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Short Stature in a Prepubescent Female with a 47.5Kb PAR1 Deletion Downstream of SHOX: A Case Suggestive of Leri-Weill Dyschondrosteosis

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ABSTRACT

A clinically significant 47.5-kilobase deletion in the pseudoautosomal region 1 (PAR1), downstream of the SHOX gene, was identified in a 13-year-old female with proportionate postnatal short stature and markedly reduced growth velocity, supporting a diagnosis of SHOX-related short stature. This finding, previously associated with Leri-Weill dyschondrosteosis (LWD) and idiopathic short stature (ISS), supports a likely diagnosis of LWD in the absence of overt Madelung deformity. Initiation of recombinant human growth hormone (rhGH) therapy led to a marked improvement in growth velocity. This case underscores the importance of considering enhancer region deletions in the diagnostic work-up of idiopathic short stature, even when clinical features are subtle or atypical.

Keywords

SHOX deficiency, Short stature, Leri-Weill dyschondrosteosis, Growth hormone therapy, PAR1 deletion.

Case Report

An 11-year-and-5-month-old female was referred to the Pediatric Endocrinology consult for evaluation of short stature.

The child was born at term following an uneventful pregnancy and delivery, with birth anthropometric measurements appropriate for gestational age. Neonatal screening was unremarkable, and no complications were reported during the neonatal period. The psychomotor development and academic performance were appropriate.

Maternal concern regarding her daughter's short stature had been present since early childhood, but became more pronounced over the past two years, particularly due to the perceived onset of puberty.

The patient was asymptomatic at the time of initial evaluation, with no systemic complaints or signs suggestive of endocrine or chronic disease. Physical examination revealed a well-nourished, active girl in good general condition, without dysmorphic features or skeletal abnormalities. She presented with Tanner stage M2P2 and no relevant findings were noted on physical examination. Her height was 131 cm (-2.5 SD), and growth velocity was markedly reduced at 1.89 cm/year (-4.43 SD). Family history revealed maternal short stature (147.5 cm; -2.25 SD).

Bone age assessment revealed a delay, corresponding to a bone age of 7 years and 9 months. Laboratory evaluation, including complete blood count, inflammatory markers, renal and hepatic function, thyroid profile, IGF-1, prolactin, adrenal and gonadal steroid levels, insulin, and celiac disease screening, was within normal limits.

A screening karyotype revealed a normal female chromosomal complement (46,XX), and sequencing of the SHOX gene did not identify pathogenic variants. However, Multiplex Ligation-dependent Probe Amplification (MLPA) analysis detected a heterozygous 47.5-kilobase deletion in the pseudoautosomal region 1 (PAR1), located downstream of the SHOX gene, consistent with a regulatory defect associated with idiopathic short stature and Leri-Weill dyschondrosteosis (LWD).

Genetic counseling confirmed the SHOX enhancer deletion as likely pathogenic and causative of the phenotype. A diagnosis of LWD was established. Although no obvious Madelung deformity was present, the phenotype was consistent with a mild form of LWD.

Given the confirmed genetic diagnosis and persistent growth impairment, recombinant human growth hormone (rhGH) therapy was initiated at a dose of 35 µg/kg/day. The patient showed excellent adherence and tolerance to treatment, with no reported adverse effects.

At the first follow-up, one month after initiating rhGH therapy, the patient's growth velocity had increased to 11.52 cm/year (+6.04 SD), and her height had reached 143 cm (-2.12 SD). At 13 years and 11 months, continued catch-up growth was observed, with a height of 146 cm (-1.99 SD) and a growth velocity of 5.77 cm/year (+2.59 SD). Pubertal development progressed appropriately, and menarche occurred at 12 years and 9 months, with regular cycles thereafter.

The patient continues to demonstrate favorable clinical evolution under rhGH therapy and remains under regular pediatric endocrinology follow-up. Growth charts are included to illustrate the patient's longitudinal growth pattern throughout the diagnostic process and follow-up (Figure 1).

