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Original Article

Various phenotypes of short stature with heterozygous *IGF-1 receptor* (*IGF1R*) mutations

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Highlights

- Patients with heterozygous *IGF1R* mutations have heterogeneous phenotypes.
- Recombinant GH therapy might be effective in treating *IGF1R*-related short stature.
- Higher IGF1 levels after rhGH treatment may indicate *IGF1R* gene mutations.

Abstract. Type 1 insulin-like growth factor receptor (IGF1R) plays an important role in normal fetal and postnatal growth. Over 30 pathogenic variants of *IGF1R* have been identified in patients with short stature. Yet, 20 years after the first report, a variety of phenotypes remain poorly defined. We analyzed the genetic and clinical data and responses to GH therapy in 11 patients using results from questionnaires. Eight of the 11 patients have already been reported in previous articles, and all of the identified mutations were heterozygous. The patients exhibited various phenotypes. At least two patients did not meet the criteria for GH treatment for small for gestational age (SGA) short stature, and two more patients showed lower serum IGF1 levels. Nine of the 11 patients had thin upper lips. Five patients with heterozygous *IGF1R* treated with GH exhibited similar height gains to those reported in previous Japanese studies on SGA short stature, which also led to extremely high serum IGF1 levels. Patients with short stature due to *IGF1R* mutations exhibit various phenotypes. Their presentation at diagnosis may be indistinguishable from common short stature. More specific clinical scoring that considers elevated IGF1 levels after GH treatment is needed to better detect *IGF1R* mutations.

Key words: Insulin-like growth factor 1 receptor (IGF1R), short stature, GH therapy, insulin-like growth factor 1 (IGF1)

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Introduction

Type 1 insulin-like growth factor receptor (IGF1R) is widely expressed in many cell types in fetal and postnatal tissues. IGF1R is activated by the secreted growth factor ligands IGF1 and IGF2, which elicit cellular responses to promote fetal somatic growth. This postnatal somatic growth is achieved through synergistic interactions between GH and IGFs (1, 2). IGF1R is important for normal fetal and postnatal growth and development (3, 4).

Almost 20 years after the first cases with *IGF1R* mutations were reported, over 30 pathogenic mutations and defects of *IGF1R* have been identified as contributing to short stature (5–17). Walenkamp *et al.* reported the detection of pathogenic *IGF1R* mutations in approximately 2% of patients with short stature who were small for gestational age (SGA) (18). Most cases had heterozygous *IGF1R* mutations or haploinsufficiency, although several compound heterozygous and two homozygous mutations of *IGF1R* have been reported (19). As *igf1r*-null mice die soon after birth due to respiratory failure, the total loss of IGF1R function in mammals is considered lethal (4). Reported cases of heterozygous IGF1R mutation or haploinsufficiency show persistent postnatal and intrauterine growth retardation with elevated serum IGF1 and microcephaly (9–12, 14). Other reported phenotypic features include mildly impaired glucose tolerance, motor and mental retardation, and mild dysmorphic features, including clinodactyly, triangular face, hypotelorism, low-set ears, thin upper lip, and high-arched palate (5, 8, 14, 15, 20). However, there are a variety of phenotypes, and the degree of growth retardation is highly variable. For instance, Klammt *et al.* reported that eight patients with an *IGF1R* mutation had a birth weight (BW) ranging from –1.5 to –3.5 standard deviation score (SDS), birth length (BL) varying from –0.3 to –5.0 SDS, and last reported height ranging from –2.1 to –5.0 SDS (21). The phenotypes of *IGF1R* mutations and defects remain poorly defined, and the variability in phenotype makes it difficult for physicians to identify patients who should be tested for *IGF1R* defects. To date, no studies on the growth profile and phenotypes in case series with heterozygous *IGF1R* mutations or haploinsufficiency have been conducted in Japan.

Recently, two studies revealed the growth profile phenotype and recombinant human GH (rhGH) therapy response in patients with heterozygous *IGF1R* mutations and defects (18, 22). Here, we present the first study of the phenotype, growth profile, and rhGH therapy response in patients with short stature and heterozygous *IGF1R* mutations in Japan.

