Identification of a novel heterozygous ACAN mutation in a patient with non-syndromic short stature

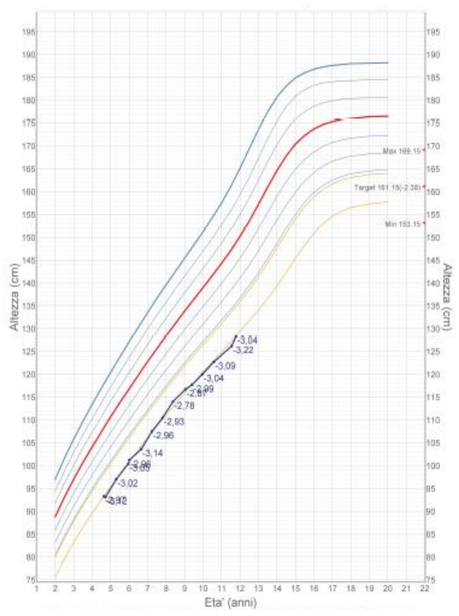
C. Partenope, D. Gallo, L. Fioretti, M. Adavastro, M. Pitea, G. Pozzobon, G. Weber
Pediatric Department, San Raffaele Hospital, Milan, Italy

Background

Short stature can be caused by decreased chondrogenesis due to mutations in any gene that directly or indirectly affects growth plate chondrocytes and the process of growth plate chondrogenesis. Aggrecan, encoded by ACAN, is a major proteoglycan component in the extracellular matrix of the growth plate. At least 25 pathological ACAN mutations have been identified in patients with highly variable phenotypes of syndromic or non-syndromic short stature.

Methods

A 6-year-old boy was referred to our Centre for short stature in familial short stature.
We collected his auxological data, including weight, height, arm span, BMI. The child also underwent X-Rays of arm, wrist and hand. Next Generation Sequencing (NGS) analysis has been performed.



H.S, I.P. ♂

- Born at 41 weeks. Birth length 49 cm (−1.17 SDS), birth weight 2840 g (−1.73 SDS).
- He had normal psychomotor development.
- **Mid-Parental target height** was 161.15 cm (-2.38 SDS). His father (height 167.3 cm) is from Ecuador; his mother of Italian origin displays a lightly disproportionate short stature (height 143 cm).
- **Growth hormone (GH) stimulation tests** showed discordant results (Dexamethasone test: GH peak 20.9 ng/mL, arginine test 5.6 ng/mL and 11.1 ng/ml). Other blood tests (liver and renal function, screening for coeliac disease, thyroid and adrenal function tests) resulted within limits.
- Brain MRI was normal.

	First evaluation		Last evaluation
Age	6 y 8 m	**START GROWTH HORMONE THERAPY (0.03 mg/Kg/die)** ⬇ **STOP THERAPY AFTER 21 MONTHS DUE TO POOR RESPONSE (+0,36 SDS) AND HIGH IGF1 LEVELS**	12 y 6 m
Height	103.60 cm (-3.14 SDS)		134 cm (-2.64 SDS)
Arm Span	103 cm		140 cm
Physical examination	No dysmorphic features		No dysmorphic features
Pubertal Status	A1 P1 G1		A1 P3 G3 (Pubertal development started at 11 y 7 m)
Bone age	Corresponds with chronological age and stature		Corresponds with chronological age, but advanced compared with stature
IGF1	120 ng/mL (52-297)		281 ng/mL (100-460)

- **Genetic analysis (Next Generation Sequencing)** showed a heterozygous variant of uncertain significance of the **ACAN gene p.(Gly676Ser).** This mutation, not characterized so far, is most likely to result in a loss of function of the protein because this position can influence splicing mechanism.

Conclusions

- ACAN haploinsufficiency is a newly discovered cause of short stature with accelerated bone age.
- Consider ACAN mutations in the genetic evaluation of patients with idiopathic short stature, even in the absence of characteristic features (early onset osteochondritis dissecans, osteoarthritis, craniofacial dysmorphisms)
- GH treatment efficacy is still controversial.

References

1. S. Dateki, “ACAN mutations as a cause of familial short stature”, Clin Pediatr Endocrinol 2017; 26(3), 119–125
2. M. Crippa et al., “A balanced reciprocal translocation t(10;15)(q22.3;q26.1) interrupting ACAN gene in a family with proportionate short stature”, J Endocrinological Investigation 2017
3. M. Van der Steen et al., “ACAN Gene Mutations in Short Children Born SGA and Response to Growth Hormone Treatment”, J Clin Endocrinol Metab, May 2017, 102(5):1458–1467