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Case Report

Short Stature in Klinefelter Syndrome From Aggrecan Mutation

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Abstract

Despite tall stature being a characteristic feature of Klinefelter syndrome, occasional cases of short stature have been reported. These cases are often attributed to GH deficiency. This case report details a unique case of a 16-year-old male with Klinefelter syndrome exhibiting proportionate short stature resulting from a heterozygous, likely pathogenic, variant in the *ACAN* gene c.7141G > A (p.Asp2381Asn). This specific variant, previously identified once in a family with a recessive inheritance pattern is reported here for the first time in an individual with Klinefelter syndrome. This report emphasizes the importance of a thorough evaluation and consideration of genetic testing for an underlying diagnosis in short-statured individuals with Klinefelter syndrome. Timely detection would enable appropriate therapeutic interventions.

Key Words: Klinefelter syndrome, aggrecan, *ACAN*, short stature, growth, advanced bone age

Abbreviations: *ACAN*, Aggrecan; *SHOX*, short stature homeobox gene.

Introduction

Klinefelter syndrome, the most common chromosomal aneuploidy in males, is characterized by the presence of 1 or more extra X chromosome, small testes, hypergonadotropic hypogonadism, infertility, intellectual disability, and tall stature [1]. Although tall stature is a common feature, there have been a few reported cases of individuals with Klinefelter syndrome having short stature. The cause of short stature has been associated with either GH deficiency or a different chromosomal variation, such as the 49,XXXXY karyotype [2, 3]. Here, we present the case of a 16-year-old male with Klinefelter syndrome with short stature secondary to a mutation in the Aggrecan *(ACAN)* gene. *ACAN* gene mutations typically present with short stature, skeletal dysplasia, and advanced bone age [4]. There are no previous reports of *ACAN* gene mutation in a patient with Klinefelter syndrome.

Case Presentation

A 16-year-old pubertal male was referred to endocrinology because of small testes identified during a physical examination at a new practice. The patient's medical history revealed a normal onset and progression of puberty, learning disability, and short stature. Short stature was noted on maternal side of the family, with normal heights on the paternal side. Only 1 data point was available on the growth chart received from the current primary care provider, with no prior growth charts available to review. The patient's weight was recorded as 47 kg and height was measured at 151.6 cm with an SD of −2.8 (Fig. 1). Mid-parental height was determined to be 172.7 cm ± 10 cm. The patient's mother and maternal grandfather were noted to also have short stature at 150 cm.

On examination, the patient exhibited relative macrocephaly and proportionate short stature without mid-facial hypoplasia or prognathism. There were no signs of gynecomastia or feminized body habitus. Genital examination revealed the patient to be Tanner stage V for pubic hair development and penile length with small testes measuring 4 to 5 mL palpated bilaterally in the scrotum. Additional physical examination findings showed that the arm span was equal to height and upper-to-lower segment ratio was 0.98.

Diagnostic Assessment

In light of the patient's short stature, a comprehensive screening of laboratory tests was conducted. The results included a normal complete blood count, erythrocyte sedimentation rate, celiac screening tests (total IgA and tissue transglutaminase IgA), and thyroid tests (TSH, free T4), which were within the normal range. IGF-1 level was 287 ng/mL (37.5 nmol/L) (reference range, 209-602 ng/mL; 27.3-78.6 nmol/L), with a *Z*-score of −1.0 and IGF binding protein-3 was 5 mg/L (0.17 nmol/L) (reference range, 3.4-9.5 mg/L; 0.12-0.33 nmol/L), which are both normal for a Tanner V male.

