



## Case Report

# Diagnosis of Chromosome 15q-Terminal Deletion Syndrome through Elevated Fasting Serum Growth Hormone Levels

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**Abstract:** Chromosome 15q26-qter deletion syndrome is a rare disease that causes prenatal and postnatal growth retardation, microcephaly, developmental delay, and congenital heart diseases, mainly due to haploinsufficiency of *IGF1R*. In addition, patients with pathogenic variants of the *IGF1R* show similar symptoms. We report the case of a 5-month-old girl with prenatal and postnatal growth retardation, microcephaly, and congenital heart disease. At 5 months of age, her length was 54.7 cm (−4.3 SD), her weight was 4.4 kg (−3.1 SD), and her head circumference was 37.4 cm (−2.8 SD), thus presenting severe growth retardation. Repeated pre-feeding serum GH levels were abnormally high (26.1–85.5 ng/mL), and IGF-1 levels (+0.16 to +1.2 SD) were relatively high. The 15q sub-telomere fluorescence in situ hybridization analysis revealed a heterozygous deletion in the 15q terminal region. Whole-genome single nucleotide polymorphism microarray analysis showed a terminal deletion of 6.4 Mb on 15q26.2q26.3. This is the first report showing that fasting GH levels are high in early infancy in patients with *IGF1R* abnormalities. In addition to relatively high IGF-1 levels, elevated fasting GH levels in early infancy may contribute to the diagnosis of *IGF1R* abnormalities.

**Keywords:** growth retardation; small-for-gestational age; congenital heart disease; growth hormone; IGF-1; *IGF1R*; 15q-terminal deletion



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## 1. Introduction

Chromosome 15q-terminal deletion syndrome (OMIM #612626) is a heterozygous deletion of chromosome 15q26-qter that causes prenatal and postnatal growth retardation, microcephaly, developmental delay, and various abnormalities [1]. Several genes in the 15q26 region, such as insulin-like growth factor 1 receptor (*IGF1R*) and nuclear receptor subfamily 2 group F member 2 (*NR2F2*), show different phenotypes resulting from heterozygous deletions. Heterozygous deletion of the *IGF1R* is associated with intrauterine growth retardation and postnatal growth deficiency, minor facial anomalies including microcephaly, micrognathia and triangular faces, and skeletal anomalies such as cubitus valgus, clinodactyly and brachydactyly [2]. Heterozygous deletion of the *NR2F2* is associated with congenital heart diseases (CHD), such as ventricular septal defect (VSD), atrial septal defect (ASD), coarctation of aorta, patent ductus arteriosus, and pulmonary stenosis [3,4]. The deletion of other genes in the 15q26 region may contribute to other phenotypic differences.

Since insulin-like growth factor 1 (IGF-1) and its receptor play an important role in skeletal growth and brain development, *IGF1R* deletions cause intrauterine and postnatal growth retardation, and mild developmental delay [5]. The binding of IGFs to its receptor results in the autophosphorylation of intracellular tyrosine residues, which activates the

phosphatidylinositide-3-kinase (PI3K)/AKT, mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) signaling pathways. This, in turn, stimulates cell proliferation and growth [6].

Similarly, several patients with pathogenic variants of *IGF1R*, mainly in the heterozygous state and rarely in the compound heterozygous state, have also been reported to exhibit growth retardation before and after birth [7,8]. Short children born small-for-gestational age (SGA) have been reported to possibly include patients with *IGF1R* pathogenic variants [9]. Indeed, variable phenotypic expression has already been reported, even in relatives carrying the same molecular defect, which makes the diagnosis of *IGF1R* defects difficult [8].

Although relatively high serum IGF-1 levels have been reported in patients with *IGF1R* abnormalities, the serum growth hormone (GH) levels in these patients remain unknown. We report the case of a girl with pre- and post-natal severe growth retardation, microcephaly, and ASD, where high serum GH levels in addition to relatively high IGF-1 levels led to a definitive diagnosis.

