

0053 - IDIOPATHIC ADVANCED BONE AGE: EXPANDING THE GENETIC SPECTRUM BEYOND ACAN

Mode: Research paper

Thematic Unit: Growth

SANTILLÁN VÁSCONEZ, Ana María | RAMOS, Carolina | DE POLLI CELLIN, Laurana | FERREIRA DE ASSIS FUNARI, Mariana | PEREIRA DE SOUZA QUEDAS, Elisangela | DA CUNHA SCALCO, Renata | DE LIMA JORGE, Alexander

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA UNIVERSIDADE DE SÃO PAULO (HC-FMUSP)

Background/Objectives: After exclusion of common clinical causes of advanced bone age, most patients remain without a defined etiology or clear guidance for management and follow-up. The aim of this study was to investigate the genetic basis of idiopathic advanced bone age associated with reduced predicted adult height.

Methods: Exome sequencing was performed in patients with at least 0.9 years of advanced bone age without a specific etiology and a Bayley–Pinneau predicted adult height below 150.4 cm for females or 162.5 cm for males (height z-score < - 2), or with parental short stature (height z-score < - 2).

Results: A total of 43 patients (25 females) were included, with a mean age of 10.3 years (range 2.8–15.1 years) and a mean height z-score of -1.60 (range - 4.0 to +2.08). Notably, half of the cohort (n = 22) did not yet present overt short stature despite impaired adult height prediction, whereas only 3 patients had adequate predicted adult height associated with parental short stature. The diagnostic yield was 39.5% (17/43). SHOX variants were more frequent (n=7) than ACAN variants (n=6), accounting for most molecular diagnoses, while variants in SMAD6, LTBP3, SRCAP, and BRAF were identified in 4 additional patients. Additionally, one patient carried a variant of uncertain significance (VUS) in ACAN, while another carried a VUS in ACAN and another VUS in SHOX. Patients with and without a molecular diagnosis had similar mean ages (10.2 vs. 10.4 years), height z-scores (-1.6 vs. - 1.7), and bone age–chronological age differences (1.6 vs. 1.6 years). However, the group without a molecular diagnosis showed a higher female predominance (69.2% vs. 41.2%).

Conclusion: This study confirms the importance of investigating ACAN in patients with idiopathic advanced bone age while expanding the phenotypic spectrum associated with SHOX deficiency. Idiopathic advanced bone age may represent a marker of monogenic growth disorders, sometimes before overt short stature develops. These findings support the inclusion of genetic testing in children with unexplained advanced bone age and impaired adult height prediction, particularly in the presence of familial short stature.

