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Case Report

Novel *IGF1R* Variants in Short Stature: Lessons from Two Patients and Outcome of Growth Hormone Therapy

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What is already known on this topic?
The growth hormone (GH)-IGF1 axis is the major regulator of longitudinal growth. IGF1 and IGF2 act through the IGF receptor type 1 (IGF1R). Monoallelic *IGF1R* gene variants result in pre-and postnatal growth failure, developmental delay, and elevated serum IGF1 levels.

What this study adds?
Clinical and molecular genetic characteristics of two patients with short stature were described. Two novel IGF1R variants were reported, one splice-site and one nonsense.

Abstract
The growth hormone (GH) – insulin-like growth factor 1 (IGF1) axis is essential for the regulation of growth. IGF1 exerts its effects through the IGF1 receptor (IGF1R) that plays a pivotal role in fetal and postnatal growth. Pathogenic monoallelic *IGF1R* variants are known to cause pre- and postnatal growth restriction, often accompanied by normal or elevated serum IGF1 levels. Herein, the clinical and genetic characteristics of two cases with *IGF1R* novel variants, emphasizing their growth patterns, endocrinological findings, and response to recombinant human growth hormone (rhGH) therapy. The first case, a 6.3-year-old boy, had a birth weight of 2,500 g (-2.5 SDS) and a current height of 101.5 cm (-3.2 SDS). Laboratory investigations revealed IGF1 and IGFBP3 levels of 117.8 ng/ml (0.9 SDS) and 4.55 µg/ml (1.3 SDS), respectively. Clinical exome sequencing (CES) identified a *novel* heterozygous c.3722+1G>A/p.(?) variant in the *IGF1R* (NM_000875.5) inherited from the mother. At 6.9 years of age, rhGH treatment was initiated at a dose of 0.035 mg/kg/day. The patient has been receiving rhGH for two years, achieving a height gain of +0.3 SDS per year, with an uneventful follow-up. The second case features a 3-year-old male with short stature and a history of being born small for gestational age (SGA) (-2.6 SDS). His height and weight were 70.0 cm (-2.1 SDS) and 8.8 kg (-1.1 SDS), respectively. He had a history of frequent respiratory infections. Pituitary hormone levels were normal, and he had no evidence of GH deficiency. CES revealed a *novel* heterozygous variant c.2275_2278 dup/p.(Ala760Glyfs*21) in the *IGF1R*. Uncovering the genetic causes of idiopathic short stature with SGA is crucial, as it facilitates more precise diagnoses, reduces unnecessary testing, and potentially enables targeted therapies. Our experience with rhGH therapy in one patient suggests a modest growth response, consistent with previous studies. However, elevated IGF1 levels during treatment highlight the importance of balancing therapeutic doses to optimize height gains without causing side effects.
Keywords: IGF1R, short stature, growth hormone, IGF-1

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Introduction
The growth hormone (GH) – insulin-like growth factor 1 (IGF1) axis plays a crucial role in human growth and metabolism (1). Among its components, the IGF1 receptor (IGF1R) mediates the effects of IGF1 and IGF2. These growth factors bind to IGF1R to promote growth both in fetal and postnatal life. Thus, dysfunctions in either *IGF1* or *IGF1R* can lead to pre- and postnatal growth restrictions (2). Structurally, IGF1R is akin to the insulin receptor and operates as a heterotetrameric transmembrane glycoprotein (3). Its alpha subunit ensures ligand binding, while the beta subunit facilitates intrinsic tyrosine kinase activity for signal transduction (4).
IGF1R gene (MIM*147370), located in chromosome 15q26.3, encompasses 21 exons. Pathogenic variants in this gene can occur in both monoallelic and biallelic forms, with the latter generally being associated with more severe clinical manifestations. Over 170 *IGF1R* variants have been documented, including missense/nonsense variants and gross deletions (5). Clinically, these variants are frequently associated with intrauterine growth restriction (IUGR), short stature, microcephaly, delayed bone age, developmental delay, and dysmorphic features, including a receding hairline, triangular face, long/smooth philtrum, thin upper lip, and fleshy lower lip. However, the expression and severity of these traits can vary, and not all individuals present with all these features, reflecting the multifactorial nature of these characteristics. In adults with IGF1R defects, a thorough evaluation is essential, particularly concerning components of metabolic syndrome and hypogonadism (6, 7).
Identifying *IGF1R* defects in short stature remains challenging due to variability in patient selection and genetic methodologies. A comprehensive approach, integrating both single nucleotide variants (SNVs) and copy number variant (CNVs) analyses, is essential for accurate diagnosis (7). Rapid advancements in high-throughput next-generation sequencing (NGS) techniques facilitate the diagnosis of patients with short stature due to *IGF1R* defects. This has reclassified numerous cases previously defined as idiopathic short stature (ISS) into distinct genetic disorders.
Herein, we present two patients with *novel* heterozygous *IGF1R* variants, detailing their clinical presentations and discussing the outcomes of recombinant human GH (rhGH) therapy in one patient.

