Clinical efficacy and safety study of rhGH treatment in children with idiopathic short stature

Dehui Zhang , WenXu Cheng , Lunmin Zhang , Zhengzhen Tang
Department of Pediatrics, The First People's Hospital of Zunyi City (the Third Affiliated Hospital of Zunyi Medical University), Guizhou 563000, China

Introduction. To compare the clinical effects and safety of long-acting and short-acting recombinant human growth hormone (rhGH) treatment in children with idiopathic short stature (ISS).

Methods. Sixty cases of children with ISS admitted to the Department of Pediatric Endocrinology, The First People's Hospital of Zunyi City, from July 2020 to July 2022 were selected. They were divided into two groups using simple randomization, with each group consisting of 30 cases. The control group received subcutaneous injection of short-acting rhGH at a dose of 0.15-0.2μ/kg once a day, while the observation group received subcutaneous injection of long-acting rhGH at a dose of 0.2mg/kg once a week. Both groups were treated continuously for 12 months. Height, weight, HtSDS value, growth rate, bone age, predicted adult height, bone age, and serum insulin-like growth factor-1 (IGF-1), fasting insulin, thyroid function, insulin-like growth factor-binding protein-3 (IGFBP3), and fasting blood glucose levels were compared before treatment, at 6 months, and 12 months of treatment. Adverse reactions in both groups were also recorded.

Results. Before treatment, the two groups were compared in terms of height, weight, height standard deviation score (HtSDS), growth rate, bone age, and predicted adult height ($P>0.05$); after 6 and 12 months of treatment, both groups showed increases in height, weight, HtSDS, growth rate, predicted adult height, bone age index, and bone age difference compared to before treatment, with the observation group higher than the control group ($P<0.05$). Before treatment, serum fasting insulin, IGF-1, IGFBP3, thyroid function, and fasting blood glucose levels were compared between the two groups ($P>0.05$); after 6 and 12 months of treatment, serum IGF-1 and IGFBP3 levels increased compared to before treatment, with the observation group higher than the control group ($P<0.05$); other parameters in both groups were compared before and between groups ($P>0.05$). The incidence of thyroid function abnormalities, transient blood sugar elevation, joint or muscle pain, and injection site swelling in the observation group was compared to the control group ($P>0.05$).

Conclusion. Long-acting rhGH treatment for ISS can increase serum IGF-1 and IGFBP3 expression, promote growth and development in affected children, and does not affect thyroid function, fasting insulin, or fasting blood glucose levels in these children.

Keywords. Recombinant human growth hormone; Idiopathic short stature; Thyroid function; Safety; Efficacy

INTRODUCTION

Idiopathic Short Stature (ISS) is a condition characterized by unexplained short stature, which may be caused by various genetic factors. It accounts for approximately 20% of children with heights below the 3rd percentile. ISS children typically have normal growth hormone secretion, but they may have defects in growth hormone receptors, leading to partial insensitivity to growth hormone. Heterozygous mutations in growth hormone receptor genes are among the possible causes of ISS. If left untreated, ISS can significantly impact a child's growth and development, as well as their psychological well-being, potentially leading to negative emotions and social withdrawal.

Currently, there is no standardized treatment protocol for ISS in clinical practice. Various medications are utilized, including recombinant human growth hormone (rhGH), gonadotropin-releasing hormone analogs, aromatase inhibitors, among others[3]. Among these, rhGH has been a significant development for ISS patients since its introduction. It can induce a transition of chondrocytes from a resting phase to a proliferative phase, thereby promoting skeletal growth and contributing to improved final height in affected children when they reach adulthood[4]. However, there is limited research on the comparative efficacy and safety of long-acting versus short-acting rhGH in the treatment of ISS, and this study aims to address this issue.

