Original Article

Two cases of autosomal dominant familial short stature associated with *COL11A2* gene variant and the therapeutic response to recombinant human growth hormone

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Background: Variants in collagen genes can cause diverse growth plate disorders frequently associated with short stature. This study aimed to evaluate clinical phenotypes in two autosomal dominant familial short stature (AD-FSS), along with the responses to recombinant human growth hormone (rhGH).

Methods: Two AD-FSS children treated with rhGH from two families were included. Next-generation sequencing (NGS) was performed to screen the gene variants that may be related to short stature. The genetic test results were evaluated using the guidelines set by the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP). The response of the children to rhGH was evaluated.

Results: The first case (child 1) was a girl aged 8 years and 7 months with a height of 118.8 cm. Her mother had a height of 145 cm. The child's maternal aunt, grandmother, grandmother's sisters, and great-grandmother were also under 150 cm in height, sharing the characteristic of short limbs. NGS revealed a c.688G>T heterozygous variant in exon 5 of the *COL11A2* gene for the girl and her mother. The second case (child 2) was a boy aged 4 years and 8 months with a height of 96 cm. A heterozygous variant c.2458G>A in exon 32 of the *COL11A2* gene was identified in the boy and his father. After 18 and 19 months of rhGH treatment, their heights increased by 15 and 20 cm, respectively, with no adverse events.

Conclusions: We presented two AD-FSS cases carrying the c.688G>T variant in exon 5 and the c.2458G>A variant in exon 32 of the *COL11A2* gene, respectively. The short-term response to rhGH treatment is promising for AD-FSS children.

Keywords: Familial short stature; *COL11A2*; variant; recombinant human growth hormone (rhGH); next-generation sequencing (NGS)

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Introduction

Axial elongation of long bones is a complex process involving endochondral ossification at the epiphyseal growth plate. This growth plate constitutes a dynamic layer of cartilage tissue comprising chondrocytes and extracellular matrix (ECM) secreted by these chondrocytes. The maturation of growth plate chondrocytes typically progresses through five stages, including quiescent, proliferative, prehypertrophic, hypertrophic, and terminal phases. At the terminal stage, blood vessels and bone tissue replace chondrocytes, ultimately halting the longitudinal bone growth. This process is a coordinated and continuous

interplay in both time and space (1). Any genetic variation influencing growth plate chondrocytes and the formation of growth plate cartilage can lead to reduced cartilage formation, resulting in short stature.

ECM homeostasis produced by chondrocytes is critical to the function of the growth plate, providing the structural foundation for cartilage compressibility and elasticity. It also regulates chondrogenesis through signaling and intermolecular interactions (2). Variants in genes encoding ECM proteins often disrupt growth plate function. As paramount ECM proteins, collagens play important structural roles by interacting with cell receptors. Additionally, they are also involved in cell growth, differentiation, and migration. The collagen family includes 28 members, with each member showing a high degree of tissue-specificity (3). In the quiescent phase, chondrocytes express the *COL2A1* gene that encodes type II collagen (COL2), while its expression is enhanced in the proliferative phase. In the pre-hypertrophic phase, chondrocytes would initiate the expression of *COL10A1* gene encoding type X collagen (COL10), which is continuously produced during the hypertrophic phase (4-6). Notably, *COL11A1* expressions in the growth plate and perichondrium are crucial for forming bone trabeculae and bone rings during endochondral ossification. *COL11A2* gene encodes the alpha-2 chain of type XI collagen, a vital component in the formation of cartilage and connective tissue (7). Its variants can disrupt normal bone development, resulting in conditions like autosomal dominant familial short stature (AD-FSS) (8).

Recombinant human growth hormone (rhGH) therapy has emerged as a promising intervention for short stature patients carrying *COL11A2* gene variants (7-9). It is a synthetic counterpart of natural growth hormone (GH), which shows the potential to foster linear growth, optimize height, and increase bone mineral density (10). In this study, we report two cases of AD-FSS associated with *COL11A2* gene variants based on next-generation sequencing (NGS). In addition, we investigated the efficacy and safety of rhGH in treating the short stature probands. The findings may offer valuable insights to clinicians, geneticists, and researchers engaged in the care of individuals grappling with AD-FSS associated with *COL11A2* gene variants.