Subjects and Methods
Clinical evaluation

Height measurements were obtained using calibrated Harpenden stadiometers (Holtain), and weight was measured with standard equipment. Standard deviation scores (SDS) for all measurements were computed using growth charts specific to Turkish children (8). Small for gestational age (SGA) was defined as a birth weight (BW) or length more than two standard deviations below the mean for gestational age (9).

Hormonal assays

Plasma GH levels were assessed using electrochemiluminescence (ECLIA, Roche Cobas). IGF1 and IGFBP3 (insulin-like growth factor binding protein 3) were analyzed by immunoassays (Immulite 2000, Siemens). IGF1 and IGFBP3 SDS were calculated using the online tool *Child Metrics* (10-12).

Molecular analyses

After obtaining informed consent from the parents, DNA isolation was performed from peripheral blood samples under the standard protocols of the QIAAmp DNA Mini kit (Qiagen, Hiden, Germany). Sequencing was performed using the Illumina NextSeq platform, and each patient was read at least 20X depth in the Clinical Exome Sequencing (CES) panel. Bioinformatic analyses and variant calling were performed using the Sophia-DDM-V5.08 bioinformatics analysis program. This test evaluates the coding regions and exon-intron boundaries in the relevant genes. During the analysis, only pathogenic (P), likely pathogenic (LP), or variants of unknown significance (VUS) were reported according to current scientific knowledge based on the ClinVar database. This database is constantly updated, and the data in the report is as of the date the report was written; changes are possible in the future. The interpretation of the variants was based on the American College of Medical Genetics and Genomics (ACMG) 2015 guideline (13). To assess the population frequency of the variants, data from gnomAD, the 1000 Genomes Project, dbSNP, and ExAC were utilized. CNVs were also examined with this analysis. Segregation analyses were performed for the parents.

Case presentations

Clinical and molecular genetic characteristics of two patients from two unrelated families were described.

Patient 1 (P1)

A 6.3-year-old boy was referred for evaluation of short stature. He was born at term with a BW of 2,500 g (-2.5 SDS), which confirmed a diagnosis of being SGA. Parents were unrelated. His neurodevelopmental milestones were normal for age, except for delayed walking, which he achieved at 3 years.

At the time of assessment, his height was 101.5 cm (-3.4 SDS), and his weight was 15.1 kg (-2.8 SDS). Body proportions were normal for his age, and head circumference (HC) was -1.8 SDS. Midparental height (MPH) was -1.7 SDS, and his mother was notably short (148.0 cm, -2.6 SDS). Pubertal examination was Tanner stage I. He had distinctive facial features, including a long philtrum and retro-micrognathia. The Bone age assessment was aligned with his chronological age, and the skeletal survey was normal. The ophthalmological evaluation identified strabismus, for which a follow-up was recommended.

Laboratory results showed normal liver, renal, and thyroid function tests. His IGF1 and IGFBP3 levels were 117.8 ng/ml (0.95 SDS) and 4.55 µg/ml (1.3 SDS), respectively. GH stimulation test revealed a peak GH concentration of 14.4 ng/ml, ruling out GH deficiency. Chromosome analysis was 46,XY.

