CASE REPORT

ACAN Pathogenic Variant as a Cause of Short Stature

Diana Reis Monteiro[1], Miguel Leão[2], Maria Adriana Rangel[3], Rosa Arménia Campos[3], Ana Luísa Leite[3]

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Abstract

Pathogenic variants of the aggrecan (*ACAN*) gene have been associated with a wide spectrum of growth modifications ranging from idiopathic short stature to severe skeletal dysplasia. We reported a case of an 8-year-old male observed in a pediatric endocrinology consultation for short stature (-3.46 standard deviation score). Investigation revealed a bone age advance of less than one year, somatotropin stimulation tests with clonidine and L-DOPA level of below 7 ng/dL, the normal value of insulin-like growth factor 1, and normal brain magnetic resonance. He started treatment with subcutaneous somatropin by 8.8 years. Over the years some traits on physical examination became more notorious, namely an upper segment longer than the lower, muscled appearance, broad thumbs, macrocranea, and mild bilateral eyelid ptosis. Clinical exome sequencing revealed a pathogenic variant c.1020del in the *ACAN* gene.

Keywords: Aggrecans/genetics; Body Height/genetics; Child; Growth Disorders/diagnosis; Growth Disorders/genetics; Growth Hormone/therapeutic use

Keypoints

What is known:

- Short stature can be associated with mutations in any gene that affects growth plate development, namely the *ACAN* gene.
- Pathogenic variants of the *ACAN* gene have been associated with a wide spectrum of clinical phenotypes, ranging from idiopathic short stature to severe skeletal dysplasia.
- How each distinct pathogenic variant leads to multiple phenotypes is unknown; however, all reported cases have short stature, and the majority also present with advanced bone age.
- Variants of growth-related genes should be considered in patients with idiopathic short stature that, even with negative somatotropin stimulation tests, show an unexpected response to growth-hormone treatment.

What is added:

- This was the first time the pathogenic variant c.1020del was described.

Introduction

Longitudinal growth is a complex and dynamic process, predominantly regulated by the configuration of the growth plate, but also modulated by genetic and environmental factors.[1-4] Short stature can be associated with mutations in any gene that directly or indirectly affects growth plate chondrocytes or growth plate chondrogenesis.[5]

Several genes contribute to the growth plate development, namely the *ACAN* gene, which encodes for aggrecan, the main proteoglycan of the extracellular matrix of the growth plate and articular cartilage.[2-4] The first human *ACAN* variant was genetically mapped in 2002[6] and since then several pathogenic variants of this gene have been associated with growth modifications ranging from idiopathic short stature to severe skeletal dysplasia.[2,5,6] These variants have been described as the second most common monogenic cause of idiopathic short stature, only surpassed in frequency by variants of the short-stature homeobox (*SHOX*) gene.[2]

Short stature, defined by the height of at least two standard deviations below the mean observed in the age and gender control population, is a very common disorder that affects around 2%-3% of the pediatric population.[2-4] Although it may be a sign of an underlying pathological process, in most cases the investigation does not reveal

1. Pediatrics and Neonatology Department, Centro Hospitalar de Entre-o-Douro e Vouga, Santa Maria da Feira, Portugal
2. Department of Medical Genetics, Centro Hospitalar de São João, Porto, Portugal
3. Pediatric Endocrinology and Nutrition Unit, Centro Hospitalar de Vila Nova de Gaia / Espinho, Vila Nova de Gaia, Portugal
Corresponding Author
Diana Reis Monteiro | E-mail: diana.reis.monteiro@gmail.com
Address: R. Dr. Francisco Sá Carneiro 4400-129, 4430-999 Vila Nova de Gaia, Portugal
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any cause that justifies growth impairment, and these patients are classified as having idiopathic short stature.[2,3] With the advance of next generation sequencing, it has become possible to identify several gene defects in children with short stature that presented only with a mild form of the disease and that were initially classified as idiopathic short stature.[1,3] One of those genes is *ACAN*, and its heterozygous mutation has been associated with short stature, premature growth cessation, and accelerated bone age maturation.[1,2,4] We reported a case of a pediatric patient with a pathogenic *ACAN* variant, occurring *de novo*, that presented with short stature and other subtle distinct body features.

