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### REVIEW

- 1002** Gut microbiota and nutrient interactions with skin in psoriasis: A comprehensive review of animal and human studies  
*Damiani G, Bragazzi NL, McCormick TS, Pigatto PDM, Leone S, Pacifico A, Todorovic D, Di Franco S, Alfieri A, Fiore M*
- 1013** Microbiota-gut-brain axis and its affect inflammatory bowel disease: Pathophysiological concepts and insights for clinicians  
*Sinagra E, Utzeri E, Morreale GC, Fabbri C, Pace F, Anderloni A*

### MINIREVIEWS

- 1026** Distal esophageal spasm: Update on diagnosis and management in the era of high-resolution manometry  
*Gorti H, Samo S, Shahnava N, Qayed E*

### ORIGINAL ARTICLE

#### Retrospective Study

- 1033** Clinical course of percutaneous cholecystostomies: A cross-sectional study  
*Er S, Berkem H, Özden S, Birben B, Çetinkaya E, Tez M, Yüksel BC*
- 1042** Clinical characteristics and 28-d outcomes of bacterial infections in patients with hepatitis B virus-related acute-on-chronic liver failure  
*Li C, Su HB, Liu XY, Hu JH*
- 1056** Application of hybrid operating rooms for treating spinal dural arteriovenous fistula  
*Zhang N, Xin WQ*
- 1065** Ruxolitinib add-on in corticosteroid-refractory graft-*vs*-host disease after allogeneic stem cell transplantation: Results from a retrospective study on 38 Chinese patients  
*Dang SH, Liu Q, Xie R, Shen N, Zhou S, Shi W, Liu W, Zou P, You Y, Zhong ZD*

### META-ANALYSIS

- 1074** Laparoscopic surgery for early gallbladder carcinoma: A systematic review and meta-analysis  
*Feng X, Cao JS, Chen MY, Zhang B, Juengpanich S, Hu JH, Topatana W, Li SJ, Shen JL, Xiao GY, Cai XJ, Yu H*
- 1087** Long-term clinical performance of flapless implant surgery compared to the conventional approach with flap elevation: A systematic review and meta-analysis  
*Cai H, Liang X, Sun DY, Chen JY*

**CASE REPORT**

- 1104** Diagnosis and management of glandular papilloma of lung: A case report  
*Wu CW, Chen A, Huang TW*
- 1108** Abnormal serum carbohydrate antigen 19-9 levels in a patient with splenic retiform haemangioendothelioma concomitant with hepatic amyloidosis: A case report  
*Sun KD, Zhang YJ, Zhu LP, Yang B, Wang SY, Yu ZH, Zhang HC, Chen X*
- 1116** Hepatoid carcinoma of the pancreas: A case report and review of the literature  
*Zeng SX, Tan SW, Fong CJTH, Liang Q, Zhao BL, Liu K, Guo JX, Tao J*
- 1129** Successful treatment of systemic sclerosis complicated by ventricular tachycardia with a cardiac resynchronization therapy-defibrillator: A case report  
*Chen YY, Yan H, Zhu JH*
- 1137** Metabolic and genetic assessments interpret unexplained aggressive pulmonary hypertension induced by methylmalonic acidemia: A case report  
*Liao HY, Shi XQ, Li YF*
- 1142** Hyoid-complex elevation and stimulation technique restores swallowing function in patients with lateral medullary syndrome: Two case reports  
*Jiang YE, Lyu QQ, Lin F, You XT, Jiang ZL*
- 1150** Microscopic removal of type III dens invaginatus and preparation of apical barrier with mineral trioxide aggregate in a maxillary lateral incisor: A case report and review of literature  
*Liu J, Zhang YR, Zhang FY, Zhang GD, Xu H*
- 1158** Cerebral venous sinus thrombosis following transsphenoidal surgery for craniopharyngioma: A case report  
*Chang T, Yang YL, Gao L, Li LH*
- 1164** Hepatoid adenocarcinoma of the stomach: Thirteen case reports and review of literature  
*Zhang ZR, Wu J, Li HW, Wang T*
- 1172** Growth hormone therapy for children with KBG syndrome: A case report and review of literature  
*Ge XY, Ge L, Hu WW, Li XL, Hu YY*
- 1180** Laparoscopic repair of complete intrathoracic stomach with iron deficiency anemia: A case report  
*Yasheng D, Wulamu W, Li YL, Tuhongjiang A, Abudureyimu K*

