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A heterozygous point mutation of the *ANKRD11* (c.2579C>T) in a Chinese patient with idiopathic short stature

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Abstract

Background: Pathogenic variants of *ANKRD11* have been reported to cause KBG syndrome characterized by short stature, characteristic facial appearance, intellectual disability, macrodontia, and skeletal anomalies. However, the direct clinical relevance of *ANKRD11* mutation with short stature is yet unknown.

Methods: Here, we report a Chinese boy with idiopathic short stature (ISS) based on clinical and genetic characteristics. Comprehensive medical evaluations were performed including metabolic studies, endocrine function tests, bone X-rays, and echocardiography. Whole-exome and Sanger sequencing was used to detect and confirm genetic mutations associated with short stature in this patient, respectively. The pathogenicity of the variant was further predicted by several in silico prediction tools and repositories of sequence variation. Twenty-four months follow-up was performed to observe the growth rate of the patient treated with recombinant human growth hormone (GH).

Results: One heterozygous point mutation (c.2579C>T) was confirmed in the *ANKRD11* gene of the patient and inherited from his mother. This mutation site was located within the highly conservative region of ANKRD11 protein and predicted to be possibly damaging in several in silico prediction programs and repositories of sequence variation. Additionally, patient underwent GH replacement therapy for 24 months exhibited good response to the treatment.

Conclusion: A heterozygous point mutation of *AKNRD11* gene was identified in a Chinese patient with short stature phenotype. The patient was treated effectively with GH supplementation.

KEYWORDS

ANKRD11, height growth, heterozygous point mutation, idiopathic short stature, whole-exome sequencing

Yabin Kang and Dongye He two contribute equal to this work and are co-first authors.

1 | INTRODUCTION

Idiopathic short stature (ISS) has classically been defined as a height more than 2 standard deviation scores (SDS) below the mean height of a specific population adjusted for age and gender without evidence of systemic diseases, growth hormone (GH) secretion disorders, nutritional abnormalities, chromosomal aberrations, or any other detectable pathology (Martucci et al., 2016). With the advent of more sophisticated chromosomal testing techniques including whole-exome sequencing (WES) and whole genome sequencing (WGS), additional etiologies of ISS are being identified, most notably mutations in *IGFALS*, *SHOX*, *NPR2*, *NPPC*, *FGFR3*, and *ACAN* (Grunauer & Jorge, 2018; Kang, 2017).

The *ANKRD11* gene (OMIM#611192), mapped to 16q24.3, encodes an ankyrin repeat domain-containing protein 11 and corresponds to the phenotype of KBG syndrome (OMIM#148050) with an autosomal dominant mode of inheritance (Goldenberg et al., 2016). KBG syndrome first described by Herrmann, Pallister, Tiddy, and Opitz (1975) as a rare genetic disorder characterized by some of the core symptoms including short stature, characteristic facial appearance, intellectual disability, macrodontia, and skeletal anomalies, is caused by haploinsufficiency of *ANKRD11* resulting from either loss-of-function mutations in the *ANKRD11* gene or microdeletions in chromosome 16q24.3, which includes *ANKRD11* (Herrmann et al., 1975; Novara et al., 2017). To date, a large amount of cases with *ANKRD11* mutation have been reported and most of these patients showed short stature phenotype (Bianchi et al., 2017). Additional laboratory study has also showed that an ENU-induced mutation in the *ANKRD11* gene resulted in an reduced body size and osteopenia-like phenotype in the mouse mutant Yoda, suggesting that this gene plays an important role in regulating bone growth and development (Barbaric et al., 2008). However, there have been no reports on *ANKRD11* mutations identified from ISS patients.

Here, we present a 14-year-old Chinese boy whose evaluation for ISS revealed by clinical and radiological features. Similar features were also identified in his mother. Genetic testing of both revealed a heterozygous point mutation in *ANKRD11* (c.2579C>T) followed by pathogenic analysis. The height of patients with *ANKRD11* gene aberrations from published literature was also reviewed. Furthermore, we reported the patient's response to recombinant human growth hormone (rhGH).