At 6.9 years of age, rhGH treatment was initiated at a dose of 0.035 mg/kg/day. The patient has been receiving rhGH for two years, achieving a height gain of +0.3 SDS per year, with an uneventful follow-up. Patient 1's mother was also evaluated for her short stature. The IGF1 and IGFBP3 levels were 251 ng/ml (-0.51 SDS) and 4.24 µg/ml, respectively. She had no evidence of insulin resistance, and her metabolic profile was normal. Clinical and laboratory findings of P1 at diagnosis and during rhGH treatment are summarized in **Table 1** and **Figure 1.**

Patient 2 (P2)

A 3-year-old boy was referred for evaluation of growth failure. He was born at term with a BW of 2,300 g (-2.6 SDS). His perinatal history raised concerns about short femur length, though no definitive diagnosis was made at birth. His parents were unrelated.

At 1 year of age, his height was 70.0 cm (-2.1 SDS), weight was 8.8 kg (-1.1 SDS), and HC was 45.0 cm (-1.4 SDS). His mother was 158.0 cm (-0.87 SDS), his father was 166.0 cm (-1.65 SDS), and the MPH SDS was -1.25. The bone age corresponded to a chronological age of 3 to 6 months. Developmental milestones for gross motor and speech skills showed mild delays. Initial evaluations revealed normal IGF1 (88.53 ng/mL, -0.9 SDS) and IGFBP3 (4.2 ng/mL, -1.1 SDS). GH deficiency was ruled out with a glucagon stimulation (peak GH: 8.0 ng/mL). The skeletal survey was normal.

At 2 years of age, his height velocity increased (+10.9 cm/year), however, height SDS remained below the expected range. At this time, his IGF1 level was elevated (164 ng/mL, 2.1 SDS), prompting further investigation for potential *IGF1R* variants.

His metabolic profile, including glucose (78 mg/dL), insulin (2.4 µIU/mL), triglyceride (35.5 mg/dL), and LDL cholesterol (85 mg/dL), were normal.

The patient had recurrent respiratory infections, and selective immunoglobulin A (IgA) deficiency was diagnosed, leading to a referral to clinical immunology for further evaluation.

At his most recent evaluation at 3.5 years old, his height and weight were 90.3 cm (-2.5 SDS) and 13.0 kg (-1.6 SDS), respectively. The arm span was 89.0 cm. The family was counseled about the possibility of initiating rhGH therapy.

The images of the patients and left-hand radiography are illustrated in **Figure 2.**

Molecular genetic results

Pedigree and Integrative Genomic Viewer (IGV) of the NGS data were demonstrated in **Figure 3.**

Analysis by CES in **P1** revealed a heterozygous c.3722+1G>A/p.(?) variant in the *IGF1R* gene (NM_000875.5). This splice-site variant was classified as LP according to ACMG criteria (PVS1, PM2). This variant was classified as 'deleterious' (MT, DANN, BayesDel) according to *in silico* prediction tools (14). For the splice-altering characteristics variant, SpliceAI is described as the 'Strong-Splice-altering'(15). This variant was not observed in the gnomAD (exomes and genomes)(16). This *IGF1R* variant was not reported by the HGMD professional database (November 2024)(5). Segregation analyses by Sanger sequencing revealed that his mother was also heterozygous for this variant.

In **P2**, the CES analysis identified a heterozygous c.2275_2278 dup/p.(Ala760Glyfs*21) variant in the *IGF1R* (NM_000875.5), which is predicted to result in frameshift and premature termination. This variant was classified as LP according to ACMG criteria (PVS1, PM2) and was not observed in the gnomAD (16). This *IGF1R* variant was not reported by the HGMD professional database (November 2024)(5). Segregation analyses revealed that this variant was *de novo*.

Discussion

This report highlights two rare cases of short stature due to novel heterozygous IGF1R variants, one involving a splice-site alteration and the other a frameshift variant. While the clinical features of our cases align with those previously reported, our findings contribute by documenting novel mutations and providing additional insights into growth response to rhGH therapy.