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Editorial Board Member of *World Journal of Clinical Cases*, Woon-Man Kung, MD, MSc, Assistant Professor, Surgeon, Department of Exercise and Health Promotion, College of Education, Chinese Culture University, Taipei 11114, Taiwan

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# Growth hormone therapy for children with KBG syndrome: A case report and review of literature

Xiu-Ying Ge, Long Ge, Wen-Wen Hu, Xiao-Ling Li, Yan-Yan Hu

**ORCID number:** Xiu-Ying Ge (0000-0002-4939-1060); Long Ge (0000-0001-5737-516X); Wen-Wen Hu (0000-0002-8228-8292); Xiao-Ling Li (0000-0001-8907-7394); Yan-Yan Hu (0000-0001-6444-8961).

**Author contributions:** Ge XY collected the data, drafted the initial manuscript, and carried out the initial analyses; Ge L was responsible for testing the patient and her parents, and data analysis; Hu WW reviewed and revised the manuscript; Li XL performed data analyses and graphics; Hu YY conceived and designed the study, performed the final data analyses, and wrote the manuscript.

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**Xiu-Ying Ge**, Department of Child Health, Maternal and Child Health Hospital of Linyi, Linyi 276000, Shandong Province, China

**Long Ge**, Department of Clinical Laboratory, Linyi People's Hospital, Linyi 276000, Shandong Province, China

**Wen-Wen Hu**, Department of Pediatrics, The People's Hospital of Lanshan District, Linyi 276000, Shandong Province, China

**Xiao-Ling Li, Yan-Yan Hu**, Department of Pediatrics, Linyi People's Hospital, Linyi 276000, Shandong Province, China

**Corresponding author:** Yan-Yan Hu, MD, Attending physician, Department of Pediatrics, Linyi People's Hospital, No. 27, East Jiefang Road, Linyi 276000, Shandong Province, China. [hyan-yansmile@hotmail.com](mailto:hyan-yansmile@hotmail.com)

## Abstract

### BACKGROUND

The incidence of short stature in KBG syndrome is relatively high. Data on the therapeutic effects of growth hormone (GH) on children with KBG syndrome accompanied by short stature in the previous literature has not been summarized.

### CASE SUMMARY

Here we studied a girl with KBG syndrome and collected the data of children with KBG syndrome accompanied by short stature from previous studies before and after GH therapy. The girl was referred to our department because of short stature. Physical examination revealed mild dysmorphic features. The peak GH responses to arginine and clonidine were 6.22 and 5.40 ng/mL, respectively. The level of insulin-like growth factor 1 (IGF-1) was 42.0 ng/mL. Genetic analysis showed a c.2635 dupG (p.Glu879fs) mutation in the *ANKRD11* gene. She received GH therapy. During the first year of GH therapy, her height increased by 0.92 standard deviation score (SDS). Her height increased from -1.95 SDS to -0.70 SDS after two years of GH therapy. There were ten children with KBG syndrome accompanied by short stature who received GH therapy in reported cases. Height SDS was improved in nine (9/10) of them. The mean height SDS in five children with KBG syndrome accompanied by short stature increased from  $-2.72 \pm 0.44$  to  $-1.95 \pm 0.57$  after the first year of GH therapy ( $P = 0.001$ ). There were no adverse reactions reported after GH treatment.

### CONCLUSION

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GH treatment is effective in our girl and most children with KBG syndrome accompanied by short stature during the first year of therapy.

**Key words:** Growth hormone therapy; KBG syndrome; *ANKRD11* gene; Short stature; Children; Case report

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**Core tip:** KBG syndrome is a rare autosomal dominant disorder. The percentage of height below 10th centile is relatively high at 66%. Children with KBG syndrome accompanied by short stature could benefit from growth hormone therapy.

