CASE REPORT

JCRPE Journal of Clinical Research in Pediatric Endocrinology

DOI: 10.4274/jcrpe.galenos.2024.2024-3-5
J Clin Res Pediatr Endocrinol 2026;18(Suppl 1):30-36

Unraveling a Genetic Puzzle: Could *MAP3K7* Be a Candidate Gene for RASopathies?

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Cite this article as: Kızılcan Çetin S, Şıklar Z, Aycan Z, Özsu E, Ceylaner S, Berberoğlu M. Unraveling a genetic puzzle: could *MAP3K7* be a candidate gene for RASopathies? J Clin Res Pediatr Endocrinol. 2026;18(Suppl 1):30-36

What is already known on this topic?

MAP3K7 variants have been associated with disorders such as cardiospondylocarpofacial syndrome and frontometaphyseal dysplasia 2. The incidence of Noonan syndrome (NS) is approximately 1:1000, and while genetic confirmation is ideal, it may not be possible for all cases. Moreover, negative genetic test results do not necessarily exclude NS, emphasizing the importance of clinical evaluation.

What this study adds?

The patient's clinical features, including short stature, valvular heart disease, and facial dysmorphismwere compatible with NS despite the *MAP3K7* variant being classified as a variant of uncertain significance. This case raises the question of whether *MAP3K7* may be a candidate gene for NS.

ABSTRACT

Noonan syndrome (NS) diagnosis may be challenging because of diverse clinical manifestations. This case report highlights a novel role for *MAP3K7* in NS. A 10.4-year-old female patient presented with short stature and clinical findings suggestive of RASopathy. Despite atypical facial features, the patient met two major van der Burgt diagnostic criteria. Initial genetic testing for known NS-associated genes did not find any variants. Later, whole exome sequencing identified a unique *de novo* heterozygous variant [c.65C>A, p.(P22H)] in *MAP3K7*. This variant, categorized as a variant of uncertain significance by the American College of Medical Genetics and Genomics criteria, raised questions about its potential role in NS. The patient's clinical presentation deviated from classical manifestations of *MAP3K7*-associated syndromes, highlighting

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Received: 10.03.2024 **Accepted:** 07.10.2024 **Epub:** 17.10.2024 **Publication Date:** 22.05.2026

the complexity of *MAP3K7* genetic and molecular mechanisms. Notably, this is the first case reported to associate *MAP3K7* variants with NS. Despite the known challenges in NS diagnosis, proper management, including recombinant growth hormone therapy, is important to optimize growth potential. The case suggests that *MAP3K7* may be a potential candidate gene for NS, but more functional genetic investigations are required to clarify the delicate interaction between genetic abnormalities, the RAS/mitogen-activated protein kinase pathway, and clinical manifestations observed in NS cases.

Keywords: Noonan syndrome, short stature, *MAP3K7*

Introduction

The group of diseases, collectively known as rasopathies, is caused by pathogenic gene changes that encode parts of the intracellular signaling pathway rat sarcoma/mitogen-activated protein kinase (RAS/MAPK). These diseases are characterized by common clinical traits, including distinctive facial features, short stature, and congenital heart disease (1). Noonan syndrome (NS) is the most predominant disorder among the rasopathies. Its prevalence ranges from 1 in 1,000 to 1 in 2,500 live births (2,3). The diagnosis of NS presents a challenge due to the wide range of clinical manifestations. However, since 1994, a scoring method devised by van der Burgt et al. (4) and van der Burgt (5) has significantly assisted in diagnosing NS accurately. A diagnosis of NS is confirmed if there is either a typical facial appearance coupled with one major and two minor clinical characteristic findings or if facial features indicative of NS are present together with two major or three minor clinical features (4,5). This system considers major criteria to include typical facial dysmorphology, cardiac anomalies (such as pulmonary valve stenosis and characteristic electrocardiographic findings), short stature (below the 3rd percentile), chest wall deformities (such as pectus carinatum, pectus excavatum), and additional features (intellectual disability, cryptorchidism, or lymphatic dysplasia). Minor criteria are suggestive facial dysmorphology, non-major heart defects, short stature (below the 10th percentile), broad chest, and suggestive features in first-degree relatives.