Case Report

An 8-year-old male was observed in a pediatric endocrinology consultation for short stature. Previous medical history records revealed that our patient was a full-term neonate, with a low birth weight of 2450 g with -2.02 standard deviation score (SDS) and a length of 45 cm (-2.58 SDS). According to his mother, in the last ultrasound during pregnancy, she was told that he had short lower limbs. There was also a history of jaundice requiring phototherapy in the neonatal period, an adenotonsillectomy at 6 years old, and corrective surgery for *linea alba* hernia at the age of 7. Neurodevelopment milestones were achieved at a normal age range. By the time of referral, the patient presented short stature with -3.46 SDS, as well as macrocephaly (greater than the 95th percentile), without other relevant features. He presented a prepubertal development, and the growth velocity in the previous year was less than 5 cm. The mid-parental target height corresponded to the 10th-25th percentile (-0.71 SDS).

Bone age assessment showed skeletal maturity of 9 years. Somatotropin stimulation tests first with clonidine and later with L-DOPA revealed a level below 7 ng/dL, with a peak value of 3.31 ng/mL. Insulin-like growth factor 1 (IGF-1) level was normal (244 ng/mL, SDS 1.83), and brain magnetic resonance did not show any changes. The remaining study carried out also excluded the coexistence of chronic disease.

The patient started treatment with somatropin at 8.8 decimal years of age, at a dose of 0.03 mg/kg/day. After starting treatment, an increase in the initial growth velocity was observed but then stabilized, remaining around the third percentile (Fig. 1).

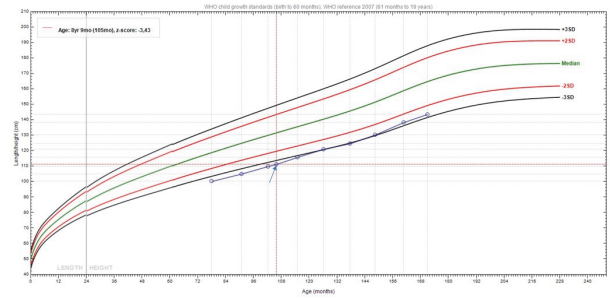

Figure 1. Patient's height curve. Treatment with somatropin was started at 8.8 decimal years, marked by the blue arrow.

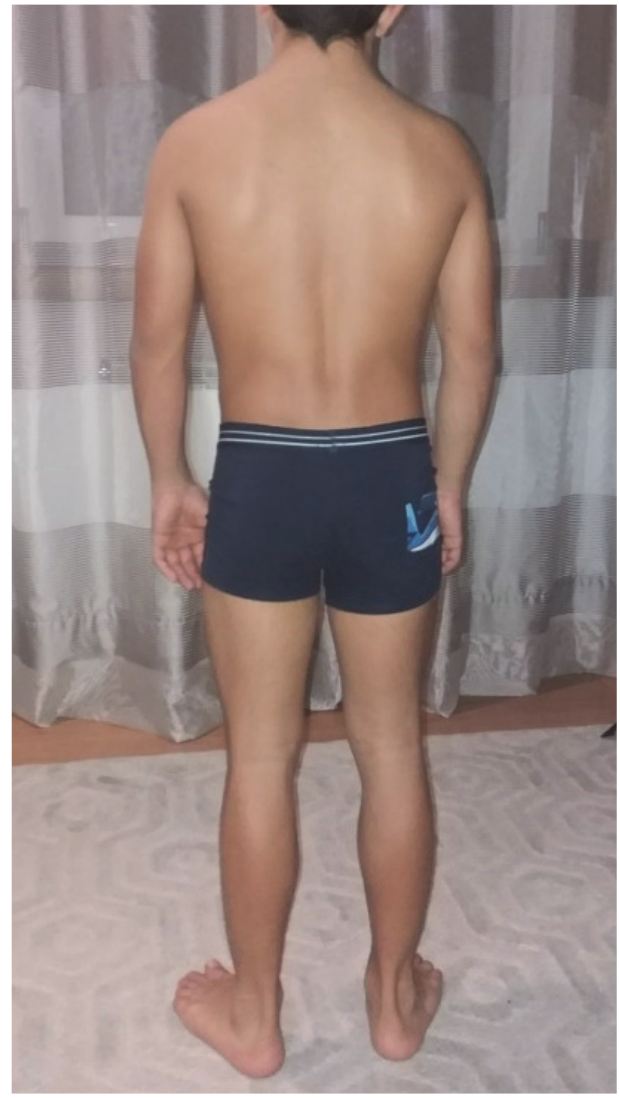

Figure 2. Patient's physical traits included macrocephaly, a slight disproportion of the limbs with an upper segment larger than the lower, and rhizomelia of the upper limbs.

Over the next three years, some traits on physical examination became more notorious, namely a slight disproportion of the limbs with an upper segment larger than the lower, rhizomelia of the upper limbs, unintentional muscled appearance, broad thumbs, and mild bilateral eyelid ptosis (Figs. 2 and 3).