Although virtually all patients with monoallelic *IGF1R* variants present with pre- and postnatal growth restrictions, its extent varies remarkably. Walenkamp et al. reported the detection of pathogenic *IGF1R* variants in approximately 2% of patients with short stature who were SGA(17). SGA-born cases represent a diverse group with varying clinical features. The reduced size at birth can be attributed to fetal, maternal, placental, and genetic factors. While many SGA achieve normal growth by the age of 2 years, about 15% remain below -2.0 SDS in height and continue to be short. Genetic factors have been identified in a limited number of short SGA children, notably having point mutations and deletions in the *IGF1* and *IGF1R* genes (18). Klammt et al. reported eight SGA patients who are in the range of -1.5 to -3.5

SDS due to *IGF1R* variants (19). Both of our patients were born SGA and were unable to catch up with growth. P2 had a history of short extremities in the prenatal evaluation; however, the postnatal examination revealed proportionate short stature.

In the study of Gonc N et al., patients with short stature without GH deficiency having either a low BW or microcephaly were evaluated to detect *IGF1R* defects, and variants were detected in 14% of the cohort. Two *IGF1R* deletions and five heterozygous variants (one frameshift, four missense) were identified. All patients with *IGF1R* defects had a height, BW, and HC lower than − 2.5 SDS,− 1.4SDS, and −1.36 SDS, respectively. IGF1 levels ranged from − 2.44 to 2.13 SDS (7). Although the height SDS of P2 was similar, in our study, P1's height SDS at presentation was below -3.0 SDS.

Features described in cases with IGF1 resistance include mild facial dysmorphism (triangular face, brachycephaly, hypotelorism, low-set and prominent ears and micro-rethognathia), neurodevelopmental delay and mild glucose intolerance (17). In our cases, some dysmorphic features like clinodactyly and micro-retrognathia were also observed. Although the patients experienced delayed attainment of certain milestones, neuromotor development remained within normal limits. There were no abnormalities in carbohydrate metabolism. Given their prepubertal age, some clinical features may emerge later, and continuous monitoring is necessary.

Cases of heterozygous *IGF1R* variants are typically characterized by IUGR, persistent postnatal growth failure, elevated serum IGF1 levels, and microcephaly (20). Our patients presented with moderately elevated IGF1 SDS values and did not exhibit microcephaly.

Most of the 170 variants identified in the *IGF1R* gene are missense/nonsense (n=107) and gross deletions (n=27). Splice altering (n=9), small deletions (n=7), small indels (n=1), gross insertions (n=6), complex rearrangements (n=3), and regulatory region (n=3) variants have also been described (5). To date, splice-site variants (n=9) described are localized in the introns 1,2, 3,7,8,9, 10, and 18.

The c.3722+1G>A is a splice-site variant occurring at the donor site of intron 20. This variant is predicted to disrupt the normal splicing process, potentially leading to the exclusion of exon 20 from the mature mRNA transcript. Exon 20 encodes a portion of the tyrosine kinase domain of the IGF1R protein (catalytic domain of insulin receptor-like protein Tyrosine kinases), which is crucial for its signaling function. Alterations in this domain can impair the receptor's ability to transduce signals, affecting growth and development processes.

The *IGF1R* c.2275_2278dup/ p.(Ala760Glyfs*21) variant is a frameshift duplication located in exon 13 of the *IGF1R* gene (NM_000875.5). This exon encodes part of the extracellular fibronectin type III domain, which is critical for ligand binding and proper receptor function (21). Variants in specific domains (e.g., fibronectin type III or tyrosine kinase) often lead to growth failure and altered IGF1 signaling, as seen in patients with short stature due to *IGF1R* variants (22).

Previous studies have highlighted significant variability in height, IGF1 levels, and intrauterine growth in individuals with the same heterozygous *IGF1R* variants. This variability is likely due to the complex structure of *IGF1R* and its interaction with the insulin receptor, which modulates IGF1 signaling. Although growth is influenced by multiple factors beyond IGF1 signaling, genetic testing for *IGF1R* alterations is crucial for accurate diagnosis, particularly in cases exhibiting elevated IGF1 levels or an exaggerated rhGH response (23, 24).