Highlight box

Key findings

- We treated two autosomal dominant familial short stature (AD-FSS) children from two families with recombinant human growth hormone (rhGH).
- Next-generation sequencing identified two *COL11A2* mutations, including c.688G>T variant in exon 5 (case 1) and c.2458G>A variant in exon 32 (case 2).
- After 18–19 months of rhGH, their heights increased by 15 and 20 cm, with no adverse events.

What is known and what is new?

- Collagen gene variants can cause growth plate disorders associated with short stature.
- This is the first study of AD-FSS carrying the c.688G>T variant in exon 5 and the c.2458G>A variant in exon 32 of the *COL11A2* gene. Short-term rhGH treatment showed promising results.

What is the implication, and what should change now?

- *COL11A2* variants were identified in two AD-FSS cases. Screening for collagen gene variants should be considered for short stature children, especially with skeletal abnormalities or a family history.

Methods

Participants

This study included two children who were admitted to the Pediatric Endocrinology Clinic of Tianjin Medical University General Hospital due to the short stature in March and September 2021. This study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by Medical Ethics Committee of Tianjin Medical University General Hospital (No. IRB2024-YX-084-01). The study was conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Physical, laboratory and imaging examinations

We measured their height, weight, growth rate, body mass index (BMI), arm span, upper/lower segment ratio, finger and toe length, breast development, and secondary sexual characteristics (Tanner staging), according to "Growth curves of body mass index for Chinese children and adolescents aged 0–18 years" (11). Blood and urine tests were performed along with evaluation of liver function and thyroid function. The concentrations of cortisol, adrenocorticotropic hormone, fasting blood glucose, fasting insulin, insulin-like growth factor-1 (IGF-1), insulin-like growth factor-binding protein-3 (IGFBP-3) were determined. Additionally, chromosomal analysis, pituitary

magnetic resonance imaging (MRI) and full-length lateral spine X-ray were conducted. Bone age was assessed in accordance with the radius, ulna, and short bones-China (RUS-CHN) method (12).

Genetic testing

The whole-exome sequencing was performed after obtaining the informed consent from their guardians. Genomic DNA was extracted from the peripheral blood (2 mL) of the patients and their parents using the Qiagen DNA Kit (Qiagen, Germany), followed by library construction using Standard Library Construction Kit from MyGenostics (Beijing, China). A biotin-labeled P039-Exome probe (MyGenostics, Beijing, China) was then used to capture exonic regions through hybridization with the library DNA. Sequencing was carried out on the Illumina NextSeq 500 platform.

For Case 1, the average sequencing depth was 202.40, with a target region coverage of 98.58% at 10× and 97.66% at 20×. In Case 2, the average sequencing depth was 188.80, with a target region coverage of 98.40% at 10× and 97.17% at 20×. The sequencing depths for the parents were 160.75 for the father and 189.39 for the mother, with a target region coverage of 98.22% and 98.15% at 10×, and 96.60% and 96.72% at 20×, respectively.

Bioinformatics analysis was then performed as follows: low-quality sequences and adapter sequences were removed using Cutadapt to generate clean data. The raw data were then aligned to the human reference genome using the Burrows-Wheeler aligner (BWA) parameters in Sentieon software. Next, the Sentieon driver parameter was applied to remove duplicates, correct base calls, and call single nucleotide polymorphisms (SNPs)/insertions and deletions (INDELs), resulting in variant call format (VCF) file generation. Variants were annotated using ANNOVAR, with pathogenicity assessed according to the guidelines set by the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) (13). Additionally, we utilized Phenolyzer and Exomiser software to filter variants based on disease phenotype associations, scoring and ranking the pathogenicity of the variants and genes. Finally, Sanger sequencing was used for familial validation of the identified variants.

Treatment and follow-up

Child 1 received subcutaneous rhGH treatment (0.05 mg/kg/day) at the age of 8 years and 9 months for a duration of 18 months. Due to the accelerated puberty, the child also received gonadotropin-releasing hormone agonist (GnRHa) treatment. Child 2 received rhGH treatment (0.05 mg/kg/day) at the age of 4 years and 10 months for a duration of 19 months. Examinations described in Section "Physical, laboratory and imaging examinations" were conducted during the treatment and follow-up periods.

Results

Clinical characteristics in the first short stature family

Proband 1 was a girl aged 8 years and 7 months who sought medical attention in September 2021 due to short stature. The child was born at full-term via cesarean section as her mother showed short stature. At birth, the child measured 50 cm [median to +1 standard deviation (SD)] in length and weighed 2,500 g (–2 to –1 SD). Her gross motor and intellectual development were normal.

