Case Report

Short stature with brachydactyly caused by a novel mutation in the *IHH* gene and response to 4-year growth hormone therapy: a case report

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Background: The etiology of short stature is heterogeneous. The disturbance of endochondral ossification and cartilage matrix synthesis caused by genetic mutations often causes short height combined with skeletal deformities in children. Some patients with minor skeletal abnormalities, such as short fingers and mild limb shortening, may be overlooked by clinicians and misdiagnosed as idiopathic short stature (ISS) or growth hormone deficiency (GHD).

Case Description: We conducted a detailed investigation of laboratory and imaging examinations on a family with short stature and non-classical brachydactyly type A1 (BDA1) and summarized the clinical features. They received whole exome sequencing (WES) to reveal the possible genetic variation. A heterozygous mutation in the Indian hedgehog gene (*IHH*) (c.387_388insC, p.Thr130Hisfs*18) was found in the two siblings and their mother. The siblings both started recombinant human growth hormone (rhGH) therapy (rhGH: 33 μg/kg/day) and followed up for 4 years. After treatment, the siblings' height improved significantly, and they acquired a significant increase in the height standard deviation score (SDS) (the boy: +2.54, the girl: +1.86) during the 4-year therapy. No noticeable adverse effect was observed during rhGH treatment.

Conclusions: We found a novel heterozygous pathogenic mutation in the *IHH* gene in a family and detailed the phenotype with short stature and non-classical BDA1. The therapy of rhGH showed promising effects. To avoid misdiagnosis, clinicians should not overlook minor skeletal anomalies in patients with short stature, especially those with a family history.

Keywords: Short stature; brachydactyly; growth hormone deficiency (GHD); Indian hedgehog gene (*IHH* gene); case report

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Introduction

Short stature refers to individuals of the same race, sex, and age whose height is less than two standard deviations of the average height of the normal population or lower than the third percentile under similar living environments. Short stature is one of the most common referrals in pediatric endocrinology clinics. It may be either a variant of normal growth or caused by diseases. Chondrogenesis is the fundamental biological process that promotes linear growth and height in children, and genetic factors play a crucial role in this process (1). Gene mutations that cause the disturbance of endochondral ossification and cartilage matrix synthesis can lead to short stature. The majority of short children with these mutations have significant skeletal deformities. However, some patients with minor skeletal abnormalities, such as short fingers and mild limb shortening, may be overlooked by clinicians. A careful examination is needed in case of short stature to find these minor abnormalities. In previous studies, it has been found that some monogenic diseases (2) affecting paracrine factors in the growth plate of the epiphysis or extracellular matrix of cartilage could simultaneously cause short stature and minor skeletal deformities. These reported genes were mainly concentrated in *ACAN*, *NPR2*, *NPPC*, *PTH1R* and *IHH* (3-5). Here, we report two short siblings combined with non-classical brachydactyly type A1 (BDA1, MIM:112500) and long-term efficacy of recombinant human growth hormone (rhGH) treatment following the CARE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-578/rc) and summarize the detailed clinical characteristics and results of genetic investigation.

Highlight box

Key findings

- We discovered a novel mutation located in the *IHH* gene in a family with short stature combined with non-classical brachydactyly type A1 (BDA1).
- The siblings with the *IHH* gene mutation both received a 4-year treatment of recombinant human growth hormone (rhGH) treatment. They acquired significant improvement in height, and no noticeable adverse effect was observed during this treatment.

What is known and what is new?

- The etiology of short stature is heterogeneous. Some patients with minor skeletal abnormalities, such as short fingers and mild limb shortening, may be overlooked by clinicians and misdiagnosed as idiopathic short stature or growth hormone deficiency. Patients with short stature caused by *IHH* mutations showed better short-term efficacy by receiving rhGH treatment in past reports, but there are no reports of long-term use.
- We showed excellent effectiveness of rhGH treatment for short patients with BDA1 patients caused by a novel mutation in *IHH*, not only in short duration but also in relatively long periods. After a 4-year therapy with rhGH, the siblings acquired a significant increase in height standard deviation score (the boy: +2.54, the girl: +1.46). No noticeable adverse effect was observed during rhGH treatment.