2 | MATERIALS AND METHODS

2.1 | Editorial policies and ethical considerations

This study was approved by the Ethics Committee of Affiliated Hospital of Jining Medical University (China). The study follows the principles outlined in the Helsinki Declaration and the parents of this patient gave written informed consent for molecular study and publication.

2.2 | Endocrine laboratory tests and imaging examination

GH was measured using a chemiluminescence method (ACCESS2, Beckman Coulter) with an analytical sensitivity of 0.010 μg/L. Serum IGF-1, IGFBP-3, and electrolytes levels were measured by the chemiluminescence immunometric method (DPC IMMULITE 1000 analyzer, SIEMENS). Measures of liver function (including alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transferase [GGT]), kidney function (including Cr, blood urea nitrogen [BUN], UA), lipid profiles (including total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], LDL-C, triglycerides [TG]), and fasting plasma glucose (FPG) were tested by a biochemical auto-analyzer (Cobas c 702, Roche). Measurements of thyroid function (including Free T3 [FT3], Free T4 [FT4], thyroid-stimulating hormone [TSH]), gonadotropin, cortisol rhythm and adreno-cortico-tropic hormone (ACTH) were tested by a luminescence immunoassay system (Cobas e 602, Roche). The SDS of IGF-1 (IGF-1 SDS) was calculated according to a previous study (Wang, Ji, Shao, Zhang, & Ban, 2018). Imaging examination included bone and chest X-rays, and brain MRI.

2.3 | DNA preparation and WES

Two milliliters of venous blood was taken from the patient and their parents, and the blood DNA of the patient and parents' peripheral blood leukocytes were extracted using the Blood DNA Midi Kit (D3494-04, Omega Bio-Tek).

Whole exome was captured by SeqCap EZ MedExome Target Enrichment Kit (Roche) and sequenced by Shenzhen Huada gene sequencing technology service co., Ltd. The sequence was read by Illumina HiSeq 2500 (Illumina). The read length of the paired end was 150 bp, and the average coverage of the capture area was about 100×. The sequencing results were compared with the human genome reference sequence (UCSC GRCh38.p12), and multiple database (eg db-SNP, OMIM, ESP, Clinvar, 1000 Genomes HGMD) annotations were used to locate candidate genes and mutations.

2.4 | Sanger sequencing

The full *ANKRD11* gene DNA sequence (NM_013275.6) was downloaded from the NCBI website. PCR primers were designed using Primer 5 software and synthesized by Sangon Biotech co., Ltd. (Shanghai, China). 2 × M5 Taq PCR Mix purchased from Sangon Biotech co., Ltd. (Cat no. MF001-01) was used for PCR amplification. Primer sequence were as follows:

upstream primer 5'-TTTTCCAAATATCCCTTCTAAGACG-3';

downstream primer 5'-TTTTATGCTTTTCGGTCTGCTC-3'.

PCR product size was 372 bp. Amplification achieved with the ANKRD11 primer was performed with an initial step at 95°C for 5 min, followed by 35 cycles at 94°C for 25 s, 50°C for 25 s and 72°C for 30 s, and a final extension step at 72°C for 5 min. After gel recovery and purification, gene sequence analysis was performed by two-way sequencing and then aligned with standard sequences.

2.5 | Pathogenicity prediction

Conservation of the identified *ANKRD11* variant was carried out using Molecular Evolutionary Genetics Analysis software version 4.0. This mutation was further analyzed with several in silico prediction programs (Align GVGD [http://agvgd.hci.utah.edu/], SIFT [http://sift.bii.a-star. edu.sg], PolyPhen 2 [http://genetics.bwh.harvard.edu/pph2/]) and repositories of sequence variation (1000 Genomes [http://www.internationalgenome.org/], EVS databases [http://evs.gs.washington.edu/EVS/], ClinVar database [https://www.clinicalgenome.org/data-sharing/clinvar/], ExAC browser [http://exac.broadinstitute.org], dbSNP database [https://www.ncbi.nlm.nih.gov/snp]) that whether the variant was pathogenic. In addition, in order to examine whether Ser 860 could be reasonable phosphorylation site, the whole ANKRD11 protein sequence was scanned and possible phosphorylation site was analyzed by NetPhos version 3.1, a widely accepted program for phosphorylation site prediction (http://www.cbs.dtu.dk/services/NetPhos/).