Nearly 20 genes (including *PTPN11, SOS1, SOS2, KRAS, NRAS, RIT1, RRAS, RASA1, RASA2, MRAS, RAF1, BRAF, MAP2K1, MAP3K8, SHOC2, PPP1CB, SPRY1, LZTR1, MYST4, A2ML1, CBL*), which are involved in the RAS/MAPK pathway and NS manifestation, have been described thus far (6,7). As a result, around 85% of cases can now be explained by known genetic factors. However, negative tests do not necessarily rule out the NS. Thus, clinical diagnosis remains vital (7,8). The etiology of the cases where the genetic pathogenesis remains unidentified provides an opportunity to expand the genetic repertoire and novel mechanisms in NS in the future, highlighting the importance of recognizing clinical features for precise diagnosis of NS.

In this case report, we present a patient with a *de novo* heterozygous variant in *MAP3K7*, c.65C>A, p.(P22H),, exhibiting facial features suggestive of NS and meeting two major van der Burgt criteria, thereby fulfilling the NS diagnostic criteria. This case highlights a potential novel role for *MAP3K7* in NS, prompting reconsideration of the intricate interplay between genetic anomalies, the RAS/MAPK pathway, and the diverse clinical manifestations observed in NS.

Case Report

A 10.4-year-old girl attended the outpatient clinic because of short stature. Her medical history revealed that she was born to non-consanguineous parents at 38 weeks of gestation, with a birth weight of 2500 g. She had undergone a number of clinical assessments. Her diagnosis had remained uncertain for a very long time. She had pulmonary valve stenosis, pectus excavatum, and failure to thrive in early infancy, so she was suspected to have NS. Karyotype was 46, XX (100 metaphases). Targeted gene panel sequencing of *PTPN11, SOS1,* and *RAF1* were unremarkable and microarray analysis was normal. On follow-up, her height was 110.8 cm [-3.3 standard deviation (SD)]. Treatment with recombinant growth hormone (rhGH) was initiated at 0.2 mg/kg/week at the age of 8.5 years. Linear growth during rhGH treatment was 5 cm/year in the first year and 8 cm/year in the second year of treatment. Whole exome sequencing (WES) revealed a novel heterozygous c.65C>A, p.(Pro22His) variant in *MAP3K7* (NM_145331.3) (Figure 1). The American College of Medical Genetics and Genomics (ACMG) criteria classify this variant as a variant of uncertain significance (VUS). The parents were informed by their doctor that all genetic tests were normal.

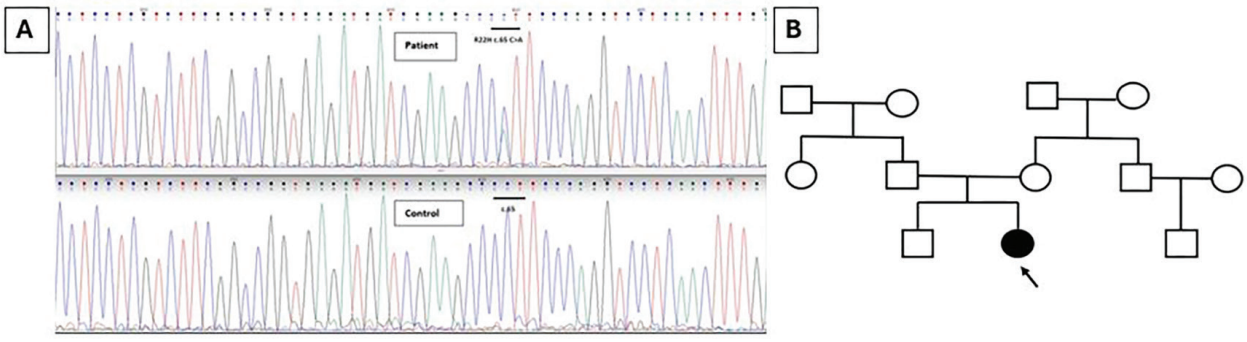

Figure 1. Electropherograms of the Sanger sequencing and the family tree of the patient

On first presentation to our clinic, her height was 124.5 cm (-2.57 SD), and her body mass index (BMI) was 14.58 kg/m^2 (-1.38 SD). The target height was 153.5 cm (-1.23 SD). Physical examination revealed phenotypic features including synophrys, prominent supraorbital ridges, mild ptosis, low set ears, full cheeks, broad nasal tip, deep elongated philtrum, thin upper vermillion, low anterior hairline, triangular face, short webbed neck, superior pectus carinatum and inferior pectus excavatum, short metacarpals and metatarsals, clinodactyly, syndactyly, intellectual disability, and dyslexia (Figure 2A).