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## INTRODUCTION

KBG syndrome (OMIM 148050) is a rare autosomal dominant disorder first reported by Herrmann *et al*<sup>[1]</sup> in 1975. They described seven affected individuals from three unrelated families. The KBG syndrome was named after the surname initials K, B, and G of the three original families. It is characterized by developmental delay, intellectual disability, specific craniofacial features, macrodontia of the upper central incisors, short stature, and skeletal abnormalities<sup>[2]</sup>. KBG syndrome is caused by mutations in the *ANKRD11* gene located on chromosome 16q24.3, which encodes an ankyrin repeat domain-containing cofactor<sup>[3]</sup>. Over 110 cases have been reported in the literature so far<sup>[4]</sup>. KBG syndrome should be distinguished from 16q24.3 microdeletion syndrome. Although the clinical manifestations of these two syndromes overlap, there are some differences in phenotypes. In 16q24.3 microdeletion syndrome, short stature and delayed bone age are often not observed<sup>[5]</sup>.

Low *et al*<sup>[2]</sup> described 31 patients affected by KBG syndrome with *ANKRD11* gene mutation in 2016. They proposed new diagnostic criteria for KBG syndrome. The major criteria included macrodontia (85%), height below the 10th centile (66%), recurrent otitis media and/or hearing loss (44%), and 1st-degree relatives with KBG syndrome (22%). The minor criteria included brachydactyly (50%), seizures (43%), cryptorchidism (31%), feeding problems (34%), palate abnormality (25%), autism (24%), and delayed closure of the anterior fontanelle (22%). KBG syndrome can be diagnosed in patients with developmental delay/learning difficulties, speech delay, or significant behavioural issues, with at least two major criteria or one major and two minor criteria.

There are no specific treatments for KBG syndrome. Based on their complex clinical symptoms, genetics, neurology, cardiology, endocrinology, surgery, rehabilitation medicine, and education need to be involved in the treatment in the form of multi-disciplinary team<sup>[2]</sup>. The incidence of short stature in KBG syndrome is relatively high. The effects of growth hormone (GH) therapy on children with KBG syndrome accompanied by short stature are not clear. It has been reported that two children with KBG syndrome showed a good response to GH therapy. They almost reached their parental target height after 3 and 5 years of GH therapy, respectively<sup>[6]</sup>. Further study was needed to determine whether GH may be successful in treating children with KBG syndrome accompanied by short stature. Data on the therapeutic effects of GH on children with KBG syndrome accompanied by short stature in previous studies have not been summarized. Therefore, we report our experience with one girl with KBG syndrome and collected the data of children with KBG syndrome accompanied by short stature from previous studies before and after GH therapy to provide evidence for the effect of GH treatment in children with KBG syndrome accompanied by short stature.

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## CASE PRESENTATION

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### **Chief complaints**

A Chinese girl aged 5 years and 6 mo presented to the Pediatric Department of our hospital complaining of short stature.

### **History of present illness**

The girl was born at term as the only child of her parents. Her birth weight was 3400 g [0.58 standard deviation score (SDS)], and her length was 50 cm (0.1 SDS). Pregnancy, delivery, and the neonatal period were uncomplicated. At 2 mo of age, a developmental delay was found by regular physical examination. She received rehabilitation therapy for 4 mo intermittently. She started walking at 17 mo of age and spoke her first words at 12 mo. Her height was below the mean for age (less than the 3<sup>rd</sup> percentile). Ordinarily, she was quiet, short-tempered, and irritable.

### **History of past illness**

Her past medical history was unremarkable except for developmental delay.

### **Personal and family history**

No specific personal history of disease was recorded. Her parents were healthy, with no significant family history. Her mother's height was 160 cm, and his father's height was 171 cm. The target height for the proband was 159.0 cm (-0.30 SDS).

### **Physical examination upon admission**

Her height was 104.7 cm (-1.95 SDS). Her weight was 15.5 kg. Her head circumference was 57.9 cm (+0.3 SDS). Physical examination revealed mild dysmorphic features, including a long triangular face, frontal bossing, large and protruding ears, broad eyebrows, a high nasal bridge, a long philtrum, macrodontia of the central incisors, and brachydactyly. No significant hearing loss or palate abnormalities were found.