Materials and Methods

Questionnaire and data analysis

Between December 2020 and March 2021, we recruited and provided a questionnaire to doctors attending to previously reported patients with *IGF1R* mutations who were identified by our comprehensive genetic testing study for unexplained growth disorders. The questionnaire asked about patient age, sex, BW, birth height (BH), head circumference (HC), peak serum GH level in the GH provocation test, serum IGF1 level, height (including final height), bone age, hemoglobin A1c (HbA1c; before, during, and after rhGH treatment), complications, and patient genotype. We carefully analyzed 11 patients based on the results of the questionnaire. The SDS values for BW, BH, HC, and height were calculated based on Japanese data regarding standard height by sex and age (23, 24). The IGF1 SDS was calculated using Japanese reference values of serum IGF1 concentrations in children by sex and age (25). Statistical analyses were performed using Microsoft® Excel® 2019 to compare groups using *t*-test and two-way ANOVA followed by Dunnel's test. The results are shown as mean ± SD. Statistical significance was set at $p < 0.05$.

Sequence analysis of IGF1R

Genomic DNA was isolated from peripheral blood lymphocytes of the patients. PCR and direct sequencing of the PCR products were performed as previously described (13). Targeted resequencing was performed on patients 9–11, using TruSight One sequencing panels (Illumina, San Diego, CA, USA), which included 4,813 genes associated with known clinical phenotypes, as previously described (26). We analyzed genes (including *GH*, *GHR*, *STAT5*, *STAT3*, *IGF1R*, *IGF1*, *IGF2*, *IGFBP3*, *IGFALS*, *IRS1*, *IRS2*, *ACAN*, *COL2A1*, *COL11A1*, *FLNB*, and *FGFR3*) associated with GH-IGF signals and growth plates, as well as other causative genes associated with short stature (*IHH*, *SHOX*, *PTPN11*, *NF1*, and *NPR2*) in the panel. Variant filtering was performed using SnpEff and SnpSift software, which collects variant-specific information by allelic frequency in all patients, and in the HGVD, GWAS, and dbSNP variant databases, as previously described (26).

In silico analysis

All variants and mutations detected in the sequence analysis described above were analyzed using three prediction algorithms (Mutation Taster, PolyPhen-2, and CADD) to calculate the prediction scores of pathogenicity in the *in silico* analysis.

Ethical approval

The Ethical Review Board of Tottori University Faculty of Medicine approved this study (questionnaire and data analysis approval: 20A068; sequence analysis approval: G173). The study was performed in accordance with the principles set out in the Declaration of Helsinki.

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Results

Identified heterozygous IGF1R mutations

We analyzed data from 11 patients with heterozygous IGF1R mutations (**Table 1**, **Fig. 1**). Eight of the 11 patients have been previously reported (7, 13, 27, 28). All of the identified mutations were heterozygous. **Table 1** shows the order of patients. The p.Arg739Gln mutation (Family A) resulted in a change in the cleavage site from Arg-Lys-Arg-Arg to Arg-Lys-Gln-Arg, which led to the failure of IGF1R proreceptor processing (13). The dominant negative effects of these mutations have not been evaluated. The p.Arg461Leu mutation (Family B) is located in the L2 domain of the IGF1R α chain, leading to a decrease in the internalization of IGF1R (7). p.Asp1135Glu (Family C) leads to a defect in tyrosine phosphorylation of IGF1R and has a dominant negative effect on IGF1R [28]. p.Gln1250* (Family D), p.Trp1249* (Family E), and p.Tyr888* (Family F) are nonsense mutations that lead to decreased or absent IGF1R protein expression, as confirmed using R^- cells transiently transfected with p.Tyr888* IGF1R (unpublished data). These findings resemble *IGF1R* haploinsufficiency (27). Family F entered our comprehensive genetic testing study for an unexplained growth disorder. With ethical approval (G173), the family underwent targeted resequencing using TruSight One sequencing panels. No alterations in any other potentially causative genes of short stature were detected in this family. We also analyzed the mutations using PolyPhen, Mutation Taster, and CADD scores. Based on previous functional analysis and *in silico* analyses, p.Arg461Leu was considered the mildest type. Although the CADD score for p.Asp1135Glu is lower than that for nonsense mutations (p.Gln1250*, p.Trp1249*, and p.Tyr888*), the p.Asp1135Glu mutation is considered the most severe missense mutation because of its dominant negative effect.

