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Case report

Long Term Growth Hormone Therapy in a Patient with *IGF1R* Deletion Accompanied by Delayed Puberty and Central Hypothyroidism

Short title: IGF1R deletion, growth hormone therapy

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What is already known on this topic:
Insulin-like growth factor-1 (IGF-1) is the main driver of growth during prenatal life. Patients with IGF1R defects exhibit variable phenotypic features. The most common symptom is pre- and postnatal growth retardation, followed by microcephaly, developmental delay, facial dysmorphism and extremity anomalies. rhGH has been used in patients with IGF1R defects with variable treatment responses

What this study adds:
Long-term rhGH with an early onset may have more beneficial effects in terms of induction of growth. Regarding the complex physiological effects of IGF1, patients should be followed for hormone deficiencies such as hypogonadism and hypothyroidism.

Abstract
Insulin-like growth factor-1 (IGF-1) is the main driver of growth during prenatal life and acts through insulin-like growth factor 1 receptor (IGF1R). Patients with IGF1R defects exhibit variable phenotypic features. A 10.9-year-old boy presented with severe short stature, microcephaly, minor dysmorphic features and mild mental retardation. Genetic analysis for *IGF1R* revealed heterozygous deletion of the complete *IGF1R*. At the age of 12.3 years, daily subcutaneous rhGH was started and continued for a total of 5.7 years in two courses with improvement of height velocity as well as final height. Puberty was delayed and eventually he could not develop full puberty suggesting partial hypogonadotropic hypogonadism. Hypothyroidism initially developed during rhGH therapy. However, low T4 levels sustained after cessation of rhGH therapy thus central hypothyroidism is a likely diagnosis. rhGH has partial effect for induction of growth in cases with *IGF1R* defects. However, long-term treatment with an early onset may have more beneficial effects. In addition, patients with *IGF1R* defects should be followed for delayed puberty-hypogonadism, and hypothyroidism.
Keywords: IGF1R, deletion, growth hormone therapy, delayed puberty, hypothyroidism

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Introduction:
Growth factors are crucial for prenatal growth. Insulin-like growth factor-1 (IGF-1) which has structural homology with proinsulin, is the main driver of growth during prenatal life and acts through insulin-like growth factor 1 receptor (IGF1R). *IGF1R* is located on the distal part on the long arm of the chromosome 15 (15q26.3) (1). In animal models, *IGF1R* null mice exhibited severe growth restriction (45% of normal size) and died soon after birth due to lung and respiratory muscle hypoplasia, ossification was delayed, epidermis was underdeveloped and there were central nervous system anomalies (2). Since the first description of patients with *IGF1R* mutation who had intrauterine growth retardation, poor postnatal growth, developmental delay and microcephaly, cumulative evidence has shown that the phenotypic characteristics of patients with *IGF1R* defects can vary over a wide range (3-5). 15q26 terminal deletions lead to contiguous gene syndrome and there is no clear genotype-phenotype correlation with a significant inter- and intra-familial variability. Homozygous or compound heterozygous mutations seems to cause more severe phenotype (3,6,7). Endocrine consequences of *IGF1R* defects other than short stature, such as delayed puberty, premature ovarian failure, growth hormone deficiency are reported very rarely (5,8-11). Central adrenal insufficiency and hypothyroidism have not been reported before.
Recombinant human growth hormone (rhGH) in SGA is approved by Food and Drug Administration and the European Medicine Agency. rhGH has been used in patients with *IGF1R* defects with variable treatment responses; it may be discontinued due to no improvement in growth velocity, continued without catch-up growth (3,10,12-15) and with mild catch-up growth (13,14,16).
We herein report a boy with 15q terminal deletion, who presented with severe growth retardation, microcephaly, developmental delay who also had delayed puberty and central hypothyroidism. We also aimed to report the long-term results of growth hormone therapy.
Case report:
A 10.9-year-old boy was referred for short stature. He was born at term to healthy nonconsanguineous parents with a so-called normal birth weight, his birth length was unknown. Maternal and paternal height were -2.8 SDS (146.7 cm) and -2.0 SDS (163.7 cm), respectively, and midparental height was -2.3 SDS (161.7 cm). There was no feeding difficulty during infancy. He was able to say his first words and walk at the age of 1.5 and 2.5 years, respectively. He had been evaluated at another health center for short stature at the age of 6 years and thyroid hormones, growth factors, and celiac antibodies were normal.
He presented with a height of -5.3 SDS (108.3 cm), a weight of -4.9 SDS (18.5 kg), and a head circumference of -4.1 SDS (48 cm) at the age of 10.9 years old. He had proportional severe short stature with no dysmorphic features except a triangular face. He was prepubertal. Neurological examination was unremarkable except for mild mental retardation detected in the Wechsler Intelligence Scale for Children-Revised test (intelligence quotient 65). Bone age (determined by the Greulich and Pyle method) was 5 years. Total blood count and blood chemistry were normal, as well as skeletal survey. In endocrine work-up, IGF-1 was 240.2 ng/mL (mean SDS), insulin-like growth factor binding protein-3

(IGFBP-3) was 4228.7 ng/mL (0.43 SDS). Growth hormone (GH) stimulation test showed a peak GH response of 10.3 ng/mL. Other pituitary hormones including adrenocorticotropic hormone (ACTH) (19.5 pg/mL [normal range 0-46]), cortisol (8.5 µg/dL), prolactin (9.3 ng/mL [normal range 2.5-18]), free T4 (1.19 ng/dL [normal range 0.9-1.7]), thyroid stimulating hormone (2.4 uIU/mL [normal range 0.3-4.2]) were normal. He had primary nocturnal enuresis and renal ultrasound revealed kidney size in the lower range for age.