Her mother showed a height of 145 cm (–3 to –2 SD) and an arm span of 132 cm, exhibiting noticeable shortness in both upper and lower limbs, without apparent shortness or widening of fingers and toes. Several women in her mother's family, including her maternal aunt, grandmother, grandmother's sisters, and great-grandmother, were also under 150 cm (–2 to –1 SD) in height, sharing the characteristic of short limbs without distinct facial features. Her father had a height of 170 cm (–1 SD to median) and a well-proportioned physique (*Figure 1*).

The patient showed a height of 118.8 cm (–2.35 SD, lower than the 3rd percentile for children of the same age and gender), and a body weight of 25.8 kg. The BMI was 18.56 kg/m^2 (located at the 90th–95th percentile for children of the same age and gender). The arm span was 110 cm, while the upper segment was 69.5 cm. The upper/lower segment ratio was 1.41:1. She had a stage II breast development, Tanner stage I external genitalia, no distinct facial features, and no obvious short fingers or toes.

Blood, urine, liver function, thyroid function, cortisol, and adrenocorticotropic hormone were all within normal range. The concentrations of IGF-1 and IGFBP-3 were 207 ng/mL and 5,890 ng/mL, respectively. The levels of fasting blood glucose and fasting insulin were 4.47 mmol/L and 6.6 mU/L, respectively. The chromosomal karyotype was 46XX. The pituitary MRI examination did not reveal any significant abnormalities. Full-length lateral spine X-ray examination showed mild scoliosis. Bone age assessment

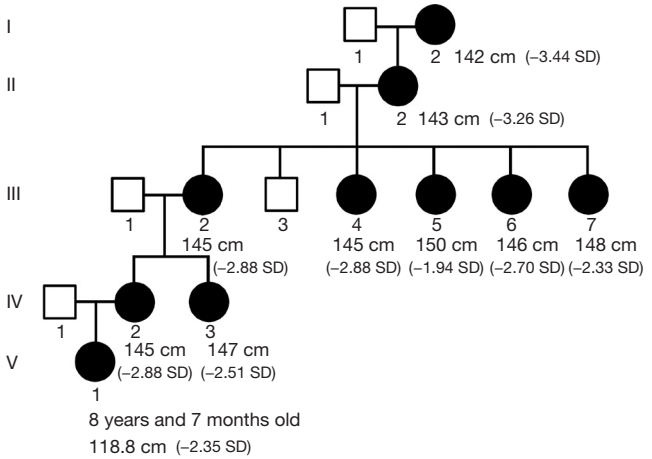

Figure 1 Family tree of the first family (family 1). White squares represent healthy males without short stature; black circles represent female proband with short stature. SD, standard deviation.

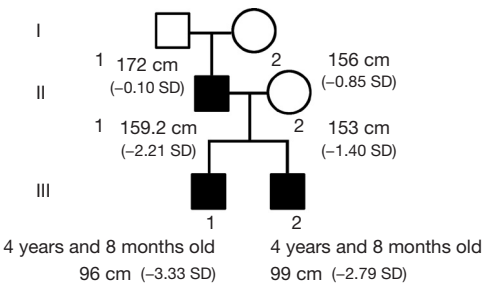

Figure 2 Family tree of the second family (family 2). White squares represent healthy males without short stature; white circles represent healthy females without short stature; black squares represent male proband with short stature. SD, standard deviation.

indicated a bone age of 10.1 years, indicating an advanced bone age of approximately 1.5 years.

Clinical characteristics in the second short stature family

Proband 2 was a boy, 4 years and 8 months old. The child was delivered vaginally at full term. At birth, the child measured 50 cm (–1 SD to median) in length and weighed 3,000 g (–1 SD to median). He showed normal gross motor and intellectual development.

His father had a height of 159.2 cm (–3 to –2 SD), with no obvious short limbs, shortness or widening of fingers (toes), and distinct facial features. The heights of his grandmother and grandfather were 156 (–1 SD to median) and 172 cm (–1 SD to median), respectively. His mother had a height of 153 cm and a well-proportioned physique, with no special limb phenotype (*Figure 2*).

The patient showed a height of 96 cm (–3.33 SD, below the 3rd percentile for children of the same age and gender), and a weight of 14 kg. The BMI was 18.56 kg/m^2 (within the 90th–95th percentile for children of the same age and gender). The arm span was 110 cm, and the sitting height was 63 cm. The upper/lower segment ratio was 1.34:1. He exhibited a well-proportioned physique, a slightly pointed mandible, mild pectus carinatum, Tanner stage I external genitalia, and no obvious short fingers (toes).