Phenotypic features

As shown in **Table 2**, almost all patients presented with short stature (below –2 SDS), while the mother in Family B and the father in Family F did not present with short stature. The Family B-mother harbored a p.Arg461Leu mutation, which led to decreased cell proliferation and decreased internalization of IGF1R, but with unaffected IGF1 signaling and cell proliferation (7). Furthermore, her CADD score was the lowest, and the prediction of amino acid substitution by Poly Phen was "benign." These findings suggest that the p.Arg461Leu

Table 1. *IGF1R* variants in this study

Patients (reference)	Nucleotide change (NM_000875.5)	Amino acid change	Prediction of amino acid substitution (Mutation taster)	Prediction of amino acid substitution (Poly phen)	CADD core (phred)
Family A-proband (13)	c.2216G>A	p.Arg739Gln	Disease-causing (*P* value, 0.9999)	Probably damaging with a score of 0.980 (sensitivity: 0.75; specificity: 0.96)	32
Family A-mother (13)	c.2216G>A	p.Arg739Gln	Disease-causing (*P* value, 0.9999)	Probably damaging with a score of 0.980 (sensitivity: 0.75; specificity: 0.96)	32
Family B-proband (7)	c.1382G>T	p.Arg461Leu	Disease-causing (*P* value, 0.9999)	Benign with a score of 0.007 (sensitivity: 0.96; specificity: 0.75)	24.3
Family B-mother (7)	c.1382G>T	p.Arg461Leu	Disease-causing (*P* value, 0.9999)	Benign with a score of 0.007 (sensitivity: 0.96; specificity: 0.75)	24.3
Family C-proband (28)	c.3405C>G	p.Asp1135Glu	Disease-causing (*P* value, 0.9999)	probably damaging with a score of 1.000 (sensitivity: 0.00; specificity: 1.00)	24.2
Family C-mother (28)	c.3405C>G	p.Asp1135Glu	disease causing (*P* value, 0.9999)	probably damaging with a score of 1.000 (sensitivity: 0.00; specificity: 1.00)	24.2
Family D-proband (27)	c.3748C>T	p.Gln1250*	Disease causing (*P* value, 1)		51
Family E-proband (27)	c.3746C>T	p.Trp1249*	Disease-causing (*P* value, 0.9999)		54
Family F-proband (–)	c.2664T>A	p.Tyr888*	Disease-causing (*P* value, 1)		33
Family F-sister (–)	c.2664T>A	p.Tyr888*	Disease-causing (*P* value, 1)		33
Family F-father (–)	c.2664T>A	p.Tyr888*	Disease-causing (*P* value, 1)		33

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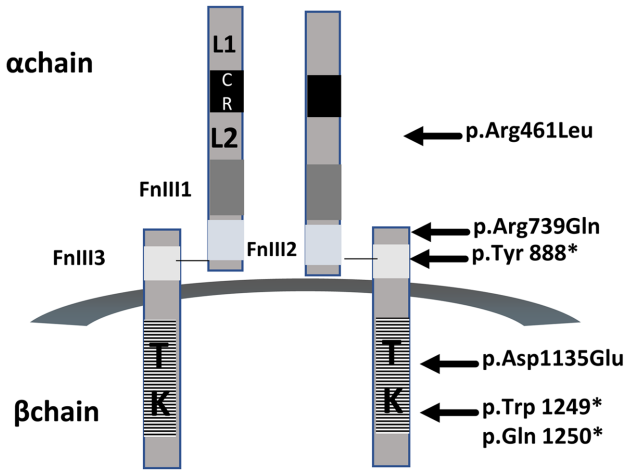

Fig. 1. *IGF1R* mutations identified in the present study. Schematic overview of IGF1R mutations in this study. All the mutations were heterozygous. The amino acid number of IGF1R refers to the IGF1R protein, including the 30 amino acid signal peptide. Abbreviations are: L1, leucine-rich region; CR, cysteine-rich region; L2, second leucine-rich region; FnIII fibronectin type 3 domain; FnIII, fibronectin type III domain; and TK, tyrosine kinase domain.

mutation is the mildest form in our study.