Karyotype analysis was 46,XY. Genetic analysis for *IGF1R* was performed in Leiden University Medical Centre. MLPA analysis of the coding region (exon 1-21) revealed heterozygous deletion of the complete *IGF1R*. SNP microarray identified a 3.3 Mb terminal deletion on the long arm of the chromosome 15 (15q26.3x1) which included the *IGF1R* and there was also a terminal duplication with a maximum size of 2.6 Mb on the short arm of chromosome 9 (9p24.3p24.2x3). The terminal 9p duplication and the terminal 15q deletion suggest the presence of an unbalanced reciprocal translocation between the short arm of chromosome 9 and the long arm of chromosome 15. MLPA and SNP microarray were normal for chromosome 9 and 15 in mother and father respectively.

At the age of 12.3 years, height was -5.27 SDS (114.2 cm), weight -5.4 SDS (19.5 kg) and growth velocity 4.1 cm/year **(IGF-1 383 mg/dL, 0.5 SDS**). Daily subcutaneous rhGH was started at a dose of 0.21 mg/kg/week (Figure 1) and the dose was increased to 0.30 mg/kg/week after three months. Treatment was continued for eighteen months; his growth velocity was 7.1 cm for the first year (height was 121.3 cm, -4.67 SDS), which then slowed down to 2.2 cm during the next six months. Treatment was withdrawn for slow growth velocity. Nine months later, rhGH treatment was restarted at a dose of 0.30 mg/kg/week due to slow growth rate (2.9 cm in nine months). During rhGH serum IGF-1 levels varied between +1 and +2 SDS.

At the age of 14.8 years, testes were 6 ml bilaterally and increased to 8 ml at the age of 15.7 years, but did not progress afterwards. At the age of 16.5 years with an observation of delayed puberty (testes volumes 6 ml bilaterally, FSH 5.27 mIU/mL [normal range 1.3-19.2], LH 0.21 mIU/mL [normal range 1.8-8.6], testosterone 29.4 ng/dL [normal range 220-800]) intramuscular testosterone (propionate 30 mg, phenylpropionate 60 mg, isocaproat 60 mg, decanoate 100 mg) was commenced at a dose of 50 mg/monthly.

At the age of 17.3 years while he was on rhGH, thyroid function tests revealed hypothyroidism (TSH 2.13 uIU/mL, [normal range 0.4-5.3]); free T4 0.51 ng/dL, [normal range 0.6-1.1]). Central adrenal insufficiency was also diagnosed (ACTH 32.5 pg/mL, peak cortisol during low dose ACTH stimulation test was 16.8 µg/dL [N:>18.9]). Thus, both hydrocortisone and levothyroxine were started. In pituitary magnetic resonance imaging, the height of the pituitary gland is 4.5 mm, and a pars intermedia cyst 2 mm in diameter was present on the anterior part of neurohypophysis.

At the age of 18.8 years, his height was -3.26 SDS (152.9 cm), weight -3.44 SDS (44.6 kg). His height increased 0.8 cm in the last 6 months, bone age was 16 years old and rhGH treatment was withdrawn. After 5.7 years of rhGH treatment in two courses, he had a height gain of 2.01 SDS. Testis volumes increased to 10 ml bilaterally (FSH 7.1 mIU/mL [normal range 0.9-11.9], LH 1.5 mIU/mL [normal range 0.5-12.0], testosterone 152.2 ng/dL [normal range 151-794] two weeks after the last dose of testosterone), and testosterone treatment was withdrawn as well. In addition, HPA axis was rechecked, peak cortisol response to low dose ACTH test was 18.9 µg/dL and hydrocortisone was discontinued with an instruction of stress coverage. At the age of 19.5 years size of testes and testosterone concentration did not increase (testes sizes were 10 ml bilaterally, FSH 8.05 mIU/mL [normal range 0.9-11.9], LH 0.84 mIU/mL [normal range 0.6-12.1], testosterone 156.9 ng/dL [normal range 47-981]), so testosterone was restarted. During the last follow-up when he was 20 years old, height was -3.06 SDS (154.8 cm), weight 45 kg (-3.45 SDS), he had not been using levothyroxine for 3 months. Thyroid function test still suggested central hypothyroidism (TSH 3.8 mIU/mL, [normal range 0.27-4.2]; free T4 0.88 ng/dL, [normal range 0.93-1.7], free T3 3.26 ng/L [2-4.4]).