What is the implication, and what should change now?

- Clinicians should not overlook minor skeletal anomalies in patients with short stature, especially those with a family history, to avoid misdiagnosis.
- *IHH* mutations can lead to familial short stature combined with non-classical BDA1; continuous use of growth hormone therapy may provide long-term benefits and have a high safety for height growth.

Case presentation

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). The study was reviewed and approved by the Ethics Committees involving Human Research in Ruijin Hospital, School of Medicine, Shanghai Jiao Tong University (No. 2012-4). Written informed consent was obtained from the patients' parents for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Patients

The proband (case 1) was a boy who presented with a significant delay in growth velocity (GV) and short stature from the age of 2 years onwards. When he was 7 years and 1 month old, he was taken to Ruijin Hospital for treatment due to his growth retardation over the past 5 years. His GV in the year before the visit was 4.7 cm/year. He did not show any delay in milestones of speech, motor, and intellectual development. He had a full-term birth by spontaneous uneventful vaginal delivery, with a birth weight and length of 2.5 kg and 48 cm, respectively, and was the first child of his parents. The target height was calculated as 167.5 cm according to this patient's parent heights (paternal: 169 cm, maternal: 153 cm).

Case 2 is the younger sister of the proband. She was the second child of this family and had a full-term, uneventful birth with vaginal delivery. She had a 2.94-kg birth weight

and a 48-cm birth length. After infancy, it was found that her height was significantly shorter than the girls of the same age. At 4 years and 11 months old, she received a medical inspection in the Department of Pediatrics at Ruijin Hospital. The GV in the year before the visit was 4 cm/year. She had no history of chronic diseases except for amblyopia in the left eye.

Both siblings and their mother had a shortening of the middle phalange of the fifth finger.

Endocrine function and imaging examination

After being admitted to the Department of Pediatrics, the two siblings received a thorough investigation of growth hormone (GH)-insulin-like growth factor 1 (IGF-1) axis function, thyroid function, adrenal function, and underwent X-ray examination for bone age and spinal morphology. The standard deviation of the serum IGF-1 level was calculated according to pediatric continuous reference intervals in the healthy Chinese children population (6). We performed GH provocative tests with arginine and clonidine. Peak GH values <10 and <5 ng/mL in the GH provocation test were used as cut-off values for diagnosing partial growth hormone deficiency (GHD) and complete GHD, respectively.

Whole-exome sequencing (WES)

Genomic DNA was extracted from the siblings' and their parents' peripheral blood mononuclear cells. A FlexiGene DNA Kit (Qiagen GmbH, Hilden, Germany) was used to extract DNA according to the manufacturer's instructions. WES was performed by the Laboratory of Molecular Genetics, Clinical Laboratory Department at Ruijin Hospital. The genetic variations were identified using online databases, such as the Single Nucleotide Polymorphism Database (dbSNP), Clinvar, the Human Gene Mutation Database (HGMD), the 1000 Genomes Project, and Online Mendelian Inheritance in Man (OMIM), to verify whether there were known pathogenic mutations. Pathogenicity was further evaluated according to the American College of Medical Genetics and Genomics (ACMG) guidelines for novel mutations not being included in the databases (7).

Sanger sequencing was used to verify the mutations in the patients revealed by WES and to test the co-segregation of variants in the kindred.

Clinical characteristics

The growth charts for Chinese children and adolescents aged 0 to 18 years were used to calculate all the standard deviation scores (SDSs) of the patient's height, weight, and BMI (8,9).