Laboratory tests reported normal hemogram and biochemical parameters including blood glucose, thyroid function, tissue transglutaminase autoantibody immunoglobin A (IgA), serum total IgA, and liver and kidney function. Her urine test results were also normal. GH stimulation tests with clonidine excluded GH deficiency (peak GH of 9.63 ng/mL). The bone age was seven years and ten months, and the bone survey was normal with incidental accessory bone, os tibiale externum. Pituitary magnetic resonance imaging (MRI), showed a hypophyseal length of 2.5 mm (normal range: 4.5±0.6 mm) and cranial MRI was normal. Before the current presentation, she had not been followed up properly, her diagnosis was not certain and the rhGH treatment was experimental. Her growth velocity slowed by 1 cm/six months during follow-up at our clinic, so rhGH was stopped. Insulin-like growth factor 1 (IGF-1) levels were within the acceptable range for pubertal stage, gender, and age. There was no pathology on laboratory tests. The radiographic bone survey was normal (Figure 3). There was no finding suggestive of skeletal dysplasia. The patient underwent regular monitoring

Figure 2. A) Physical characteristics of the patient (synophrys, prominent supraorbital ridges, mild ptosis, low set ears, full cheeks, broad nasal tip, deep elongated philtrum, thin upper vermillion, low anterior hairline, short webbed neck, superior pectus carinatum, and inferior pectus excavatum. **B)** Pointed chin appearance of the patient