The phenotype of short stature associated with *IGF1R* variants is not fully elucidated, and no approved therapy is currently available. However, effectiveness of rhGH treatment was studied (17, 25, 26). In our study, P1 was treated with rhGH, and the height SDS gain was +0.3 at the first year and +0.6 SDS at the second year. Patients with heterozygous *IGF1R* variants may respond to rhGH treatment, aligning with previous reports. However, the response remains variable (25). Çelik et al. concluded in their recent review that rhGH has a partial beneficial effect in cases with *IGF1R* defects, particularly when initiated early and administered long-term. Nearly half of the patients achieved a height gain of more than 1 SDS over the long term (26). Walenkamp MJE et al. suggested that higher IGF1 levels may need be tolerated during the treatment to achieve a clinically significant increase in height SDS due to the partial insensitivity to IGF1 in these patients (17). The reluctance to increase the rhGH due to elevated IGF1 SDS levels may have contributed to suboptimal treatment response in our case. Higher IGF1 levels after rhGH therapy may indicate *IGF1R* gene variants.

The correlation between *IGF1R* defects and clinical presentation remains unclear, and the wide phenotypic variability complicates the selection of patients for *IGF1R* variant testing. However, advancements in NGS technologies have enabled the massively parallel sequencing of multiple genes and genomic regions with high precision, significantly enhancing diagnostic yield. By capturing both coding and non-coding regions, NGS facilitates the comprehensive identification of pathogenic variants, including SNVs, small in/dels, and CNVs, thereby revolutionizing the diagnostic approach to genetically heterogeneous disorders (27).

In conclusion, uncovering the genetic causes of idiopathic growth failure is crucial, as it facilitates more precise diagnoses, reduces unnecessary testing, and potentially enables targeted therapies. Our experience with rhGH therapy in one patient suggests a modest growth response, consistent with previous studies. A +0.6 SDS gain over two years aligns with prior reports of partial responsiveness in *IGF1R* variant carriers. However, elevated IGF1 levels during treatment highlight the importance of balancing therapeutic doses to optimize height gains without causing side effects.

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Data Availability Statement

All data generated or analysed during this study are included in this article. For further information, please contact the corresponding author.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Statement of Ethics

Written informed consent was obtained from the patient's parents for the publication of details of their medical case and any accompanying images.

Author contributions

M.E., H.S., S.A., and Z.Y.A. clinically characterized the patient. S.C. and M.H.Y. performed and analyzed the sequencing data and evaluated the results. M.E., S.A., and Z.Y.A. prepared the draft manuscript. All authors contributed to the study’s conception, design, and discussion of results and edited and approved the final.

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Table 1. Clinical and laboratory findings of P1 at the time of diagnosis and during rhGH therapy			
	At presentation	**1st year of rhGH**	**2nd year of rhGH**
Age, years	**6.3**	**7.5**	**8.4**
Height, SDS	**-3.4**	**-3.1**	**-2.8**
Height Velocity, SDS	**-**	**0.08**	**0.23**
BMI, SDS	**-0.62**	**-0.74**	**-0.9**
Bone Age, years	**6.0**	**7.0**	**8.0**
MPH SDS	**-1.7**		
Tanner stage	**I**	**I**	**I**
GH stimulation test (Peak GH) (ng/ml)	**14.4**		
IGF1 (ng/ml) RR: 57.5-216.0	**117.8**	**177.1**	**278.1**
IGF1, SDS	**0.95**	**2.42**	**5.0**
IGFBP3 (µg/L) RR:1.5-6.0	**4.55**	**4.39**	**4.24**
IGFBP3, SDS	**1.29**	**2.42**	**0.74**
Fasting glucose (mg/dl)	**82.0**	**80.0**	**83.0**
Fasting insulin (µIU/mL)	**4.1**	**4.0**	**4.3**
Triglyceride (mg/dL)	**NA**	**NA**	**36.0**
LDL Cholesterol (mg/dL)	**NA**	**NA**	**63.0**

GH: Growth hormone; BMI: Body Mass Index; SDS: Standart Deviation Score; MPH: Midparental height; IGF1:Insulin like growth factor 1, IGFBP3: Insulin like growth factor binding protein 3; NA: Not available; RR: Reference range

