

CASE REPORT

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# Isolated growth hormone deficiency type IA due to a novel *GH1* variant: a case report

Xi Yang<sup>1</sup>, Mingming Yuan<sup>1</sup>, Zhuoguang Li<sup>1,2</sup>, Yanqin Ying<sup>1</sup>, Ling Hou<sup>1\*</sup> and Xiaoping Luo<sup>1</sup>

## Abstract

**Background:** A case of isolated growth hormone deficiency type IA (IGHD IA) caused by novel compound heterozygous mutation in the *GH1* gene was reported in this study, which aimed to provide insights that will benefit future diagnosis and treatment.

**Case presentation:** We analyzed and summarized the clinical data and genetic test results from a patient with IGHD admitted in March 2019 to the Department of Pediatrics Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. We described the results from a 1-year-9-months old female, whose chief complaint was “growth retardation for more than one year”. Her birth length was 49.0 cm, and her birth weight was 3.05 kg. Suboptimal intake (breastfeeding) jaundice lasted for approximately two months following birth. When evaluated at the age of 1-year-9-months old, the patient’s height was 61.0 cm (− 7.24 SD), and her weight was 6.4 kg (− 1.50 SD). The patient’s physical characteristics included yellowish hair, large and unclosed anterior fontanelles, raised forehead, and a low and flat nose. The major abnormalities observed from the auxiliary examinations included low GH (< 0.05 µg/l), low IGF-1 (16.99 µg/l), and elevated TSH (6.97 mIU/l). Genetic testing revealed two heterozygous variants: a splicing mutation (NG\_011676.1(NM\_022560.4): c.10 + 1G>T, inherited from her mother) in intron 1 of the *GH1* gene and a deletion that encompassed the same gene (chr17: 61973811–61996255, inherited from her father). After hormone replacement therapy with L-thyroxine and recombinant human GH (rhGH), the patient’s thyroid function returned to normal, and her serum IGF-1 level significantly improved, which resulted in an accelerated increase in height.

**Conclusion:** This study described a case of IGHD caused by novel compound heterozygous mutations in the *GH1* gene. This study suggested that closer attention should be directed to genetic testing and diagnosis based on clinical characteristics to avoid misdiagnosis.

**Keywords:** Isolated growth hormone deficiency, GH1, Gene, Mutation

## Background

Isolated growth hormone deficiency (IGHD) is a common disease affecting the growth and development of children, with an incidence of 1/4000–1/10,000. IGHD can be classified as sporadic and familial, with the latter being rare (approximately 3% to 30%) [1]. IGHD can

be subdivided further into three categories, IA (OMIM: 262400) and IB (OMIM:612781) (autosomal recessive inheritance), II(OMIM:173100) (autosomal dominant inheritance), and III (OMIM:307200) (X-linked inheritance) [2]. In 1970, Ruth Illig first reported three cases of IGHD IA, exhibiting growth hormone deficiency and severe growth retardation [3]. In 1972, Illig and Prader observed patients with IGHD IA who also presented distinctive facial features and a tendency to produce growth hormone antibodies that affected treatment in addition to the observed growth disorders. *GH1*(OMIM:139250) deletions resulting in IGHD IA have been reported,

\*Correspondence: houlingtj@163.com

<sup>1</sup> Department of Pediatrics, Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, No. 1095 Jie Fang Avenue, Hankou, Wuhan 430030, People’s Republic of China  
Full list of author information is available at the end of the article



ranging in size from 6.5 to 45 kb. Deletions of 6.7 kb due to unequal recombination and crossover within the *GH* gene cluster during meiosis are the most common. In addition, heterozygous frameshift mutations and a homozygous nonsense mutation have been reported [4]. In patients with these mutations, severe growth retardation occurs in the first six months of life (height standard deviation score (HtSDS) less than - 4.50), GH is not detected, and the patients tend to produce GH antibodies that affect the therapeutic effects of exogenous rhGH. This study analyzed clinical data from a case of IGHD IA admitted to the Department of Pediatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology in March 2019 to improve the basic understanding of this disease.