Blood, urine, liver function, thyroid function, cortisol, and adrenocorticotropic hormone were all within normal range. The levels of IGF-1 and IGFBP-3 were 67.8 ng/mL and 3,920 ng/mL, respectively. The levels of fasting blood glucose and fasting insulin were 4.25 mmol/L and 8.25 mU/L, respectively. The chromosomal karyotype was 46XY. The pituitary MRI examination findings were normal. Full-length lateral spine X-ray examination showed mild scoliosis. Bone age assessment indicated a bone age of 2.5 years, indicating a delayed bone age of approximately 2.1 years.

Genetic testing results

NGS revealed a c.688G>T (p.G230W) heterozygous variant in exon 5 of the *COL11A2* gene of the proband from the first family (family 1) (*Figure 3A*), resulting in the substitution of glycine with tryptophan at position 230, which was a missense variant. The pathogenic evidence of this variant was BS1 (allele frequency is greater than expected for disorder) according to the ACMG guidelines. However, pedigree analysis confirmed a heterozygous variant at this site in her mother, while the father showed no variant. The maternal grandmother and aunt also carried this variant. In addition, bioinformatic algorithms analyzed the detected variants, with rare exome variant ensemble learner (REVEL) and PolyPhen-2 predicting it as unknown, sorting intolerant from tolerant (SIFT) as harmful, and Mutation Taster and genomic evolutionary rate profiling ++ (GERP++) as benign. These sequencing results and bioinformatics analysis results were inconsistent with the ACMG classification, which indicated that the pathogenicity of this variant was uncertain (*Table 1*).

A heterozygous variant c.2458G>A in exon 32 of the *COL11A2* gene was detected in the proband of the second family (*Figure 3B*), resulting in an amino acid change of