Because of the presence of small testes, pediatric FSH and LH assays were obtained, revealing elevated levels of 62.24 mIU/mL (62.24 IU/L) (reference range, 0.85-8.74 mIU/mL) and 21.82 mIU/mL (21.82 IU/L) (reference range, 0.29-4.77 mIU/mL), respectively, confirming primary gonadal failure. Testosterone levels

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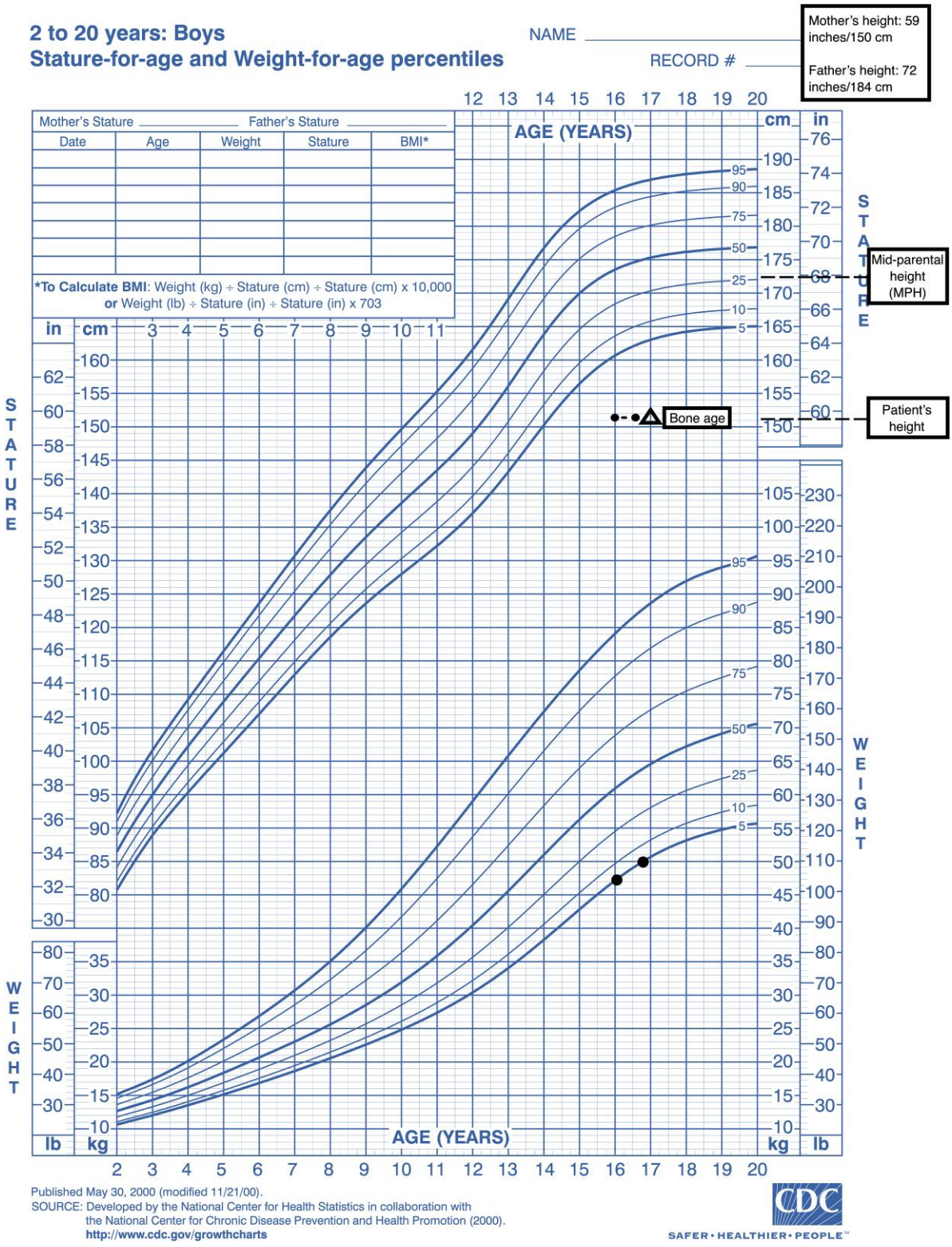

Figure 1. Centers for Disease Control and Prevention's boys growth chart: height and weight.

were in the low-normal range at 286 ng/dL (9.9 nmol/L) (reference range, 110-975 ng/dL; 3.8-33.8 nmol/L).