**Case presentation**

**Clinical data**

**General data**

The proband, a 1-year-9-months old female, was admitted to the hospital in March 2019 for “growth retardation of more than one year”. She was born at term gestation to a G1P1(G is gravida, meaning the number of pregnancies; P is pregnancy, indicating the number of births) mother via cesarean section delivery. Her birth weight was 3.05 kg (25<sup>th</sup>–50<sup>th</sup> centile), and her birth height was 49.0 cm (25<sup>th</sup>–50<sup>th</sup> centile). She was breastfed to the age of one year, then fed with a combination of breastfeeding and formula. The child’s appetite was normal. However, she experienced postnatal jaundice when consuming breast milk that lasted for approximately two months. The child’s comprehension and memory were normal.

The child’s parents were from two unrelated families, and there was no family history of inherited or metabolic diseases. The heights of her father and mother were 171.0 cm and 167.0 cm, respectively. The body length of the child was monitored by her parents for the first nine months after birth, as seen in Table 1.

**Physical examination**

The child’s height at the time of admission was 61.0 cm (- 7.24 SD), and her weight was 6.4 kg (- 1.50 SD). Specific physical characteristics included yellowish hair, large and unclosed anterior fontanelles, a raised forehead, a

low and flat nose, and 12 erupted baby teeth. No apparent abnormalities were observed during cardiopulmonary auscultation. Her abdomen was soft, and her liver and spleen were palpable and exhibited normal size, smoothness, and firmness.

**Auxiliary examinations**

No discernible abnormalities were found in the blood gas analysis, liver and kidney function assays, and serum electrolytes. The thyroid function indicators, including total triiodothyronine (TT3) (2.06 nmol/l), total thyroxine (TT4) (107.00 nmol/l), and free thyroxine (FT4) (1.15 ng/dl), were in the normal range. However, the TSH (6.97 mIU/l) level was elevated. The serum ACTH (29.80 pg/ml) and cortisol (414.16 nmol/l) levels were normal, but the IGF-1 (16.99 ng/ml) level was low, and the level of growth hormone was exceedingly low (<0.05 µg/l). Fasting blood glucose (3.44 mmol/l) and insulin (0.16 mIU/l) levels also were low. The child’s karyotype was determined to be 46, XX.

