

Case Report

Early-Life Presentation and Phenotypic Variability of the *IGF1R* c.3595G>A (p.Gly1199Arg) Variant: A Case ReportOktay MA et al. *IGF1R* Gly1199Arg and Growth FailureMehmet Ali Oktay¹, Aylin Kılınç Uğurlu¹, Esra Döğeri¹, Gülsüm Kayhan², Mahmut Orhun Çamurdan¹, Aysun Bideci¹¹Gazi University Faculty of Medicine, Department of Pediatric Endocrinology, Ankara, Türkiye²Gazi University Faculty of Medicine, Department of Genetics, Ankara, Türkiye

Abstract

Most infants born small for gestational age (SGA) achieve spontaneous catch-up growth within the first two years of life; however, a subset remains growth-restricted and warrants further evaluation. Persistent short stature accompanied by microcephaly should prompt consideration of an underlying monogenic disorder. We report a term male infant born with severe SGA (birth weight -3.8 SDS; birth length -2.2 SDS) and microcephaly. At 16 months of age, his height was -2.7 SDS and head circumference -3.1 SDS. Initial insulin-like growth factor 1 (IGF-1) concentration was mildly decreased (-1.0 SDS) with normal insulin-like growth factor binding protein-3 (IGFBP-3, +1.0 SDS). Following nutritional optimization, IGF-1 increased to supranormal levels (+2.0 SDS), yet linear growth remained persistently below -2 SDS without sustained catch-up. Genetic analysis identified a heterozygous *IGF1R* c.3595G>A (p.Gly1199Arg) variant inherited from his short-statured mother. The variant was absent in population databases, localized within the intracellular tyrosine kinase domain, and predicted to be deleterious by multiple in silico tools (REVEL 0.98; AlphaMissense 1.0), supporting likely pathogenic classification. Previously reported individuals carrying this variant were evaluated later in childhood or adolescence. This case represents the earliest documented presentation and highlights a biochemical-auxological dissociation characterized by elevated IGF-1 levels without proportional linear growth, consistent with impaired receptor-mediated signaling. This report broadens the phenotypic and temporal spectrum of the *IGF1R* Gly1199Arg variant and underscores the importance of early molecular evaluation in SGA infants with persistent microcephaly and inadequate catch-up growth.

Keywords: *IGF1R*, Gly1199Arg, small for gestational age, microcephaly, growth failure

What is already known on this topic?

Heterozygous *IGF1R* variants cause SGA with persistent postnatal growth failure and microcephaly. Circulating IGF-1 levels are often normal or elevated due to receptor-level resistance.

What this study adds?

The youngest reported individual carrying the *IGF1R* Gly1199Arg variant. Detailed early-life biochemical dynamics demonstrating nutritional IGF-1 recovery without proportional linear growth. Practical clinical indicators supporting early genetic referral in SGA infants with microcephaly.

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Introduction

The insulin-like growth factor (IGF) signaling pathway plays a pivotal role in human prenatal and postnatal growth. The insulin-like growth factor 1 receptor (*IGF1R*) encodes a transmembrane tyrosine kinase receptor that mediates the biological effects of insulin-like growth factor 1 (IGF-1) and insulin-like growth factor 2 (IGF-2) through activation of intracellular signaling cascades regulating cellular proliferation, differentiation, and survival (1-6). Disruption of this pathway results in impaired fetal growth and persistent postnatal growth failure.

Heterozygous pathogenic variants in *IGF1R* are increasingly recognized as an important monogenic cause of small-for-gestational-age (SGA) birth associated with microcephaly and failure of postnatal catch-up growth (1, 2, 5). In contrast, biallelic mutations typically lead to more severe phenotypes including profound intrauterine growth restriction (IUGR), intellectual disability, and congenital anomalies (2, 5). Among SGA children who do not demonstrate adequate catch-up growth, *IGF1R* defects represent one of the few identifiable molecular etiologies.

Clinically, *IGF1R*-related growth failure may overlap with other conditions such as Silver-Russell syndrome (SRS) and SHORT syndrome (short stature, hyperextensibility, ocular depression, Rieger anomaly, and teething delay); however, microcephaly remains a distinguishing and highly suggestive feature (7-9). Moreover, circulating IGF-1 concentrations are often normal or mildly elevated, reflecting partial receptor-level resistance rather than impaired hormone production (1, 9).