Figure 1. IGF1 and IGFBP3 levels of P1 under GH treatment

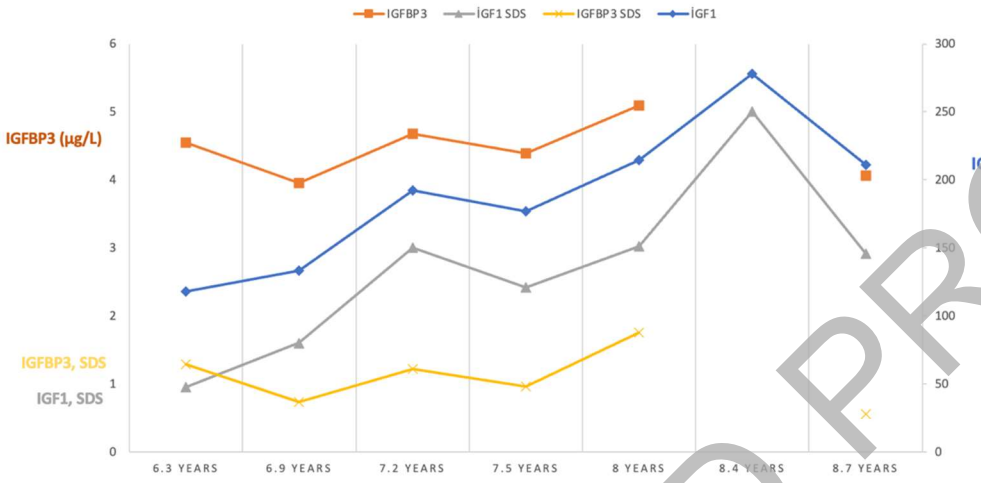
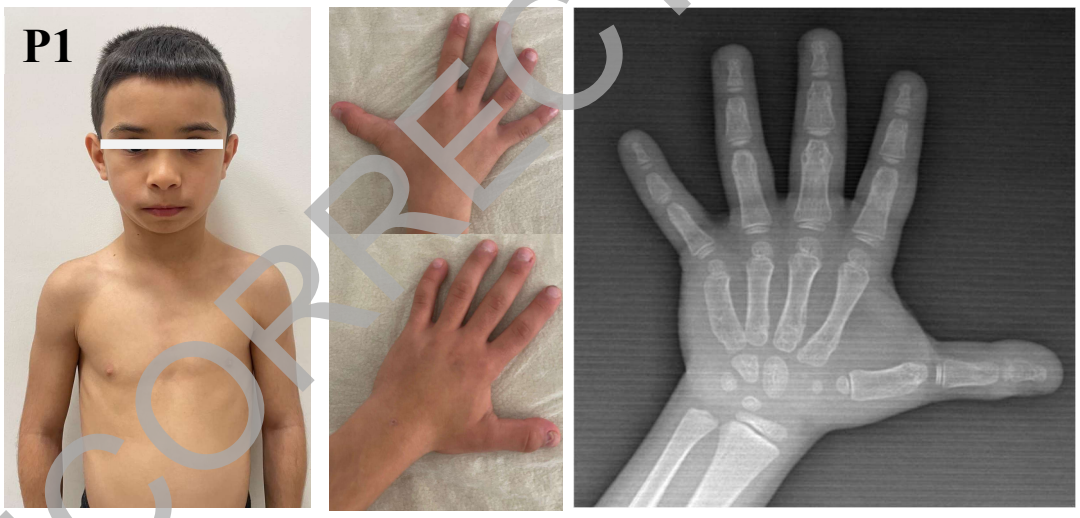


Figure 2. The pictures and left-hand radiography images of P1 and P2
P1: Long philtrum, retro-micrognathia, and clinodactly. The bone age is consistent with chronological age without any obvious pathological appearance.
P2: Long philtrum, micrognathia, mildly low-set ears, and clinodactly The bone age is consistent with chronological age with clinodactly.