Case 1

The boy was 7 years and 1 month old. His height was 109.3 cm (SDS: –2.88). His weight was 18.8 kg (SDS: –1.35), and his body mass index (BMI) was 15.73 kg/m^2 (SDS: 0.15). He was a symmetrical boy, without abnormal facial features or obvious bone deformity. The laboratory tests showed normal function of the liver, kidney, thyroid, parathyroid, and adrenal glands. The level of IGF-1 was 155 ng/mL (SDS: –0.88). GH provocation test using arginine and clonidine was performed, and the result suggested this boy had complete GHD (GH peak value: 2.317 ng/mL). The X-ray film of his left hand and wrist showed his bone age was 4.5 years old (chronological age: 7.08 years). Besides, the film also showed a shortening deformity of the middle phalange of the fifth finger in his left hand (*Figure 1A*), which was a milder feature of BDA1. No clinodactyly was found.

Case 2

The sister was 4 years and eleven months old. She was 97.9-cm tall (SDS: –2.2), weighed 14.2 kg (SDS: –2.09), and had a BMI of 15.4 kg/m^2 (SDS: 0.26) at the time of visit. Similar to her sibling, the patient was well-proportioned, with no apparent facial nor bone abnormalities. Her laboratory test results were almost normal, except the GH peak value was 7.48 ng/mL after the provocation test using arginine and clonidine, and her serum IGF-1 level was 101 ng/mL (SDS: –1.4). Her bone age was 3.0 years (chronological age: 4.92 years). The X-ray film also found a shortening deformity of the middle phalange of her fifth finger (*Figure 1B*).

Whole exome sequencing results of this family

A heterozygous mutation in the Indian hedgehog gene (*IHH*) (c.387_388insC, p.Thr130Hisfs*18) was found in the two siblings and their mother by WES. The father had a wild type of *IHH*. This result was certified by Sanger sequencing (*Figure 2*). According to the guidelines of

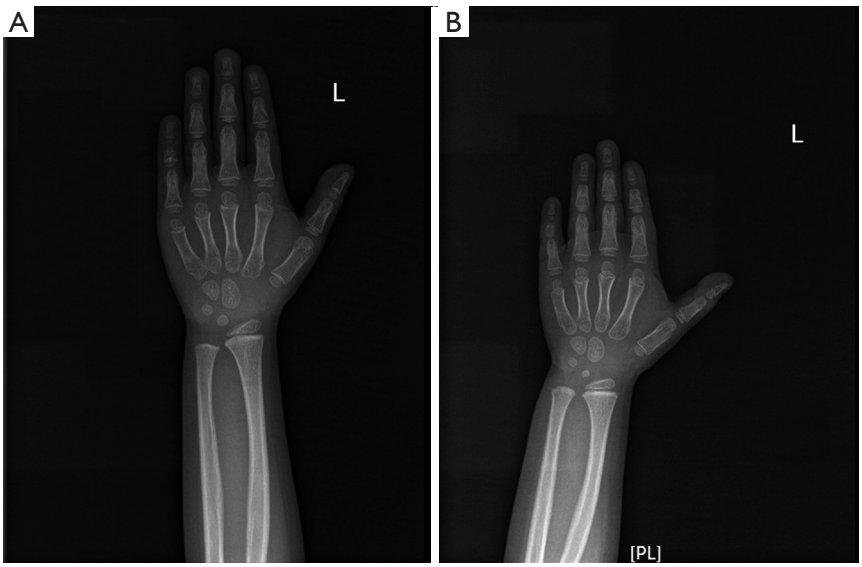

Figure 1 The X-ray revealed a significant lag in bone age and a short digit deformity in the middle phalanx of the fifth finger in both children. (A) Case 1; (B) case 2. L, left; PL, posterior and left.