1 MATERIALS AND METHODS

1.1 General data

60 children diagnosed with ISS were selected from the Department of Pediatric Endocrinology at the First People's Hospital of Zunyi City between July 2020 and July 2022. Inclusion criteria: (1) Refer to the ISS standard in the 'Guidelines for the diagnosis and treatment of children with short stature'[5]. (2) Age 2-12 years old, not limited to gender. (3) Normal feeding. (4) No previous history of rhGH, protein

anabolic hormone and other drug treatment. (5) The children and their parents agreed to join the study. Exclusion criteria: (1)Physiologically short stature. (2) With asthma, liver and kidney dysfunction, congenital heart disease and other chronic systemic diseases. (3) With rickets or other orthopedic diseases. (4) Hypothyroidism. (5) Long-term glucocorticoid therapy or nutritional deficiency. (6) Developmental deformity. Excluded criteria: (1) Failure to complete 12 months of treatment as required, poor compliance. (2) Automatic exit midway. (3) Lost to follow-up. (4) Incomplete examination data. The patients were divided into two groups using simple randomization, with each group consisting of 30 cases. The control group received short-acting rhGH treatment, while the observation group received long-acting rhGH treatment. General patient information between the two groups was compared (P>0.05). See Table 1

Table 1 Comparison of two groups of general data（n=30）

General information	Control group	Observation group	χ^2/t	P
Sex（n）				
Male	17（56.67）	16（53.33）	0.067	0.795
Female	13（43.33）	14（46.67）		
Gestational age（weeks）	39.25±0.47	39.14±0.52	0.860	0.394
Birth weight（kg）	3.12±0.54	3.17±0.50	0.372	0.711
Birth length（cm）	51.05±0.83	51.11±0.84	0.278	0.782
Age distribution（n）				
Pre-school age	11（36.67）	14（46.67）	0.617	0.432
School age	19（63.33）	16（53.33）		
HtSDS value	-2.71±0.41	-2.68±0.45	0.270	0.788
Growth rate（cm/years）	5.14±0.77	5.08±0.81	0.294	0.770
Paternal height（cm）	171.85±3.47	171.74±3.29	0.126	0.900
Maternal height（cm）	163.25±2.41	163.28±2.33	0.049	0.961

1.2 Methods

The control group received subcutaneous injections of short-acting rhGH at a dose of

0.15-0.2 μg/kg, once daily, administered subcutaneously half an hour before bedtime. The observation group received subcutaneous injections of long-acting rhGH at a dose of 0.2 mg/kg, once a week. Both groups received continuous treatment for 12 months.

1.3 Detect methods

Before treatment, at 6 months of treatment, and at 12 months after treatment, the heights and weights of two groups of pediatric patients were measured using the Su Heng brand height and weight scale. GV = (height before treatment - height after treatment) / number of months between measurements × 12. HtSDS = (height - average height of the same age and gender in a normal population) / standard deviation of normal height for the same age and gender. The reference values for normal height standards for different age groups were obtained from the "2015 Survey of Physical Development in Children Under Seven Years Old in Nine Cities in China"[6] and the "Analysis of Physical Development Status in Urban Children in Zunyi City"[7].

Before treatment, at 6 months of treatment, and at 12 months after treatment, 6ml of fasting venous blood samples were collected from two groups of pediatric patients. The samples were kept at 4°C for half an hour and then centrifuged at a speed of 3000r/min for 10 minutes. Serum samples were analyzed using an enzyme immunoassay instrument, the MK3 model from Thermo Fisher Scientific, to measure the levels of serum IGF-1 and IGFBP3. The enzyme-linked immunosorbent assay (ELISA) kits used for this analysis were products from Shanghai Jianglai Biotechnology Co., Ltd. Fasting insulin, fasting blood glucose, and thyroid function indicators including FT3, FT4, and TSH levels were measured using a fully automated biochemical analyzer, specifically the Hitachi 7600 model from Hitachi, Ltd. in Japan.

The incidence rates of thyroid function abnormalities, transient blood sugar elevation, joint or muscle pain, and injection site swelling were recorded for both groups.

1.4 Statistical processing

The data were processed by SPSS25.0, and the measurement indexes of normal distribution were expressed as ($\bar{\chi}\pm s$). The t test was used for comparison, and the

count data were described by n (%). The comparison was performed by $\chi 2$ test or correction test, and $\alpha=0.05$ was the standard.

