The first description of large pathogenic deletion in ACAN gene and additional cases with novel pathogenic ACAN variants

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Introduction: Defining the underlying etiology of idiopathic short stature (ISS) in children and adolescents improves their overall management. The main objective of our single-center cohort study was to assess the frequency of pathogenic variants in the aggrecan gene (ACAN) in selected individuals with ISS.

Results: Systematic phenotyping of study cohort yielded 37.5% (6/16) ACAN-positive probands, with all novel pathogenic variants, including the first intragenic deletion, detected by array comparative genomic hybridization (array CGH) and exome data analysis (figure 1, 2). All variants co-segregated with short stature phenotype, except in one family member with the intragenic deletion who had an unexpected growth pattern within the normal range (-0.5 SDS) (figure 3). One patient presented with otosclerosis, a sign not previously associated with aggrecanopathy.

Methods: From the baseline cohort of 50 children and adolescents with ISS, 16 probands were selected upon defined inclusion criteria: (i) height below -2 SDS, (ii) advanced bone age and/or (iii) autosomal dominant inheritance pattern of short stature; and exclusion criteria: (i) growth hormone deficiency, (ii) hypothyroidism, (iii) skeletal dysplasia and/or syndrome, and (iv) cytogenetically detectable chromosomal abnormalities. Additionally, 15 family members of ACAN positive probands were included.

Genetic analysis: Exome sequencing in all probands, additional copy number variation (CNV) detection in probands with a distinct ACAN-associated phenotype (ii)+(iii).

Figure 2. Three methods detecting heterozygous deletion in ACAN gene: a) NGS CNVkit detection algorithm, b) Array CGH, c) Long-range PCR with NGS sequence analysis.

Figure 1. Structure of the aggrecan protein (above) and the ACAN gene (bottom) with the reported pathogenic variants in study patients.

Figure 3. a) Pedigrees of 6 unrelated families with ACAN pathogenic mutation. b) Growth charts of family members with heterozygous multiple-exon deletion in ACAN gene. Legend: Green points – P1, red points - P15 with atypical growth pattern (without being on growth hormone (GH) therapy), black points - P15, horizontal arrow- advanced bone age, vertical arrow- starting of GH therapy, cross signs- final mother’s (above) and father’s (below) height, P1- proband no. 1, P15 – sister of proband no. 1, P1F- father of proband no. 1.

Conclusion: ACAN pathogenic variants presented a common cause of familial ISS. The reported selection criteria used in our study indicated high yield of ACAN positive probands. Our results expanded the number of pathogenic ACAN variants, including the first intragenic deletion, and suggested CNV evaluation in patients with typical clinical features of aggrecanopathy as reasonable.

References:  