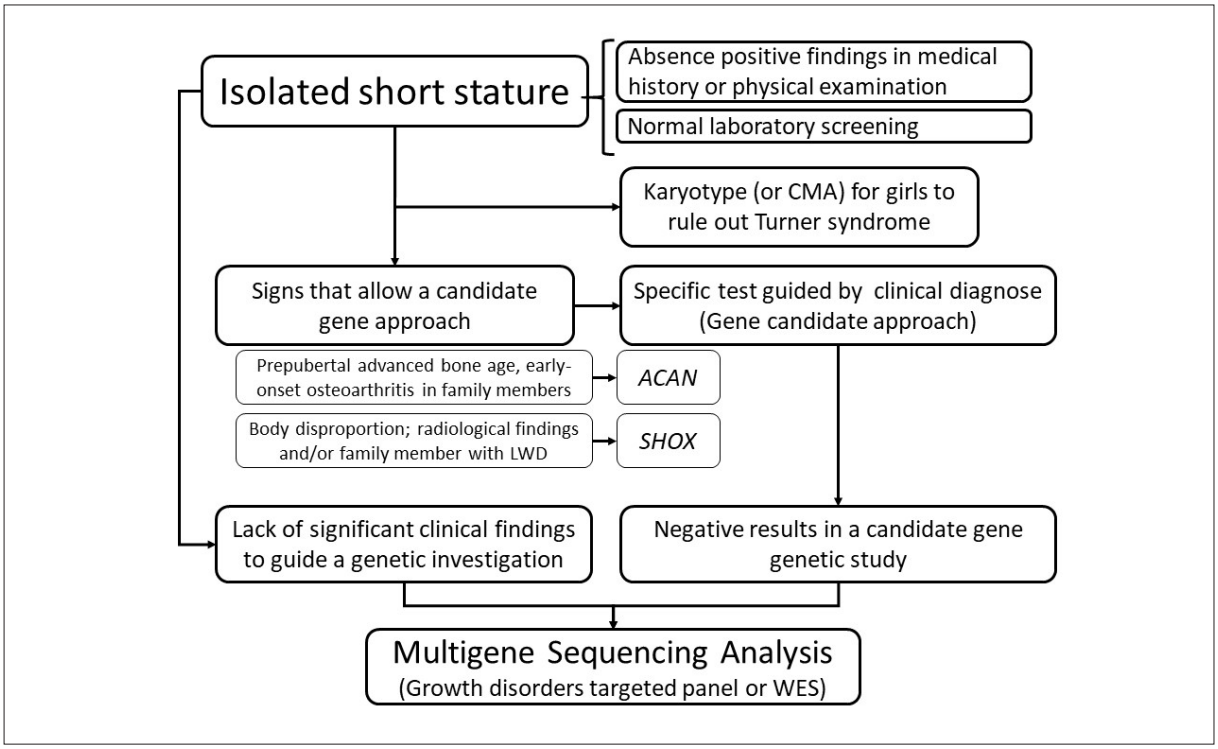

Figure 1. Flowchart suggesting how to proceed to genetic evaluation of a child with isolated short stature. CMA = chromosomal microarray. Leri-Weill dyschondrosteosis = LWD. Whole exome sequencing = WES.

limited. However, it is expected that new protocols will be proposed aiming at a more accurate approach to treat growth disorders based on their genetic cause.

Conflicts of interests

AALJ has received consulting fees from NovoNordisk and Biomarin.

References

1. Collett-Solberg PF, Jorge AAL, Boguszewski MCS, et al. Growth hormone therapy in children; research and practice - A review. Growth Horm IGF Res. 2019;44:20-32.

2. Jelenkovic A, Sund R, Hur YM, 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. Yengo L, Sidorenko J, Kemper KE, et al. Meta-analysis of genome-wide association studies for height and body mass index in approximately 700000 individuals of European ancestry. Hum Mol Genet. 2018;27(20):3641-9.

4. Marouli E, Graff M, Medina-Gomez C, et al. Rare and low-frequency coding variants alter human adult height. Nature. 2017;542(7640):186-90.