2 RESULTS

2.1 Comparison of the general level of the two groups

Before treatment, the general conditions of both groups were compared (P>0.05). However, after 6 and 12 months of treatment, the observation group and the control group showed increases in height, predicted adult height, weight, HtSDS values, and growth velocity compared to before treatment. Additionally, the observation group demonstrated higher values than the control group (P<0.05). See Table 2

Table 2 Comparison of the general level of the two groups（n=30）

Index	Time	Control group	Observation group	t	P
Height（cm）	Before treatment	124.12±6.78	122.94±7.03	0.662	0.511
	Treatment for 6 months	128.98±7.87*	132.75±6.47*	2.027	0.047
	Treatment for 12 months	135.84±6.88*	139.75±7.02*	2.179	0.033
Weight（kg）	Before treatment	26.15±5.22	26.20±4.97	0.038	0.970
	Treatment for 6 months	29.34±4.45*	31.72±4.17*	2.138	0.037
	Treatment for 12 months	32.54±4.82*	35.23±5.02*	2.117	0.039
HtSDSvalue	Before treatment	-2.71±0.41	-2.68±0.45	0.270	0.788
	Treatment for 6 months	-2.46±0.35*	-2.22±0.31*	2.812	0.007
	Treatment for 12 months	-2.11±0.28*	-1.94±0.23*	2.570	0.013
Growth rate（cm/years）	Before treatment	5.14±0.77	5.08±0.81	0.294	0.770
	Treatment for 6 months	9.72±1.42*	13.64±1.89*	9.082	0.000
	Treatment for 12 months	11.71±1.77*	16.81±2.23*	9.811	0.000
Predicted adult height（cm）	Before treatment	160.95±4.89	161.01±4.47	0.050	0.961
	Treatment for 6 months	164.96±4.36*	167.78±4.67*	2.418	0.019
	Treatment for 12 months	168.11±4.02*	170.44±4.23*	2.187	0.033

Compared with the group before treatment, * P < 0.05 .

2.2 Comparison of bone age levels between the two groups

Before treatment, the bone ages of the two groups were compared (P>0.05). However, after 6 and 12 months of treatment, the bone age index and the difference in bone age compared to chronological age increased in both the observation group and the control group compared to before treatment. Additionally, the observation group showed higher values than the control group (P<0.05). See Table 3

Table 3 Comparison of bone age levels between the two groups（n=30）

Group	Bone age index			Bone age difference		
	Before treatment	Treatment for 6 months	Treatment for 12 months	Before treatment	Treatment for 6 months	Treatment for 12 months
Control group	0.90±0.06	0.94±0.05*	0.98±0.03*	-0.63±0.10	-0.48±0.07*	-0.39±0.05*
Observation group	0.91±0.07	0.97±0.04*	1.00±0.03*	-0.61±0.12	-0.41±0.06*	-0.32±0.04*
t	0.594	2.566	2.582	0.701	4.159	5.988
P	0.555	0.013	0.012	0.486	0.000	0.000

Compared with the group before treatment, * P < 0.05 .

2.3 Comparison of IGF-1 and IGFBP3 levels between the two groups

Before treatment, the levels of IGF-1 and IGFBP3 in both groups were compared (P>0.05). However, after 6 and 12 months of treatment, the levels of IGF-1 and IGFBP3 increased in both the observation group and the control group compared to before treatment. Additionally, the observation group showed higher levels than the control group (P<0.05). See Table 4

Table 4 Comparison of IGF-1 and IGFBP3 levels between the two groups（n=30）

Group	IGF-1（ng/mL）			IGFBP3（g/L）		
	Before treatment	Treatment for 6 months	Treatment for 12 months	Before treatment	Treatment for 6 months	Treatment for 12 months
Control group	208.85±74.15	284.59±85.23*	347.88±77.48*	2.12±0.46	2.59±0.52*	3.07±0.69*
Observation group	212.22±70.89	332.89±92.07*	389.96±82.23*	2.09±0.51	2.91±0.57*	3.68±0.71*
t	0.180	2.109	2.040	0.239	2.272	3.375
P	0.858	0.039	0.046	0.812	0.027	0.001

Compared with the group before treatment, * P < 0.05 .

2.4 Comparison of thyroid function levels between the two groups

The levels of FT3, FT4, and TSH were compared between and within the two groups before treatment, at 6 months of treatment, and at 12 months of treatment (P>0.05). See Table 5

Table 5 Comparison of thyroid function levels between the two groups（n=30）

Index	Time	Control group	Observation group	t	P
FT3（pmol/L）	Before treatment	6.16±1.08	6.08±0.97	0.302	0.764
	Treatment for 6 months	6.03±1.14	6.15±1.03	0.428	0.670
	Treatment for 12 months	6.25±0.94	6.32±0.95	0.287	0.775
FT4（pmol/L）	Before treatment	14.31±1.85	14.24±1.76	0.150	0.881
	Treatment for 6 months	14.25±1.77	13.98±1.89	0.571	0.570
	Treatment for 12 months	13.88±2.03	14.12±1.94	0.468	0.641
TSH（mIU/L）	Before treatment	2.60±0.74	2.57±0.81	0.150	0.881
	Treatment for 6 months	2.37±0.88	2.54±0.76	0.801	0.427
	Treatment for 12 months	2.42±0.79	2.49±0.85	0.330	0.742

Compared with the group before treatment, * P < 0.05 .