**Gene sequencing analysis**

**Gene sequencing**

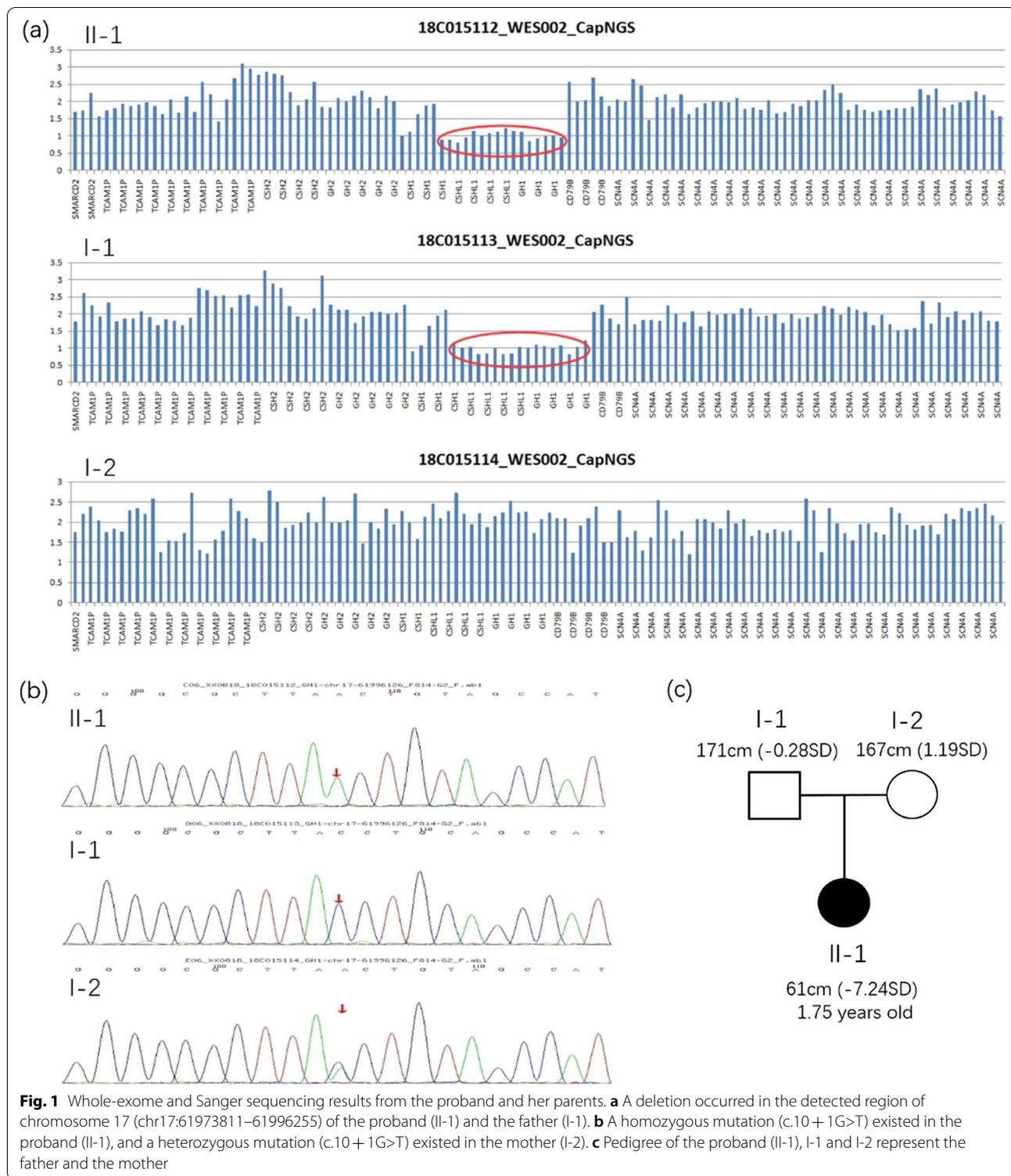
After obtaining written, informed consent from her parents, whole-exome sequencing (WES) analysis and whole-genome copy number variation (CNV) detection (Beijing MyGenostics Inc.) were performed on the proband and her parents. A genome library was constructed using a standard library construction kit, and WES covered all exons of all genes (estimated to be approximately 20,000–25,000 genes) with a total number of captured exons estimated to be approximately 180,000 coding exons. The average coverage for all genes was greater than 97% at an average depth of 20X or higher. Suspected candidate mutations were screened by comprehensively considering the genetic pattern of the disease and the clinical characterization of the patient. Whole-genome CNV detection was performed by carrying out genome-wide CNV scanning on the samples, and the disease-free CNV region in the DGV database, specifically, the candidate CNV region, was filtered out.

**Genetic testing results**

The genome-wide CNV detection found that the proband exhibited a 22 kb deletion in the chr17q23.3 region, suggesting that it might result in a pathogenic variant. The coverage of this genomic region by WES was decreased in both the proband and his father, suggesting that they might carry a heterozygous deletion encompassing this region (Fig. 1a). Moreover, a splicing mutation (NG\_011676.1(NM\_022560.4): c.10+1G>T) in the *GHI* gene intron 1 was inherited from her mother (Fig. 1b). The splicing mutation had not been reported previously.

**Table 1** Body length and SDS scores of the proband aged 0 to 9 months

Age (month)	0	2	4	6	9
Body length (cm)	49.0	51.0	54.0	57.0	58.0
Height SD score	- 0.41 SD	- 2.95 SD	- 4.10 SD	- 4.22 SD	- 5.14 SD



According to the 2019-ACMG Standards and Guidelines [5], the splicing mutation was a pathogenic variant due

to the evidence of pathogenicity for PVS1 (nonsense, splicing variant), PP3 (harmful effects on genes or gene

products), and PM2 (low-frequency variation in the normal population database).

