SGA Short Stature Bearing with a Novel Nonsense Mutation (p.W1249X) in the IGF1R Gene

Masanobu Fujimoto, Yuki Kawashima, Takashi Hamajima*, Naoki Miyahara,
Rei Nishimura, Keiichi Hanaki, Susumu Kanzaki
Division of Pediatrics and Perinatology, Tottori University Faculty of Medicine, Yonago, Japan
* Department of Pediatric Endocrinology and Metabolism, Aichi Children's Health and Medical Center, Aichi, Japan

Introduction

The type 1 insulin-like growth factor receptor (IGF1R) is widely expressed in nearly all mammalian tissues. The hormones IGF1 and -2 exert somatic growth effects, initiated by binding to IGF1R. IGF1 is an essential mediator of growth hormone (GH) activity, which is required during fetal and postnatal growth. Therefore, the interaction between IGF1 and IGF1R is critical for these developmental stages.

Heterozygous *IGF1R* mutations that are found concomitant with intrauterine and postnatal growth retardation have been identified in over 20 families. Some of them are linked to the etiology of short stature in previous studies.

We previously reported that a heterozygous nonsense mutation (p.Q1250X) led to decrease IGF1R protein expression through endoplasmic reticulum-associated protein degradation (ERAD) mechanism, resulted in growth failure.

In this report, we describe the clinical features of the patient with a novel mutation (p.W1249X) in the *IGF1R* gene and to evaluate the molecular characteristics of it.

Patient data & Results

Patient was a 3-year-old Japanese girl, who was born at 40 weeks of gestation, with a birth weight of 2,110 g (-3.0 SD), birth height of 44.3 cm (-2.8 SD), and head circumference of 30.0 cm (-2.1 SD). She had no family history of short stature (Figure 1). At the age of 2.4 years, her basal serum GH level was high (10.5 ng/mL), but serum IGF-1 level showed upper limit of normal [185 ng/ml (normal range: 32-213)]. At the age of 3.2 years, she presented with missing catch-up growth; her height was 82.9 cm (-3.1 SD); head circumference, 46.0cm (-1.6 SD) (Figure 2). Her karyotype was normal (46, XX). MRI of her brain showed within normal limit. The GH stimulation test showed a basal serum GH level of 2.42 ng/mL, which peaked at 20.76 ng/mL and 28.32 ng/mL after stimulation with arginine and clonidine, respectively. She had no signs of developmental delay and hearing impairment. Serum IGF-I level was normal [144 ng/ml (normal range: 40-227)].

Recombinant human GH therapy (0.25 mg/kg/wk) was initiated at the age of 3 years and 4 months. She responded well to the GH therapy after the 2 months of treatment (Figure 2).

Fig. 1. The family tree of the proband.

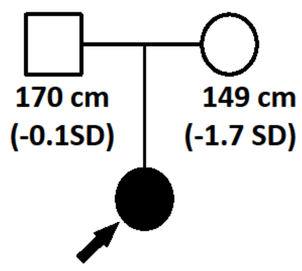
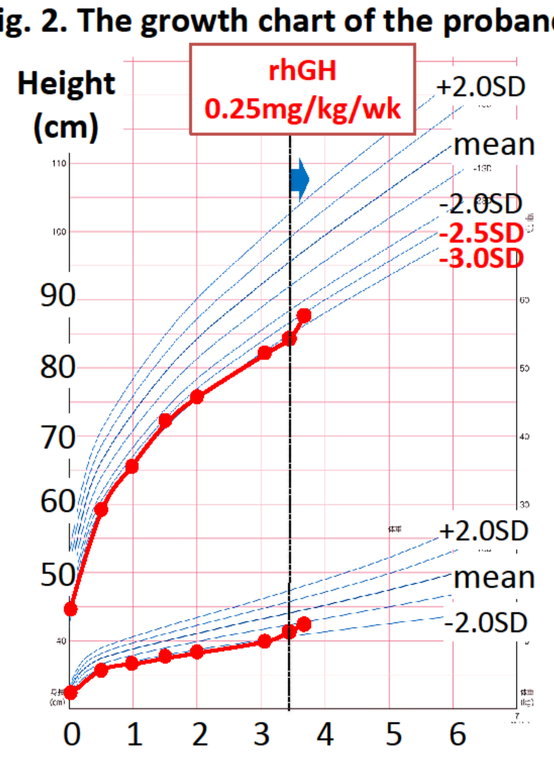


Fig. 2. The growth chart of the proband.