Chromosomal analysis was done, confirming a 47,XXY karyotype using G-Band (digital analysis: MetaSystems/Ikaros) with 50 cells counted, with band Level 525-600 and 5 cells analyzed and karyotyped. All laboratory tests were performed at Quest diagnostics.

Bone age obtained at chronological age of 16 years, 2 months, was advanced at 17 years with epiphyseal growth plate fusion.

Given that the initial screening laboratory tests did not determine the underlying etiology for short stature, further testing for possible skeletal dysplasia was pursued. A sponsored Invitae discover dysplasia panel was sent after collecting a buccal swab from the patient. On evaluation of 358 genes,

a heterozygous likely pathogenic variant c.7141G > A (p.Asp2381Asn), also known as c.6799G > A (p.D2267N), in the *ACAN* gene was identified. This variant is associated with skeletal dysplasia and was considered a potential genetic cause for the observed short stature in the patient.

Treatment

Our patient presented late at the age of 16 years with advanced bone age of 17 years and fused epiphyseal growth plates. Unfortunately, because of the advanced bone age, growth-enhancing therapy is not beneficial at this stage. Despite the diagnosis of Klinefelter syndrome, the patient exhibited spontaneous onset and progression of puberty, reaching full masculinization. Notably, he did not display features of gynecomastia or a female body habitus and his testosterone levels, although in the low-normal range, did not warrant immediate testosterone therapy initiation. The patient and his mother were educated on both diagnoses. Counseling on fertility preservation was also provided and referrals to urology and a genetic counselor were made.

Outcome and Follow-up

At the 6-month follow-up, the patient's weight remained at the 5th percentile and his height showed no significant change. He continued to have learning disabilities in school, necessitating considerable academic support. He remained asymptomatic for testosterone deficiency. Although parental genetic testing for *ACAN* gene mutation was offered, the family opted not to pursue it at this time. Follow-up laboratory assessments revealed a total testosterone level of 240 ng/dL and so weekly subcutaneous testosterone 50 mg was initiated after discussion with the patient and his family. He had a normal baseline complete blood count, fasting lipid panel, and hemoglobin A1c.

Discussion

Klinefelter syndrome, 47,XXY, has an estimated prevalence of 1.5 per 1000 males. Many cases remain undiagnosed or are diagnosed late, with only approximately 25% of cases identified because of the diverse clinical presentation. For individuals with Klinefelter syndrome, >95% present with small testes (< 6 mL), up to 99% experience infertility, and 75% have intellectual disabilities [1]. A distinctive feature in Klinefelter syndrome is tall stature. It is thought that the additional X chromosome could potentially lead to the overexpression of short stature homeobox (SHOX), a gene recognized for its crucial involvement in skeletal development and height regulation. Individuals with a 47,XXY karyotype carry 3 copies of the pseudoautosomal region where SHOX is situated, contributing to the tall stature [5].

In our patient's case, the presence of small testes and intellectual disability aligns with Klinefelter syndrome; however, notable variations included the absence of tall stature, gynecomastia, or a feminine body habitus. There are few reported cases in which individuals with Klinefelter syndrome exhibit short stature. In many of these instances, the cause of short stature was attributed to GH deficiency [2]. There has been documented a case of a patient with a 49,XXXXY variant of Klinefelter syndrome with a clinical phenotype characterized by short stature, cubitus varus, foot deformity, hypogonadism, and intellectual disability [3].

Genetic testing for monogenic cause of short stature was supported in this patient's case. Factors that increase the likelihood of diagnosing genetic cause of short stature include height below −3.0 SD or −2.5 SD with additional features, including a single parent with significant short stature, dysmorphic features, and a predicted height more than 2 SD below the mid-parental target height [6]. Additionally, the presence of intellectual disability is another consideration for genetic testing, although in our case, the intellectual delay could be attributed to Klinefelter syndrome.