## 2. Case Presentation

The female patient presented with severe fetal growth retardation at 19 weeks of gestation. Fetal echocardiography revealed pericardial effusion and septal hypertrophy. She was delivered at 38 weeks of gestation by emergency cesarean section due to fetal distress. Her father's height was 174 cm, and her mother's height was 156 cm. Her birth weight was 2034 g (−2.6 SD), body length was 42 cm (−3.2 SD), and head circumference was 30.5 cm (−1.9 SD); she was born SGA. She had no skeletal abnormalities or dysmorphic facial features. Echocardiogram revealed an ASD type II and VSD. At one week of age, she presented with inspiratory stridor due to laryngomalacia, and required a high-flow oxygen nasal cannula to maintain oxygenation. In addition, nasogastric tube feeding was required due to feeding difficulties until 2 months of age. At 5 months of age, her length was 54.7 cm (−4.3 SD), her weight was 4.4 kg (−3.1 SD), and her head circumference was 37.4 cm (−2.8 SD). She showed delayed motor development, achieved head control at 5 months of age and could not rollover. On the other hand, her social and language skills were not delayed: her social smile was noted at 3 months of age and babbling at 4 months. The patient showed severe growth retardation; thus, she was referred to a pediatric endocrinologist. Repeated pre-feeding serum GH levels were abnormally high, and serum IGF-1 levels were slightly above the age-average levels (Table 1). Although the blood glucose level decreased at 3 months of age, the fasting blood glucose remained at the lower limit of normal between 60 and 90 mg/dL. No severe hypoglycemia was observed during the first 3 months, and after 3 months of age, blood glucose levels were in the normal range. Other tests, such as renal function, liver function, metabolic markers, thyroid function, and chromosomal G-band test also did not reveal any abnormalities. Abdominal ultrasonography showed no morphological abnormalities of the kidneys, and head MRI showed no structural abnormalities of the brain.

**Table 1.** Pre-feeding serum GH levels and IGF-1 levels.

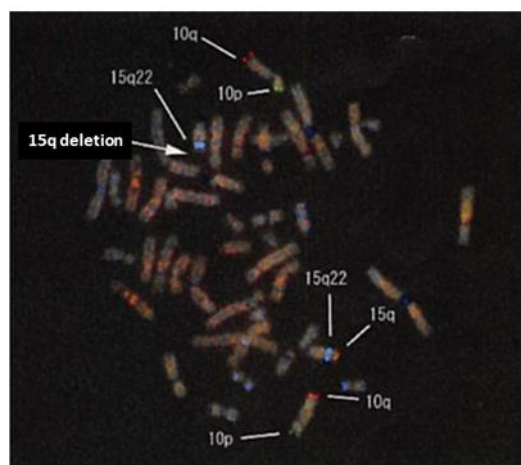
Age in Months	3 Months	4 Months	5 Months
Serum GH (ng/mL)	85.5	8.5	26.1
IGF-1 (ng/mL) (SDS) *	NA	75 (+0.16)	126 (+1.2)
Blood glucose (mg/dL)	57	NA	NA

GH, growth hormone; IGF-1, insulin-like growth factor 1; SDS, standard deviation score; NA, No data available; \*, The IGF-1 SDS values were calculated by the LMS method using the IGF-1 calculator ([https://pfizerpro.jp/cs/sv/ghw/support/igf1\\_checker.html](https://pfizerpro.jp/cs/sv/ghw/support/igf1_checker.html) (accessed on 19 June 2021) based on reference [10].

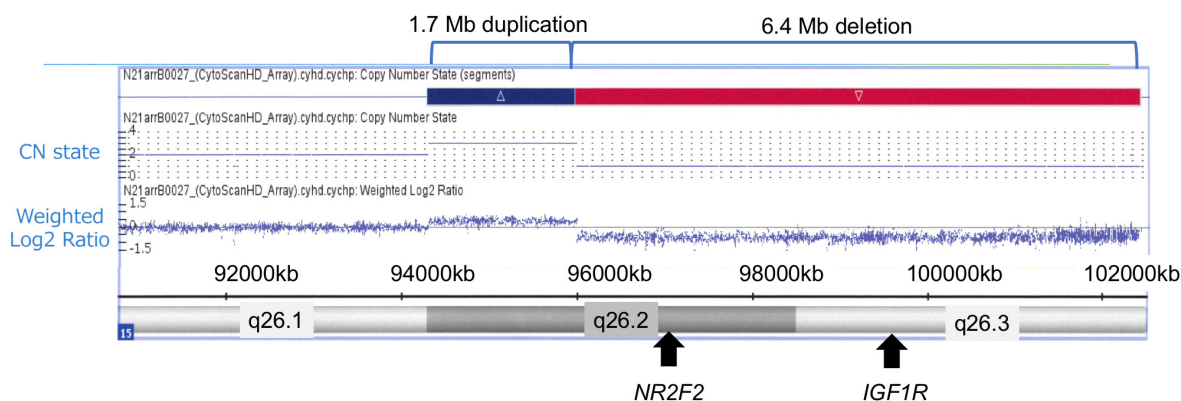
## 3. Diagnostic Assessment: Genetic Testing