3 | RESULTS

3.1 | Clinical findings

The patient was born at 40 weeks gestation by natural childbirth, with a birth weight of 3.2 kg (−0.3 *SD*) and a body length of 50 cm (−0.2 *SD*). The proposita was the first child of both healthy and nonconsanguineous parents, besides the short stature of his mother (149.2 cm, −2.0 *SD*). The patient was born without suffocation and hypoxia, and his mother denied abnormal placenta and amniotic fluid. He was breastfed upto 1 year old, began to teethe at 7 months of age, spoke, and walked independently at one and a half years. The boy was observed to grow slower than the same age children since he was 4 years old. When 14 years old, he was admitted to the Department of Endocrinology, Affiliated Hospital of Jining Medical University on July 27, 2015 due to his short stature (142.1 cm, −3.3 *SD*). He had normal intelligence without secondary sex characteristics, and his testicular volume was 9 ml. Patient family pedigree was shown in Figure 1.

Levodopa GH test results showed that peak GH level of this patient was 18.882 ng/ml. Insulin hypoglycemia stimulation test showed a maximum GH secretion of 8.48 ng/ml. IGF-1 level was 337 μg/L (12 years old reference value: 143–693) and IGFBP-3 level was 6.77 mg/L (12 years old reference value 2.7–8.9). Additional laboratory measurements included thyroid function, liver function and kidney function, electrolytes, lipid profiles, FPG, ACTH and gonadotropin levels over 24 hr, all within normal results. Additionally, pituitary MRI plain scan showed the normal pituitary (Figure 2a). The average bone age of the left hand was about 12 years old by bone X-ray, demonstrating a delayed bone age of the patient (Figure 2c).

3.2 | Identification of *ANKRD11* mutations

One heterozygous point mutations in *ANKRD11* (NM_013275.6), c.2579C>T (p.S860L), were both found in the patient and his mother (Figure 3). The conservative analysis result indicated that the 860st amino acid serine of ANKRD11 was located in the highly conserved region in all seven species available on NCBI (Figure 4). The variant was predicted to be possibly damaging in several in silico prediction programs (Align GVGD: C65 (GV: 0.00 - GD: 144.08), SIFT: Neutral (score: −1.540), PolyPhen 2: predicted to be probably damaging (HumDiv score 0.996 (sensitivity 0.55, specificity 0.98) and

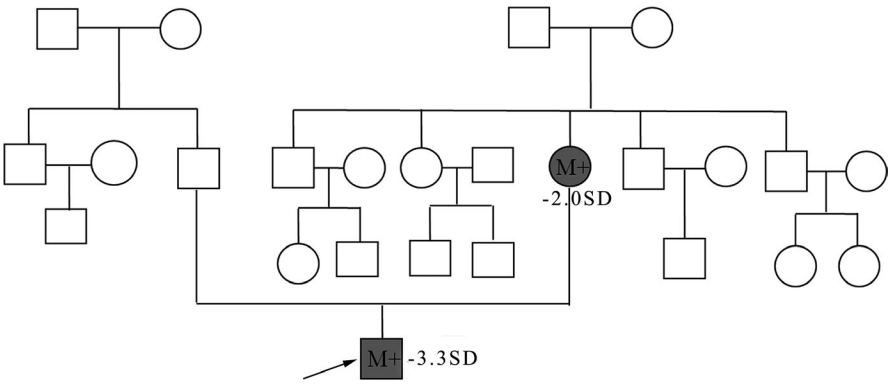

FIGURE 1 Pedigree of the patient's family. Filed symbols represent family members with short stature, whereas the open symbol represents wild-type. Nearby these symbols height SDS is displayed. M+: heterozygous point mutation of the ANKRD11 (c.2579C>T) is present. M-: heterozygous point mutation of the *ANKRD11* (c.2579C>T) is not present (Reference transcript NM_013275.6).