Discussion:

We report a boy with *IGF1R* deletion presenting with severe short stature, microcephaly, mental retardation and mild dysmorphic features. Growth hormone therapy for a total of 5.7 years in two courses improved height velocity as well as final height. Also, puberty was arrested and eventually he could not develop full puberty suggesting partial hypogonadotropic hypogonadism. Hypothyroidism developed during GH therapy which may be associated with isolated GH deficiency during GH therapy (17). However, low T4 levels persisted after cessation of GH therapy thus central hypothyroidism is a likely diagnosis.

Patients with *IGF1R* defects exhibit variable phenotypic features. The most common symptom is pre- and postnatal growth retardation, followed by microcephaly, developmental delay, facial dysmorphism and extremity anomalies. Although birth weight or height below -2 SDS were used as the inclusion criteria in studies evaluating *IGF1R* defects (15), patients showed wide variation in these parameters; birth weight between -4.1 and -0.8, birth length -5.8 and -1.0, and head circumference -5.7 and 0.8 SDS (3,6,12,14). Patients with terminal 15q deletions could exhibit additional features involving other organ systems such as cardiac, genitourinary, respiratory, ocular (7,14) disorders attributed to defects in contiguous genes, some of which may impact growth. Our patient had only mild dysmorphic features and neurodevelopmental delay, without involvement of major organ systems.

rhGH therapy has been recommended for patients with *IGFR1* defects in higher than usual doses to overcome receptor resistance (15). Growth promoting effects of rhGH is less pronounced in comparison to patients with SGA, and response is quite variable among patients with *IGF1R* defects (18). Although the rhGH response in the first year is lower than in SGA patients, the constant growth velocity in the following years could emphasize the importance of long-term treatment (18). The dose of rhGH is expected to be important, however, Göpel et al (18) did not find any association between dose and treatment response. In addition, it has been a matter of debate whether genotype influences rhGH treatment response. Walenkamp et al (4) found no difference in 3-year rhGH response between twelve patients with mutations and seven with deletions who received rhGH therapy at similar ages. Göpel et al (18) reported that the ratio of patients with a good response to treatment was higher in carriers of mutations within the intracellular part of IGF1R compared to the extracellular part. However, it should be emphasized that number of patients were limited due to the rarity of *IGF1R* defects.

We reviewed 28 patients with *IGF1R* defects who received rhGH (Table 1). Thirteen (46%) had terminal 15q deletions or ring chromosome, fourteen (50%) heterozygous mutations, and one (4%) compound heterozygous mutation. Sixty one percent of patients with terminal 15q deletions or ring chromosome, and 35% of patients with *IGF1R* mutations exhibited ≥ 0.5 SDS increase in height during the first year of rhGH. Sixty nine percent of patients with terminal 15q deletions or ring chromosome, and 42% of patients with mutations had a height gain of ≥ 1 SDS based on the last evaluation or final height. One of the two patients with the worst treatment response had a compound heterozygous mutation and the other with 15q26 deletion had hypoplastic left heart. Forty six percent of patients who did not gain ≥ 0.5 SDS in the first year of treatment achieved ≥ 1 SDS with prolonged treatment. Our patient had a height gain of 0.6 SDS at the first year of rhGH treatment, and 2.01 SDS with a 5.7 year-long treatment.

The presence of IGF-1 and IGF-1R has been demonstrated in various cells including the pituitary (19). IGF-1 is a mitogenic hormone that induces proliferation and differentiations of various cells and participates in physiological regulations. IGF-1 is the key modulator of GH actions, on the other hand it also participates in regulation of the hypothalamo-pituitary-gonad (HPG) axis. The expression of GH and IGF1 receptors in the elements of HPG axis and reproductive organs has been demonstrated in molecular studies. GH and IGF1 participate in various stages of maturation of reproductive axis including intrauterine stages, mini-puberty and onset of puberty. Cryptorchidism was reported in two patients with *IGF1R* deletion (7,20). Although contiguous gene syndrome cannot be excluded as an etiology of cryptorchidism, IGF1R haploinsufficiency could still be the causative factor emphasizing intrauterine effects. In vitro animal models showed that IGF-1 both induces proliferation of gonadotrophs and secretion of gonadotropins (21) which emphasizes the importance of growth factors for induction of puberty and its progression. IGF-1 participates in functions of testis and ovary in terms of Sertoli and granulosa cell survival and production of gonadal steroid hormones (22,23), and hypergonadotropic hypogonadism was also reported in patients with *IGF1R* defects (5,24). It is interesting that cases with *IGF1R* duplication had azoospermia. These data suggest that an intact IGF-1 system is necessary for the maturation and maintenance of the

reproductive system. Our patient exhibited features of hypogonadotropic hypogonadism. Puberty started at the age of 14.8 years, and did not progress appropriately, so sex steroid replacement was established. Patients with delayed puberty were reported previously with *IGF1R* defects, but none of them required sex steroids since puberty progressed spontaneously (8,9).