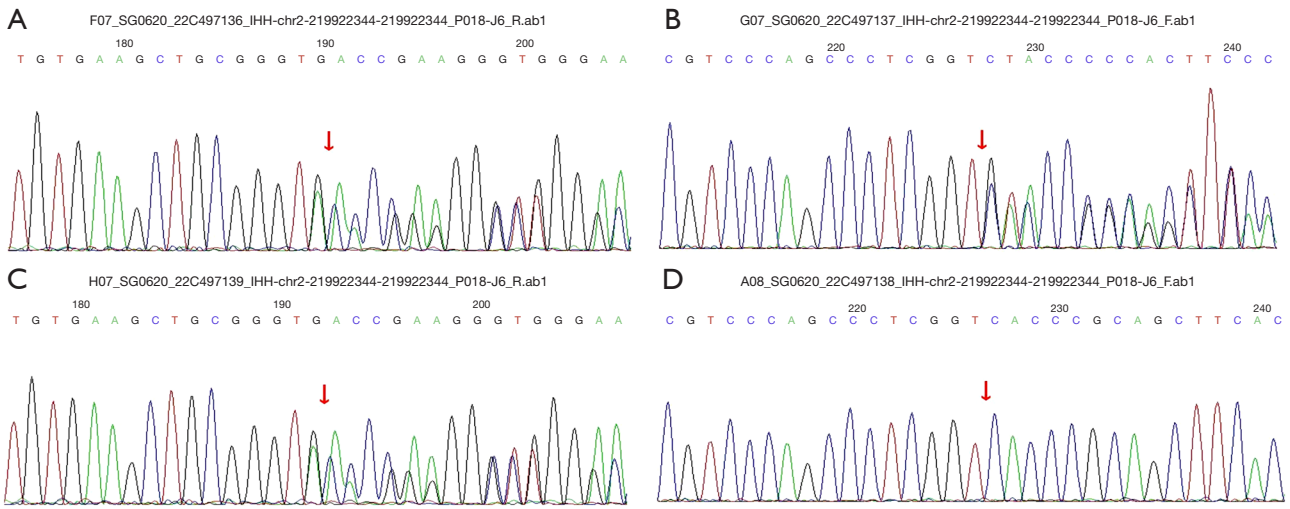

Figure 2 A novel heterozygous mutation (c.387_388insC, p.Thr130Hisfs*18) in the *IHH* gene was found in the two siblings and their mother by whole-exome sequencing, and the father was a wild type. This mutation was subsequently verified by Sanger sequencing. The red arrow indicates the position of the mutation. (A) Case 1; (B) case 2; (C) mother; (D) father.

ACMG (7), this mutation was classified as pathogenic (PVS1_very strong + PM2_supporting + PM5).

Treatment and follow-up

The siblings both started rhGH therapy (GH: 33 μg/kg/day) 1 month after the visit. The children had excellent adherence to rhGH therapy, with regular nightly injections as prescribed. With the treatment, the siblings' height improved significantly, accompanied by a marked increase in GV and IGF-1 levels. The height (SDS) and GV in case 1 were 117.8 cm (–2.25) and 8.5 cm/year (1-year treatment); 126.9 cm (–1.46) and 9.1 cm/year (2-year treatment); 135.3 cm (–0.75) and 8.4 cm/year (3-year treatment); and