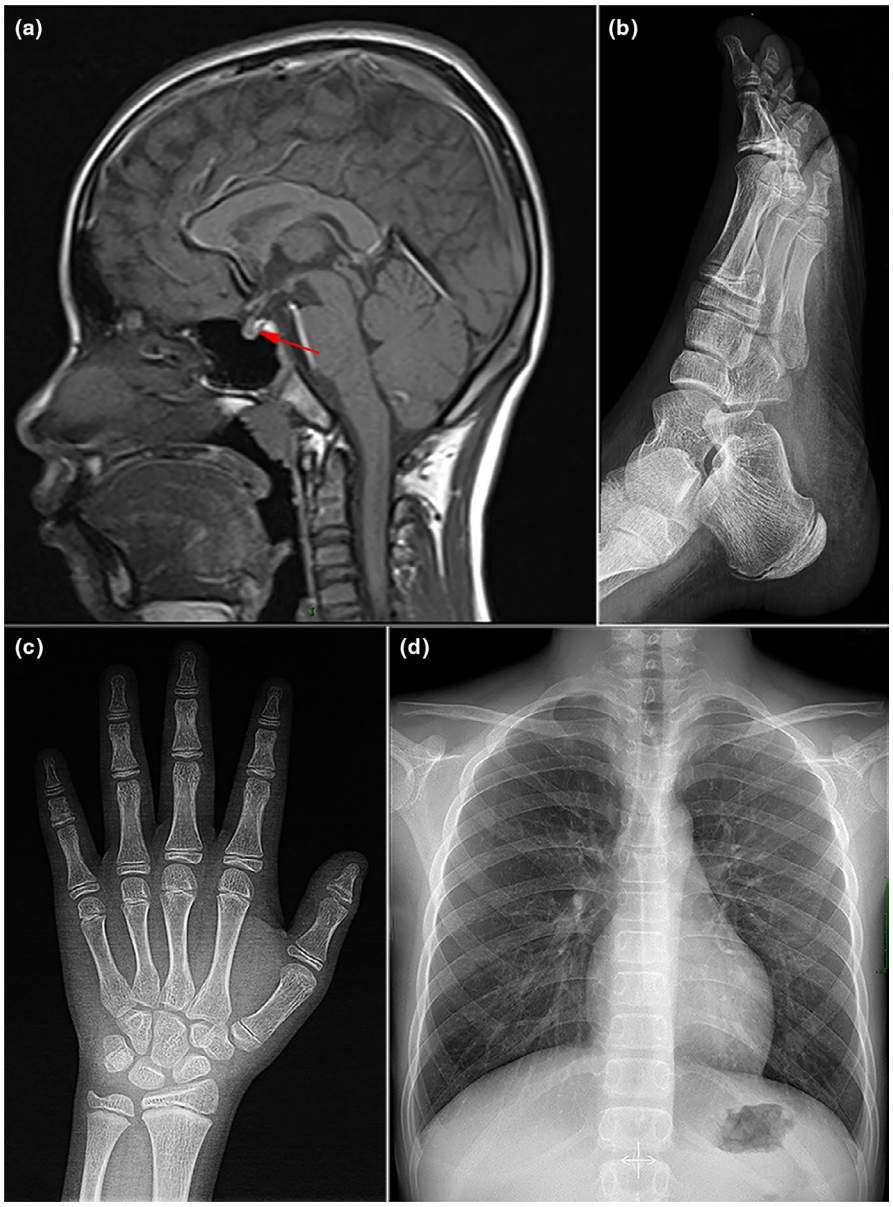

FIGURE 2 Brain MRI and bone X-rays of the index patient at the age of 14 years. (a) Brain MRI shows normal pituitary. (b and c) Bone X-rays of the left foot and left hand show delayed ossification. (d): Normal chest X-ray