One of the consequences of rhGH therapy is alterations in thyroid hormones. GH induces the activity of deiodinase, thus freeT4 (fT4) level may decrease and freeT3 (fT3) level may increase during rhGH therapy. TSH concentration is not expected to increase in the face of increased fT3. Thus rhGH therapy can either mimic or unmask central hypothyroidism (17). Our patient developed central hypothyroidism during rhGH therapy, however, this condition continued even after cessation of rhGH. Since *IGF1R* expressed in pituitary somatotrophs participates in negative feedback on the somatotropic axis, receptor resistance may disrupt negative feed-back leading to an increase in growth hormone. Elevation in GH levels may induce somatostatin from the hypothalamus which is a weak inhibitor of TSH (25). Studies on salmon pituitary cells have shown that IGF-1 can stimulate thyrotropin beta subunit transcript in a dose-dependent manner (26). In addition, GH-IGF1 axis has important effects on the thyrocytes. In invitro animal studies, GH and IGF-1 showed synergistic effects with TSH on thyroid gland growth and hormone production (27). Thus, *IGF1R* defects may be expected to impact thyroid function in multiple levels. Interestingly, no patient with hypothyroidism have been reported to date, thus, it is not possible to ensure that alterations in thyroid function in the current patient is a direct consequence of IGF-1 resistance. Also, a pars intermedia cyst was detected on MRI. Pars intermedia cysts, remnant of Rathke's pouch, rarely causes symptoms and symptoms are related to the mass effect or pituitary hormone deficiency (28). Some reports suggested a positive correlation between cyst size and impairment of pituitary function (29), other reports an association between symptoms and chronic inflammation around the cyst wall (28). However, small cysts are asymptomatic and detected incidentally or at autopsy (29), frequency of pituitary hormone deficiency increases in ≥10 mm cysts (30). Therefore, pituitary hormone deficiency is not expected in a 2 mm diameter pars intermedia cyst.

IGF-1 immunoreactivity was detected in the same secretory granules of the corticotroph cells, indicating a concomitant secretion and release of both hormones (19). Despite the coexistence of both hormones, recent studies showed no effect of IGF-I on ACTH secretion and the corticotroph responsiveness to CRH (19). Instead, corticotroph cells may require IGF-I to protect them against apoptosis, especially in the case of stressful situations (19). The first low dose ACTH test that was performed before levothyroxine treatment revealed an inadequate serum cortisol peak, and the second one was just above the lowest reference range. We could not definitively exclude the diagnosis of central adrenal insufficiency, due to the technical limitations of the low dose ACTH test and its lower sensitivity and specificity compared to the insulin tolerance test. However, the lack of protective effects of IGF1 could make these patients vulnerable to apoptosis of corticotroph cells.

In conclusion, rhGH has partial beneficial effect on growth in cases with *IGF1R* defects if long-term, early-onset treatment has been instituted. Even if the treatment response to rhGH is not sufficient during the first year, it is important to continue the treatment since 42% of the patients have a height gain of more than 1 SDS on long-term. In addition, patients with *IGF1R* defects should be followed for hormone deficiencies.

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Declaration of competing interest: All co-authors declare no conflicts of interest.

References:

1. Walenkamp MJ, Losekoot M, Wit JM. Molecular IGF-1 and IGF-1 receptor defects: from genetics to clinical management. Endocr Dev. 2013;24:128-137.
2. Liu JP, Baker J, Perkins AS, Robertson EJ, Efstratiadis A. Mice carrying null mutations of the genes encoding insulin-like growth factor I (Igf-1) and type 1 IGF receptor (Igf1r). Cell. 1993;75(1):59-72.
3. Abuzzahab MJ, Schneider A, Goddard A, Grigorescu F, Lautier C, Keller E, Kiess W, Klammt J, Kratzsch J, Osgood D, Pfäffle R, Raile K, Seidel B, Smith RJ, Chernausek SD. IGF-I receptor mutations resulting in intrauterine and postnatal growth retardation. N Engl J Med. 2003;349(23):2211-2222.
4. Walenkamp MJE, Robers JML, Wit JM, Zandwijken GRJ, van Duyvenvoorde HA, Oostdijk W, Hokken-Koelega ACS, Kant SG, Losekoot M. Phenotypic Features and Response to GH Treatment of Patients With a Molecular Defect of the IGF-1 Receptor. J Clin Endocrinol Metab. 2019;104(8):3157-3171.
5. Gonc EN, Ozon ZA, Oguz S, Kabacam S, Taskiran EZ, Kiper POS, Utine GE, Alikasifoglu A, Kandemir N, Boduroglu OK, Alikasifoglu M. Genetic IGF1R defects: new cases expand the spectrum of clinical features. J Endocrinol Invest. 2020;43(12):1739-1748.
6. Prontera P, Micale L, Verrotti A, Napolioni V, Stangoni G, Merla G. A New Homozygous IGF1R Variant Defines a Clinically Recognizable Incomplete Dominant form of SHORT Syndrome. Hum Mutat. 2015;36(11):1043-1047.
7. Choi JH, Kang M, Kim GH, Hong M, Jin HY, Lee BH, Park JY, Lee SM, Seo EJ, Yoo HW. Clinical and functional characteristics of a novel heterozygous mutation of the IGF1R gene and IGF1R haploinsufficiency due to terminal 15q26.2->qter deletion in patients with intrauterine growth retardation and postnatal catch-up growth failure. J Clin Endocrinol Metab. 2011;96(1):E130-134.
8. Walenkamp MJ, van der Kamp HJ, Pereira AM, Kant SG, van Duyvenvoorde HA, Kruithof MF, Breuning MH, Romijn JA, Karperien M, Wit JM. A variable degree of intrauterine and postnatal growth retardation in a family with a missense mutation in the insulin-like growth factor I receptor. J Clin Endocrinol Metab. 2006;91(8):3062-3070.
9. Kruis T, Klammt J, Galli-Tsinopoulou A, Wallborn T, Schlicke M, Müller E, Kratzsch J, Körner A, Odeh R, Kiess W, Pfäffle R. Heterozygous mutation within a kinase-conserved motif of the insulin-like growth factor I receptor causes intrauterine and postnatal growth retardation. J Clin Endocrinol Metab. 2010;95(3):1137-1142.
10. Ester WA, van Duyvenvoorde HA, de Wit CC, Broekman AJ, Ruivenkamp CA, Govaerts LC, Wit JM, Hokken-Koelega AC, Losekoot M. Two short children born small for gestational age with insulin-like growth factor 1 receptor haploinsufficiency illustrate the heterogeneity of its phenotype. J Clin Endocrinol Metab. 2009;94(12):4717-4727.
11. Yoon JS, Hwang IT. Microdeletion in the IGF-1 receptor gene of a patient with short stature and obesity: a case report. J Pediatr Endocrinol Metab. 2021;34(2):255-259.
12. Labarta JI, Barrio E, Audí L, Fernández-Cancio M, Andaluz P, de Arriba A, Puga B, Calvo MT, Mayayo E, Carrascosa A, Ferrández-Longás A. Familial short stature and intrauterine growth retardation associated with a novel mutation in the IGF-I receptor (IGF1R) gene. Clin Endocrinol (Oxf). 2013;78(2):255-262.
13. Walenkamp MJ, de Muinck Keizer-Schrama SM, de Mos M, Kalf ME, van Duyvenvoorde HA, Boot AM, Kant SG, White SJ, Losekoot M, Den Dunnen JT, Karperien M, Wit JM. Successful long-term growth hormone therapy in a girl with haploinsufficiency of the insulin-like growth factor-I receptor due to a terminal 15q26.2->qter deletion detected by multiplex ligation probe amplification. J Clin Endocrinol Metab. 2008;93(6):2421-2425.
14. Veenma DC, Eussen HJ, Govaerts LC, de Kort SW, Odink RJ, Wouters CH, Hokken-Koelega AC, de Klein A. Phenotype-genotype correlation in a familial IGF1R microdeletion case. J Med Genet. 2010;47(7):492-498.
15. Leal AC, Montenegro LR, Saito RF, Ribeiro TC, Coutinho DC, Mendonca BB, Arnhold IJ, Jorge AA. Analysis of the insulin-like growth factor 1 receptor gene in children born small for gestational age: in vitro characterization of a novel mutation (p.Arg511Trp). Clin Endocrinol (Oxf). 2013;78(4):558-563.