The Family F-father harbored the p.Tyr888* nonsense mutation. His final height was –1.93 SDS. He has a lower BW (–1.82 SDS). Data for his BH and HC were not available. Patients harboring mutations with higher CADD scores or dominant negative effects (p.Asp1135Glu) had relatively shorter statures than patients with other mutations. Patients with pathogenic *IGF1R* mutations are usually born with low BW. In the present study, all patients presented with a BW SDS below –1.26, but they did not always present SGA (< –10% tile [1.33 SDS]). Furthermore, BW and BH for the Family A-proband and Family F-sister did not meet the criteria for GH treatment for SGA short stature (both BW and BL were below –10% percentile; BW or BL must be below –2 SD), and were not able to receive GH treatment despite their short stature. Although the Family F-mother did not have the mutation, the proband, sister, and father in Family F harbored the same nonsense mutation (p.Tyr888*). However, they exhibited different phenotypes. The Family F-proband had SGA short stature, Family F-sister had short stature without SGA, and Family F-father was born SGA, but attained a normal height. These individuals did not show any other symptoms except growth problems. Surprisingly, serum IGF1 levels before rhGH treatment were not elevated in all patients (–0.56–3.44 SDS), and the proband and sister in Family F had lower serum IGF1 levels (–0.45, –0.56, respectively). Some patients (Family B-proband, Family C-proband, Family E-proband) showed elevated GH peak levels in the GH provocation test. All patients (Family A-proband, Family B-proband, Family C-proband Family D-proband, Family E-proband, Family F-proband and sister) with relevant data showed bone age delay (chronological age: bone age; mean 1. 68 ± 0.81, data not shown). Two of the patients had complications. Family A-proband displayed mental retardation (IQ score: 60). Family C-mother, who had the p.Asp1135Glu mutation, had type 2 diabetes. Although we could not evaluate whether the p.Asp1135Glu mutation has a dominant effect on the insulin receptor (unpublished data), the mutation might also have an effect on the insulin receptor. Although all patients had no clinodactyly, triangular face, hypotelorism, or a high-arched palate, nine of 11 patients had thin upper lips.

In summary, patients with heterozygous *IGF1R* mutations exhibited various phenotypes. The genotype may affect the phenotype, but not all patients exhibited short stature, had elevated serum IGF1 levels, or were born SGA.

rhGH therapy for patients with heterozygous IGF1R mutation

To date, many patients with *IGF1R* gene mutations have been administered rhGH treatment without side effects (5, 6, 9, 15, 17, 18, 22, 29). In this study, five patients (Family B-proband, Family C-proband, Family D-proband, Family E-proband, Family F-proband) received rhGH therapy for SGA-related short stature (**Table 3**, **Fig. 2**). Two patients (Family B-proband, and Family C-proband) completed rhGH therapy because of epiphyseal closure. Therapy was stopped for one patient (Family D-proband) at the patient's request before epiphyseal closure. The patient's growth rate had decreased as the physician had reduced the rhGH dose to 0.2 mg·kg^{-1}week^{-1} due to a markedly high IGF1 level. The patient did not show any other side effects, except an elevated serum IGF1 level. Family E-proband and Family F-proband continued rhGH treatment. All patients started GH therapy with low doses of rhGH (0.23–0.25 mg·kg^{-1}week^{-1}). Family C-proband and F-proband received higher doses of rhGH (0.31–0.35 mg·kg^{-1}week^{-1}) 1 yr after the start of therapy. Family C-proband also received an increased dose of rhGH (0.45 mg·kg^{-1}week^{-1}) 2 yr after the start of therapy. Family B-proband received rhGH as a trial for low-dose rhGH treatment for SGA short stature for 3 yr. She restarted rhGH treatment at 10 yr of age and was treated with a gonadotropin-releasing hormone analog from 10 to 12.4 yr of age. We only used data from rhGH treatment (**Table 3** and **Fig. 2A and B**). None of the patients experienced any obvious complications. The mean height ΔSDS for chronological age 1 yr after the initiation of rhGH treatment was 0.62 ± 0.278 SDS, which is similar to the effect reported in Japanese studies of rhGH therapy for SGA short stature (0.63 ± 0.32 SDS) (30). The other annual height ΔSDS we observed was also similar to previous reports on SGA-related short stature in Japan (30–32). The rhGH treatment to the heterozygous *IGF1R* mutation (Family C-proband, Family D-proband, Family E-proband) for 5 yr resulted

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Table 2. Patient characteristics