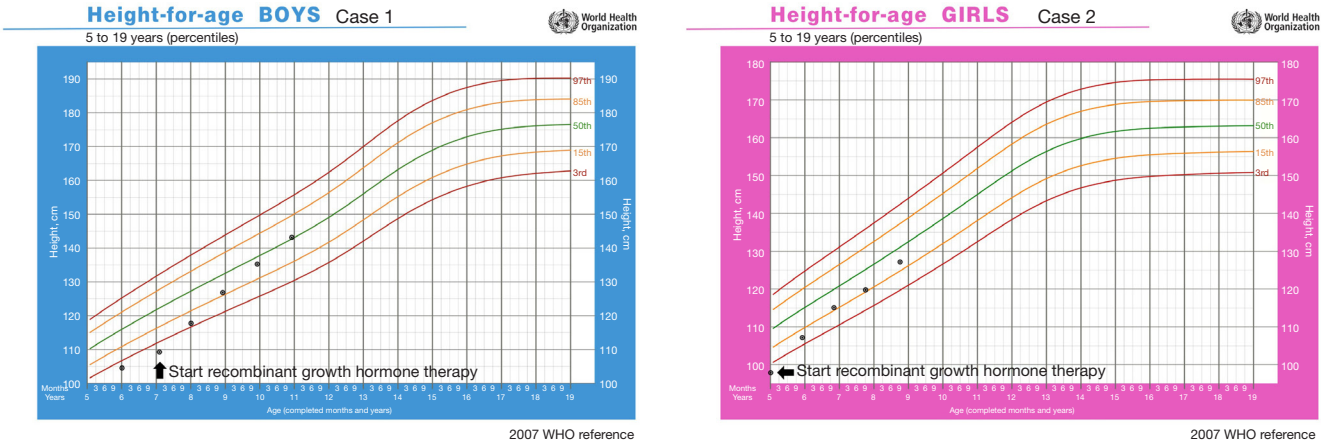

Figure 3 Changes in height during 4-year therapy of recombinant human growth hormone. Black dots indicate height, and black arrows indicate the start of growth hormone therapy. Boy's chart for case 1 and girl's chart for case 2. WHO, World Health Organization.

143.2 cm (–0.34) and 7.9 cm/year (4-year treatment), respectively (*Figure 3*). In case 2, the corresponding changes in height (SDS) and GV were 107.2 cm (–2.17) and 9.3 cm/year (1-year treatment); 115.1 cm (–1.34) and 7.9 cm/year (2-year treatment); 119.8 cm (–1.65) and 4.7 cm/year (3-year treatment); and 127.2 cm (–0.74) and 7.4 cm/year (4-year treatment), respectively (*Figure 3*). Overall, in case 1 and case 2, the increase in height SDS was 2.54 and 1.46 respectively after 4-year rhGH therapy. No noticeable adverse effect was observed during rhGH treatment. Routine blood and urine tests showed normal glucose, lipids and endocrine profile findings. At the age of 10.25 years, case 1 started his puberty and his testes were bigger than 4 mL.

Discussion

Short stature is a common clinical manifestation. However, the etiology of short stature is heterogeneous. Many factors are involved in controlling linear growth in children, such as prenatal, nutritional, hormonal, environmental, or genetic (10-13). However, to familial short stature (FSS), genetic factor is particularly important. Milder types may be the results of a combination of polygenic inheritance and other factors. Severe familial growth retardation suggests more likelihood of autosomal dominant inherited short stature due to monogenic mutation. In recent studies, Plachy *et al.* and Zhou *et al.* revealed that approximately 50% of severe short-stature patients had the monogenic condition (1,14). And a high prevalence of growth plate gene variants was found in FSS (14).

We reported herein two siblings of height SDS of –2.88 and –2.2. Both had an uneventful delivery with normal birth weight and length, a very low GV (<5.0 cm/year), a delayed bone age, and a well-proportioned body. GH peak value during the provocative tests was 2.317 and 7.48 ng/mL. In standard clinical practice, the siblings could be diagnosed with GHD according to guidelines (15,16). However, GH provocative tests showed a low specificity, about 14.9% to 49% (17). In a previous study, short children were misdiagnosed with GHD frequently. And the authors showed that 7 in 23 GHD children had a known causative genetic variant with short stature but was irrelevant to GH secretion (14). However, the siblings did not have typical features of GHD, such as accumulation of abdominal and facial fat. The level of serum IGF-1 in case 1 was not significantly reduced. Meanwhile, we found a phenotype of BDA1 in the two siblings and their mother, who also had a short height (153 cm, SDS: –1.41). For the above reasons, we performed WES for the two siblings and the parents.

Although we did not find any pathogenic variations associated with GHD, the sequencing result revealed that both children and their mother carried a novel heterozygous mutation in *IHH* (c.387_388insC, p.Thr130Hisfs*18), which inserted cytosine between the coding sites 387–388 in exon 2. Consequently, this insertion causes a frame-shift mutation in IHH protein starting from the 130th threonine to be substituted by a histidine and a premature termination at 148th amino acid thereafter. Although we did not perform functional test, this mutation shows convincing evidence for the pathogenicity. It is a null variant (frame-shift) in *IHH* and is predicted to cause nonsense-mediated RNA decay (NMD). Loss of function is a known mechanism of short

stature and BDA1 caused by *IHH* mutation (18,19). The exon 2 contains 22 pathogenic variants, and this truncated region has 21 pathogenic variants according to VarSome database (https://varsome.com/) (20). Although this variant is not found in gnomAD genomes and exomes, a missense variant T130N in *IHH* has been reported in BDA1 cases (21,22). Therefore, when using evidence PVS1_very strong, PM2_supporting, and PM5, this mutation is recognized as a pathogenic variant.