The c.3595G>A (p.Gly1199Arg) variant has previously been reported in the European EPIGROW cohort and in a large *IGF1R* series by Giabicani et al. (10, 11). However, previously described individuals were evaluated during late childhood or adolescence, and detailed early-life phenotypic and biochemical characterization of this specific variant remains limited. Here, we report the youngest described patient carrying the *IGF1R* Gly1199Arg variant, presenting in infancy with severe SGA, persistent growth failure, and microcephaly. By comparing our findings with previously published cases, we aim to refine the phenotypic spectrum and provide additional insight into early clinical recognition and biochemical dynamics associated with this variant.

Case Presentation

A 16-month-old boy was referred to our pediatric endocrinology clinic for evaluation of persistent growth failure. He was born at 38 weeks of gestation to healthy, non-consanguineous parents following an uneventful pregnancy without maternal hypertension, diabetes, or infection. Birth weight was 1,975 g (-3.8 standard deviation score [SDS]) and birth length was 45 cm (-2.2 SDS), consistent with SGA status. Head circumference at birth was below -2 SDS.

Parental heights were 147 cm (-2.7 SDS) for the mother and 182.4 cm (+1.0 SDS) for the father, resulting in a mid-parental target height of 171.2 cm (-0.8 SDS). Maternal head circumference was 53.5 cm (-2.11 SDS), consistent with mild microcephaly. Maternal serum IGF-1 concentration was within the normal range (+1.0 SDS).

At presentation (1 year 4 months), length was 72.5 cm (-2.7 SDS), weight 6.8 kg (-4.0 SDS), and head circumference 43.5 cm (-3.1 SDS), confirming proportionate short stature with microcephaly. Body mass index (BMI) was 12.9 kg/m² (-3.2 SDS). Physical examination revealed reduced subcutaneous fat and mild hypotonia without limb asymmetry or disproportion. Mild craniofacial dysmorphic features were noted, including triangular head configuration with brachycephaly, epicanthal folds, upslanting palpebral fissures, retrognathia, broad nasal bridge, thin lips, prominent ears with a prominent antitragus, sparse eyelashes, and hypoplastic fingernails. Testicular volume was 2 mL bilaterally, and penile length was appropriate for age. There was no hepatosplenomegaly.

Laboratory investigations showed normal thyroid function, liver enzymes, renal parameters, and negative celiac serology. Serum albumin and prealbumin levels were within normal limits, suggesting mild rather than severe malnutrition. Serum IGF-1 was 46.1 ng/mL (-1.0 SDS), and insulin-like growth factor binding protein 3 (IGFBP-3) was within the normal range (+1.0 SDS). Bone age corresponded to chronological age. Brain magnetic resonance imaging and abdominal ultrasonography were unremarkable. At 2 years of age, developmental evaluation using the Denver Developmental Screening Test II showed a marked delay in the language domain and mildly below age-expected performance in the fine motor domain, while social interaction was preserved.

Nutritional optimization was initiated. Over subsequent follow-up, caloric improvement was associated with a marked increase in IGF-1 levels, reaching +2.0 SDS at 2 years 7 months and +1.5 SDS at 3 years, while IGFBP-3 increased to +2.5 SDS. Despite biochemical normalization and transient improvement in growth velocity, height SDS remained persistently around -2.0 without sustained catch-up growth. Longitudinal auxological and biochemical data are summarized in Table 1.

Given persistent postnatal growth failure in the context of SGA and microcephaly, targeted next-generation sequencing was performed. A heterozygous *IGF1R* c.3595G>A (p.Gly1199Arg) variant (NM_000875.5) was identified. Sanger sequencing confirmed maternal inheritance. According to American College of Medical Genetics and Genomics (ACMG) criteria, this variant was classified as likely pathogenic (Figure 1). The absence of the variant in population databases (PM2), its location within the intracellular tyrosine kinase domain of *IGF1R*, a critical functional region (PM1), supportive computational evidence predicting a deleterious effect (REVEL score: 0.98; AlphaMissense score: 1.0; PP3), and segregation with short stature in the mother collectively supported this classification. Taken together, these criteria fulfill the ACMG framework for a likely pathogenic variant and provide molecular evidence consistent with the observed clinical phenotype.

Recombinant growth hormone (rGH) therapy was discussed as a potential therapeutic option; however, the family declined treatment.

Discussion

Heterozygous *IGF1R* variants represent a well-established genetic cause of SGA associated with persistent postnatal growth failure and microcephaly (1, 2, 5). The *IGF1R* protein functions as a transmembrane tyrosine kinase receptor mediating IGF-1-dependent activation of intracellular signaling pathways, primarily the MAPK/ERK and PI3K-AKT cascades, which regulate cellular proliferation and survival (6). Disruption of this signaling axis results in impaired fetal growth and variable postnatal growth trajectories.