2.5 Comparison of fasting insulin and blood glucose levels between the two groups

The levels of fasting insulin and fasting blood glucose were compared between the two groups before treatment, at 6 months of treatment, and at 12 months of treatment (P>0.05). See Table 6

Table 6 Comparison of fasting insulin and blood glucose levels between the two groups（n=30）

Group	Fasting insulin（pmol/L）			Fasting blood glucose（mmol/L）		
	Before treatment	Treatment for 6 months	Treatment for 12 months	Before treatment	Treatment for 6 months	Treatment for 12 months
Control group	10.66±1.98	9.84±2.14	10.84±2.01	4.89±0.51	5.00±0.44	4.97±0.47
Observation group	10.27±2.05	10.44±1.97	10.37±1.96	4.93±0.47	4.97±0.52	5.01±0.53
t	0.749	1.130	0.917	0.316	0.241	0.309
P	0.457	0.263	0.363	0.753	0.810	0.758

Compared with the group before treatment, * P < 0.05 .

2.6 Comparison of adverse reaction levels between the two groups

The incidence rates of thyroid function abnormalities, transient blood sugar elevation, joint or muscle pain, and injection site swelling in the observation group were compared to those in the control group (P>0.05). See Table 7

Table 7 Comparison of adverse reaction levels between the two groups（n=30）

Group	Thyroid dysfunction	Transient hyperglycemia	Joint or muscle pain	Injection site edema
Control group	2（6.67）	2（6.67）	2（6.67）	4（13.33）
Observation group	0（0.00）	1（3.33）	1（3.33）	0（0.00）
Calibration check	0.517	0.000	0.000	2.411
P	0.472	1.000	1.000	0.121

3 DISCUSSION

Epidemiological surveys have found that the incidence rate of ISS in Chinese children is approximately 3%, with a higher incidence rate in boys compared to girls[8]. ISS is characterized by normal secretion of growth hormone in affected children, despite their short stature or growth retardation. However, the exact mechanisms underlying the development of ISS are currently not well understood. Existing research suggests that the occurrence of ISS may be related to factors such as insensitivity of growth hormone receptors, inadequate nutrition, lack of physical activity, insufficient sleep, and adverse environmental conditions[9-10]. Early treatment and intervention are helpful in improving the final adult height of children with ISS. Currently, in clinical practice, rhGH is the main treatment for ISS. RhGH can bind to growth hormone receptors in target organs, stimulate the synthesis of IGF-1, which, in turn, promotes the proliferation of cartilage cells and improves growth velocity[11]. Research has shown that rhGH treatment for children with ISS is highly effective, promoting their growth and development, improving their quality of life, and having few complications[12].

Currently, both long-acting rhGH and short-acting rhGH are used in the treatment of ISS, and both have a certain growth-promoting effect[13-14]. However, some studies suggest that short-acting rhGH requires daily administration, and children's compliance with this regimen is often poor, leading to instances of medication non-compliance[15].

This study compared the efficacy of long-acting rhGH and short-acting rhGH in the treatment of ISS. The findings indicated that after 6 and 12 months of treatment, both groups showed increases in height, weight, HtSDS values, growth velocity, predicted adult height, bone age index, and the difference between bone age and chronological age compared to before treatment. Furthermore, the observation group exhibited higher improvements in these parameters compared to the control group. This suggested that long-acting rhGH treatment for ISS can better promote the growth and development of affected children. Basic research supports the notion that the mechanism by which growth hormone promotes skeletal growth is related to stimulating the synthesis of IGF-1[16]. IGFBP3 is the primary binding protein for IGF-1, and the binding of IGF-1 to IGFBP3 in target organs and tissues enables its