HumVar score 0.713 (sensitivity 0.78, specificity 0.85)). This variant exists in the 1000 Genomes and EVS databases, and also present in the dbSNP database (rs145730800) as a SNV. It was found in ExAC browser in six African and one Latino out of 60,706 subjects and the mutation allele frequency (AF) is 5.771e-05, which is lower than the filtering AF (0.000252). The mutation (c.2579C>T) was not recorded in the ClinVar database. However, there are two mutation types recorded in the ClinVar database closest to the mutation, NM_013275.5 (*ANKRD11*): c.2589dupA (p.Asp864Argfs, pathogenic) and NM_013275.5 (*ANKRD11*): c.2535G>T (p.Leu845Phe, uncertain significance). Additionally, the result obtained from NetPhos 3.1 analysis indicated that Ser 860 was very reasonable phophorylation site (CDK5, Score: 0.529; p38MAPK, Score: 0.512) and this mutant site (p.S860L) predicted to be desphosphorylated.

3.3 | Treatment and follow-up

The growth rate after treatment was significantly improved by subcutaneous injection of rhGH (0.15 units per kilogram of body weight per day; Figure 5). On a return visit 3 months later, his body height was 145.7 cm (−3.3 *SD*) with an increase of 3.6 cm. On a return visit 6 months later, his height was 151.2 cm (−2.5 *SD*), gained 5.5 cm. On a return visit 12 months later, his height was 152.8 cm (−2.6 *SD*). On a return visit 15 months later, his height was 154.8 cm (−2.6 *SD*). On a return visit 21 months later, his height was 157.9 cm (−2.2 *SD*) with an increase of 3.1 cm. On a return visit 24 months later, his height reached 159.2 cm (−2.0 *SD*), gained 17.1 cm. No side effects were observed. By the end of December in 2018, he is 17 years old and 5 months and his body height was 167.0 cm (−0.8 *SD*).

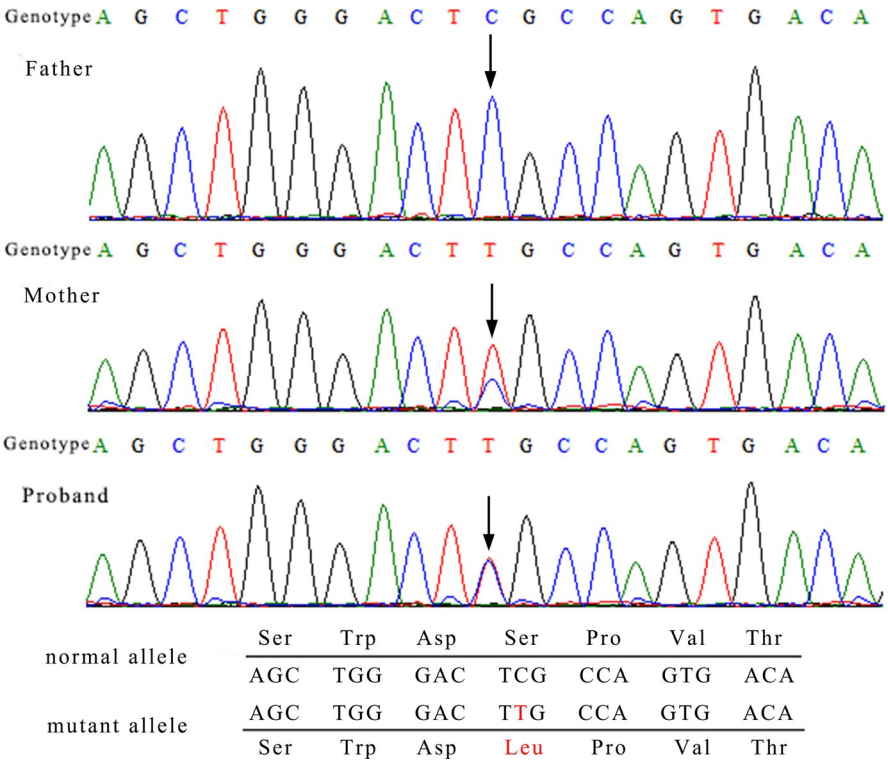

FIGURE 3 Sanger sequencing results of identified *ANKRD11* (Reference transcript NM_013275.6) mutations. A novel heterozygous point mutation c.2579C>T inherited from the patient's mother. Affected residues are indicated with arrows