Cohort-based studies indicate that heterozygous *IGF1R* defects account for a small but clinically relevant subset of persistent short stature in children born SGA. In clinically selected short SGA cohorts without adequate catch-up growth, *IGF1R* defects have been identified in approximately 1.5-3% of patients, supporting their role as a rare but recurrent cause of SGA-associated short stature (12, 13). Consistent with this, prenatal growth impairment is highly prevalent among individuals with confirmed *IGF1R* defects. In the cohort reported by Giabicani et al., 90.9% of affected individuals were born SGA, while Walenkamp et al. reported mean birth weight and birth length SDS values of -2.1 and -2.7, respectively, further supporting the prominent prenatal impact of impaired *IGF1R* signaling on growth (9, 11). In a Japanese series, 4 of 13 patients carrying heterozygous pathogenic *IGF1R* variants did not fulfill SGA criteria at birth, indicating that although SGA is a prominent and highly suggestive feature of *IGF1R*-related disease, its absence does not exclude the diagnosis (14).

The c.3595G>A (p.Gly1199Arg) variant has previously been described in the European EPIGROW cohort (10) and in the large *IGF1R* series reported by Giabicani et al. (11). However, previously published individuals were evaluated during late childhood or adolescence. In contrast, our patient was diagnosed at 16 months of age, representing the youngest reported individual carrying this specific variant to date. This early presentation underscores that *IGF1R*-related growth impairment may be clinically recognizable within the first two years of life, particularly in infants presenting with severe SGA and microcephaly.

Comparison of reported cases (Table 2) demonstrates notable phenotypic variability associated with the same variant. In the EPIGROW cohort, the affected adolescent exhibited severe short stature (height SDS -4.23) and microcephaly (-3.03 SDS), with only moderate prenatal growth restriction (birth weight SDS -1.44) (10). In the Giabicani series, the patient presented with SGA birth (-2.1 SDS), marked microcephaly (-3.7 SDS), and achieved a height gain of +1.4 SDS following rGH therapy, although final height remained -2.9 SDS (11). In contrast, our patient demonstrated more severe prenatal growth restriction (birth weight -3.8 SDS) and early postnatal growth failure, further expanding the phenotypic spectrum of the Gly1199Arg variant.

Beyond prenatal growth restriction, *IGF1R*-related disorders show substantial phenotypic and biochemical heterogeneity during postnatal follow-up. In the series reported by Walenkamp et al., height SDS at presentation ranged from -5.5 to -1.7 and head circumference SDS from -4.2 to -0.5, illustrating the broad variability in postnatal growth failure and microcephaly among affected individuals (9). Final or near-final height outcomes are likewise variable: in the cohort reported by Giabicani et al., final height was -2.3 SDS overall (range, -4.2 to 1.0), while untreated individuals had a median final height of -2.0 SDS (range, -4.2 to 1.0) (11). Additional manifestations reported across studies include feeding difficulties, failure to thrive, mild dysmorphic features, and variable neurodevelopmental outcomes, ranging from developmental delay in some patients to normal intelligence in others (9, 11, 14, 15). Serum IGF-1 concentrations are also heterogeneous. Although IGF-1 levels are often normal or elevated in *IGF1R* defects, low concentrations have also been described in several patients, particularly in association with poor appetite, failure to thrive, or nutritional compromise (9, 12, 15). Consistent with this, IGF-1 values ranged from -2.44 to +2.13 SDS in the cohort reported by Göncü et al. (15), and in the Japanese series by Kawashima et al., only 3 of 12 patients had IGF-1 levels above +2 SDS, whereas 3 had values below 0 SDS (14). Larger cohorts have also expanded the adult spectrum of *IGF1R*-related disease by describing metabolic complications such as diabetes, hypertension, hyperlipidemia, and occasional gonadal dysfunction (11, 15). Overall, these data highlight that both the phenotypic presentation and biochemical profile of *IGF1R*-related disorders are variable, providing an important framework for interpreting the longitudinal findings observed in our patient.