We first suspected *IGF1R* deletion based on the severe growth retardation before and after birth, CHD, high GH levels, and relatively high IGF-1 levels, and performed

subtelomere fluorescence in situ hybridization (FISH) analysis focusing only on 15q. The 15q subtelomere FISH analysis revealed a heterozygous deletion in the 15q terminal region (Figure 1). Whole-genome single nucleotide polymorphism (SNP) array analysis using the Affymetrix Genome-Wide Human SNP Array 6.0 (Affymetrix, Santa Clara, CA, USA) showed a terminal deletion of 6.4 Mb on chromosome 15q26.2-26.3, which contains disease-causing OMIM genes, *NR2F2*, *IGF1R*, *MEF2A*, *ADAMTS17*, *CERS3*, *LINS1*, *ALDH1A3* and *CHSY1*, and 1.7 Mb duplication on 15q26.2 which does not contain the disease-causing OMIM gene (Figure 2). No other pathogenic copy number variation or copy number neutral loss of heterozygosity were observed in the SNP array. We diagnosed her with chromosome 15q26-qter deletion syndrome.



**Figure 1.** The result of fluorescent in situ hybridization (FISH) analysis of the peripheral blood sample.



**Figure 2.** The result of whole-genome single nucleotide polymorphism array analysis.

FISH was performed using the TelVysion multi-color FISH probe panel No.10. It contains probe for 10p (green), 10q (red), 15q (orange) and 15q22 (blue). The arrow indicates a deletion in the 15q terminal region.

The physical positions correspond to GRCh37/hg19 of the human genome assembly. The arrows indicate the positions of *NR2F2* and *IGF1R* on 15q26.2-26.3, contained in the deletion range.

#### 4. Discussion

Herein, we describe a 5-month-old girl with a chromosome 15q-terminal deletion syndrome, pre- and postnatal severe growth retardation, microcephaly, CHD, and high fasting GH levels in addition to relatively high IGF-1 levels. Among her 15q-terminal deletions, *NR2F2*, *IGF1R*, and *MEF2A* are genes in which heterozygous deletions cause clinical phenotypes. Among these, heterozygous deletion of *NR2F2* cause CHD and heterozygous

deletion of *IGF1R* cause pre- and post-natal severe growth retardation [1,11]. *MEF2A* has been reported to be associated with autosomal dominant inherited coronary artery disease [12]. Therefore, her current clinical features can be explained by the heterozygous deletion of *NR2F2* and *IGF1R*.

Early diagnostic markers for *IGF1R* abnormalities have not yet been identified. Most of the patients reported so far have been diagnosed after the age of 2 years due to the short stature of children born SGA. Walenkamp et al. [13] proposed a clinical score to drive molecular investigations of *IGF1R* abnormalities. This score includes the following 4 criteria: birth length or weight  $<-1$  SD, head circumference at first presentation  $<-2$  SD, height at first presentation  $<-2.5$  SD and serum IGF-1 levels above the mean for age and sex. While our patient was diagnosed in early infancy, she met all of these criteria. However, the initial IGF-1 level was only slightly above the age-average level, making it difficult to suspect *IGF1R* abnormalities.

It is known that newborns and young infants have low IGF-1 levels due to immaturity of the GH-IGF-1 axis [14]. However, IGF-1 levels in early infancy have not always been reported to be low, reflecting immaturity of the GH-IGF-1 axis. For example, the average IGF-1 level at 3–4 months of age has been reported to be 37.3–93 ng/mL [14]. Since undernourished infants with poor weight gain, such as our case, usually tend to have low IGF-1 levels, the serum IGF-1 levels in the case were determined to be relatively high IGF-1 levels. If IGF-1 levels are low, we also consider abnormalities in GH-IGF-1 signaling pathways such as Laron syndrome, IGF-1 deficiency, *STAT5B*, *ALS*, and *PAPPA2* deficiencies [15].