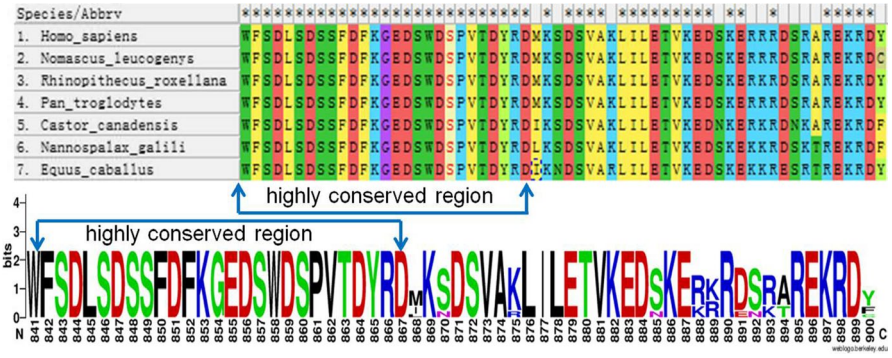

FIGURE 4 The conservative analysis of the amino acid at the mutant site in ANKRD11 protein (*ANKRD11* reference transcript NM_013275.6). The 860st amino acid serine of ANKRD11, which was changed into leucine in the patient, is highly conserved in all the following species that were available on NCBI: *Homo sapiens*, *Nomasous leucogeys*, *Rhinopithecus roxellana*, *Pan troglodytes*, *Castor canadensis*, *Nannospalax galili*, *Equus caballus*

4 | DISCUSSION

A large amount of cases with *ANKRD11* mutation have been reported and most of these patients showed short stature phenotype. This study described the clinical and molecular data of a mother-son pair who shared ISS and a missense mutation in *ANKRD11* (c.2579C>T). This C-to-A transversion at nucleotide c.2579 in exon 9 was predicted to result in an amino acid alteration from Serine to Leucine inside the nuclear localization sequence in codon 860 (p. Ser860Leu). This mutation affects a highly evolutionarily conserved amino acid of the nuclear localization signal region in the ANKRD11 protein and seems to cause a loss of function by altering location of the protein within cells. Additionally, predictions from functional effect studies demonstrated that this mutation is probably damaging with a high score (Align GVGD, SIFT, PolyPhen 2).

ANKRD11 protein, a relatively conservative and widely expressed non-histone transcription factor, belongs to ANCOS protein family. It consists of 2,663 amino acid residues and contains multiple functional domains including two transcriptional repression domains (RD1 and RD2), one transcriptional activation domain (AD), one ankyrin repeat domain and several nuclear localization signals (Figure 6; Barbaric et al., 2008). As a transcriptional factor localized in the nucleus, ANKRD11 has been reported to regulate