A particularly informative aspect of our case is the dynamic biochemical profile. Initial IGF-1 levels were mildly decreased in the context of undernutrition but increased to supranormal values (+2.0 SDS) following nutritional optimization, confirming preserved hepatic IGF-1 production capacity. Although normal or elevated IGF-1 concentrations are commonly observed in *IGF1R*-related disorders due to receptor-level resistance (1, 9–11), the absence of proportional catch-up growth in our patient despite supranormal IGF-1 levels supports impaired receptor-mediated signaling rather than primary hormone deficiency. Importantly, this biochemical dissociation was observed in the absence of rGH therapy, distinguishing our case from previously reported patients in whom IGF-1 elevation was mainly documented during growth hormone treatment. These findings further emphasize that biochemical normalization of IGF-1 does not exclude receptor-level dysfunction in SGA infants with microcephaly.

Compared with previously reported individuals carrying the same p.Gly1199Arg variant, our patient demonstrated a relatively milder degree of postnatal short stature during follow-up, with height improving from -2.7 SDS at presentation to approximately -2.0 SDS after nutritional optimization. Several factors may contribute to this observation. First, our patient was evaluated substantially earlier than previously reported cases, and long-term growth outcomes remain unknown. Second, the father's normal-to-tall stature (height SDS +1.0) may have partially offset the growth-restricting effect of the variant and contributed to a relatively favorable growth trajectory. Third, improvement in nutritional status was associated with increased growth velocity and partial catch-up growth. Nevertheless, stature remained around -2 SDS during follow-up, and it remains uncertain whether complete catch-up growth will occur. Continued longitudinal follow-up will therefore be necessary to determine whether adult height approaches the target range.

The localization of the Gly1199 residue within the tyrosine kinase domain further supports a functional impact on receptor signalling, consistent with the deleterious predictions obtained from *in silico* analyses. The presence of mild craniofacial dysmorphic features in our patient aligns with previously reported *IGF1R*-associated phenotypes, strengthening the genotype–phenotype correlation and reinforcing the clinical suspicion prior to molecular confirmation.

Microcephaly was consistently observed across reported cases and remains a key clinical clue in differentiating *IGF1R* related growth failure from other SGA associated conditions such as Silver–Russell syndrome (8, 9). Application of the clinical scoring system proposed by Walenkamp et al. (9) further supports the indication for molecular testing in our patient, who fulfilled three of four criteria at initial evaluation and subsequently met the biochemical criterion during follow-up.

Regarding treatment, response to rGH therapy in *IGF1R* defects has been heterogeneous (9, 11). Although some individuals demonstrate moderate height gain, circulating IGF-1 levels are often elevated at baseline or rise markedly during treatment, potentially limiting dose escalation (9, 11). Even when growth acceleration is achieved, final height may remain below target range, reflecting the intrinsic receptor-level signaling defect (11). Recently, Çelik et al. reported long-term recombinant rGH therapy in a patient with an *IGF1R* deletion associated with delayed puberty and central hypothyroidism. Despite the complex phenotype, prolonged rGH treatment resulted in improved linear growth, although final height remained below the target range, further supporting the variable therapeutic response observed in *IGF1R*-related disorders and suggesting that treatment outcomes may also be influenced by the underlying molecular defect and associated clinical features (16). These observations suggest that while rGH may offer benefit in selected cases, therapeutic expectations should remain cautious and individualized. While rGH therapy was declined in our case, early molecular diagnosis may facilitate realistic counseling and informed treatment decisions. In addition, long-term follow-up of patients with *IGF1R* variants should include metabolic surveillance, as altered insulin signaling and features of metabolic syndrome have been reported in adulthood (11). Intrafamilial variability was also evident, as the variant was inherited from the short-statured mother, consistent with previously reported variable expressivity in heterozygous *IGF1R* mutations (2, 11).

Taken together, our findings refine the phenotypic characterization of the *IGF1R* Gly1199Arg variant by demonstrating that receptor-level dysfunction may become clinically evident during infancy. The combination of severe SGA, persistent microcephaly, and biochemical dissociation between circulating IGF-1 levels and linear growth represents a clinically recognizable pattern that should prompt early molecular evaluation. Although the Gly1199Arg variant has previously been reported, detailed early-life clinical and biochemical dynamics have not been described. By documenting these features, our case broadens the temporal and phenotypic spectrum of *IGF1R*-related growth impairment and underscores the importance of considering receptor-level defects in SGA infants who fail to demonstrate adequate catch-up growth despite normalization of IGF-1 concentrations.

Conclusion

This report expands the clinical spectrum of the *IGF1R* Gly1199Arg variant by describing the earliest reported presentation and detailed early-life biochemical dynamics. Severe SGA combined with microcephaly should prompt consideration of *IGF1R* defects. Early genetic evaluation allows timely diagnosis and individualized management planning.