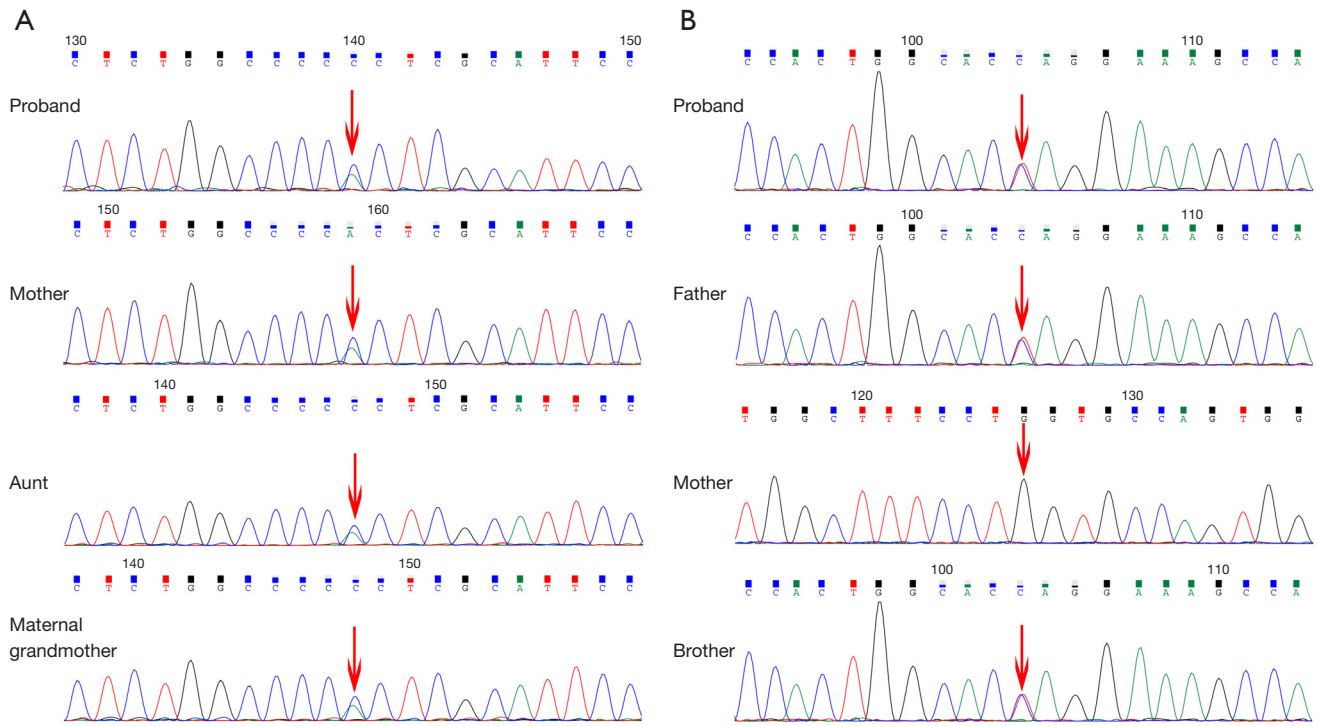

Figure 3 Sequencing results of the *COL11A2* gene for the proband and family members in the two family. (A) A heterozygous c.688G>T (p.G230W) variant was detected in exon 5 of the *COL11A2* gene of the proband from family 1. (B) A heterozygous variant c.2458G>A was detected in exon 32 of the *COL11A2* gene in the proband of the family 2.

Table 1 The evaluation of gene variants in both probands based on the ACMG guidelines

Proband	Gene variant	Amino acid change	ACMG criteria	Pathogenicity	Associated with AD-FSS
Proband 1	*COL11A2*, exon 5, c.688G>T	p.G230W	BS1	Uncertain	Yes
Proband 2	*COL11A2*, exon 32, c.2458G>A	p.G820S	PM2-Supporting, PP3-Strong	Uncertain	Yes

ACMG, American College of Medical Genetics and Genomics; AD-FSS, autosomal dominant familial short stature; BS1, allele frequency is greater than expected for disorder; PM2, absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project 1000 Genomes Project, or Exome Aggregation Consortium; PP3, multiple lines of computational evidence support a deleterious effect on the gene or gene product.

p.G820S. Pedigree verification analysis showed that his father had a heterozygous variant at this site. These results suggested that the variant appeared to be pathogenic, but it was not classified as a pathogenic variant by the ACMG guidelines. The pathogenic evidence of this variant in the ACMG guidelines was PM2 (absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project 1000 Genomes Project, or Exome Aggregation Consortium) and PP3 (multiple lines of computational evidence support a deleterious effect on the gene or gene product). Therefore, the pathogenicity of this variant was uncertain (*Table 1*).

Treatment and follow-up

The height standard deviation score (SDS) of the probands in both families was below −2 SD and 3rd percentile for children of the same age and gender, meeting the diagnostic criteria for short stature. Considering clinical manifestations, as well as laboratory and genetic test results, the two patients were diagnosed with short stature carrying *COL11A2* gene variants. The height changes of the two children during the follow-up period are depicted in *Figure 4*.

Child 1 received subcutaneous injections of rhGH treatment (0.05 mg/kg/day) at the age of 8 years and