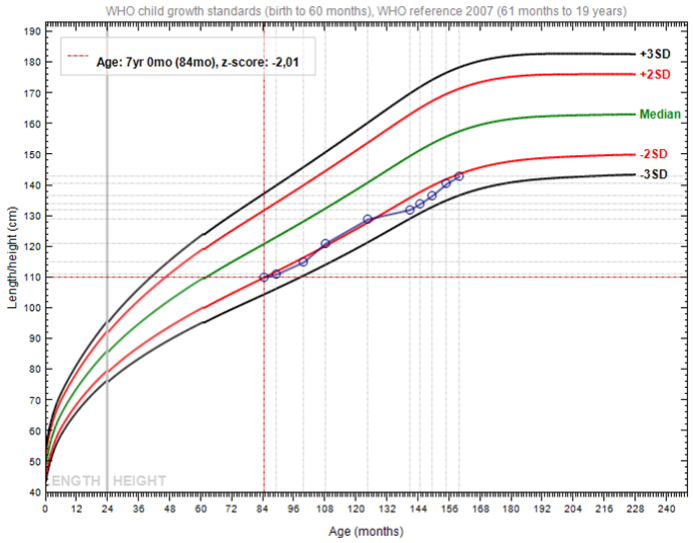

Figure 1: Longitudinal growth chart showing the patient's height trajectory in SD score over time, including the period before and after rhGH therapy.

Discussion

SHOX haploinsufficiency is a known cause of short stature, and while exonic mutations are well documented, deletions in non-coding regulatory regions—particularly in the PAR1 region—can also significantly impact gene expression [2,3]. This case illustrates the importance of extended molecular analysis (e.g., MLPA) when initial sequencing is negative. Despite lacking classical features such as Madelung deformity, the phenotype was consistent with LWD.

Patients with SHOX haploinsufficiency typically present with postnatal proportionate short stature that may become disproportionate over time, with subtle mesomelic shortening and reduced arm span-to-height ratio or sitting height-to-leg length discrepancies [2,4]. In many cases, including the one described here, these disproportionate features may be mild or absent during early childhood. Growth impairment is often most pronounced during the pubertal years, as the expected pubertal growth spurt tends to be blunted or absent [5]. This highlights the importance of early identification and intervention, ideally before or at the onset of puberty, to maximize height outcomes and mitigate the impact of SHOX-related growth failure.

The therapeutic response to rhGH further supports the diagnosis and highlights its value in improving final height in such patients [4,6]. Continued follow-up will be essential to monitor skeletal development, final adult height, and potential development of subtle skeletal deformities [7].

Conclusions

This case emphasizes the need for comprehensive genetic evaluation in children with short stature and a family history of short stature. Enhancer region deletions near SHOX should be considered even in the absence of classical radiological findings.

References

1. Rao E, Weiss B, Fukami M, et al. Pseudoautosomal deletions encompassing a novel homeobox gene cause growth failure in idiopathic short stature and Turner syndrome. Nat Genet. 1997; 16: 54-63.
2. Binder G. Short stature due to SHOX deficiency: genotype, phenotype, and therapy. Horm Res Paediatr. 2011; 75: 81-89.
3. Benito Sanz S, Royo JL, Barroso E, et al. Identification of the first recurrent PAR1 deletion in Léri-Weill dyschondrosteosis and idiopathic short stature reveals the presence of a novel SHOX enhancer. J Med Genet. 2012; 49: 442-450.
4. Donze SH, Renes JS, van Doorn J, et al. The growth response to GH treatment is greater in patients with SHOX enhancer deletions compared to SHOX defects. Eur J Endocrinol. 2015; 173: 611-621.
5. https://www.ncbi.nlm.nih.gov/books/NBK1215/
6. Blum WF, Ross JL, Zimmermann AG, et al. GH treatment to final height produces similar height gains in patients with SHOX deficiency and Turner syndrome. J Clin Endocrinol Metab. 2013; 98: 1383-1392.
7. Soucek O, Lebl J, Snajderova M, et al. Bone geometry and volumetric bone mineral density in girls with SHOX haploinsufficiency. Bone. 2011; 49: 819-826.