Theoretically, in addition to relatively high serum IGF-1 levels, serum GH levels should also be high in *IGF1R* abnormalities. A summary of *IGF1R* abnormalities with the described GH levels is presented in Table 2. Previous reports have shown that basal GH levels vary among patients but tend to be higher at younger ages. In the GH stimulation tests, GH peak levels were subnormal to mildly elevated in most cases. All but one of the patients were diagnosed after the age of one year. Typically, GH levels are high at birth, then fall sharply for the first few weeks, and slowly over the next few months reaching pre-pubertal levels around 6 months of age [16]. In particular, SGA newborns had higher serum GH levels at birth than normal newborns in all trimesters, but serum GH levels at 3 days after birth were not significantly different between the 2 groups [17]. Nevertheless, basal GH levels are clearly implicated in the alterations of GH secretion observed in various physiological states (stress, sleep, bleeding, fasting, hypoglycemia, exercise, etc.), and their assessment should be determined in the setting of age, blood glucose levels, and blood sampling procedures. Our patient had significantly higher basal GH levels at 3 months of age, which could be attributed to the testing in early infancy, relatively low blood glucose levels, and venipuncture procedures. High basal GH levels may also be a marker for suspicion of GH-IGF-1 insensitivity disorders in early infancy.

The mechanism of the deletion of the 15q26 region is unclear. The range of *IGF1R* deletions varies from deletion of the *IGF1R* exon level to an identifiable size by G-band analysis, with no specific deletion. In previous reports, *IGF1R* deletions have ranged from 19 kb to 11.2 Mb [8,18]. Besides the deletion of the 15q26.2–26.3 region, a 1.7 Mb duplication was observed in our patient, suggesting that the 15q26-ter deletion may have been caused by an inverted duplication although we have not actually confirmed this. In fact, a 15q-terminal deletion by inverted duplication has been reported [19]. The 1.7 Mb duplicated region upstream of the deletion region does not contain any OMIM disease-related genes. Therefore, we consider it unlikely that this duplication is involved in the phenotype.

*NR2F2* plays an important role in angiogenesis and heart development by participating in signaling between the endothelial and mesenchymal compartments [20]. The expression of *NR2F2* in the developing human fetal heart including the atria, coronary vessels, and aorta has been substantiated, and *NR2F2* mutations have been causally linked to isolated congenital heart disease, including atrio ventricular septal defect, tetralogy of Fallot, aortic

stenosis, VSD, coarctation of the aorta and hypoplastic left heart syndrome [11]. In this case, loss of function of *NR2F2* due to 15q26-ter deletion caused ASD and VSD.

In summary, to our knowledge, this is the first report showing that fasting GH levels are high in early infancy in patients with *IGF1R* abnormalities. Previous reports may not necessarily have shown high GH levels because the patients with *IGF1R* abnormalities were diagnosed after the age of 1 year. However, this study has several limitations. Firstly, since blood was drawn at the same time as the venipuncture, a stress-induced GH elevation cannot be ruled out. Secondly, blood glucose levels were not measured at the same time as the GH test except for once; therefore, we do not know the contribution of hypoglycemia to high serum GH levels. Further clinical studies are needed for analyzing more cases.