growth-promoting effects. The levels of IGF-1 and IGFBP3 in the blood can reflect the growth status of the body[17]. This study, through the measurement of serum IGF-1 and IGFBP3, found that long-acting rhGH treatment for ISS can increase the expression of serum IGF-1 and IGFBP3, thereby promoting the growth and development of affected children more effectively. This is because the amino acid sequence and composition of rhGH are identical to endogenous growth hormone. Long-acting rhGH, when introduced into the body, is released at a constant rate, which allows it to bind more stably to growth hormone receptors. This sustained binding stimulates the pituitary gland to synthesize IGF-1, promotes cartilage ossification and bone formation, and results in a relative deficiency of calcium and phosphorus. This, in turn, leads to compensatory increases in blood vitamin D levels, improving bone metabolism and increasing the growth velocity of affected children[18]. In contrast, short-acting rhGH requires daily administration and may not maintain stable blood drug concentrations. Instances of medication non-compliance can, to some extent, impact its effectiveness.

Long-term administration of rhGH treatment may potentially lead to thyroid function impairment. This is because elevated levels of growth hormone can trigger a reactive increase in somatostatin secretion. Elevated somatostatin levels can inhibit the secretion of TSH, thereby causing thyroid function impairment[19]. Additionally, rhGH treatment may also impact the function of pancreatic β-cells, leading to temporary increases in fasting insulin and fasting blood sugar levels in affected children[20]. This study found that after 6 and 12 months of treatment, fasting insulin levels, fasting blood sugar levels, and thyroid function levels were similar between the two treatment groups. The study also observed that the incidence rates of thyroid function abnormalities, transient blood sugar elevation, joint or muscle pain, and injection site swelling were similar between the observation group and the control group. These results suggested that the effects of long-acting rhGH and short-acting rhGH treatment for ISS on thyroid function, fasting insulin, and fasting blood sugar levels in affected children are comparable, and their safety profiles are similar.

In summary, long-acting rhGH treatment for ISS has been found to increase the expression of serum IGF-1 and IGFBP3, promoting the growth and development of affected children, while not affecting their thyroid function, fasting insulin, and fasting blood sugar levels. However, it's important to note that this study had a

relatively small sample size, with only 30 cases in each group, which could introduce bias into the results. In future clinical work, it is crucial to focus on accumulating a larger sample size and extending the follow-up period. Large-scale and long-term studies should be conducted to further investigate the effectiveness and safety of long-acting rhGH and short-acting rhGH treatment for ISS.

FUND NAME

(A comparative study of long-acting growth hormone and short-acting growth hormone in the treatment of idiopathic nanosomia) Zunshi Medical Support HZ (2020) 111

REFERENCES

[1]PALTOGLOU, GEORGE, DIMITROPOULOS, IOANNIS, KOURLABA, GEORGIA, et al. The effect of treatment with recombinant human growth hormone (rhGH) on linear growth and adult height in children with idiopathic short stature (ISS): a systematic review and meta-analysis[J]. Journal of pediatric endocrinology & metabolism: JPEM,2020,33(12):1577-1588.

[2]WEINBERG, ADI, DROR, NITZAN, MOTIN, KATYA, et al. The Effect of Growth Hormone Treatment on Physical Performance Indices in Children With Idiopathic Short Stature[J]. Pediatric exercise science,2021,33(2):70-73.

[3]ASHRAF SOLIMAN, ALAN D. ROGOL, SOHAIR ELSIDDIG, et al. Growth response to growth hormone (GH) treatment in children with GH deficiency (GHD) and those with idiopathic short stature (ISS) based on their pretreatment insulin-like growth factor 1 (IGFI) levels and at diagnosis and IGFI increment on treatment[J]. Journal of pediatric endocrinology & metabolism: JPEM,2021,34(10):1263-1271.

[4]SHAHAB NOORIAN, NAMI MOHAMMADIAN KHONSARI, SHAHRAM SAVAD, et al. Whole-Exome Sequencing in Idiopathic Short Stature: Rare Mutations Affecting Growth[J]. Journal of pediatric genetics,2021,10(4):284-291.

[5]Endocrine Genetic Metabolism Group of Pediatrics Branch of Chinese Medical Association. Guidelines for the diagnosis and treatment of children with short stature [J].Chinese Journal of

Pediatrics, 2008,46 (6): 428-430.

[6]Capital Institute of Pediatrics, Collaboration Group of Children 's Physical Development Survey in Nine Cities. 2015 Physical Development Survey of Children under Seven Years Old in Nine Cities of China [J].Chinese Journal of Pediatrics, 2018,56 (3): 192-199.