**Diagnosis, treatment, and follow-up**

After two weeks of treatment with L-thyroxine tablets, the child’s thyroid function returned to normal. The gene testing results indicated the suspect lesions. When these results were combined with the clinical characteristics of the affected child, we diagnosed IGHD IA caused by a *GHI* gene mutation. The child was treated with rhGH (0.03 mg/kg per day) via subcutaneous injection. After initiating the rhGH treatment, the child’s growth velocity (GV) and serum IGF-1 levels increased significantly. No adverse reactions were observed. The height and weight of the child that were monitored starting at the time of the voluntary diagnosis are shown in Fig. 2.

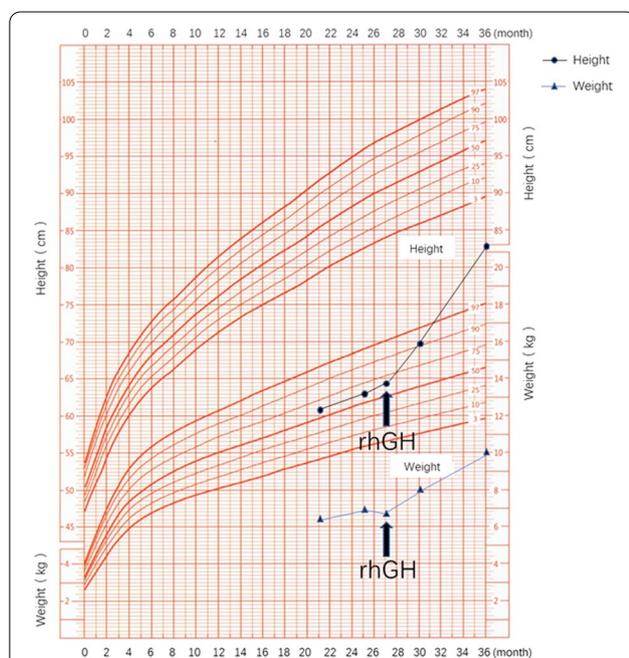
**Discussion and conclusions**

IGHD Type IA is an autosomal recessive hereditary disease. It is clinically characterized by short stature accompanied by a decreased growth rate and severe growth retardation in the first six months of life (with a height SDS score less than -4.50 SD). The GH levels of patients with IGHD Type IA are undetectable, and anti-GH antibodies occur after exposure to rhGH [6]. Although the initial reaction to rhGH treatment might be favorable, there is a tendency to produce antibodies that adversely affect treatment [7]. Although children with IGHD