**Table 2.** Summary of *IGF1R* abnormalities with described serum GH levels in the previous literatures.

IGF-1 (ng/mL) (Range * or SDS **)	Basal GH (ng/mL)	Peak GH (ng/mL)	<i>IGF1R</i> Abnormalities (Deletion Size)	Age	Sex	Authors (Reference Number)
126 (+1.2) **	8.5–85.5	NA	15q26.2- > 15qter (6.4 Mb)	5 m	F	Our case
72 (33–102) *	NA	7.6	p.Asp1105Glu	7 m	M	Solomon-Zemler et al. [21]
231 (+2.9) **	8.0	NA	p.Arg1256Ser	1 y 5 m	M	Juanes et al. [22]
211 (+1.7) **	1.2	NA	p.Tyr865Cys	1 y 9 m	F	Juanes et al. [22]
NA	2.7	10.0	15q26.1- > 15qter (5 Mb)	1 y 10 m	F	Okubo et al. [23]
16 (−4.67) **	7.6	NA	p.Tyr487Phe	2 y	F	Labarta et al. [24]
102 (51–303) *	6.9	17.3	p.Met1247Thr	2 y 1 m	F	Yang et al. [25]
185 (32–213) *	10.5	Normal	p.Trp1249X	2 y 5 m	F	Fujimoto et al. [26]
58 (+0.5) **	0.27	NA	p.Asn359Tyr	2 y 8 m	M	Juanes et al. [22]
344 (+3.3) **	7.6	NA	p.Arg431Leu	3 y 0 m	F	Kawashima et al., 2012 [27]
298.4 (+3.8) **	NA	Normal	p.Gln1250X	3 y 0 m	M	Fujimoto et al. [26]
268 (+2.1) **	2.4	14.3	15q26.2- > 15qter	3 y 1 m	F	Gonc et al. [7]
NA (−0.8 to +1.4) **	NA	9.8	p.Arg59X	3 y 2 m	M	Raile et al. [28]
239 (+1.6) **	NA	62	p.Gly1050Lys	3 y 3 m	F	Walenkamp et al. [29]
253 (54–161) *	High	High	p.Glu1211Lys/p.Glu234Lys	3 y 4 m	M	Fang et al. [30]
Normal	Normal	Normal	15q26.1- > 15qter (9.15 Mb)	4 y	F	Benbouchta et al. [31]
159 (+2.6) **	NA	Normal	p.Tyr387X	4 y	M	Mohn et al. [32]
63 (NA)	NA	51	p.Arg108Gln/p.Lys115Asn	4 y 5 m	F	Abuzzahab et al. [33]
203 (+2.5) **	2.5–7.5	NA	15q26.2- > 15qter (5.2 Mb)	4 y 5 m	F	Walenkamp et al. [34]
222 (+2.3) **	NA	5.7–21.2	p.Arg59X	5 y 3 m	M	Abuzzahab et al. [33]
NA (+1.1) **	3.0	12.1	p.Arg511Trp	5 y 8 m	F	Leal et al. [35]
344 (+3.3) **	NA	Normal	p.Asp1105Glu	6 y 0 m	F	Kawashima et al., 2014 [36]
145 (−0.66) **	NA	3.72	15q26.2- > 15qter (3.9 Mb)	6 y 5 m	F	Yoon et al. [37]
200 (+0.76) **	0.9–2.4	Normal	p.Gly1125Ala	7 y 5 m	F	Kruis et al. [38]
NA (+1.2 to +2.2) **	NA	4.4–21	p.Arg59X	8 y 5 m	M	Raile et al. [28]
164 (123–275) *	0.42	7.6–9.1	p.Met1123Argfs * 14	9 y 6 m	M	Fang et al. [5]
509 (51–303) *	0.36	15.4	p.Cys248Trp	10 y 8 m	F	Yang et al. [25]
291 (+1.53) **	0.15	11.2	15q26.3- > 15qter	12 y 8 m	M	Gonc et al. [7]
350 (+0.6) **	3.7	12.9	p.Ile678Val	13 y	M	Gonc et al. [7]
950 (+7) **	0.86	NA	p.Arg10Leu	13 y 5 m	F	Gannagé-Yared et al. [39]
100 (−1.11) **	0.46	10	p.Arg461His	13 y 5 m	M	Gonc et al. [7]
404.3 (165–300) *	7.4	10.6	p.Arg481Gln	13 y 6 m	F	Inagaki et al. [40]
671 (+2.13) **	25.3	NA	p.Thr79Met	13 y 8 m	F	Gonc et al. [7]
112 (−2.44) **	0.63	20.3	p.Lys704Arg	15 y	M	Gonc et al. [7]
389.8 (244–787) *	NA	18.8	p.Ala140Glyfs * 5	15 y	F	Wang et al. [41]
537 (+0.85) **	0.7	11.7	p.Leu19Profs * 27	16 y 3 m	M	Gonc et al. [7]

IGF-1, insulin-like growth factor 1; GH, growth hormone; SDS, standard deviation score; NA, data not available; y, years; m, months; M, male; F, female; Peak GH, GH peak was assessed in stimulation test; \*, The ranges of IGF-1 levels are those described in the respective manuscripts; \*\*, Patients' IGF-1 SDS values reported in the respective manuscripts.

## 5. Conclusions

In addition to relatively high IGF-1 levels, elevated fasting GH levels in early infancy may contribute to the diagnosis of *IGF1R* abnormalities. Routine testing of specific parameters when growth retardation is detected during pregnancy will definitely enhance the knowledge of the relation to elevated GH and IGF-1 levels.



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