The etiologic investigation proceeded with skeleton radiography and array comparative genomic hybridization, both described as normal. The patient was evaluated by an expert in genetics, and clinical exome sequencing was proposed, which revealed a pathogenic variant c.1020del in the *ACAN* gene. The genetic investigation was performed in both parents, without any abnormal findings, leading to the conclusion that this pathogenic variant occurred *de novo*. Bone age was frequently reassessed and showed a slight advance compared to chronological age, with a difference of less than two years.

From the beginning of the treatment until now, his response to somatropin was variable, showing a growth velocity of between 3.5 cm/year to 8.1 cm/year, with a median of 5.5 cm/year.

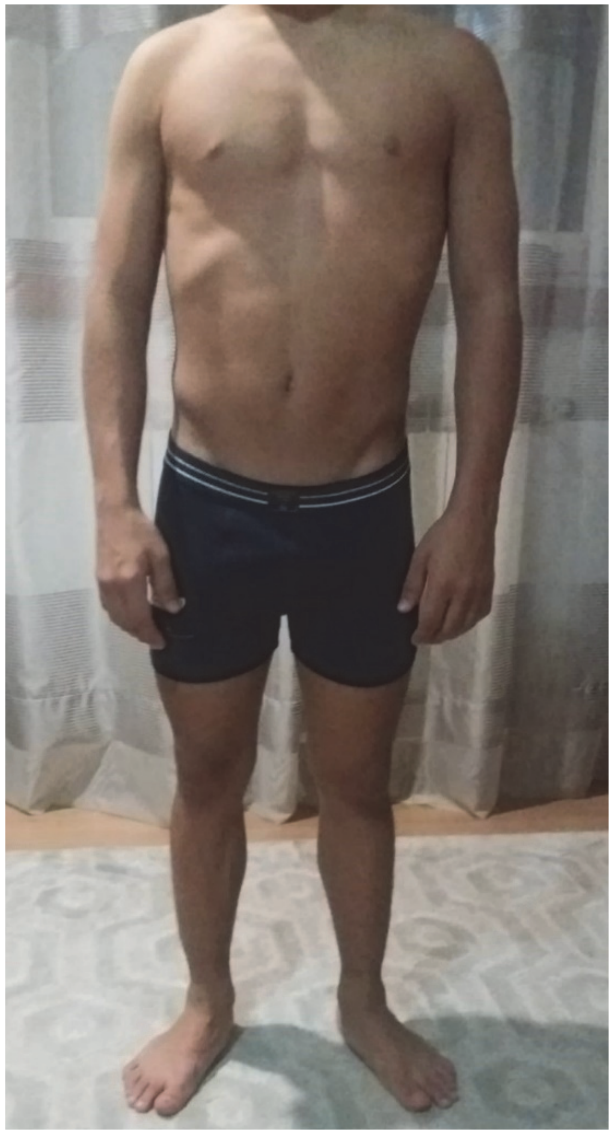

Figure 3. Patient's physical traits included a slight disproportion of the limbs with an upper segment larger than the lower, muscular appearance, and broad thumbs.

At present, he is 14 years old, 143.5 cm tall (-2.75 SDS), and currently on tanner stage 4. He still shows a muscled appearance but is slightly more proportionate. His growth velocity was 5.2 cm/year last year and 8.1 cm/year the year before, which might be partially attributable to a growth spurt. He is evaluated regularly, and we are considering stopping treatment with somatropin in the next appointment.

Discussion

ACAN is located on chromosome 15q26.14 and it is responsible for encoding aggrecan, the main proteoglycan in the extracellular matrix of the growth plate and articular cartilage, explaining the effects on joints and growth when a pathogenic variant occurs.[1,5,7,8] To date, 93 pathogenic *ACAN* variants have been reported in patients with highly variable phenotypes of syndromic or non-syndromic short stature[9]; however, the molecular cause of short stature remains undiagnosed in a large fraction of affected children.[8] To our knowledge, this was the first time the pathogenic variant c.1020del was described.