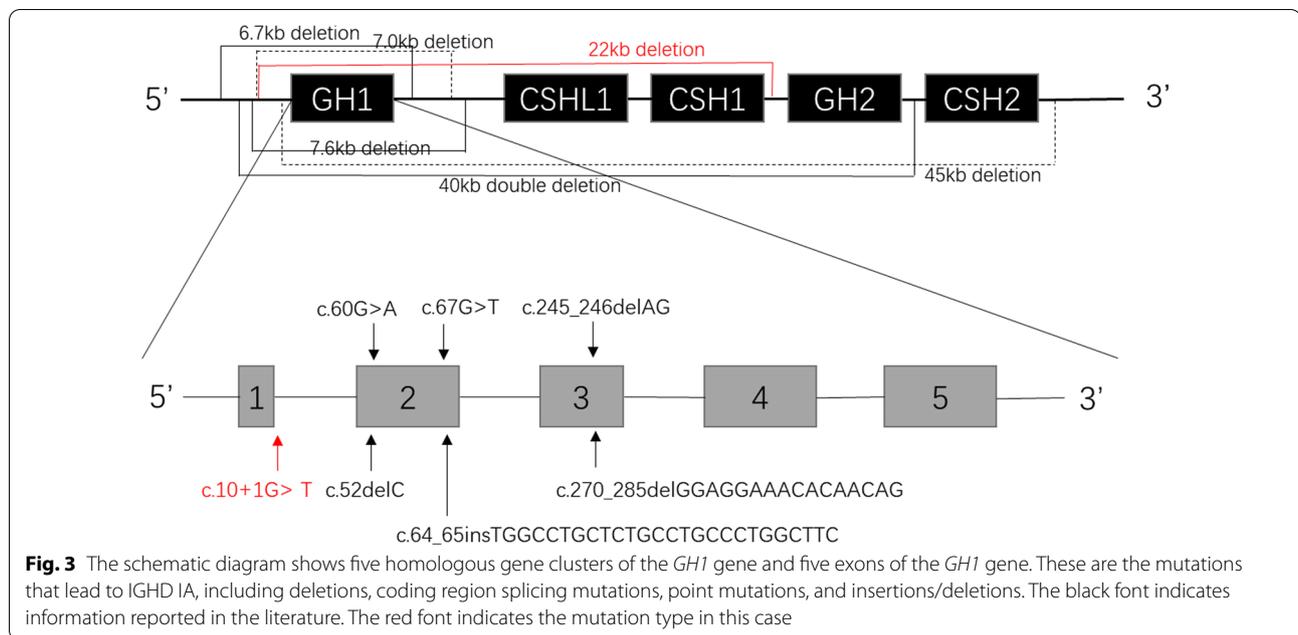
exhibit normal body length and weight at birth, GHD caused by *GHI* gene mutations inhibits growth in body length after birth. Some patients may have small penises or exhibit fasting hypoglycemia. Other common characteristics reported in the literature include truncal obesity, a raised forehead, and a low and flat nasal bridge [8, 9]. Currently, most cases of IGHD reported in the literature are familial, and sporadic cases are rare. Therefore, IGHD should be considered as a differential diagnosis for children with severe growth retardation. Differential diagnosis was made on the basis of normal birth length and weight, growth retardation after birth, severe deficiency of growth hormone, combined with the results of gene mutation and pedigree analysis. For example, the children with Silver-Russel syndrome (RSS) (OMIM:180860) also showed short stature, but their growth hormone level were normal. Moreover, their birth length and weight were lower than those of children of the same gestational age due to intrauterine growth restriction, and they also had clinical characteristics such as postnatal feeding difficulties, special facial features, and limb asymmetry, which could be distinguished from IGHD IA. The need to improve early biochemical detection and genetic analysis is critical to provide a prompt etiological diagnosis, prevention, and treatment.

The facial and clinical features of the patient reported in this case were consistent with those reported in the literature for the most part. In this case, the patient exhibited severe growth retardation after birth until the initiation of treatment. Her growth hormone level (<0.05 ng/ml) was extremely low, and her growth rate increased rapidly after initiating rhGH treatment. This patient exhibited a compound combination of two *GHI* gene mutations, including a splicing mutation in intron 1 inherited from her mother (NG\_011676.1 (NM\_022560.4): c.10 + 1G>T) and a missing fragment inherited from her father, which resulted in a *GHI* gene deletion. Based on the analysis of the family diagram, we speculated that both parents carried mutations. Therefore, two alleles, each with a mutation, were passed on to the child resulting in a compound heterozygous mutation of the *GHI* gene, which produced the phenotypic characteristics of IGHD Type IA (Fig. 1c). The gene mutations reported in the literature that cause IGHD Type IA are summarized and compared with this case, as seen in Fig. 3.

The most common genetic causes of IGHD include mutations in *GHI* and *GHRHR*. In addition, IGHD can be caused by mutations in transcription factors (*HESX1*, *SOX3*, and *OTX2*) or the development of a multi-pituitary hormone deficiency [10]. The *GHI* gene is located on the long arm of chromosome 17 (17q22-24). It is composed of five homologous genes, which are, in sequence, from 5’ to 3’, *GHI*, *CSHL1*, *CSH1*, *GH2*, and *CSH2*,



**Fig. 2** The figure shows the height and weight gain of the child before and after initiation of rhGH injections



and spans a region that is approximately 65 KD [11]. This gene cluster is consistent with respect to the coding region, insertion sequence, and flanking sequence. These homologous sequences appear upstream and downstream of the *GH1* gene, providing the basis for the unequal recombination of the *GH1* gene, which results in the deletion of the gene. Several published reports have described deletions in the *GH1* gene of different lengths, including 6.7 kb, 7.7 kb, 7.6 kb, 45 kb, and double deletions, that all resulted in IGHD IA. Of these reported deletions, the 6.7 kb deletion was the most common (80%). Heterozygous frameshift variants and a homozygous nonsense mutation also have been reported [4].