Ethics Informed Consent: An informed consent form was obtained from the patient's parents. **Acknowledgments:** The authors thank the patient and his family for their consent to publication.

Conflict of Interest: None declared.

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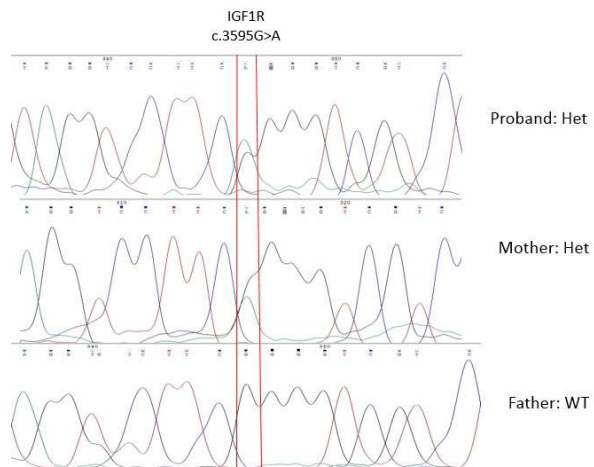


Figure 1. Sanger sequencing chromatograms of the *IGF1R* family

Sanger sequencing chromatograms demonstrating the heterozygous *IGF1R* c.3595G>A (p.Gly1199Arg) variant in the proband and his mother. The electropherogram shows a G>A substitution confirming maternal inheritance of the variant.

Chronological age (years-months)	Bone age	Height (cm)/SDS	Weight (kg)/SDS	BMI (kg/m ²)/SDS	Height velocity (cm/year)	IGF1 (ng/mL)/SDS	IGFBP3 (ng/mL)/SDS
1 y 4 m	-	72.5/-2.7	6.8/-4.0	12.9/-3.2	7.5	46.1/-1.0	3008/+1.0
2 y 2 m	-	81.2/-2.18	8.5/-3.7	12.8/-3.0	11.6	-	-
2 y 7 m	-	85.5/-2.1	9.6/-3.3	13.1/-2.6	8.5	196.6/ +2.0	-
3 y	2 y 8 m	86.6/-2.0	10.1/-3.3	13.4/-2.0	5.8*	162.8/+1.5	4728/+2.5

*Velocity calculated over the preceding interval
 BMI: body mass index; IGF-1: insulin-like growth factor 1; IGFBP-3: insulin-like growth factor binding protein 3, SDS: standard deviation score

Parameter	EPIGROW (Perchard 2020)	Giabicani 2020	Present Case
Sex	Male	Male	Male
Zygosity	Heterozygous	Heterozygous	Heterozygous
ACMG classification	Reported	Pathogenic	Likely pathogenic
Segregation	Unknown	Maternal	Maternal
Gestational age	NA	38.5 weeks	38 weeks
Birth weight SDS	-1.44	-2.1	-3.8
Birth length SDS	-0.84	-3.7	-2.2
Head circumference SDS (birth/first evaluation)	-3.03	-3.7	-3.1
Age at first evaluation	14.5 years	11.7 years (GH initiation)	1.4 years
Height SDS at first evaluation	-4.23	-4.3	-2.7
BMI SDS (initial)	-0.73	-2.9	-3.2
Initial IGF-1 SDS	-0.37	-0.2	-1.0
IGFBP-3 SDS	-1.16	NA	+1.0
IGF-1 dynamic change	Not reported	+3.0 SDS with GH therapy	+1.5 SDS after nutritional optimization
GH therapy	Not reported	Yes	Recommended, not initiated
Age at GH initiation	NA	11.7 years	NA
Duration of GH therapy	NA	4.1 years	NA
Height gain with GH	NA	+1.4 SDS	NA
Final height SDS	NA	-2.9	NA
Target height SDS	-2.23	-1.6	-0.8
Clinical score (Walenkamp 2019)	3/4	4/4	4/4
Neurodevelopment	Limited data	Normal	Mild delay
Microcephaly	Present	Present	Present

Clinical comparison of previously reported individuals and the present patient carrying the *IGF1R* Gly1199Arg variant. The table illustrates differences in severity of prenatal growth restriction, age at presentation, and biochemical findings.
 BMI: body mass index; GH: growth hormone; IGF-1: insulin-like growth factor 1; IGFBP-3: insulin-like growth factor binding protein 3; SDS: standard deviation score; NA: not available