Physical Examination

Birth Height	44.3 cm	(-2.8 SDS)
Birth Weight	2,110 g	(-3.0 SDS)
Birth Head Circumference	30.0 cm	(-2.1 SDS)
At the age of 3.2 yrs		
Present Height	82.9 cm	(-3.1 SDS)
Present HC	46.0 cm	(-1.6 SDS)

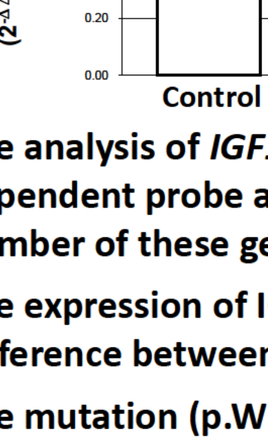
Laboratory data

GH	10.5 ng/mL	(at the age of 2.4 yrs)
	2.42 ng/mL	(at the age of 3.2 yrs)
IGF-1	144 ng/mL	(+0.6 SDS)
IGF-1 under GH treatment		
	277 ng/mL	(at the age of 3.4 yrs)

GH stimulation test (* Arginine 0.5g/kg, † Clonidine 0.10mg/m²)

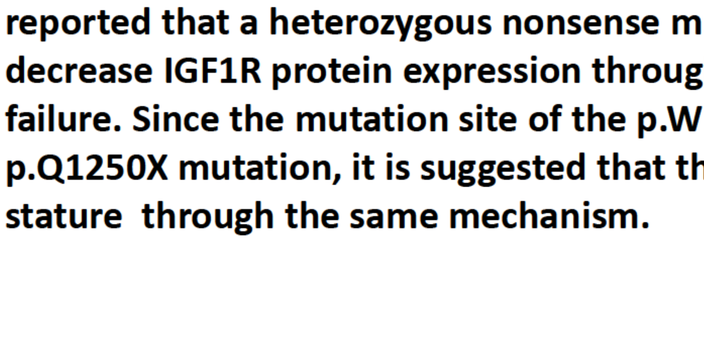
Time (min)	0	30	60	90	120
GH (ng/ml)*	2.65	4.73	20.8	8.25	3.75
GH (ng/ml)†	2.19	5.44	28.3	11.3	6.75

Fig. 3. The chromatogram of the case.



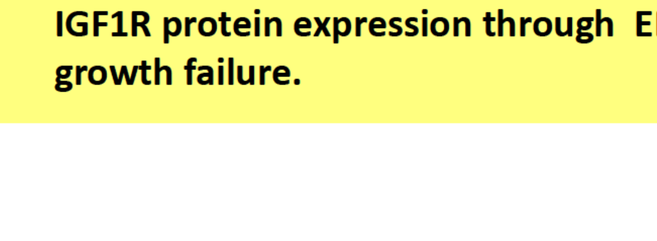
Sequencing of exon 21 of the *IGF1R* gene on the case shows a heterozygous point mutation from G to A (p.W1249X).
Her mother does not carry this mutation, and her father has not been gene-analyzed.

Fig. 4. Quantitative Real-time PCR analysis of IGF1R mRNA expression in whole blood cells from patients bearing with the W1249X or Q1250X mutation of IGF1R.



The expression of IGF1R mRNA showed no difference between the p.W1249X / p.Q1250X mutation and normal of IGF1R.

Fig. 5. The Expression of IGF1R protein in R⁻ cells transiently transfected with pcDNA6.1 encoding the wild-type IGF1R (WT) or p.W1249X mutant IGF1R.



The R⁻ cells transfected with p.W1249X showed the reduced IGF1R protein.

- The analysis of *IGF1R*, *ALS* and *IGFBP3* gene by multiplex ligation-dependent probe amplification (MLPA) was performed. The copy number of these genes was normal.
- The expression of IGF1R mRNA in whole blood cells showed no difference between p.W1249X mutation and normal of IGF1R.
- The mutation (p.W1249X) leads to decrease IGF1R protein expression.
- Mis-folded or mutated proteins are degraded by ERAD which is a cellular quality control mechanism for proteins. Previously, we reported that a heterozygous nonsense mutation (p.Q1250X) led to decrease IGF1R protein expression through ERAD, resulted in growth failure. Since the mutation site of the p.W1249X is located next to the p.Q1250X mutation, it is suggested that the p.W1249X result in short stature through the same mechanism.

Conclusions

- ✓ We identified a novel heterozygous nonsense mutation (p.W1249X) of the *IGF1R* gene in a 3-yr-old Japanese girl with SGA short stature.
- ✓ It is suggested that the mutation (p.W1249X) lead to decrease IGF1R protein expression through ERAD mechanism, result in growth failure.

ESPE 2015 405--P2
GH and IGF Physiology
Masanobu Fujimoto
DOI: 10.3252/pso.eu.54espe.2015
Poster presented at: 54th Annual Meeting 1-3 October ESPE 2015 BARCELONA European Society for Paediatric Endocrinology
PosterSessionOnline.com