IGHD can be divided into four types, including autosomal recessive (IA and IB), autosomal dominant (II), and X-linked (III). The phenotypic characteristics of IGHD IA have been described above. IGHD IB is primarily caused by *GH1* or *GHRHR* mutations. Compared with IGHD IA, patients with IGHD IB exhibit more variable phenotypes. Children exhibit short stature, a slow growth rate, delayed bone age, low but detectable growth hormone concentrations, and respond favorably to exogenous growth hormone treatment [12, 13]. IGHD II is the most common genetic form of IGHD, and children show considerable variability in the time of onset and severity of GHD. Over time, they might develop deficiencies in other pituitary hormones [14, 15], requiring lifelong follow-up assessments. IGHD III can be caused by mutations in *SOX3* or *BTK* genes [16], and patients often exhibit mental retardation, craniofacial malformations, hypoglycemia, and agammaglobulinemia [17–19]. The phenotypic

characteristics of each genetic form of IGHD are similar, but they also exhibit specific phenotypic characteristics, which should be distinguished through clinical assessments. In addition, *GH1* gene mutations can cause IGHD IB, IGHD II, and Kowarski syndrome. Patients with these conditions exhibit exceedingly short stature, although their specific clinical phenotypes are not identical because of the type and site of the mutations. Overall, the *GH1* genotype is closely associated with the phenotype of short stature caused by the *GH1* mutations.

Despite the increasing number of genes known to be involved in IGHD etiology, mutations in known genes account for only a small number of cases. Therefore, understanding emerging, newly discovered mutations can guide clinical diagnosis and facilitate patient treatment. Early application of rhGH to treat IGHD IA has demonstrated favorable results. However, antibodies to rhGH eventually are produced during treatment. Therefore, long-term follow-up assessments must be conducted. Also, the presence of circulating growth hormone antibodies will substantially influence the ongoing treatment of these children, making it difficult for them to reach their expected height. Thus, further research is needed to improve the prognosis for the affected children.

**Abbreviations**

IGHD: Isolated growth hormone deficiency; CNV: Copy number variation; GH: Growth hormone; IGF-1: Insulin-like growth factor-1; TSH: Thyroid stimulating hormone; rhGH: Recombinant human growth hormone; HtSDS: Height standard deviation score; TT3: Total triiodothyronine; TT4: Total thyroxine; FT4: Free thyroxine; ACTH: Adrenocorticotropic hormone; ACMG: American College of

Medical Genetics; GHRHR: Growth hormone releasing hormone receptor; GV: Growth velocity; CSHL1: Chorionic somatomatotropin hormone like 1; CSH1: Chorionic somatomatotropin hormone 1; GH2: Growth hormone 2; CSH2: Chorionic somatomatotropin hormone 2; HESX1: HESX homeobox 1; SOX3: SRY-box transcription factor 3; OTX2: Orthodenticle homeobox 2.

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### Authors' contributions

XY and MMY were actively involved in the patient follow-up and the acquisition, analysis and interpretation of data. LH and XPL designed and organized the study. ZGL and YQY carried out the molecular genetic studies. XY and LH wrote the manuscript. All authors edited and approved the final manuscript.

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### Availability of data and materials

The *GH1* variant can be found in NCBI Nucleotide under the accession number NM\_022560. The raw datasets generated and analyzed during the current study are not publicly available in order to protect participant confidentiality. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

### Declarations

#### Ethics approval and consent to participate

This study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (Approval number: TJ-IRB20201214) and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from the parents of the patient.

#### Consent for publication

Written informed consent to publish was obtained from the patient's parents.

#### Competing interests

The authors declare that there are no conflicts of interest regarding the publication of this paper.

#### Author details

<sup>1</sup>Department of Pediatrics, Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, No. 1095 Jie Fang Avenue, Hankou, Wuhan 430030, People's Republic of China. <sup>2</sup>Department of Endocrinology, Shenzhen Children's Hospital, Shenzhen 518038, People's Republic of China.

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