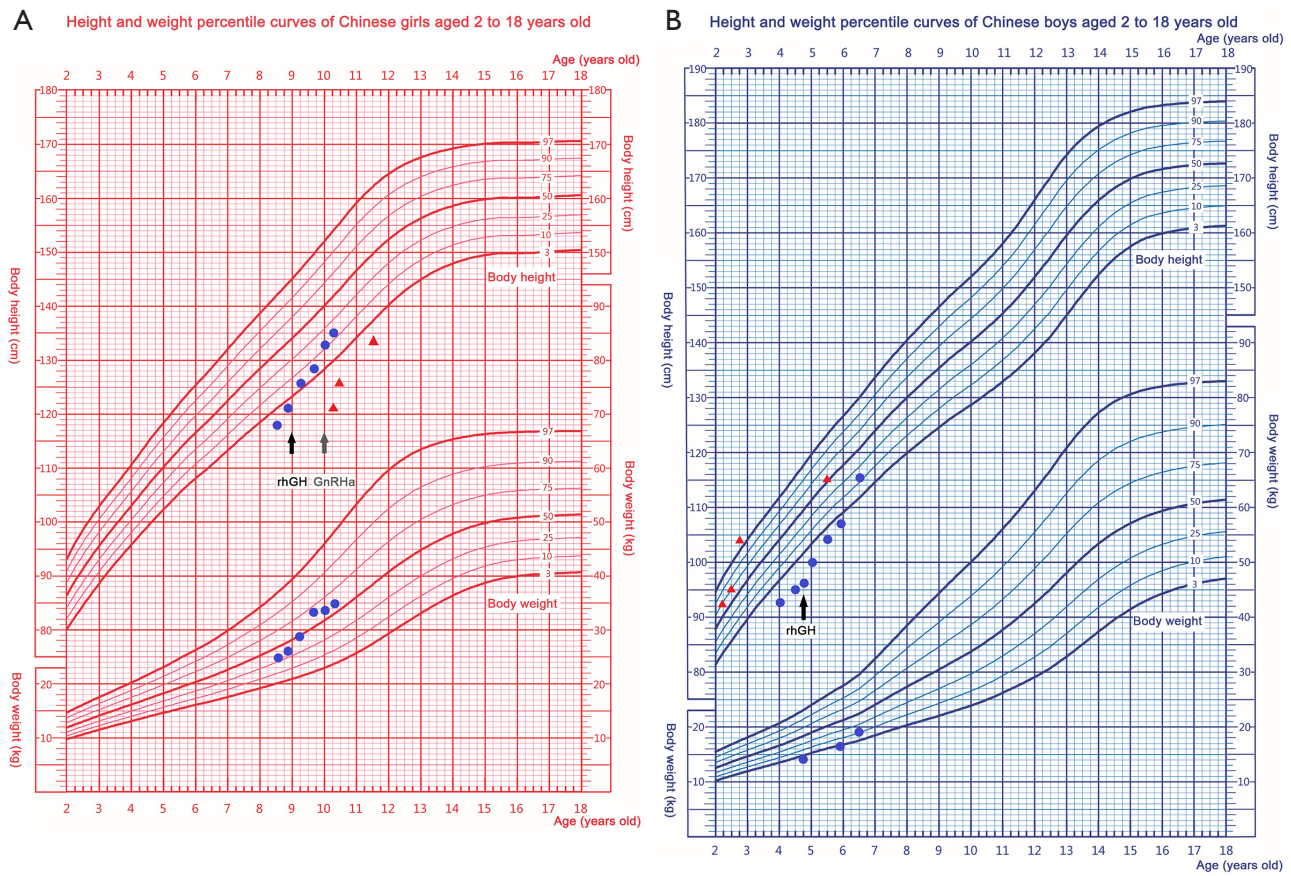

Figure 4 Changes in the heights of proband 1 (A) and proband 2 (B) during follow-up. Comparisons were performed based on the height and weight percentile curves of Chinese girls and boys aged 2 to 18 years old, respectively. The blue dot represents the proband's height or weight, and the red triangle represents the proband's bone age. rhGH, recombinant human growth hormone.

9 months, causing a significantly increased growth rate. During a follow-up examination at 9 years and 8 months, breast development was observed, and the bone age was measured to be 11.9 years (+2.1 years). Ultrasound results indicated a uterus size of 25×10×19 cm^3 with a linear endometrium. The left and right ovaries were measured 4.06 and 1.99 mL, respectively. Sex hormone tests revealed luteinizing hormone (LH) at 0.87 IU/L, follicle-stimulating hormone at 2.49 IU/L, and estrogen at 15 pg/mL. Given the accelerated progression of pubertal development, GnRHa treatment was initiated. Currently, after 18 months of rhGH therapy, the child has experienced a height increase of 15 cm, averaging 10.0 cm per year. The height SDS increased from −2.88 to −1 SD. Her current height is between the 10th and 25th percentiles for children of the same age and gender. Breast tissue had regressed to prepubertal levels, and LH had decreased to 0.21 IU/L.

Child 2 received rhGH treatment (0.05 mg/kg/day) at the age of 4 years and 10 months. Following a cumulative 19 months of treatment, his height increased by 20 cm, averaging 12.6 cm per year. The SDS increased from −3.33 to −1.02 SD. Presently, his height is between the 10th and 25th percentiles for children of his age and gender (*Figure 4*).

No adverse events were observed in the two children during the treatment, and their blood routine, thyroid function, blood glucose and insulin levels were all within the normal range. IGF-1 remained in a range of −1 to +1 SD. Spine evaluation was performed every 3 months, with no worsening scoliosis after treatment.

Discussion

In this study, the AD-FSS in both families was associated with *COL11A2* variants of c.688G>T and c.2458G>A.