Pathogenic variants of this gene have been associated with growth modifications ranging from idiopathic short stature to severe skeletal dysplasias.[2,3] Such a wide phenotypic spectrum may explain the high number of undiagnosed patients, particularly in situations less clinically evident, such as isolated short stature.[1] A common trait of all described cases is the reduced height of the patients,[2] and the majority also present with advanced bone age, which helps to differentiate them from idiopathic short stature that usually shows delayed bone age.[3-5] However, there are reported cases among Chinese individuals with *ACAN* nonsense mutations that present short stature without advanced bone age.[1]

While some reported cases of this mutation only show mild changes with accelerated bone maturation and progressive growth failure, without any other syndromic findings, other patients have syndromic short stature conditions.[1,3-6] Aggrecan-related bone diseases include five clinical phenotypes, namely spondyloepimetaphyseal dysplasia, aggrecan type (OMIM 612813), macrocephaly with multiple epiphyseal dysplasia (OMIM 607131), spondyloepiphyseal dysplasia, Kimberley type (OMIM 608361), familial osteochondritis dissecans, short stature, and early-onset osteoarthritis (OMIM 165800), and various undefined short stature syndromes associated with accelerated bone maturation, like the case presented.[1,3,4,6,7,10]

How each distinct mutation in the *ACAN* gene leads to a wide range of phenotypes is unknown; however, in all published studies, affected individuals had short stature

and early growth arrest.[7] After the poor pubertal spurt, these patients usually present early growth arrest, with subsequent lower height SDS as adults and, often, body disproportion.[3-5] The case we presented showed short stature with a slight disproportion with an upper segment larger than the lower and other distinct features similar to the cases described in the literature, like very muscled appearance, broad thumbs, macrocephaly, and mild bilateral eyelid ptosis.

Regarding treatment options, growth hormone is sometimes administered to try to compensate for height deficiency and prevent additional height loss.[1] Since growth hormone stimulates IGF-1 production and chondrocyte differentiation, aggrecan deficiencies are unlikely to be repaired by growth hormone alone.[1] Previous publication reported that patients with mutations in the *ACAN* gene have shown large variations in response to growth hormone[1,8,11] and show a general trend of gradually diminishing yearly height growth over the course of treatment in variant-carrying children.[1] Some reports considered effective the combined treatment with a gonadotropin-releasing hormone analog that suppresses puberty and blocks early growth cessation along with growth hormone to achieve the best height outcome possible, and these patients were described as 5-8 cm taller than their same-sex family members with the same variant.[1,4,5] Regarding our case, the patient had already started his pubertal development when he was evaluated by genetics; therefore, we did not consider treatment with a gonadotropin-releasing hormone analog.

These patients may present with such a wide phenotypic spectrum, without a group of unique characteristics, that necessitates the performance of genetic studies to make an accurate diagnosis.[3] Molecular genetic studies using next generation sequencing (like panels of genes or exome analysis) should become part of the investigation of isolated short stature in children, especially in cases of advanced bone age and the presence of the dysmorphic features previously mentioned.[3,5,7] Early genetic diagnosis could prevent children from unnecessary tests and allow the best treatment options when available or the identification of potential therapeutic targets. Also, genetic diagnosis allows us to give more accurate information to the patient about probable growth outcomes and provide adequate and timely genetic counseling.[3,6]

Author Contribuitions

DRM and ML participated in the study conception or design. DRM and ML participated in acquisition of data. DRL and DRM participated in the analysis or interpretation of data. ALL authors participated in the drafting of the manuscript. ALL authors participated in the critical revision of the manuscript. All authors approved the final manuscript and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

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Confidentiality of data

The authors declare that they have followed the protocols of their work center on the publication of patient data.

Consent for publication

Consent for publication was obtained.

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Variante Patogénica *ACAN* como Causa de Baixa Estatura

Resumo:
As variantes patogénicas do gene aggrecan (*ACAN*) têm sido associadas a um amplo espetro de alterações do crescimento, desde baixa estatura idiopática a displasia esquelética severa. Reportamos o caso de uma criança de 8 anos, do sexo masculino, que foi observada numa consulta de endocrinologia pediátrica por baixa estatura (-3.46 pontuação do desvio). A investigação efetuada revelou uma idade óssea com um avanço inferior a um ano, um doseamento de somatotropina inferior a 7 ng/dL nas provas de estimulação com clonidina e L-DOPA, um valor normal de fator de crescimento semelhante à insulina tipo 1 e uma ressonância magnética cerebral sem alterações. Iniciou tratamento com somatropina subcutânea pelos 8.8 anos. Nos anos seguintes foram-se evidenciando algumas particularidades no exame físico, nomeadamente um segmento superior maior que o inferior, aparência musculada, dedos largos, macrocefalia e discreta ptose palpebral bilateral. O exoma clínico revelou a variante patogénica c.1020del no gene *ACAN*.

Palavras-Chave: Agrecanas/genética; Alterações do Crescimento/diagnóstico; Alterações do Crescimento/genética; Criança; Estatura/genética; Hormona do Cresicmento/uso terapêutico