### **Laboratory examinations**

After two stimulation tests (arginine test and levodopa test), the peak GH responses to arginine and levodopa were 6.22 ng/mL and 5.40 ng/mL, respectively. The cut-off peak GH value for GH deficiency was  $\leq 10$  ng/mL. GH deficiency was confirmed. Serum GH level was measured using chemiluminescence assay (Cobas E170, Roche Diagnostics, Germany). The level of insulin-like growth factor 1 (IGF-1) was 42.0 ng/mL. Serum IGF-1 were measured using chemiluminescence assay (Siemens Healthcare Diagnostics, USA). Other biochemical examinations, such as of thyroid function, sex hormones, adrenal function, and blood glucose, were normal.

Written informed consent for clinical whole-exome detection was obtained from her parents. Clinical whole-exome detection was offered by Sino-Science in Beijing, China.

### **Imaging examinations**

Her bone age was 4.5 years. Bone age was estimated using the atlas of Greulich-pyle. Pituitary magnetic resonance imaging (MRI) and echocardiography were normal.

### **Intelligence testing**

She had a borderline intellectual disability with a total IQ of 79 (WISC-R).

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## FINAL DIAGNOSIS

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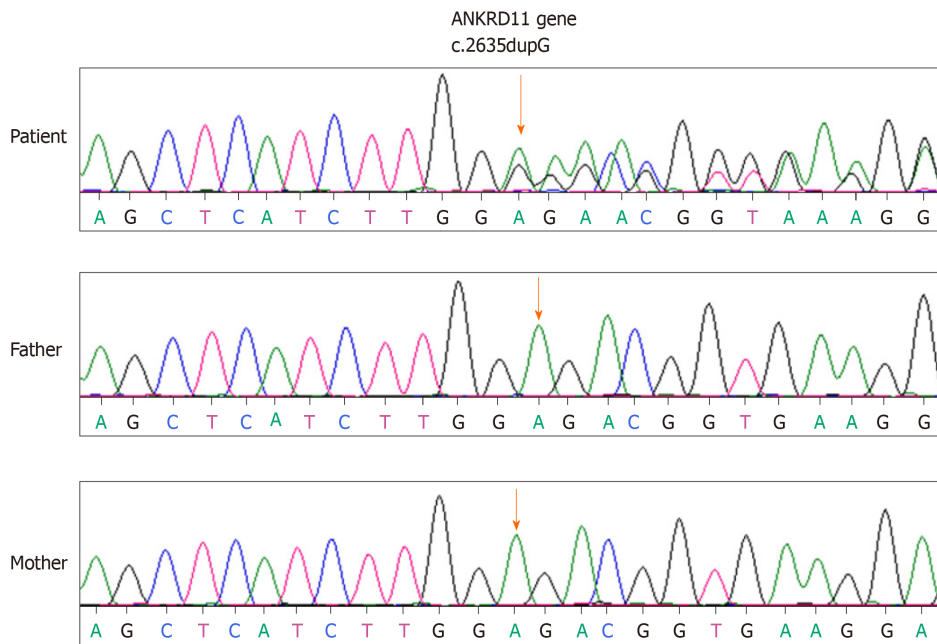
A novel *de novo* mutation (c.2635 dupG, p.Glu879fs) was identified in the *ANKRD11* gene. The variant was interpreted as pathogenic based upon the *de novo* variant in a family without a disease history (PS2) according to the guidelines of ACMG. KBG syndrome was confirmed. Sanger sequencing was employed for our girl and her parents (Figure 1). No mutation of the *ANKRD11* gene was present in her parents.

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## TREATMENT

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The patient was treated with recombinant human GH injections (50  $\mu$ g/kg/d, GenSci, Changchun, Jilin Province) starting at age 5 years and 6 mo.



**Figure 1** Electropherograms of the patient and her parents. A *de novo* heterozygous single base pair duplication at position 2635 (c.2635 dupG) in the *ANKRD11* gene was found in the patient, and was not inherited from her parents.

## OUTCOME AND FOLLOW-UP

Follow-up was performed every 3 mo for two years. During the first year of GH therapy, her height increased by 0.92 SDS. Over the two years of GH, her height increased from -1.95 SDS to -0.70 SDS (Figure 2). Thyroid function and blood glucose were normal during the two-year follow-up.