Our patient's genetic testing revealed a heterozygous mutation in the *ACAN* gene located on chromosome 15q26, which is responsible for encoding the aggrecan protein. Aggrecan, a proteoglycan present in the extracellular matrix of growth plates and cartilaginous tissues, plays a crucial role in chondrogenesis [4, 7]. The majority of *ACAN* gene mutations identified so far are autosomal dominant, presenting with a spectrum ranging from proportionate short stature to skeletal dysplasia with disproportionate short stature. These mutations are associated with advanced bone age, early-onset osteoarthritis, and intervertebral disc disease [4, 7].

In a review on *ACAN* gene mutations summarizing 25 mutations, all are autosomal dominant except for 1 missense mutation, c.7141 G > A (Asp2381Asn), which is autosomal recessive [7]. Our patient is heterozygous for this autosomal recessive mutation, affecting the C-type lectin domain within the G3 domain of aggrecan on exon 15. This variant, also known as c.6799 G→A, predicts a p.D2267N amino acid substitution, influencing the aggrecan-tenascin interaction in chondrogenesis [8]. The primary mechanism underlying aggrecan-related disease is truncated protein haploinsufficiency impairing growth plate chondrogenesis [4]. Our patient is the second case with this variant described so far. There is only 1 prior documentation of this specific novel variant in a family from Zacatecas, Mexico. The 3 homozygous affected siblings, aged 16 to 26 years, exhibited a severe phenotype of spondyloepimetaphyseal dysplasia with profound short stature (66-71 cm adult final height) and various craniofacial abnormalities. These individuals presented with rhizomelia, mesomelia, and brachydactyly in their extremities. In contrast, the parents and a half-sibling who were carriers displayed a milder phenotype with proportionate short stature (150-152 cm), similar to our patient. An unaffected sister in the family was notably taller, measuring 178 cm in height [8].

Interestingly, it has been reported that individuals with spondyloepimetaphyseal dysplasia of the aggrecan type and carriers of the mutation do not typically exhibit an early-onset osteoarthritis phenotype. This is in contrast to the milder spondyloepiphyseal dysplasia Kimberly phenotype, which is associated with early-onset osteoarthritis [7–9]. The knees are commonly affected in spondyloepiphyseal dysplasia Kimberly, but other joints may also be involved [7, 8]. Both our patient and his mother deny experiencing knee or back pain so far.

Individuals with *ACAN* gene mutations often exhibit advanced bone age, leading to early growth cessation [4]. Although our patient was postpubertal at presentation, we hypothesize that he likely had advanced bone age in his early teens, contributing to the premature hypertrophic chondrocyte maturation. Despite the potential impact of SHOX overdosage in our patient, his phenotype prominently featured significant short stature, underscoring the importance of the role of the *ACAN* gene in determining stature. Therapy with GH in patients with *ACAN* gene mutation has been shown to improve their height from 5.2 cm/year (range, 3.8-7.1) to

8.3 cm/year (range, 7.3-11.2) with a median height SD Δ of +0.62 (range, +0.35 to +1.39) [10]. Unfortunately, our patient was not considered a candidate for GH therapy because of late presentation with already fused epiphyseal growth plates.

This case underscores the importance of conducting a comprehensive workup for short stature, including the consideration of genetic testing for skeletal dysplasia, in short patients with Klinefelter syndrome. Timely identification of underlying genetic factors can inform appropriate interventions and management strategies for these individuals.

Learning Points

- A thorough physical examination is important for timely detection of Klinefelter syndrome.
- Short stature in Klinefelter is unusual and warrants a thorough workup, including consideration for genetic testing.
- Timely detection of *ACAN* gene mutation may allow therapeutic intervention with GH and can improve height outcomes.

Contributors

All authors made individual contributions to authorship. S.S. was responsible in the diagnosis and management of this patient. A.F. and S.S. prepared the manuscript submission. All authors reviewed and approved the final draft.

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient's relatives or guardians.

Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

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