Although the pathogenicity of the identified variants remains uncertain, our study emphasized a strong association between *COL11A2* variants and short stature. Both cases in our study underwent NGS, and no other potentially pathogenic variants were identified, further suggesting that *COL11A2* could be a key contributor to the observed phenotype. Both families with *COL11A2* variants exhibited consistent clinical features, including short stature and limb shortening. In contrast, family members without the variant did not present these phenotypes. Interestingly, short stature is the only observed phenotype in our study, although the broad distribution of collagen type XI in various tissues (e.g., articular cartilage, tendons, trabecular bone, and skeletal muscle). To investigate the potential causes of short stature, we conducted a thorough examination of the two reported cases. In family 1, we observed limb shortening in the proband, along with her mother and maternal aunt. However, in family 2, aside from AD-FSS, no additional abnormalities were identified. Notably, other collagenopathies, including those associated with collagen types II, IX, and X, have also been reported with short stature as the sole clinical manifestation (9). A possible explanation for this phenotype variability is that different gene variants may result in distinct clinical presentations, potentially influenced by factors such as genetic background, modifier genes, or compensatory mechanisms. Moreover, *COL11A2* plays a known role in chondrocyte proliferation and development, suggesting that its variant could disrupt these processes and lead to the phenotypic traits in our cases. Therefore, despite the classification of the variants as of uncertain significance, the consistent clinical presentation across family members with the variant, along with the known biological roles of *COL11A2*, supports its consideration as a likely cause of short stature in these families.

In variants of several genes affecting the growth plate, a wide phenotypical spectrum has been described. A typical example is the *SHOX* gene (14,15). Recently, Zhang *et al.* published a study in which variants in the *COL2A1* gene caused short stature in 9 of 82 (11%) Chinese patients with signs of bone dysplasia (16). Our study has extended the phenotypical spectrum of collagenopathies by proving that AD-FSS is associated with variants in the *COL11A2* gene encoding collagen molecules. *COL11A2* (NM_080680.2; 6p21.32) encodes the α2(XI) collagen chains, a part of type XI collagen (17). Type XI collagen is a cartilage-specific ECM protein essential for cartilage collagen fibril formation, ECM organization, and the integrity and proper development of the skeleton (18). Variants in *COL11A2* can lead to structural alterations in the α2(XI) chain, potentially disrupting the proper assembly of collagen type XI heterotrimers. Such disruption may impair fibril formation and stability, thereby affecting the biomechanical properties of cartilage and bone. Additionally, defective *COL11A2* may affect the interaction between collagen type XI and other ECM components, further compromising tissue integrity. It is worth mentioning that the c.688G>T variant in exon 5 of the *COL11A2* gene is classified as benign in other studies and databases. Nevertheless, multiple studies have reported that otospondylomegaepiphyseal dysplasia (OSMED) patients harbor homozygous pathogenic variants in *COL11A2*. Certain findings such as midface hypoplasia and dysplastic skeletal changes were consistently present across all cases (17). Furthermore, variants in the *COL11A2* gene have been shown to cause hearing loss (19,20). The mechanism in these cases involves the disruption of collagen function. In summary, *COL11A2* is crucial for the formation of type XI collagen. Our study and other studies together demonstrated that variants in this gene can lead to significant clinical conditions affecting bones and hearing (9,20). Understanding these variants is essential for the diagnosis and management of related disorders.

The treatment of short stature in the absence of GH deficiency remains a clinical challenge. While GH has been approved for treating short stature associated with certain syndromic diseases such as Noonan syndrome, Prader-Willi syndrome and Silver-Russell syndrome (21), its effectiveness in cases of short stature caused by collagen gene variants is unclear. In a GeNeSIS observational program involving 521 children with SHOX deficiency, the respective ages, GH treatment durations and SDS gains for patients prepubertal at baseline (n=42) were 9.2 years, 6.0 years and 1.19 (0.76–1.62), and for the clinical trial cohort they were 9.2 years, 6.0 years and 1.25 (0.92–1.58). No new GH-related safety concerns were reported (22). In a recent study, Plachy *et al.* evaluated the efficacy of GH treatment (21–45 μg/kg/day) in children with growth plate collagenopathies. A likely pathogenic variant in the collagen genes (*COL2A1*, *COL9A1*, *COL9A2*, *COL9A3*, *COL10A1*, *COL11A1*, and *COL11A2*) was found in 10 of 87 (11.5%) children. Their height improved from a median of −3.1 to −2.6 SD and to −2.2 SD after 1 and 3 years of therapy, respectively (8). Chen *et al.* found that among 106 patients with short stature and skeletal abnormalities, 26 (24.5%)