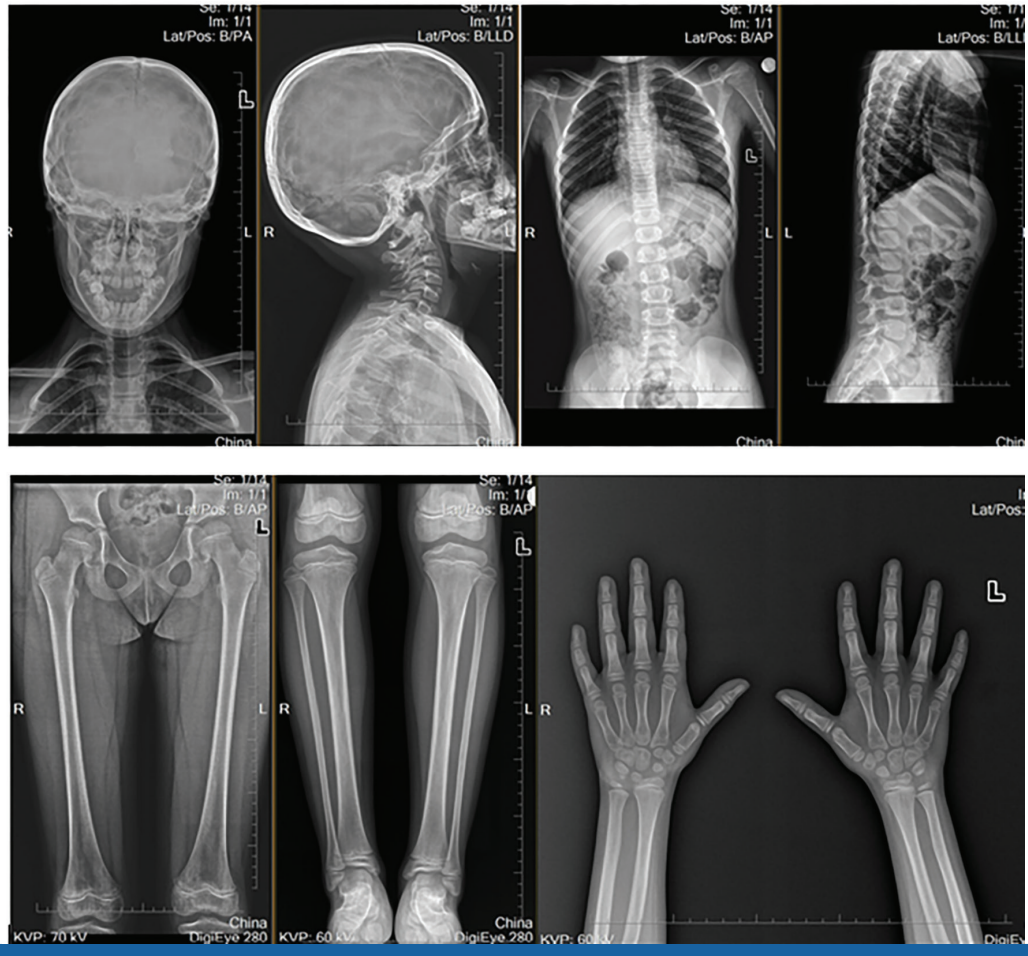

Figure 3. The radiographic bone survey of the patient

through electrocardiography, echocardiography, and abdominal and pelvic ultrasonography, which revealed no abnormal ultrasonographic findings. Subsequent echocardiograms showed a minimal atrial septal defect with no evidence of hypertrophic cardiomyopathy.

The *MAP3K7* c.65C>A variant was not identified in either parent through family segregation analysis, indicating a *de novo* occurrence. Clinically, the patient was diagnosed with NS based on Van der Burgt scoring (characterized by NS-like facial appearance, major short stature, cardiac symptoms, and pectus excavatum). Puberty (Tanner stage 2) began at 10.6 years of age.

Throughout follow-up, height velocity of only 1 cm/6 months was noted so rhGH treatment was restarted at 0.35 mg/kg/week, which was the recommended dosage for NS. Adjustments were made to the dose based on IGF-1 levels, eventually reducing it to 0.20 mg/kg/week (Figure 2).

At the latest evaluation, at 13 years of age, the patient was Tanner stage 3 with a height of 138 cm (-3.2 SD) and a BMI of 15.23 kg/m^2 (-2.18 SD score). During the approximately 3-years clinical follow-up at our clinic, a more pronounced pointed-chin appearance has become evident (Figure 2B). Yearly follow-ups included abdominal and pelvic ultrasonography and echocardiographic assessments, all revealing no pathological findings.

Methods

Genomic DNA was isolated from the patient's peripheral blood samples using established protocols. Genetic analyses were conducted through next-generation sequencing (Miseq, Illumina, San Diego, CA, USA) in accordance with the manufacturer›s guidelines.

Results

The identified variant in the patient is exceptionally rare (gnomAD Allele Frequency 6.207e-7) and results in a change within a highly conserved gene across species. Computational tools predict it to be "disease causing," supported by MutationTaster, and deleterious with a Combined Annotation Dependent Depletion score of 23.0. Notably, this variant has not been documented in major databases such as ClinVar or dbSNP.

Discussion

Diagnosing NS in patients who lack the phenotypic characteristics presents a clinical challenge and atypical clinical anomalies may lead to a misdiagnosis. This diagnostic difficulty may also delay appropriate management and interventions. Although genetic testing has advanced, it is noteable that around 15% of patients with a clinical diagnosis of NS lack a definitive genetic diagnosis (7). Therefore, clinical assessment remains important even though there is widespread availability of genetic testing. Moreover, understanding and interpretation of WES findings is important for identifying potential variants related to NS, as the 15% of NS patients without genetic confirmation suggest there may be a number of variants or genes that play a pathogenic role in NS that are yet to be identified. Effective collaboration between clinicians and geneticists with expertise in dysmorphology and disease-specific features may help to identify these unidentified genetic associations. The guidelines established by the ACMG provide a framework for analyzing VUS, highlighting the need for collaboration between doctors and genetics professionals in resolving these uncertainties. The evolution of VUS classifications from "uncertain significance" to "likely pathogenic" or "pathogenic" is characteristic of the dynamic nature of genetic research and the potential for reclassification as our understanding improves (9).

MAP3K7 (MIM*602614) is a 17-exon gene located on chromosome 6q15. The MAPKs, (MAPKs), also known as extracellular signal-regulated kinases, are activated by a wide range of stimuli and serve as a convergence point for signaling pathways (1). Of note, with an autosomal inheritance pattern, NS is often caused by *de novo* variants (7). Segregation analysis, which demonstrates that neither of the proband's parents had the detected *MAP3K7* variant, supports the suggestion that the variant presented in the case described earlier was pathogenic. However, it is important to consider the effect of incomplete penetrance and variable expressivity, particularly in dominantly inherited conditions like those observed in RASopathy spectrum disorders. The parents might have also carried the variant with milder or asymptomatic presentations, highlighting the complexity of genetic inheritance and phenotypic expression in RASopathy spectrum disorders.