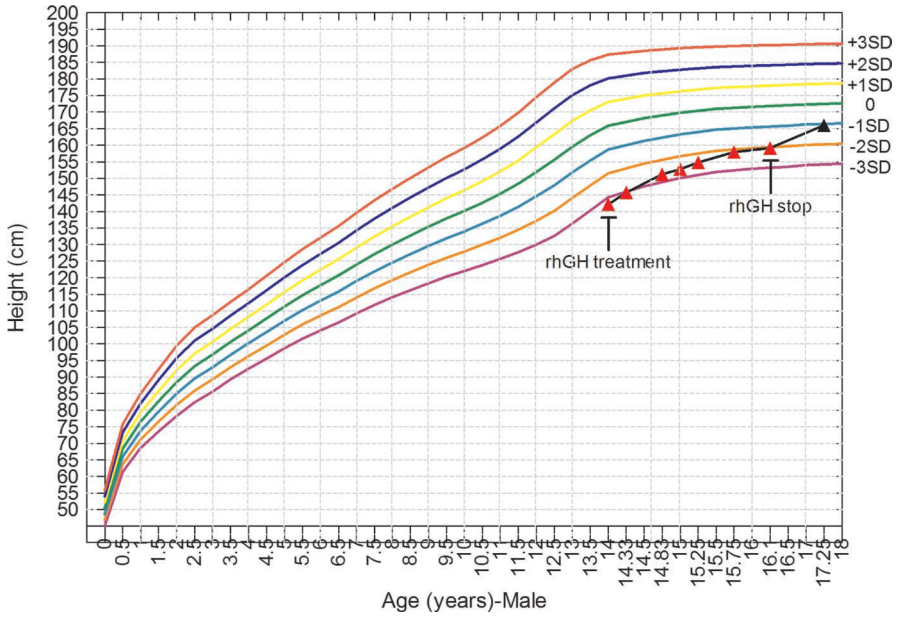

FIGURE 5 Growth chart of the patient. Height standard deviation score (SDS) shown on the extreme right. The triangle indicates the height measurements. The arrow marks the beginning of rhGH therapy and end of the therapy

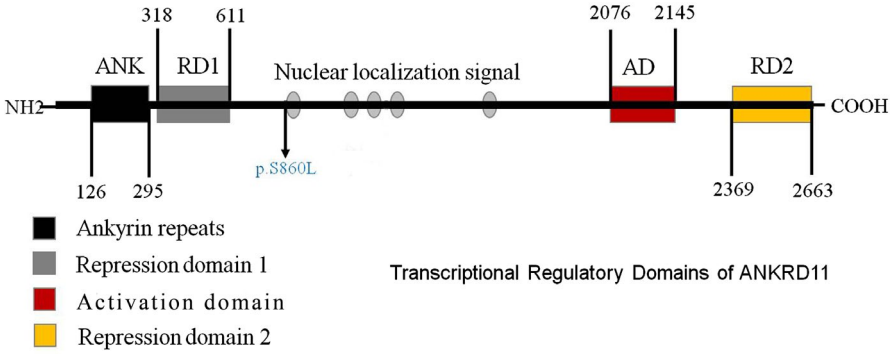

FIGURE 6 The structure diagram of ANKRD11 (Reference transcript NM_013275.6) and its coding product. *ANKRD11* is located at 16q24.3. It contains 13 exons, and 11 are coding exons. ANKRD11 contains 2,663 residues and 4 domains. The mutation in the patient was a transition in exon 9 of *ANKRD11* (reverse sequencing). This mutation changes the 860st serine into leucine, which is adjacent to the nuclear localization

many physiological and pathological processes and its abnormal expression is strongly associated with pathogenesis of many disorders, especially bone development (Barbaric et al., 2008; Gallagher et al., 2015). Previous studies have found that ANKRD11 participated in transcription inhibition by interacting with histone deacetylases and histone molecules, resulting in the inhibition of ligand-dependent transcription, as well as interacted with histone acetyltransferases such as p160 coactivator family members and activates gene transcription (Ka & Kin, 2018). In our study, although this variant existed in the 1000 Genomes, EVS databases, dbSNP database and ExAC browser, population frequencies of the detected variant was quite low. In addition, there are two mutation types recorded in the ClinVar database closest to the identified mutation, NM_013275.5 (*ANKRD11*): c.2589dupA (p.Asp864Argfs, pathogenic) and NM_013275.5 (*ANKRD11*): c.2535G>T (p.Leu845Phe, uncertain significance). Taken together, this information indicated that the variant plausibly caused disease. Interestingly, the 860st amino acid (Serine) of ANKRD11 protein was a reasonable phosphorylation site analyzed by NetPhos 3.1, suggesting that Ser-to-Leu mutation of ANKRD11 protein in codon 860 might lead to impaired bone development through by engaging mechanisms of epigenetic regulation. However, further functional studies are needed to fully understand the mechanisms of *ANKRD11* mutation in bone formation and development.

