univerzitetni klinični center ljubljana
University Medical Centre Ljubljana

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

Stavber L[1], Hovnik T [1], Avbelj Stefanija M [2], Kotnik P [2], Bertok S [2], Dovč K [2,4], Lovrečič L [3], Kovač J [1], Tesovnik T [1], Debeljak M [1], Battelino T [2,4].

[1] Unit for Special Laboratory Diagnostics, University Children's Hospital, UMC, Ljubljana, Slovenia [2] Department of Pediatric Endocrinology, Diabetes and Metabolic Diseases, University Children's Hospital, UMC, Ljubljana, Slovenia, [3] Clinical Institute of Medical Genetics, UMC, Ljubljana, Slovenia, [4] Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia.

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.

Methods: From the baseline cohort of 50 children and adolescents with ISS, 16 probands were selected upon defined inclusion criteria: *(ia)* height below -2 SDS, *(iia)* advanced bone age and/or *(iiia)* 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 (*(iia)+(iiia)*).

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.

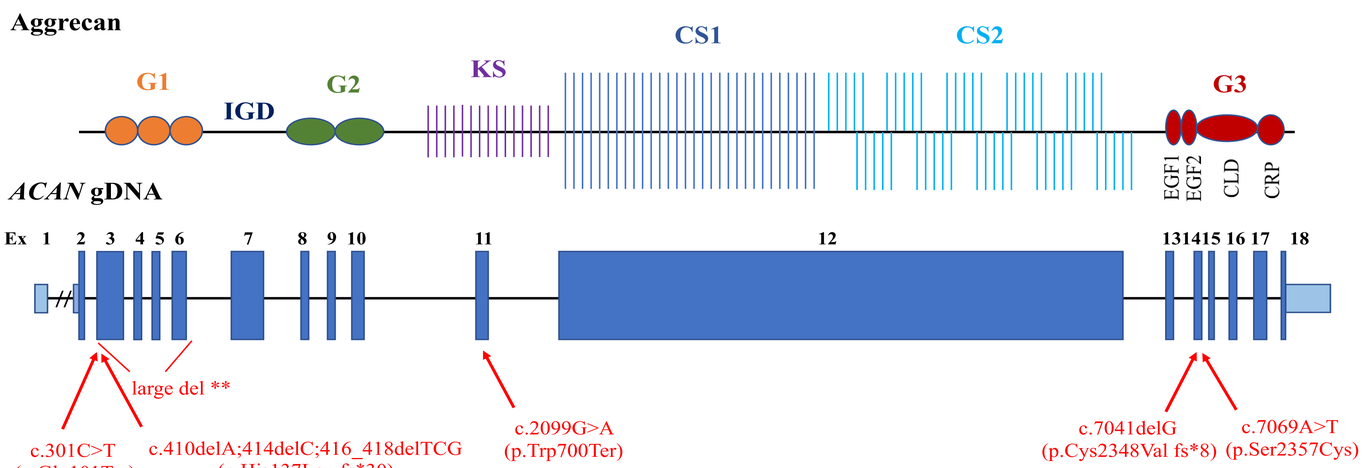

Figure 1. Structure of the aggrecan protein (*above*) and the *ACAN* gene (*bottom*) with the reported pathogenic variants in study patients.