[7]Wu Zhongyong. Analysis of physical development of children in Zunyi City [C]. 2016 ' Chinese Journal of Hospital Pharmacy ' Academic Annual Meeting, 2016 : 439.

[8] PARK, SE-JUN, LEE, KEUN-HO, LEE, CHONG-SUH, et al. Impact of growth hormone treatment on scoliosis development and progression: analysis of 1128 patients with idiopathic short stature[J]. Journal of pediatric endocrinology & metabolism: JPEM,2021,34(2):243-250.

[9]KAWASHIMA, SAYAKA, YAGI, HIROKO, HIRANO, YASUHIRO, et al. Screening for imprinting disorders in 58 patients with clinically diagnosed idiopathic short stature[J]. Journal of pediatric endocrinology & metabolism: JPEM,2020,33(10):1335-1339.

[10]TORLINSKA-WALKOWIAK, NATALIA, MAJEWSKA, KATARZYNA ANNA, SOWINSKA, ANNA, et al. Skeletal and dental age discrepancy and occlusal traits in children with growth hormone deficiency and idiopathic short stature[J]. Clinical oral investigations,2022,26(10):6165-6175.

[11]ANILKUMAR, VANDANAJAIN, MADHUMITA ROYCHOWDHURY, et al. Pathogenic/likely pathogenic variants in the SHOX, GHR and IGFALS genes among Indian children with idiopathic short stature[J]. Journal of pediatric endocrinology & metabolism: JPEM,2020,33(1):79-88.

[12] ANILKUMAR, VANDANAJAIN, MADHUMITA ROYCHOWDHURY, et al. Pathogenic/likely pathogenic variants in the SHOX, GHR and IGFALS genes among Indian children with idiopathic short stature[J]. Journal of pediatric endocrinology & metabolism: JPEM,2020,33(1):79-88.

[13] ANILKUMAR, VANDANAJAIN, MADHUMITA ROYCHOWDHURY, et al. Pathogenic/likely pathogenic variants in the SHOX, GHR and IGFALS genes among Indian children with idiopathic short stature[J]. Journal of pediatric endocrinology & metabolism: JPEM,2020,33(1):79-88.

[14] RENATA STAWERSKA, MARZENA KOLASA-KICIŃSKA, ANNA ?UPIŃSKA, et al. Comparison of nocturnal and morning ghrelin concentration in children with growth hormone deficiency and with idiopathic short stature[J]. Chronobiology International,2020,37(11):1629-1635.

[15] STAVBER, L., HOVNIK, T., KOTNIK, P., et al. High frequency of pathogenic ACAN variants including an intragenic deletion in selected individuals with short stature[J]. European journal of

endocrinology,2020,182(3):243-253.

[16] SINGH, ACHINTYA D., SINGH, PRASHANT, FAROOQUI, NABA, et al. Prevalence of celiac disease in patients with short stature: A systematic review and meta-analysis[J]. Journal of gastroenterology and hepatology,2021,36(1):44-54.

[17] Ma JY, Cruz J, Jin J, Peng XY, Zhang AM, Cheng XD. Therapeutics of integrative medicine ameliorate immunological disorders of the nervous system: A meta-analysis. World J Tradit Chin Med 2022;8:153-67.

[18] MERGULHAO, BEATRIZ, ALMEIDA, JOSE PAULO, MOREIRA, HELENA, et al. Quality of Life of Children and Adolescents with Short Stature: The Twofold Contribution of Physical Growth and Adaptive Height-Related Cognitive Beliefs[J]. Journal of clinical psychology in medical settings,2022,29(2):466-475.

[19] ELAINE ZHOU, BENJAMIN ROLAND HAUSER, YOUN HEE JEE. Genetic evaluation in children with short stature[J]. Current opinion in pediatrics,2021,33(4):458-463.

[20] SENTCHORDI-MONTANE, LUCIA, BENITO-SANZ, SARA, AZA-CARMONA, MIRIAM, et al. High prevalence of variants in skeletal dysplasia associated genes in individuals with short stature and minor skeletal anomalies[J]. European journal of endocrinology,2021,185(5):691-705.

Corresponding Author:

Zhengzhen Tang

Department of Pediatrics, The First People's Hospital of Zunyi City (the Third Affiliated Hospital of Zunyi Medical University), Guizhou 563000, China

E-mail: Tangzz957150@163.com