The *IHH* gene was first discovered in the 1980s when studying drosophila genes. *IHH* belongs to the hedgehog family and is expressed in prehypertrophic as well as early hypertrophic chondrocytes. *IHH* can maintain bone homeostasis and recovery by regulating the interaction between mesenchymal stem cells and osteoblasts. It can also stimulate the prechondrogenic stem cells' proliferation and thus inhibit the development of osteoblasts in cartilage (23). The *IHH*-related signaling pathway is highly conserved among species and has a critical regulatory role in various biological processes, such as embryonic growth and development, postnatal stem cell homeostasis, organ damage repair, and tumor occurrence and development (24,25). Particularly, this pathway is the core of regulating chondrocyte proliferation and differentiation (26-29). IHH is secreted by early hypertrophic chondrocytes in the growth plate and acts on the cartilage cells in the resting area by paracrine. One of the critical functions of IHH is promoting the secretion of parathyroid hormone-related protein (PTHrP) by Col2 chondrocytes to maintain the pool of proliferative chondrocytes (30). In this way, IHH promotes the accumulation of calcium deposits and the formation of a primary ossification center, which is crucial to the regulation of osteogenic differentiation during the process of endochondral osteogenesis. In mice, *IHH* mutations could lead to abnormal skeletal development, including the bones of the skull (31), mandible (32), and spine (33), resulting in associated phenotypes such as short stature, short fingers (19,34), cleft lip and palate (35), craniofacial dysplasia (36,37), and osteoarthritis (38).

Patients with heterozygous mutations in *IHH* have the phenotype of BDA1, which is an autosomal dominant inherited disease characterized as short middle phalange in digits along with short stature (18,19). However, clinical phenotypes with heterozygous mutations in *IHH* have been reported to be very heterogeneous. Previous research in 16 patients with *IHH* heterozygous variants reported atypical manifestations: 2 patients had short stature without typical phalange shortening, 5 had phalange shortening with normal height, and the other nine patients had both features (39). Some mild skeletal anomalies such as metacarpal shortening, isolated clinodactyly, cone-shaped epiphysis, and slight micromelia were also reported (31,39). Clinicians easily overlooked these mild bone defects and diagnosed these patients as idiopathic short stature (ISS) or isolated GHD.

A standardized treatment protocol is currently unavailable for bone anomalies and short stature due to *IHH* mutations. The treatment with rhGH has been used in short stature of various causes, including GHD, small for gestational age, Turner syndrome, Noonan syndrome, chronic kidney disease, and ISS in some countries. These diseases respond well to rhGH. However, rhGH therapy for short stature due to defects in cartilage development has been unsatisfactory or ineffective, such as achondroplasia. Vasques *et al.* reported a good response in five patients with heterozygous *IHH* variants with 1-year rhGH treatment (18). The mean change in their height SDS was 0.6 (18). We also used rhGH to treat the siblings, and they acquired a significant increase in height SDS (the boy: +2.54, the girl: +1.86) during the 4-year therapy. No severe side effects had been noticed in our patients. These preliminary results may indicate that rhGH is effective in short stature with *IHH* mutation.

Conclusions

We found a novel heterozygous pathogenic mutation in *IHH* gene in a family and detailed the phenotype with short stature and non-classical BDA1. The therapy of rhGH showed promising effects. Clinicians should not overlook minor skeletal anomalies in patients with short stature, especially those with a family history, to avoid misdiagnosis of ISS or GHD.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-23-578/rc

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-23-578/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-578/coif). The authors have no conflicts of interest to declare.

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. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). The study was reviewed and approved by the Ethics Committees involving Human Research in Ruijin Hospital, School of Medicine, Shanghai Jiao Tong University (No. 2012-4). Written informed consent was obtained from the patients' parents for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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