

0119 - CLINICAL IMPACT OF PROSPECTIVE EXOME SEQUENCING IN CHILDREN INITIALLY CLASSIFIED AS HAVING IDIOPATHIC SHORT STATURE

Mode: Research paper

Thematic Unit: Growth

CELLIN, Laurana1 | F. A. FUNARI, Mariana2 | ANDRADE, Nathalia1 | SOLBERG, Paulo Ferrez3 | MALAQUIAS, Alexsandra C.4 | C. LEAL, Andrea5 | ARAUJO, Jacqueline6 | C. DEMARTINI, Adriane7 | V. ATIQUE, Patricia8 | F. COSTALONGA, Everlayny9 | L. GOMES, Nathalia10 | M. SANTILLAN-VASCONEZ, Ana1 | CARNEIRO REZENDE, Raíssa1 | P. S. QUEDAS, Elisangela1 | R. CURI, Samara1 | E. COSTA, Marcia8 | G. TELES, Milena1 | ANTONINI, Sonir Roberto Rauber8 | LONGUI, Carlos Alberto1 | J P ARNHOLD, Ivo1 | BILHARINHO DE MENDONCA, Berenice1 | C. SCALCO, Renata1 | DE LIMA JORGE, Alexander1

FACULDADE DE MEDICINA DA UNIVERSIDADE DE SÃO PAULO1; Universidade de São Paulo2; UNIVERSIDADE DO ESTADO DO RIO DE JANEIRO (UERJ)3; IRMANDADE DA SANTA CASA DE MISERICÓRDIA DE SÃO PAULO4; UNIVERSIDADE DO ESTADO DO PARÁ5; UNIVERSIDADE FEDERAL DE PERNAMBUCO6; UNIVERSIDADE FEDERAL DO PARANÁ7; FACULDADE DE MEDICINA DE RIBEIRÃO PRETO - UNIVERSIDADE DE SÃO PAULO8; UNIVERSIDADE FEDERAL DO ESPÍRITO SANTO (UFES)9; SANTA CASA DE BELO HORIZONTE10

Background/Objectives: Introduction: Most children referred for short stature evaluation are ultimately categorized as having idiopathic short stature (ISS). While exome sequencing (ES) has increasingly uncovered monogenic etiologies in this group, the extent to which these findings influence clinical management has not been systematically documented. Objectives: To investigate the diagnostic yield, potential for novel etiologic insights, and clinical utility of prospective ES in children meeting rigorous ISS criteria.

Methods: We performed ES in 235 children classified as having ISS, as part of the initial evaluation and before major management decisions whenever possible. Family segregation studies were undertaken in positive cases, and variants were classified according to ACMG guidelines.

Results: Pathogenic or likely pathogenic (P/LP) variants were identified in 36 patients, corresponding to a diagnostic yield of 15.3%. Variants in genes already recognized in association with ISS were found in 20 children, while 16 harbored variants in genes classically linked to skeletal dysplasias or syndromic disorders, despite the absence of their characteristic phenotypes. Genetic diagnoses had a measurable clinical impact in 29 of the 36 positive cases. Main

consequences included refinement of diagnosis, reverse phenotyping, individualized surveillance strategies, therapeutic decision-making, and cascade evaluation of relatives. Treatment-related implications were observed in 16 children: ES findings supported recombinant human growth hormone therapy in eight, whereas in the remaining eight they supported treatment discontinuation, discouraged treatment initiation, explained poor therapeutic response, or contraindicated rhGH treatment. In addition, molecular findings



prompted targeted clinical reassessment in nine children and facilitated diagnosis in other affected relatives from five families.

Conclusion: A meaningful subset of children initially labeled as having ISS carry an identifiable monogenic disorder affecting growth. Our findings highlight that incorporating genomic investigation early in the evaluation of ISS may provide benefits extending beyond etiologic diagnosis, contributing to patient reclassification, personalized management, surveillance, and family counseling.