Patients (reference)	Amino acid change	Sex	Age	BW (SD)	BH (SD)	HC (SD)	Height*	GH therapy (duration of GH therapy)	Final height (SD)	Serum IGF-1 (SD)	GH peak value (μg/L)	Mild dysmorphic features	Complication	GnRH therapy (duration)
Family A-proband (13)	p.Arg739Gln	F	24	–1.26	–0.78			No	–2.30	1.41		Thin upper lip	Mental retardation	No
Family A-mother (13)	p.Arg739Gln	F	53	–2.29				No	–2.85	1.81		Thin upper lip		No
Family B-proband (7)	p.Arg461Leu	F	20	–1.66	–2.77		–3.43	Yes (2 y, and 4.5 y)	–1.81	0.09	37.4 (L-DOPA)	Thin upper lip		Yes (2 yr: 10.4 yr old→12.4 y)
Family B-mother (7)	p.Arg461Leu	F	46	–1.55	–0.24			No	–1.15			Thin upper lip		No
Family C-proband (28)	p.Asp1135Glu	F	18	–1.3	–2.16		–3	Yes (7.9 y)	–1.61	3.22	35.2 (Arginine)	Thin upper lip		Yes (4 mo: 12.3 yr)
Family C-mother (28)	p.Asp1135Glu	F	53	–2.23	–2.36			No	–3.98			Thin upper lip	Type 2 Diabetes	No
Family D-proband (27)	p.Gln1250*	M	18	–3.37	–2.08	–3.7	–3.09	Yes (6.4 yr)	–3.60	3.44	15.6 (Arginine)			No
Family E-proband (27)	p.Trp1249*	F	10	–3.01	–2.83	–2.63	–3	Yes (6 yr, ongoing)		0.36	28.32 (Clonidine)			No
Family F-proband (–)	p.Tyr888*	M	5	–2.49	–2.67	–1.66	–3.38	Yes (1 yr, ongoing)		–0.45	30.5 (GHRP-2)	Thin upper lip		No
Family F-sister (–)	p.Tyr888*	F	8	–1.27	–0.86	–0.12	–2.68	No		–0.56	65.5 (GHRP-2)	Thin upper lip		No
Family F-father (–)	p.Tyr888*	M	42	–1.82				No	–1.93			Thin upper lip		No

*Height before rhGH treatment or recent height.

in similar height gain (–3.03 ± 0.04–1.64 ± 0.57 SDS) compared with previous Japanese studies on rhGH therapy for SGA-related short stature (–3.02 ± 0.65–1.23 ± 0.91 SDS) (32). There was a significant difference ($p < 0.05$) between the heights 2–5 yr after rhGH treatment and the height before rhGH treatment. Interestingly, in Family C, the proband (p.Asp1135 Glu) had a normal final height (–1.61 SD) after rhGH treatment, while the Family mother, who had not received GH treatment, had severely short stature (–3.98 SD) (**Fig. 2D**, **Fig. 3**). **Figure 2C** shows the Δ height SDS with rhGH treatment (start to the final height). The Family D-proband, though had stopped rhGH therapy before epiphyseal closure. Height gain with rhGH treatment had been poor. The other two patients (probands in Family B and C) showed increased height gain with rhGH treatment (**Fig. 3**). These results, as well as those shown in **Figs. 2A, 2D**, and **Fig. 3**, suggest that rhGH therapy for patients with the heterozygous *IGF1R* mutation can be considered somewhat effective, which is consistent with previous studies (18, 29). Furthermore, the mean serum IGF1 level after rhGH treatment was significantly increased (**Table 3**, **Fig. 2B**). Although mean serum IGF1 at baseline was within the normal range (–1.23 ± 1.05 SDS), mean serum IGF1 SDS 1 yr after rhGH treatment exceeded 3 SDS (3.84 ± 1.29 SDS), increased to over 5.0 SDS (5.0 ± 1.27 SDS) after 2 yr of treatment, and reached 6.1 SDS (6.1 ± 0.34 SDS). There was no significant increase between from 2–5 yr after the treatment. Since Horikawa *et al.* (32) reported that the mean serum IGF1 SDS 1 and 5 yr after GH treatment of SGA short stature was 0.10 ± 1.68 and < 0 SD, respectively, the serum IGF1 level after GH treatment in patients with the heterozygous *IGF1R* mutation can be considered to have been extremely elevated in our study. There was a significant difference ($p < 0.05$) in serum IGF1 levels 5 yr after rhGH treatment and serum IGF1 levels before rhGH treatment.

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Table 3. GH treatment for heterozygous *IGF1R* mutations