Pathogenic variants in *MAP3K7* have recently been linked to two disorders; cardiospondylocarpofacial syndrome (CSCFS) and frontometaphyseal dysplasia 2 (FMD2) (10,11,12,13,14,15). Interestingly, her presentation was not consistent with the typical features associated with either CSCFS or FMD2, particularly the absence of spinal and bone fusions in CSCFS (10,11,12) and the incongruence with flexion contractures of the elbow seen in FMD2 (13,14,15). The unique clinical manifestation, combined with the discovery of a novel likely pathogenic variant [c.125_127del, p.(Val42del)] in *MAP3K7* in another case reported by AbuBakr et al. (16), reinforces the benefit of comprehensive functional studies to clarify the precise mechanisms linking these genetic variants to the observed phenotypic traits. However, the patient described by AbuBakr et al. (16) displayed spinal and bone fusions in the hands and feet, which were associated with CSCFS (10,11,12), and elbow flexion contractures, a characteristic of FMD2 (13,14,15), though not CSCFS; the patient exhibited apparent "opposite" features. The two *MAP3K7*-associated syndromes that overlap may indicate the presence of a single disorder. This patient was misdiagnosed as NS for years based on the Var der Burgt criteria (16). The complexity of this case extends beyond the phenotypic range of CSCFS and FMD2, raising concerns about the underlying genetic and molecular mechanisms. The clinical features resembled the underlying mechanism of neurofibromatosis-NS (NFNS). NF1 and NS may exhibit similar features in some patients, leading to NFNS. The genetic basis of NFNS is not fully understood, and there is an ongoing debate about whether NFNS represents a variable manifestation of NF1 or NS or a distinct clinical entity. Some NFNS patients have variants in both *PTPN11* and *NF1*, but the majority only have *NF1* variants. As a result, most authors attribute NFNS to *NF1* variants (17,18). In another case report, an Asian male with CSCFS presented with a novel missense variant in *MAP3K7* (NM_145331.3: c.467A>T: p.Asp156Val)) and exhibited a mixed phenotype resembling Ehlers-Danlos syndrome and NS. This overlap in phenotypes suggested potential diagnostic implications for identifying CSCFS. In contrast, our case is exceptional because she did not exhibit clinical features typical of either CSCFS or FMD2 (19). This highlights the variability in clinical presentations associated with *MAP3K7* variants, contributing to the complexity of clinical diagnosis and genetic characterization. At the time of writing, *MAP3K7* had not been associated with NS. The patient's comprehensive bone X-ray examination revealed no findings of skeletal dysplasia, which ruled out both CSCFS or FMD2. The intriguing possible association between *MAP3K7* and NS may suggest a new insight into the underlying genetics of this condition.

This finding encouraged us to further investigate the interplay between genetic variants, the RAS/MAPK pathway, and the variable clinical manifestations. To further explore the potential impact of the c.65C>A, p.(Pro22His) variant in *MAP3K7*, according to the Kyoto Encyclopedia of Genes and Genome pathway database was interrogated. The *MAP3K7* is a key gene in the MAPK signaling pathway (hsa04010), which interacts with several other genes known to cause RASopathies, such as *KRAS, BRAF*, *RAF1, SOS1* and *NF1*. The involvement of *MAP3K7* in this pathway underscores its potential role in the pathogenesis of RASopathies. In our case, the absence of evidence of skeletal dysplasia suggested *MAP3K7* as the direct cause of the NS clinical presentation. Whether this gene is directly related to the NS clinical condition in our patient or if its interaction with a different

gene in the RASopathy pathway is a question that remains to be answered, ideally through future functional analysis studies. The absence of functional testing to support this assumption is the major limitation of our case report. Remarkably, our patient is the second documented case featuring a *MAP3K7* variant that did not result in the two recognized types of skeletal dysplasia and, more importantly, the first case with clinical evidence of its relationship with NS, based on the Van der Burgt criteria. We suggest that *MAP3K7* may be a candidate gene for NS. While this association is encouraging, more functional genetic research focusing on the precise pathways to which *MAP3K7* variants contribute is necessary to establish a definitive connection. The identified variant in the patient is exceptionally rare (gnomAD allele frequency=6.207e-7). Functional validation through protein structure modeling or *in vitro* studies will be crucial to elucidate this specific variant's impact on protein function and disease pathogenesis and to establish a definite association or not.