## DISCUSSION

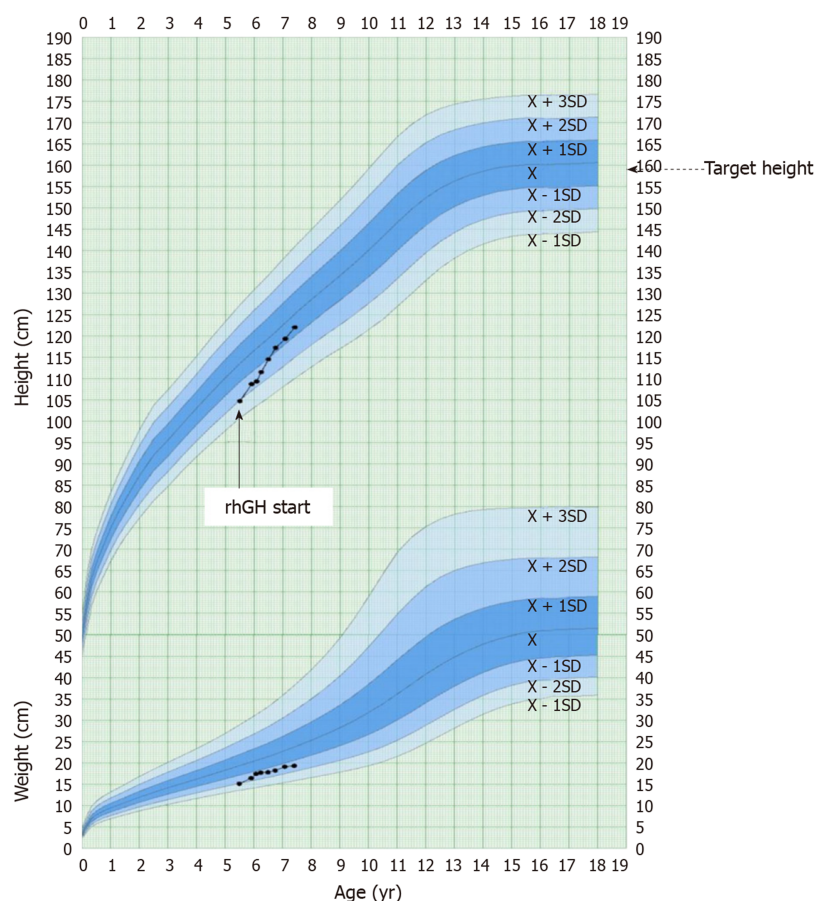
In this study, we collected the data of children with KBG syndrome accompanied by short stature. To observe the effects of GH therapy on the height of children with KBG syndrome accompanied by short stature, we mainly analyzed growth velocity during the first year by comparing those with and those without GH therapy.

Children with KBG syndrome accompanied by short stature without description of changes in height were excluded from our research. A total of ten children with KBG syndrome accompanied by short stature who received GH therapy (P1-P10) were included<sup>[4,6-10]</sup>. Three children with KBG syndrome accompanied by short stature who did not receive GH therapy (P11, P12, and P13) were also included<sup>[5,11]</sup>.

Clinical features of children with KBG syndrome accompanied by short stature who received GH therapy are shown in Table 1 (P1-P8). P8 is our patient. Two children (P9 and P10) without detailed clinical information are not shown in Table 1. The birth length in three (3/5) children was below the 50th percentile. Height SDS was below the 3rd percentile in all children (10/10). GH deficiency was suggested in four (4/6) children. Levels of IGF-1 were low in three (3/4) children. Delayed bone age was found in six (6/8) children.