cases carried 24 pathogenic or likely pathogenic variants in collagen genes, with *COL2A1* variants being the most common, accounting for approximately 57.7%. They also identified other common variants associated with skeletal development, including *FGFR3*, *ACAN*, *NPR2*, *COMP*, and *FBN1* (9). For children with short stature caused by skeletal collagen gene variants, the average height Z-score of 9 patients who received rhGH treatment improved from a median of −3.2±0.9 to −2.2±1.3 SDS after 2.8±2.1 years. The most significant height Z-score improvement of 2.3 and 1.7 SDS was seen in two patients who received treatment for more than 6 years (9). Both children in this study received rhGH treatment, resulting in significant height improvement. The child in family 1 received 18 months of treatment, experiencing a height increase of 15 cm. In addition, the child received GnRHa treatment due to her advanced bone age and sex hormone levels. GnRHa is the established treatment of central precocious puberty (23) and can postpone premature closure of the growth plates (24). In family 2, the child received rhGH for 19 months, resulting in a height increase of 20 cm. Our results together with previous studies demonstrated the efficacy of rhGH in treating short stature carrying collagen gene variants. Genes such as *COL2A1* and *COL11A2* encode collagens that play multiple roles in the cartilage ECM (9). Their variants may disrupt ECM integrity, reduce chondrocyte proliferation and differentiation, and consequently lead to cartilage developmental disorders, skeletal deformities, and short stature. Previous studies have described several genes in which rare deleterious variants cause short stature with no other characteristics or with only subtle phenotypes. These genes were mainly involved in the GH/IGF-1 axis and growth plate physiology (25). RhGH may promote IGF-1 secretion by binding to GH receptors on hepatocytes and chondrocytes (26,27). IGF-1 acts on chondrocytes in the growth plate, stimulating their proliferation and differentiation, enhancing ECM synthesis, and ultimately promoting longitudinal bone growth (27). It is worth mentioning that limb and spinal deformities are common concerns in children with skeletal collagenopathies. While there is no available data on whether rhGH treatment affects the prevalence or severity of such symptoms, especially scoliosis, the two children in this study did not exhibit these issues during more than 1 year of treatment period.

There are some limitations in the current study. Firstly, the lack of comprehensive sequencing of all family members in Case 1 restricts a full segregation analysis, which could provide stronger evidence for the pathogenic role of *COL11A2* variants. Although family members with the variant exhibited consistent phenotypic features, all family members sequencing would enhance our understanding of the inheritance pattern and help to identify any potential involvement of other genetic factors. In future studies, we recommend whole-exome sequencing of all family members to facilitate segregation analysis, which could provide more definitive evidence for the pathogenicity of *COL11A2* variants. Additionally, functional studies on exploring the biological impact of the identified variants and their roles in short stature would further enhance our understanding of the causal relationship. Furthermore, this study only reports the response to GH treatment in two children with AD-FSS. Other factors, such as the timing of GH treatment initiation and the dosage of GH, may affect growth outcomes. Therefore, larger-scale studies with longer follow-up periods are required. Moreover, the present study lacks a clear mechanistic explanation for the therapeutic response to rhGH in patients with *COL11A2* variants. A possible explanation is that rhGH may modulate paracrine signaling pathways involved in endochondral ossification, thereby promoting chondrocyte proliferation and matrix remodeling despite the underlying collagen deficiency. However, further studies are required to elucidate the potential mechanisms by investigating the interactions between rhGH signaling and ECM components, along with exploring potential biomarkers that could predict therapeutic efficacy in patients with *COL11A2* variants.

Conclusions

Two heterozygous *COL11A2* variants (c.688G>T and c.2458G>A) were identified in a girl and a boy with familial short stature. After rhGH treatment, their heights increased by 15 cm and 20 cm, with no adverse events. In children with short stature and skeletal dysfunction, screening of collagen gene variants is recommended, especially in the multiple family members showing short stature. Collagen gene variants may lead to simple short stature, with or without minor skeletal dysfunction. In terms of short-term efficacy, rhGH is effective for treating children with growth plate collagen gene variants as it can enhance growth rates and offer substantial growth benefits. However, vigilant monitoring for potential skeletal dysfunction is crucial during treatment.

Acknowledgments

None.

Footnote

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-2024-551/dss

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Ethical Statement: The authors 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. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by Medical Ethics Committee of Tianjin Medical University General Hospital (No. IRB2024-YX-084-01). The study was conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

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