Without functional analysis, the pathogenicity of this variant and its role in the phenotypic presentation of NS remains unproven.

Moreover, the delayed diagnosis of NS has a domino effect on initiating appropriate medical interventions. In NS, rGH is effective and positively contributes to final height (20,21). Most adults' heights remain below the 3rd percentile without rGH treatment (21). Other pathologies that would cause low BMI were not suggested by clinical or laboratory evaluations. In NS patients, the growth response is more favorable when rGH treatment is initiated earlier and maintained longer. The duration of rGH usage before puberty and the height at the onset of puberty also impact near-final height (21). Delayed diagnosis will likely postpone growth hormone therapy initiation, limiting optimal growth potential, as was the situation with the current case. The relationships within the RAS/MAPK pathway will vary, depending on specific genotypic variations. In addition, differences in growth characteristics may depend on whether other pathways related to RAS/MAPK, including the PI3K/AKT and JAK2/STATb5 pathways, are affected or unaffected (21).

It is well-established that the RAS/MAPK pathway is implicated in various malignancies (20). Therefore, it will also be important to investigate the incidence of cancers in disorders associated with *MAP3K7* mutations, particularly in relation to the decision to initiate rGH therapy. In the presented case, detailed information was provided to the family, and rGH therapy was initiated with their consent. The patient was monitored at three-month intervals, including close IGF-1 level monitoring and abdominal-pelvic imaging studies.

She also had a low BMI. There is no difference in macronutrient intake in NS patients compared to healthy children, which might be attributed to increased energy expenditure (22). The distinctive chest deformity of the presented case with pectus carinatum in the upper section and pectus excavatum in the lower part of the chest is a remarkable anomaly (23,24). The dysmorphic characteristics of NS exhibit variations depending on age, with more pronounced characteristics in infancy, while facial features may not be readily noticeable during adolescence and adulthood. During the adolescent and young adult periods, the face takes on a more triangular contour (25). Throughout approximately three years of follow-up, there was a notable enhancement of the patient's jawline. All clinical findings were consistent with NS.

In conclusion, the identification of a novel *de novo* heterozygous variant [c.65C>A, p.(P22H)] in the *MAP3K7* raises intriguing questions about a potential role in NS pathogenesis. This is the first documented case associating a *MAP3K7* variant with clinically diagnosed NS, potentially expanding our understanding of genetic factors implicated in NS although functional *in silico* and/or *in vitro* studies will be required to strengthen this association. The unique clinical presentation in the described case, with no features of the classical manifestations of *MAP3K7*-related syndromes, highlights the intricate nature of genetic and molecular mechanisms. This finding raises questions about how the RAS/MAPK system, clinical symptoms seen in NS patients, and *MAP3K7* variants interact.

Ethics

Informed Consent: Informed consent for publication was obtained from the patient's parents.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Sirmen Kızılcan Çetin, Zeynep Şıklar, Zehra Aycan, Elif Özsu, Serdar Ceylaner, Merih Berberoğlu, Concept: Sirmen Kızılcan Çetin, Zeynep Şıklar, Merih Berberoğlu, Design: Sirmen Kızılcan Çetin, Zeynep Şıklar, Serdar Ceylaner, Merih Berberoğlu, Data Collection or Processing: Sirmen Kızılcan Çetin, Zeynep Şıklar, Zehra Aycan, Elif Özsu, Merih Berberoğlu, Analysis or Interpretation: Sirmen Kızılcan Çetin, Zeynep Şıklar, Zehra Aycan, Elif Özsu, Literature Search: Sirmen Kızılcan Çetin, Zeynep Şıklar, Elif Özsu, Serdar Ceylaner, Writing: Sirmen Kızılcan Çetin, Zeynep Şıklar, Elif Özsu, Merih Berberoğlu.

Conflict of Interest: One author of this article, Merih Berberoğlu is a member of the Editorial Board of the Journal of Clinical Research in Pediatric Endocrinology. However, she did not involved in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions. The other authors declared no conflict of interest.

Financial Disclosure: The authors declared that this study received no financial support.

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