

0151 - SHORT STATURE ASSOCIATED WITH A SPLICING ACAN VARIANT: PHENOTYPIC SPECTRUM IN FOUR UNRELATED FAMILIES

Mode: Research paper

Thematic Unit: Growth

Thematic Unit 2: Rare Diseases

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Background/Objectives: Aggrecan, encoded by ACAN gene, plays a crucial role in cartilage function and bone growth. Heterozygous loss-of-function ACAN variants were initially identified in individuals with postnatal growth retardation, accelerated bone age (BA) and osteoarthritis. Subsequently, a broader phenotypic spectrum of short stature (SS) with minor skeletal defects and facial dysmorphisms, with or without advanced BA was described. Aim: To describe the phenotypic spectrum in four families with SS caused by the same ACAN splicing variant.

Methods: We included 6 patients (4 girls, 2 boys) with SS and/or body disproportion and 7 affected adult relatives from 4 non-consanguineous unrelated families (F: A,B,C,D). Clinical evaluation included detailed anthropometry and phenotyping, BA assessment and radiological screening. Frequent causes of SS were ruled out. SS candidate genes were studied by NGS with a custom gene panel or WES in index cases. Sanger sequencing was used to confirm the prioritized variant and to study family relatives. ACMG/AMP criteria and ClinGen guidelines were used for variant classification.

Results: The SS phenotype was inherited as an autosomal dominant pattern in the 4 families. All affected subjects (13) shared the same pathogenic ACAN splicing variant: NM_001369268.1:c.7302+1G>A (PM2_supp, PVS1, PS4), which has only been found in South American individuals. Median age at admission was 1.8y (0.8-9.2). Patient IV-1(FA, girl), born SGA, presents SS, relative macrocephaly, body disproportion, brachydactyly, joint hypermobility, and adequate BA at 8.3y. Both patients from FB (III-2 & III-3, girls), born AGA from SS affected father, show relative macrocephaly, body disproportion and advanced BA. The older sister developed early puberty. Patients from FC, 2 boys born SGA, have adequate BA, disproportionate SS and relative macrocephaly; one of them with autistic spectrum disorder. Patient III-2(FD, girl), born SGA from a SS mother, presented with clinical suspicion of skeletal dysplasia. Heterogeneous mild dysmorphic features and skeletal findings were observed within this cohort. After a median follow up of 4.8y (2.2-7.1), height ranged from -2.9 to -4.9 SDS.



Conclusion: These findings emphasize the challenges in recognizing ACAN-related SS based solely on clinical features and underscore the importance of molecular testing for establishing an etiological diagnosis in primary growth disorders.