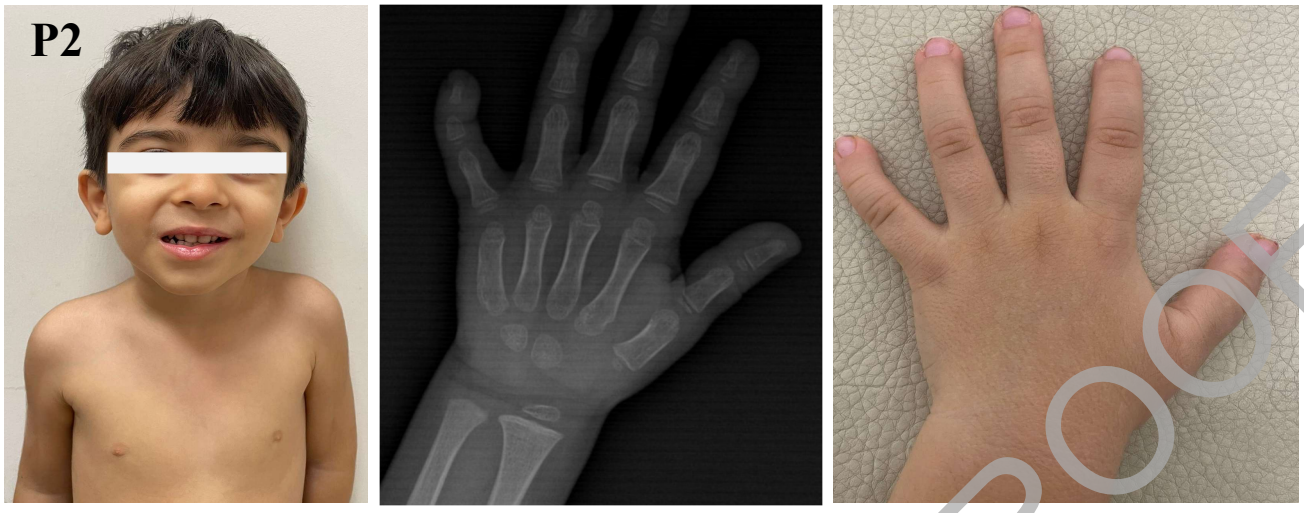


Figure 3. Pedigree and Integrative Genomic Viewer (IGV) results of the patients

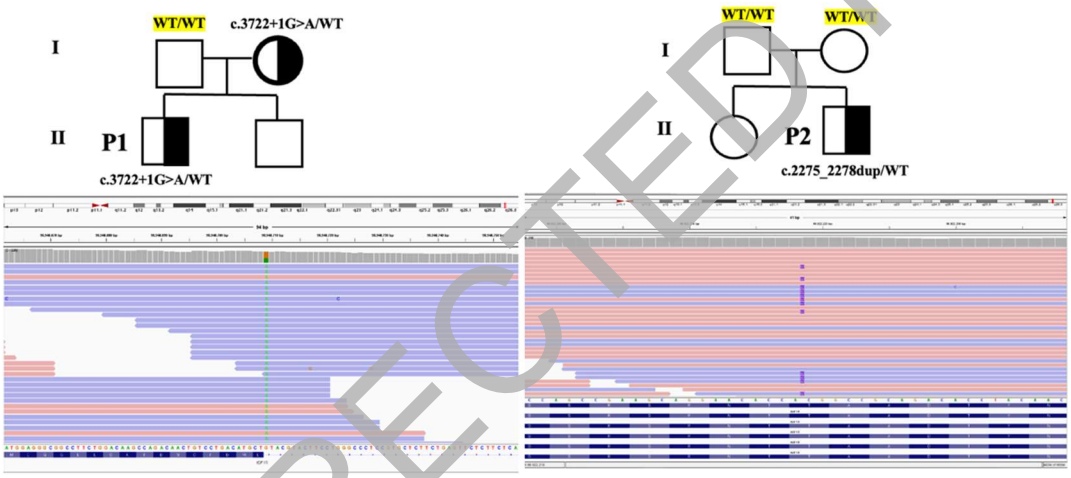


Figure 3. Pedigree and Integrative Genomics Viewer (IGV) of the *IGF1R* gene variant in P1 and P2

The heterozygous (NM_000875.5) : c.3722+1G>A/p.(?) *IGF1R* variant in P1 and c. 2275_2278dup/p.(Ala760Glyfs*21) variant in P2. Segregation analysis was performed on the parents, while it was not conducted in clinically unaffected siblings. Future decisions regarding segregation analysis in siblings will be made based on their follow-up assessments.