16. Mahmoud R, Naidu A, Risheg H, Kimonis V. Response to Growth Hormone Treatment in a Patient with Insulin-Like Growth Factor 1 Receptor Deletion. J Clin Res Pediatr Endocrinol. 2017;9(4):380-386.
17. Kucharska AM, Witkowska-Sędek E, Rumińska M, Pyrżak B. Thyroid Hormone Changes Related to Growth Hormone Therapy in Growth Hormone Deficient Patients. J Clin Med. 2021;10(22).
18. Göpel E, Rockstroh D, Pfäffle H, Schlicke M, Pozza SB, Gannagé-Yared MH, Gucev Z, Mohn A, Harmel EM, Volkmann J, Weihrauch-Blüher S, Gausche R, Bogatsch H, Beger C, Klammt J, Pfäffle R. A Comprehensive Cohort Analysis Comparing Growth and GH Therapy Response in IGF1R Mutation Carriers and SGA Children. J Clin Endocrinol Metab. 2020;105(4).
19. Eppler E, Jevdjovic T, Maake C, Reinecke M. Insulin-like growth factor I (IGF-I) and its receptor (IGF-1R) in the rat anterior pituitary. Eur J Neurosci. 2007;25(1):191-200.
20. Rudaks LI, Nicholl JK, Bratkovic D, Barnett CP. Short stature due to 15q26 microdeletion involving IGF1R: report of an additional case and review of the literature. Am J Med Genet A. 2011;155a(12):3139-3143.
21. Huang YS, Rousseau K, Le Belle N, Vidal B, Burzawa-Gérard E, Marchelidon J, Dufour S. Insulin-like growth factor-I stimulates gonadotrophin production from eel pituitary cells: a possible metabolic signal for induction of puberty. J Endocrinol. 1998;159(1):43-52.
22. Dance A, Kastelic J, Thundathil J. A combination of insulin-like growth factor I (IGF-I) and FSH promotes proliferation of prepubertal bovine Sertoli cells isolated and cultured in vitro. Reprod Fertil Dev. 2017;29(8):1635-1641.
23. Monte APO, Barros VRP, Santos JM, Menezes VG, Cavalcante AYP, Gouveia BB, Bezerra MES, Macedo TJS, Matos MHT. Immunohistochemical localization of insulin-like growth factor-1 (IGF-1) in the sheep ovary and the synergistic effect of IGF-1 and FSH on follicular development in vitro and LH receptor immunostaining. Theriogenology. 2019;129:61-69.
24. O'Riordan AM, McGrath N, Sharif F, Murphy NP, Franklin O, Lynch SA, O'Grady MJ. Expanding the clinical spectrum of chromosome 15q26 terminal deletions associated with IGF-1 resistance. Eur J Pediatr. 2017;176(1):137-142.
25. Takano K, Ajima M, Teramoto A, Hata K, Yamashita N. Mechanisms of action of somatostatin on human TSH-secreting adenoma cells. Am J Physiol. 1995;268(4 Pt 1):E558-564.
26. Fleming MS, Maugars G, Martin P, Dufour S, Rousseau K. Differential Regulation of the Expression of the Two Thyrotropin Beta Subunit Paralogs by Salmon Pituitary Cells In Vitro. Front Endocrinol (Lausanne). 2020;11:603538.
27. Feldt-Rasmussen U. Interactions between growth hormone and the thyroid gland -- with special reference to biochemical diagnosis. Curr Med Chem. 2007;14(26):2783-2788.
28. Nishioka H, Haraoka J, Izawa H, Ikeda Y. Magnetic resonance imaging, clinical manifestations, and management of Rathke's cleft cyst. Clin Endocrinol (Oxf). 2006;64(2):184-188.
29. Trifanescu R, Ansorge O, Wass JA, Grossman AB, Karavitaki N. Rathke's cleft cysts. Clin Endocrinol (Oxf). 2012;76(2):151-160.
30. Dadej D, Skraba K, Matyjaszek-Matuszek B, Świrska J, Ruchała M, Ziemnicka K. Presenting symptoms and endocrine dysfunction in Rathke cleft cysts - a two-centre experience. Endokrynol Pol. 2021;72(5):505-511.

Figure 1. Growth chart of the patient. The patient had two courses of growth hormone therapy. Normative data for boys is from the Centers for Disease Control and Prevention.