In children with KBG syndrome accompanied by short stature who received GH therapy (P1-P10), Patient 5 showed no response to GH therapy, though specific height velocity data were missing. The authors did not explain why the child showed no response. The height velocities of children with KBG syndrome accompanied by short stature who received GH therapy (P1-P4 and P6-10) were compared with those who did not receive GH therapy (P11, P12, and P13). Among them, Patient 3 was followed for 9 mo, Patient 13 was followed for 8 mo, and three patients (P4, P9, and P10) were followed for an unspecified time. Their height changes are shown in Figure 3. Height SDS was improved in nine (9/10) children with KBG syndrome accompanied by short stature after GH therapy. The mean height SDS in five children with KBG syndrome accompanied by short stature (P1, P2, and P6-8) increased from  $-2.72 \pm 0.44$  to  $-1.95 \pm 0.57$  after the first year of GH therapy ( $P = 0.001$ ). In children with KBG syndrome accompanied by short stature who did not receive GH therapy, height SDS did not change in 8 mo (from -1.25 to -1.25) in P13, increased mildly (from -2.3 to -1.9) in the





**Figure 2** Changes of height and weight in our patient with KBG syndrome during 2 years of growth hormone therapy. GH: Growth hormone.

first year in P12, and decreased (from -3.2 to -3.5) in approximately one year in P11. The dosages of GH were not given in the literature. There were no adverse reactions (such as hypothyroidism, hyperglycemia, intracranial hypertension, and scoliosis) reported after GH treatment.

The use of GH therapy obviously promoted growth in the girl with KBG syndrome accompanied by short stature. There were no abnormalities in thyroid function or glycemic status during the two years of follow-up. In the previous literature, most children with KBG syndrome showed a good response to the first year of GH therapy compared with untreated children affected by KBG syndrome. Our results are consistent with other reported cases<sup>[6]</sup>. Based on the review of previously reported cases and the experience obtained from our KBG case, we conclude that GH treatment is effective in our girl and most children with KBG syndrome accompanied by short stature during the first year of therapy.

It was reported<sup>[9]</sup> that only one child with KBG syndrome was diagnosed with acute myeloid leukemia. Down-regulation of the *ANKRD11* gene might be associated with breast cancer<sup>[12]</sup>. The *ANKRD11* gene was found to enhance the transcription of *p53*, as *ANKRD11* was thought to be a *p53* coactivator<sup>[13]</sup>. However, the role of the *ANKRD11* gene in cancer was not confirmed<sup>[8]</sup>. Therefore, we need further evidence from long-term follow-up and close monitoring for tumors during GH therapy in patients with KBG syndrome. There is a pressing need to establish guidelines for GH therapy in patients with KBG syndrome.

This study had several limitations, such as incomplete data and short-term follow-up. The long-term effects of GH therapy on children with KBG syndrome and its benefits to adult height are not clear. A large-scale case-control and long-term follow-up study is necessary to better understand the effects of GH therapy on children with KBG syndrome accompanied by short stature.

## CONCLUSION

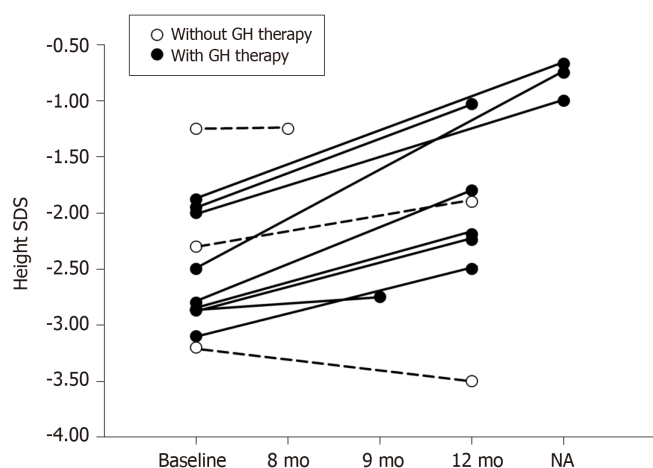
In conclusion, our girl with KBG syndrome showed a good growth response to the

**Table 1** Clinical features of seven previously reported children and our girl with KBG syndrome using growth hormone therapy