5. Zoledziewska M, Sidore C, Chiang CWK, et al. Height-reducing variants and selection for short stature in Sardinia. Nat Genet. 2015;47(11):1352-6.

6. Scalco RC, Hwa V, Domene HM, et al. STAT5B mutations in heterozygous state have negative impact on height: another clue in human stature heritability. Eur J Endocrinol. 2015;173(3):291-6.

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

8. Freire BL, Homma TK, Funari MFA, et al. Multigene Sequencing Analysis of Children Born Small for Gestational Age With Isolated Short Stature. J Clin Endocrinol Metab. 2019;104(6):2023-30.

9. Hauer NN, Popp B, Schoeller E, et al. Clinical relevance of systematic phenotyping and exome sequencing in patients with short stature. Genet Med. 2018;20(6):630-8.

10. Wang SR, Carmichael H, Andrew SF, et al. Large-scale pooled next-generation sequencing of 1077 genes to identify genetic causes of short stature. J Clin Endocrinol Metab. 2013;98(8):E1428-37.

11. Goddard AD, Covello R, Luoh SM, et al. Mutations of the growth hormone receptor in children with idio-

pathic short stature. The Growth Hormone Insensitivity Study Group. N Engl J Med. 1995;333(17):1093-8.

12. Millar DS, Lewis MD, Horan M, et al. Novel mutations of the growth hormone 1 (GH1) gene disclosed by modulation of the clinical selection criteria for individuals with short stature. Hum Mutat. 2003;21(4):424-40.

13. Abuzzahab MJ, Schneider A, Goddard A, et al. IGF-I receptor mutations resulting in intrauterine and postnatal growth retardation. N Engl J Med. 2003;349(23):2211-22.

14. Domene HM, Bengolea SV, Martinez AS, et al. Deficiency of the circulating insulin-like growth factor system associated with inactivation of the acid-labile subunit gene. N Engl J Med. 2004;350(6):570-7.

15. Pantel J, Legendre M, Cabrol S, et al. Loss of constitutive activity of the growth hormone secretagogue receptor in familial short stature. J Clin Invest. 2006;116(3):760-8.

16. Batey L, Moon JE, Yu Y, et al. A novel deletion of IGF1 in a patient with idiopathic short stature provides insight Into IGF1 haploinsufficiency. J Clin Endocrinol Metab. 2014;99(1):E153-9.

17. Dauber A, Munoz-Calvo MT, Barrios V, et al. Mutations in pregnancy-associated plasma protein A2 cause short stature due to low IGF-I availability. EMBO Mol Med. 2016;8(4):363-74.

18. Klammt J, Neumann D, Gevers EF, et al. Dominant-negative STAT5B mutations cause growth hormone insensitivity with short stature and mild immune dysregulation. Nat Commun. 2018;9(1):2105.

19. Rao E, Blaschke RJ, Marchini A, Niesler B, Burnett M, Rappold GA. The Leri-Weill and Turner syndrome homeobox gene SHOX encodes a cell-type specific transcriptional activator. Hum Mol Genet. 2001;10(26):3083-91.

20. Vasques GA, Amano N, Docko AJ, 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.

21. Nilsson O, Guo MH, Dunbar N, et al. Short stature, accelerated bone maturation, and early growth cessation due to heterozygous aggrecan mutations. J Clin Endocrinol Metab. 2014;99(8):E1510-8.

22. Kant SG, Cervenkova I, Balek L, et al. A novel variant of FGFR3 causes proportionate short stature. Eur J Endocrinol. 2015;172(6):763-70.

23. Hisado-Oliva A, Ruzafa-Martin A, Sentchordi L, et al. Mutations in C-natriuretic peptide (NPPC): a novel cause of autosomal dominant short stature. Genet Med. 2018;20(1):91-7.

24. Vasques GA, Funari MFA, Ferreira FM, 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.

25. Plachy L, Dusatkova P, Maratova K, et al. Familial short stature - a novel phenotype of growth plate collagenopathies. J Clin Endocrinol Metab. 2021;dgab084. doi: https://doi.org/10.1210/clinem/dgab084. Online ahead of print.