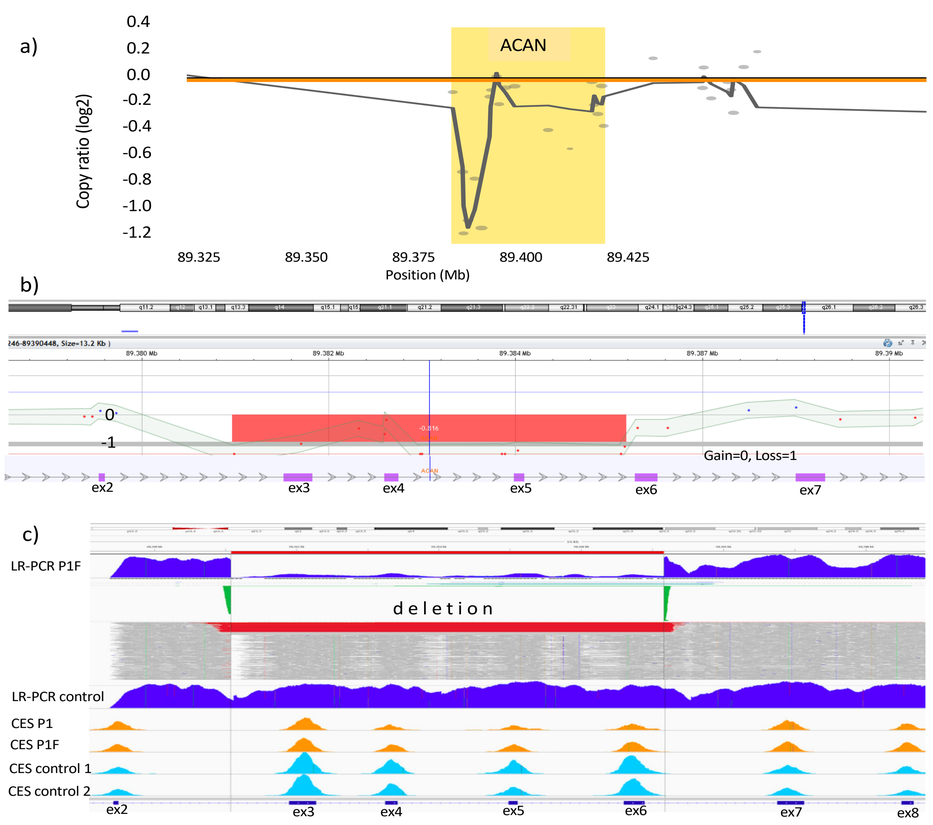

Figure 2. Three methods detecting heterozygous deletion in *ACAN* gene: a) NGS CNVkit detection algorithm, b) Array CGH, c) Long-range PCR with NGS sequence analysis.

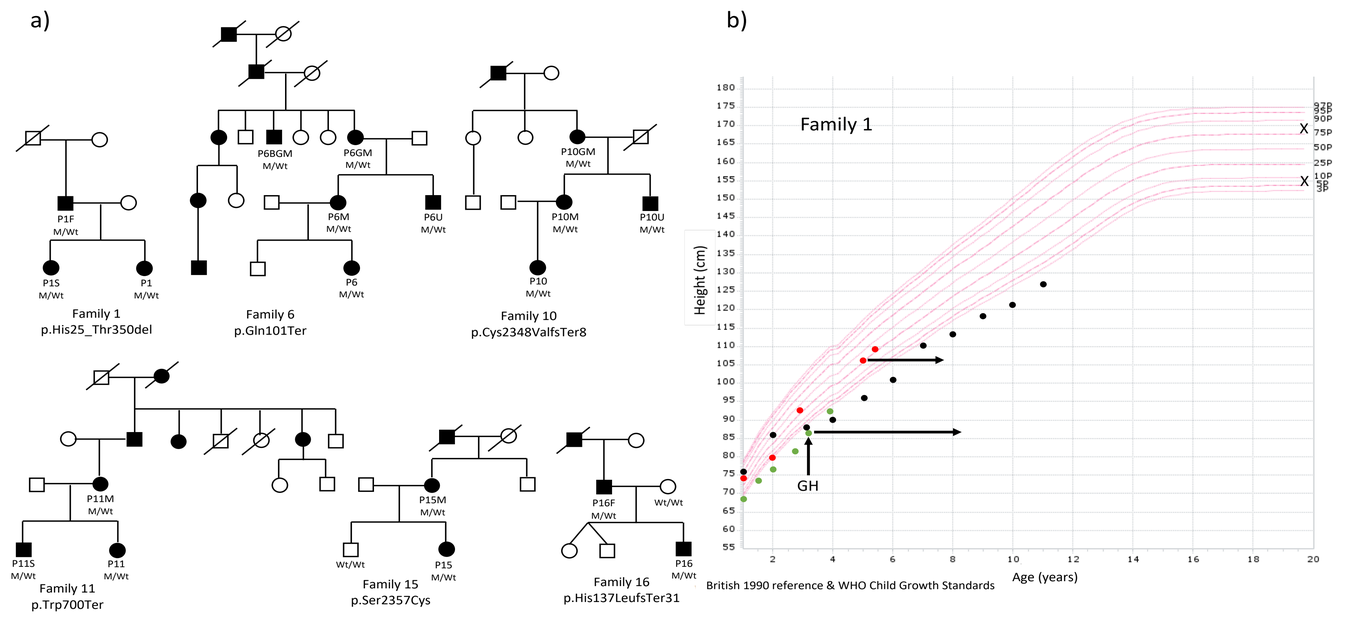

Figure 3. a) Pedigrees of 6 unrelated families with *ACAN* pathogenic mutation. b) Growth charts of family members with heterozygous multiple-exon deletion in *ACAN* gene. Legend: *Green points* – P1, *red points* - P1S with atypical growth pattern (without being on growth hormone (GH) therapy), *black points* - P1F, *horizontal arrow*- advanced bone age, *vertical arrow*- starting of GH therapy, *cross signs*- final mother's (*above*) and father's (*bellow*) height, P1- proband no. 1, P1S – 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:

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Growth and syndromes (to include Turner syndrome)
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