		0 years	1 year	2 years	3 years	4 years	5 years
Family B-proband (p.Arg461Leu)	Height SDS	–3.43	–2.81	–2.34	–2.11		
	rhGH dose (mg·kg^{-1}week^{-1})	0.25	0.25	0.25	0.25		
	Annual Δ height SDS		0.62	0.47	0.23		
	Serum IGF1 level (SDS)	–0.32	1.72	1.61	2.72		
Family C-proband (p.Asp1135Glu)	Height SDS	–3	–2.7	–2.37	–2.06	–1.89	–2.01
	rhGH dose (mg·kg^{-1}week^{-1})	0.23	0.35	0.45	0.45	0.45	0.45
	Annual Δ height SDS		0.3	0.33	0.31	0.17	–0.12
	Serum IGF1 level (SDS)	3.22	4.36	5.04	4.36	4.94	5.59
Family D-proband (p.Gln1250*)	Height SDS	–3.09	–2.77	–2.53	–2.65	–2.46	–2.08
	rhGH dose (mg·kg^{-1}week^{-1})	0.23	0.23	0.23	0.2	0.2	0.2
	Annual Δ height SDS	0.32	0.24	–0.12	0.19	0.38	0
	Serum IGF1 level (SDS)	4.77	8.7	8.75	6.66	7.46	6.92
Family E-proband (p.Trp1249*)	Height SDS	–3	–2.09	–1.46	–1.28	–0.82	–0.82
	rhGH dose (mg·kg^{-1}week^{-1})	0.25	0.31	0.35	0.34	0.32	0.35
	Annual Δ height SDS	0.91	0.63	0.18	0.46	0	0
	Serum IGF1 level (SDS)	–0.22	4.2	4.51	4.76	3.97	5.78
Family F-proband (p.Tyr888*)	Height SDS	–3.38	–2.43				
	rhGH dose (mg·kg^{-1}week^{-1})	0.25	0.25				
	Annual Δ height SDS		0.95				
	Serum IGF1 level (SDS)	–1.28	0.22				
Mean (±SD)	Height SDS	–3.18 ± 0.19	–2.56 ± 0.27	–2.18 ± 0.42	–2.03 ± 0.49	–1.72 ± 0.68	–1.64 ± 0.58
	rhGH dose (mg·kg^{-1}week^{-1})	0.24 ± 0.0009	0.28 ± 0.045	0.32 ± 0.088	0.31 ± 0.095	0.32 ± 0.102	0.33 ± 0.102
	Annual Δ height SDS		0.62 ± 0.278	0.42 ± 0.148	0.12 ± 0.157	0.21 ± 0.165	0.065 ± 0.188
	Serum IGF1 level (SDS)	1.234 ± 1.045	3.84 ± 1.29	4.98 ± 1.27	4.63 ± 0.70	5.46 ± 0.85	6.10 ± 0.34

