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

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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.

<table>
<thead>
<tr>
<th>Age</th>
<th>First evaluation</th>
<th>START GROWTH HORMONE THERAPY (0.03 mg/Kg/die)</th>
<th>Last evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 y 8 m</td>
<td></td>
<td>12 y 6 m</td>
</tr>
<tr>
<td>Height</td>
<td>103.60 cm (−3.14 SDS)</td>
<td></td>
<td>134 cm (−2.64 SDS)</td>
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<tr>
<td>Arm Span</td>
<td>103 cm</td>
<td></td>
<td>140 cm</td>
</tr>
<tr>
<td>Physical examination</td>
<td>No dysmorphic features</td>
<td></td>
<td>No dysmorphic features</td>
</tr>
<tr>
<td>Pubertal Status</td>
<td>A1 P1 G1</td>
<td></td>
<td>A1 P3 G3 (Pubertal development started at 11 y 7 m)</td>
</tr>
<tr>
<td>Bone age</td>
<td>Corresponds with chronological age and stature</td>
<td></td>
<td>Corresponds with chronological age, but advanced compared with stature</td>
</tr>
<tr>
<td>IGF1</td>
<td>120 ng/mL (52-297)</td>
<td></td>
<td>281 ng/mL (100-460)</td>
</tr>
</tbody>
</table>

- 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 dysm morphisms)
- GH treatment efficacy is still controversial.

References