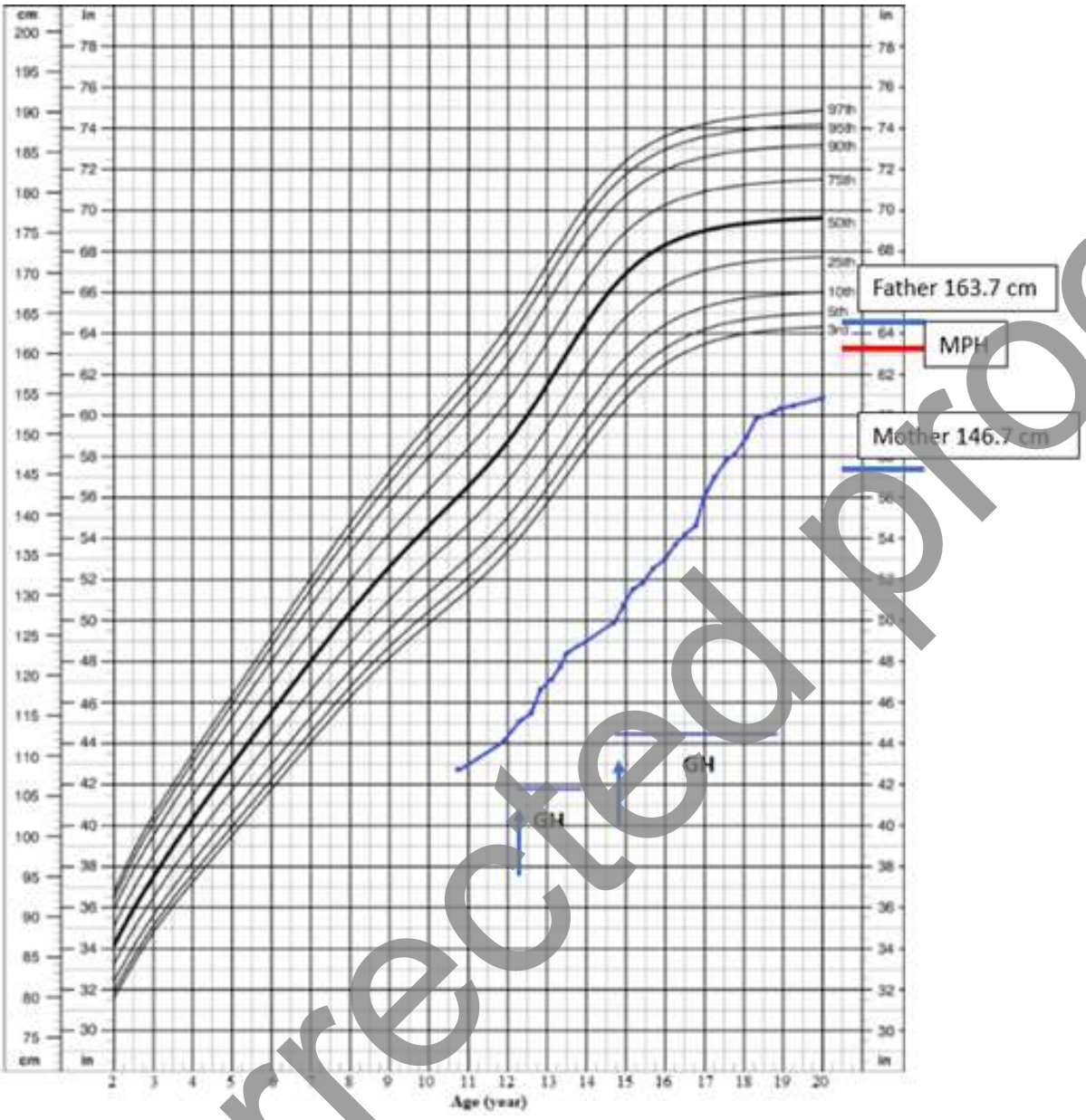

Table 1. Features of genotype, auxology and phenotype of patients who were administered rhGH.

Author (year)	Deletion/ mutation	Gender (F/M)	Birth weight/ length/ head circumference	Age at first evaluation; Height (SDS)	Age at the start of rhGH (year); Height (SDS)	Duration (year)	Height gain at the first year of rhGH (SDS)	Age (year) at last evaluation; Height (SDS)	Final height	Other features	Affected family member	Other hormonal deficiencies
Ho et al (1)	46,XX,r(15)(p11q26.3)	F	-0.8 / NA / NA	0.4; -5.6	1.8; -5.3	12.4	+1	NA; -2.1	-2.1	DD	NA	NA
Ho et al (1)	46,XX,r(15)(p13q26.2)	F	-1.6 / NA / -3.3	0.5; -4.4	2.6; -3.3	12.2	+0.5	NA; -2.5	-2.5	Hip dislocation, DD	NA	NA
Ho et al (1)	46,XY,del(15)(q26.3)	M	-1.6 / NA / NA	1.5; -3.7	5.2; -4.0	11.8	+0.7	NA; -2.6	-2.6	Bilateral talipes, DD	NA	NA
Ester et al (2)	15q26.3 deletion, exons 3-21	M	-1.9 / -2.2 / NA	3.0; -3.84	7; -3.57	10	+0.83	17; -1.89	NA	DD, DF, EA, HL	No	NA
Gkourogianni et al* (3)	c.3364G > T p.Gly1122Cys	M	NA	NA	9.1; -3.5	9.6	+0.2	18.7; -1.8	−1.8 SDS	No DF.	Mother; -2.1 SDS	DP
Abuzzahab et al (4)	Compound heterozygousArg108Gln, Lys115Asn, exon 2.	F	-3.5 / NA / NA	NA	4.1 yr, for 2 years and at 8.7 yr old restarted	7.9 yrs in two courses	+0.17 in the first course	NA	-4.8 SDS	DD and psychiatric disorders.		Menarche at the age of 12.5 yr.
Walenkamp et al (5)	15q26.2-qter	F	-3 / -1.3 / -2	4.5; -3.5	5.3; NA	6.7	NA	NA	-1.6 SDS	DD	No	NTF. Puberty started at the age of 12.8 yr.
Yang et al* (6)	c.3740T>C, p.M1247T	F	-1.9 / NA / NA	2.1; -3.85	2.8; -3.36	6	+0.6	8.8; -2.4	NA	No DD	Mother; -1.96 SDS	NA
Ho et al (1)	46,XX,del(15)(q26.2)	F	-2.9 / NA / -3.7	3.0; -4.9	5.0; -4.9	5.8	+0.1	NA; -4.9	-4.9	Hypoplastic left heart, DD, dysplastic kidney	NA	NA
Leal et al (7)	c.1531C>T, p.Arg511Trp, exon 7	F	-2.5 / NA / NA	5.8; -2.7	8.4; -2.9	5	+0.9	13.3; -1.7	NA	No DD. Mild DF.	Mother; -2.9 SDS	NP
Veenma et al (8)**	15q26.3 microdeletion	M	-1.7 / -2.3 / 0.88	12; -4.2	13.8; NA	4.6	+0.1	NA, the overall catch-up growth was +1.8SDS	NA	DD, DF, café-au-lait, strabismus, refraction anomalies of lens	Mother; -4.42 SDS	NP
Labarta et al (9)	c.1549A>T, p.Y487F, exon 7	F	-3.46 / -4.9 / -5.7	1.5; -2.84	3.4; -3.19	4.1	+0.31	7.5; -2.39	NA	Slightly retarded	Mother; -1.6 SDS	Mother menarche at the age of 13 yr
Ester et al (2)	15q26.3 deletion, exons 1-21	F	-1.28 / -2.21 / NA	2.3; -3.46	4; -3.42	4	+1.02	8.3; -1.68	NA	DD, DF, EA, HL, hyperlaxity	No	NA
Nuutinen et al (10)	46,XY, r(15)(pll.2q26.2).		-3.2 / -4.0 / NA	0.6; -6.2	2.2; -6.2	2	+1.2	4.2; -4.4	NA	DD, DF, café-au-lait	NA	NTF