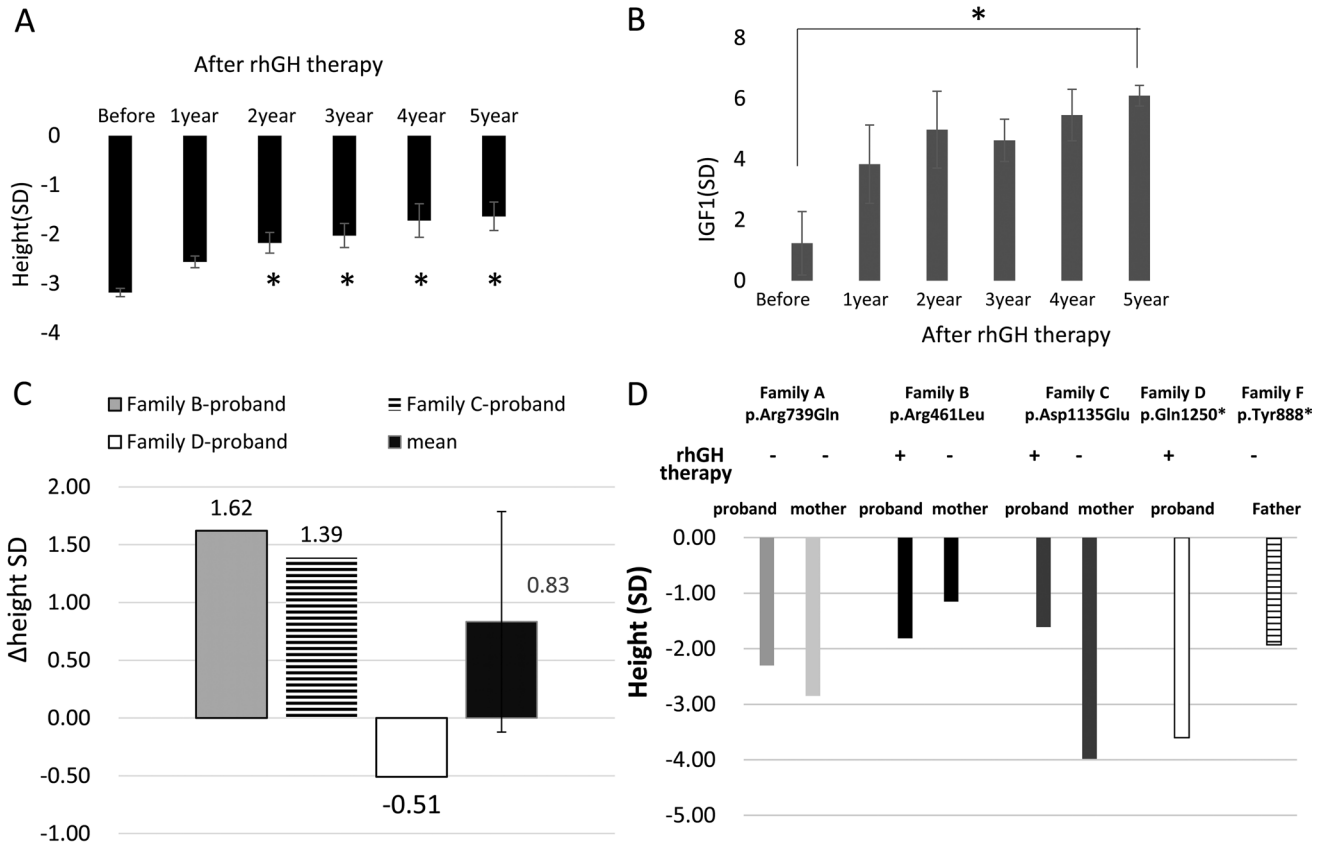

Fig. 2. Growth profiles and serum IGF1 after rhGH treatment from patients with *IGF1R* mutations. A: Change in height SDS during 5 yr of GH treatment. * $p < 0.05$ compared with the height before rhGH treatment, B: Change in mean serum IGF1 standard deviation score (SDS) during the 5 yr of GH treatment. *$p<0.05$. C: The Δ height SDS with rhGH treatment (start to the final height) D: Individual final height for patients with *IGF1R* mutations with or without rhGH treatment. Data are presented as median ± standard deviation.

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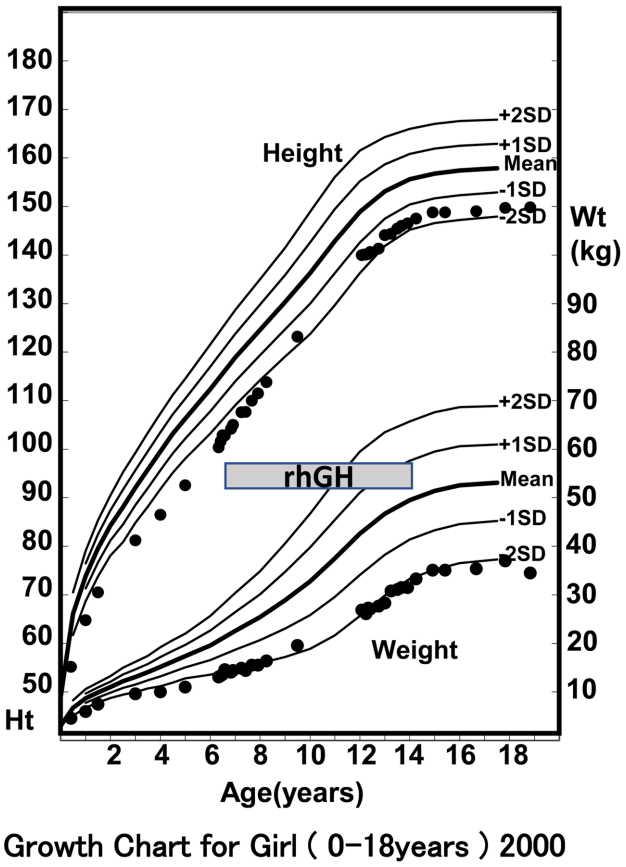

Fig. 3. Growth curve of Family C-proband. Height and weight were plotted on a cross-sectional growth chart for Japanese girls (0–18 yr) in 2000. Family C-proband was treated with rhGH treatment from 6–14 yr.

Discussion

The phenotype of short stature with *IGF1R* mutations remains poorly understood, and there is no approved therapy for short stature with *IGF1R* mutations, although a previous study reported the efficacy of GH treatment (5, 6, 9, 15, 17, 18, 22, 29). In this study, we report the genetic, clinical, and biochemical data of 11 patients with heterozygous *IGF1R* mutations. Five of the patients had heterozygous nonsense mutations. The other six had heterozygous missense mutations. The various phenotypes of heterozygous *IGF1R* mutations were determined. The data revealed that rhGH therapy in patients with heterozygous *IGF1R* mutations led to extreme increases in serum IGF1 levels, resulting in height gain without complications.