Case	P1	P2	P3	P4	P5	P6	P7	P8
Gender	Male	Male	Female	Male	Female	Male	Female	Female
Country	Sweden	Sweden	China	Australia	Australia	Italy	Italy	China
Pregnancy complication	Normal	Polyhydramnios	Normal	Advanced maternal age	Normal	Normal	Normal	Normal
Gestational age	38.5 wk	40 wk and 6 d	Full term	40 wk	32 wk	Full term	Full term	Full term
Delivery	Breech presentation	Normal	Vaginal delivery	Vaginal delivery; Fetal distress and meconium liquor	Cesarean section	Cesarean section	Cesarean section	Vaginal delivery
Birth length, cm	47 (-1.5 SDS)	50 (-0.5 SDS)	48 (-0.90 SDS)	50th	NA	NA	NA	50 (0.1 SDS)
Birth weight, g	2940 (-0.6 SDS)	3945 (1 SDS)	2400 (-2.19 SDS)	NA (< 10th)	NA (90th)	NA	NA	3400 (0.58 SDS)
Referred age, yr	5.5	7	7.6	15	4	9	4	5.5
Chief complain	Short stature	Short stature	Short stature	NA	NA	NA	NA	Short stature
Height SDS	-2.4 SDS	-2.8 SDS	-2.82 SDS	< -1.88 SDS	< -1.88 SDS	-2.58 SDS	-3.25 SDS	-1.95 SDS
Midparental height	-1.2 SDS	-0.3 SDS	-1.6 SDS	NA	NA	NA	NA	-1.6 SDS
Peak GH	40.3 mU/L	10 mU/L (GH deficit)	5.7 ng/mL	NA	NA	No GH deficit	5.1 ng/mL	6.22 ng/mL
IGF-1	88 ng/mL	51, 76, and 56 ng/mL	271 ng/mL	NA	NA	NA	NA	42 ng/mL
Thyroid function	Normal	Normal	Normal	NA	NA	Subclinical hypothyroidism	Small thyroid	Normal
Delayed bone age, yr	Delayed 3.0	Delayed 1.5	Delayed 3.6	Yes	No	Yes	No	Delayed 1.0
Pituitary MRI /Brain imaging	NA	Normal	Normal	NA	Neonatal seizures; Multiple calcific foci in brain; Arachnoid cyst; Germinolytic cysts	Unspecific structural abnormalities	Enlarged cisterna magna; Leptomeningeal cyst	Normal
GH therapy started age	10.5 yr	7.4 yr	7.9 yr	15 yr	Not known	11 yr	5.2 yr	5.5 yr
Height SDS	-3.1 SDS	-2.8 SDS	-2.87 SDS	< -1.88 SDS	Not known	-2.86 SDS	-2.87 SDS	-1.95 SDS
GH dose	35 µg/kg/d	30 µg/kg/d	52 µg/kg/d	NA	NA	NA	NA	50 µg/kg/d
Others	Triptorelin was added at 12.5 yr	No	Intermittent treatment	No	No response to rhGH therapy	No	No	No
ANKRD11 aberrations	c.3836del (p.Ser1279fs)	c.1903_1907del (p.Lys635Glnfs*26)	c.6972dupc (p.p2271pfs*8)	No genetic testing	c.6472G > T (p.Glu2158)	c.7534C > T (p.Arg2512Trp)	c.3339G > A (p.Trp1113Ter)	c.2635 dupG (p.Glu879fs)

Two children with KBG syndrome accompanied by short stature with GH therapy (P9 and P10) who had no detailed clinical information are not shown in this table. NA: Not applicable; P: Patient.

first year of GH therapy. We reviewed and analyzed the changes in the height of children with KBG syndrome accompanied by short stature during the first year of therapy in the reported cases. We conclude that GH treatment is effective in our girl and most children with KBG syndrome accompanied by short stature during the first year of therapy. Our results provide evidence for GH treatment in children with KBG syndrome accompanied by short stature.



**Figure 3** Changes of height SDS of children with KBG syndrome accompanied by short stature in the reported literature and in our study. There were nine children with KBG syndrome accompanied by short stature who received growth hormone (GH) therapy (P1-P4 and P6-10) (black circle). Patient 5 showed no response to GH therapy without specific data of height velocity were not included in the figure. There were three children with KBG syndrome accompanied by short stature who did not receive GH therapy (P11, P12, and P13) (white circle). We mainly recorded growth velocity in the first year of GH therapy. Patient 3 was followed by 9 mo, Patient 13 was followed by 8 mo, and three patients (P4, P9, and P10) did not show specific follow-up time. GH: Growth hormone; NA: Not applicable; P: Patient.

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