Choi et al* (11)	c.420del, p.Ala110fsX20, in exon 2	F	-2.1 / NA / NA	6.8; -3.56	8; -3.56	1	+1.18	9; -2.38	NA	No DD or DF	Father; -4.19 SDS	NTF
Ho et al (1)	46,XX,r(15)(p13q26.3)	F	-2.5 / NA / -2.0	0.5; -3.0	3.3; -3.8	1.0	+0.8	4.3; -3.0	NA	DD, DF	NA	NA
Choi et al* (11)	c.420del, p.Ala110fsX20, in exon 2	M	-1.96 / NA / NA	9.5; -3.47	10.5; -3.42	1	+0.64	11.5; -2.78	NA	NA	Father; -4.19 SDS	NA
Ho et al (1)	46,XY,del(15)(q26.3)	M	-1.4 / NA / NA	3.2; -4.8	6.2; -4.6	1.6	+0.6	7.8; -3.4	NA	DD, DF	NA	NA
Raile et al (12)	Arg59Ter, exon 2	M	-3.5 / -5.8 / NA	1.1; -3.8	6.4; -2.51	2	+0.55	8.5; -1.5	NA	DD, DF	Mother; -2.6 SDS	NTF, NAF, normal prolactin
Wallborn et al* (13)	c.1886T>A, p.V599E	F	-2.26 / -1.82 / <3p	NA	7.42; -2.27	1.5	+0.43	9.02; -1.4	NA	DD, ADHD	Mother; -3.3 SDS	NTF
Mahmoud et al* (14)	15q26.2q26.3 deletion	M	-3 / -3.2 / NA	2.5; -9.3	3.4; -3.4	2.6	+0.33	6; -1.5	NA	Mild DD, DF	No	NTF
Gkourogianni et al* (3)	c.3364G>T p.Gly1122Cys	M	-2.0 / -1.6 / -2.15	6.8; -2.3	7.9; -2.2	2.6	+0.23	10.5; -1.15	NA	Attention deficit disorder	Father; -1.8 SDS	NA
Ho et al (1)	46,XX,del(15)t(15;16)(q26.1:q22.3)	F	-1.6 / NA / NA	5.0; -5.4	12.4; -5.9	2.2	+0.2	14.6; -5.7	NA	DD, EA, VSD, subglottic stenosis	NA	NA
Fang et al* (15)	19Dup in exon 18	M	-3.04 / -1.5 / NA	9.6; -3.6	10; -3.65	2	+0.03	12; -3.05	NA	Bifid uvula, ADHD	Mother; -4.6 SDS	NTF, NAF
Inagaki et al (16)	c.1577G>A, p.R481Q, exon 7	F	-3.1 / -4.9 / NA	13.6; -5	NA	0.5	0 SDS	NA	NA	Mild DF.	Mother; -5.7 SDS	T2P2 at presentation.
Mohn et al (17)	c.1161C>A, p.Tyr387X, exon 5	M	-2.03 / -3.08 / NA	4; -4.58	8; NA	1	No improvement in GV	18; -3.08	NA	No DD	Father; -2.94 SDS	NP
Kawashima et al (18)	c.3405C>A	F	-1.5 / -2.5 / NA	6; -3.0	6; -3.0	3	NA	9; -1.5	NA	DD	Mother; -4.0 SDS	NA
Kawashima et al (19)	c.1382G>T, R431L	F	-1.8 / -3.2 / NA	3; -2.9	5; -3.0	2	NA	8; -2.7	NA	No DD	Mother; -1.2 SDS	NA
Fujimoto et al (20)	c.3798C>T, p.Q1250X, exon 21	M	-3.3 / -2.1 / -3.7	3; -3.2	6; -3.1	2	NA	8.7; -2.6 (at the end of the rhGh -2.5)	NA	No DD	No	NA

*GV, height SDS calculated from growth charts. **In the first 2 years also received GnRHa. ADHD: attention deficit hyperactivity disorder, CA: cardiac anomaly, DD: developmental delay, DF: dysmorphic features, DP: delayed puberty, EA: extremity anomalies, GV: growth velocity, HL: hearing loss, MR: mental retardation, NAF: normal adrenal function, NP: normal puberty, NTF: normal thyroid function