The classical and typical phenotypes of short stature with pathogenic *IGF1R* mutations and defects are SGA birth, elevated serum IGF1 levels, and GH peak values in the provocation test (9–12, 14). However, recent studies have revealed that some patients have a mild phenotype (normal stature, normal BW and BL, non-elevated serum IGF1 levels) (18, 21), which is consistent with our study. Surprisingly, Family A-proband was not born with SGA. Her height was approximately –2 SD, although her final height became more severely negatively impacted (–2.3 SD). The serum IGF1 for the proband and sister in Family F was < 0 SD. Normally, IGF1 is controlled by GH and IGF1R, and by nutrition and insulin. Furthermore, most of the serum IGF1 is composed of ternary complexes with IGFBP3 or IGFBP5 and IGFALS. This means that the serum IGF1 level does not accurately reflect the insensitivity of IGF1. The proband and sister in Family F did not have any major nutritional problems. Mild malnutrition might be hidden. However, the actual cause of low serum IGF1 levels is unknown. Furthermore, IGF1R is expressed in almost all tissues and cells, and there are tissue-specific differences in its distribution. This variability in the phenotype of Family F might correlate with the differential distribution of mutated IGF1R. Further studies are required to clarify this.

This phenotypic variability leads to the important issue of which patients should be tested for *IGF1R* mutations. Walenkamp *et al.* (18) determined the clinical score for molecular defects of *IGF1R* as follows: BW and/or BL, < –1 SDS; height SDS at presentation: < –2.5 SDS, HC at presentation: < –2 SDS, IGF1: > 0 SDS. A score of > 3 had 87% specificity (18). Scores > 3 had 55% sensitivity in our study. This lower sensitivity in our study might be related to the lack of information on HC at birth. However, the Family F-proband and sister, who had normal birth HC, had a score of 2 which means that the clinical score by Walenkamp *et al.* is insufficient for the diagnosis. Since both our study and previous studies reported higher serum IGF levels after GH treatment, and 9 of 11 patients had thin upper lips, the extremely higher serum IGF levels after GH treatment and thin upper lip may also be added to the clinical score. These findings highlight the need for a more specific clinical score for the detection of *IGF1R* mutations.

There are cases with *IGF1R* mutations that showed less response to GH treatment compared with most other SGA patients, and this lower response to GH is considered to be associated with IGF1 resistance. Some older reports classified SGA patients with GH resistance as having *IGF1R* gene anomalies (33, 34). However, patients with *IGF1R* mutations and defects have received GH treatment in many studies (5, 6, 9, 15, 17, 18, 22, 29), with all patients achieving moderately effective height gains without side effects. Furthermore, Göpel *et al.* (22) reported that some patients with *IGF1R* mutations respond poorly to therapy, while others are good responders, for reasons still unknown. Although our sample size was small, we observed a similar height gain compared with previous reports on Japanese patients undergoing rhGH therapy for SGA-related short stature (30–32). The present and previous findings suggest that rhGH therapy may be a first-line approach for short stature resulting from *IGF1R* mutations. There is no approved therapy for short stature due to *IGF1R* mutations or defects in Japan. Since patients with *IGF1R* mutations and defects without SGA cannot receive rhGH

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treatment in Japan (e.g., Family F-sister), an approved treatment for short stature due to *IGF1R* mutations is needed. rhGH treatment is a candidate option.

This study has several limitations. The sample size was small. Only five patients received rhGH therapy for SGA-related short stature. Of these, only three patients had reached their final height. One of these three patients (Family D-proband) stopped rhGH therapy because of elevated IGF1 levels before epiphyseal closure. Moreover, two of five patients (probands in Family E and F) were receiving ongoing rhGH treatment. The sample size was be greater to conclusively assess the efficacy of rhGH therapy for short stature due to *IGF1R* mutations.

This study provides the first data of the phenotype, growth profile, and rhGH therapy response in Japanese individuals with short stature and heterozygous *IGF1R* mutations. There are various phenotypes of heterozygous *IGF1R* mutations, including extremely high serum IGF1 levels, resulting in height gain without complications after rhGH therapy. Higher serum IGF1 levels after GH treatment are considered an important sign of *IGF1R* gene mutations. Since short stature due to IGF1R mutations has various phenotypes, and because diagnosis may be difficult, we need a more specific clinical score for the detection of *IGF1R* mutations.

Conflict of interests: None of the authors have any potential conflicts of interest associated with this research.

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