To date, a number of evidences have proved that heterozygous loss-of-function variants in the *ANKRD11* gene at 16q24.3 can result in KBG syndrome (Goldenberg et al., 2016; Novara et al., 2017; Ockeloen et al., 2015) One of the core features of patients with KBG syndrome is the short stature, and the direct correlation between *ANKRD11* gene aberration and short stature phenotype has not been reported. We extensively reviewed the literature, and compiled

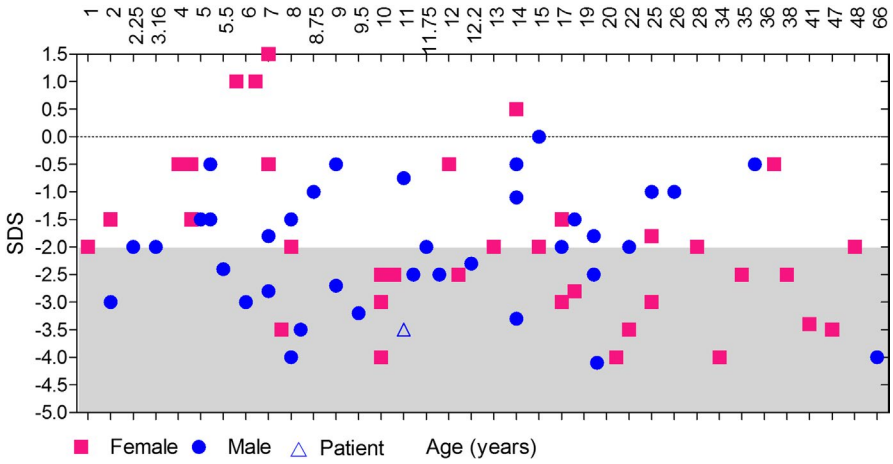

FIGURE 7 Height SDS of 72 patients with ANKRD11 aberration (Crippa et al., 2015; Goldenberg et al., 2016; Isrie et al., 2012; Li et al., 2018; Novara et al., 2017; Ockeloen et al., 2015; Reynaert et al., 2015; Sirmaci et al., 2011; Walz et al., 2015; Xu et al., 2013). The height of 42 patients below −2.0 *SD* account for 58% of 72 total. The patient represented by blue triangular symbols is the ISS boy in our report

72 patients with *ANKRD11* gene aberrations (Crippa et al., 2015; Goldenberg et al., 2016; Isrie et al., 2012; Li et al., 2018; Novara et al., 2017; Ockeloen et al., 2015; Reynaert et al., 2015; Sirmaci et al., 2011; Walz et al., 2015; Xu et al., 2013). To further study height in children and adults with *ANKRD11* mutation/deletion, we pooled the data from the literature and from our unreported an ISS patient. Additionally, patients with a deletion of the 16q24.3 region, including the *ANKRD11* and additional genes (*ZNF778*, *SPG7*, *CPNE7* or *CDH15*) leading to the 16q24.3 microdeletion syndrome, are not included in the data analysis because the contribution of flanking genes on the height of patients could influence the results (Novara et al., 2017). The height SDS was reported in a total of patients with ANKRD11 aberrations: 50 children and 22 adults (Figure 7), and stature below −2.0 *SD* was observed in approximately 58% of all cases (54% of children and 68% of adults). Most strikingly, most patients with *ANKRD11* aberrations showed short stature phenotype with various degrees, demonstrating the clinical relevance of short stature phenotype and *ANKRD11* aberrations. In addition, the growth velocity of ISS patient in our study was improved significantly after treatment rhGH, thus appearing that *ANKRD11* gene mutation does not seem to limit a response to exogenous GH treatment during childhood.

In conclusion, a heterozygous point mutation of *AKNRD11* gene was identified in a Chinese patient with short stature phenotype. The variant (c.2579C>T) occurred at the maternal allele and plausibly caused disease. This information expands the spectrum of *ANKRD11* mutations, which is critical in establishing an accurate diagnosis and developing a treatment strategy for ISS patient based on available clinical and genetic molecular information.

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CONFLICT OF INTEREST

None declared.

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