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Clinical Variability in a Family with Noonan Syndrome with a Homozygous *PTPN11* Gene Variant in Two Individuals

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What is already known on this topic?

Noonan syndrome (NS) is an inherited multisystem disease, with a reported prevalence of 1/1000-2500. The most common findings in NS are short stature, distinctive facial features (ptosis, hypertelorism, low-set ears, low hairline), mane neck, chest deformity, bleeding diathesis, cryptorchidism, learning disability, congenital heart defects and varying levels of intellectual disability. While NS is inherited in an autosomal dominant manner, it is noteworthy that approximately half of the cases manifest sporadically.

What this study adds?

A previously described variant in *PTPN11* was present in nine members of two consanguineous families of the same kindred and was inherited in a homozygous fashion in two members. To the best of our knowledge, these are the first published homozygous *PTPN11* cases. The patients with homozygous inheritance had lower height standard deviation scores than family members with heterozygous inheritance.

Abstract

Objective: Noonan syndrome (NS) is characterized by dysmorphic facial features, short stature, congenital heart defects, and varying levels of developmental delays. It is a genetic, multisystem disorder with autosomal dominant inheritance and is the most common of the RASopathies. In approximately 50% of patients, NS is caused by variants in the Protein Tyrosine Phosphatase Non-Receptor Type 11 (*PTPN11*) gene. The aim of this study was to evaluate two patients with a previously reported *PTPN11* homozygous variant for the first time and seven other kindred members carrying the same heterozygous variant in terms of clinical, biochemical, genetic, and response to treatment.

Methods: Nine patients diagnosed with NS due to the same variants in the *PTPN11* gene were included in the study.

Results: The median (range) age at diagnosis was 11.5 (6.8-13.9) years and the mean follow-up duration was 4.7 (1-7.6) years. In eight patients (88.9%), short stature was present. The height standard deviation score of the patients on admission was -3.24 ± 1.15. In six of the patients, growth hormone treatment was initiated. Cardiovascular or bleeding disorders were not detected in any of the patients. Three (33.3%) had hearing loss, two (22.2%) had ocular findings and one (11.1%) had a horseshoe kidney. The mean psychomotor development performance score was 84.03 ± 17.09 and the verbal score was 82.88 ± 9.42. Genetic analysis revealed a variant in the *PTPN11* gene [c.772G > A; (p.Glu258Lys)] that had been previously described and was detected in all patients. Two patients were homozygous for this variant and short stature was more severe in these two.

Conclusion: A previously described in *PTPN11* affected nine members of the same kindred, two with homozygous inheritance and the remainder being heterozygous. To the best of our knowledge, these are the first homozygous *PTPN11* case reports published, coming from two related consanguineous families.

Keywords: *PTPN11*, Noonan syndrome, short stature

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Introduction

Noonan syndrome (NS) is an inherited disease that affects many different systems, and its prevalence has been reported as 1/1000-2500 (1,2). The most common findings in NS are short stature, distinctive facial features (ptosis, hypertelorism, low-set ears, low hairline), mane neck, chest deformity, bleeding diathesis, cryptorchidism, learning disability, congenital heart defects, and varying levels of intellectual disability (2).

Although NS is inherited in an autosomal dominant pattern in a significant proportion of patients, it occurs sporadically in approximately half of the patients. NS is caused by variants in genes that encode proteins in the RAS-Mitogen-Activated Protein Kinase (RAS-MAPK) pathway. The RAS-MAPK pathway is vital for many cellular functions such as proliferation and differentiation (3). Many genes including *PTPN11, SOS1, KRAS, RAF1, NRAS, BRAF, SHOC2,* and *RIT1* have been identified that may cause NS. The use of next-generation sequencing (NGS) techniques has improved the identification of new genes and increased the rate of reaching a molecular genetic diagnosis in patients (4,5). The Protein Tyrosine Phosphatase Non-Receptor Type 11 (*PTPN11*) gene (MIM*176876) is located in the chromosome 12q24.13 region and comprises 16 exons. The first described phenotype caused by pathogenic/likely pathogenic alterations in this gene, which has been implicated in the genetic etiology in 50-60% of individuals with NS, is called NS type 1. In individuals with *PTPN11* variants, short stature is observed more often due to resistance to growth hormone (GH) (6,7). However, the pathophysiology of short stature in patients with NS is not yet fully understood. Various likely mechanisms have been postulated. In terms of GH, it has been suggested that GH deficiency, GH neurosecretory dysfunction, or mild GH resistance may be present. *PTPN11* encodes SHP2, a cytoplasmic protein tyrosine phosphatase that positively regulates RAS signaling. SHP2 binds to its phosphotyrosyl-containing signaling partners through the SH2 domain, which controls its sub-cellular localization and functional regulation. While alterations in the *PTPN11* gene are observed more frequently in patients with pulmonary stenosis and short stature, they are very rare in patients with hypertrophic cardiomyopathy (HCM) and/or severe intellectual disability. It has been shown that the type of variants are mostly missense and these affect the function of SHP2 through different mechanisms (8). Children with NS are prone to juvenile myelomonocytic leukemia (JMML), and somatic variants in the *PTPN11* gene have been detected in approximately one-third of children with non-syndromic JMML and in patients with other childhood myeloid and lymphoid malignancies at varying rates.

Methods

Nine patients who presented to Diyarbakır Children's Hospital Pediatric Endocrinology Outpatient Clinic and were diagnosed with NS due to a variant in the *PTPN11* gene were included in the study. There was consanguinity between the parents in all patients. The presenting complaints, age, body weight (BW), height, BW and height standard deviation scores (SDS), maternal and paternal height, bone age, and detailed physical examination findings of the participants included in the study were recorded. In all patients, ophthalmology examinations and hearing tests were performed. All patients underwent echocardiography performed by an experienced pediatric cardiologist to detect cardiovascular pathologies. Kent EGY and Porteus Maze tests were used to evaluate the neurocognitive functions of all patients. Abdominal ultrasound was requested to detect other accompanying pathologies. Complete blood count, prothrombin time, and activated partial thromboplastin time tests were requested for hematologic disorders that may accompany NS. *PTPN11* gene analysis was requested in all patients. In addition, informed consent was obtained from all patients included in the study.

Molecular Analysis

After written consent was obtained from the families of the affected individuals, molecular analyses were planned. To determine the genetic etiology, molecular analyses were performed by using a targeted NGS panel (TruSight One Sequencing Panel by Illumina). Nextera XT DNA Library Preparation Kit (Illumina Inc., San Diego, CA, USA) was used according to the manufacturer's instructions for target enrichment. Paired-end sequencing was performed on all samples using the Illumina NextSeq platform (Illumina Inc., San Diego, CA, USA). NGS data were analyzed using the Illumina VariantStudio software and Integrative Genomics Viewer (IGV) (https://www.igv.org/). The frequency of the identified variant was investigated in different databases: NCBI dbSNP build141 (http://www.ncbi.nlm.nih.gov/SNP/), 1000 Genomes Project (http://www.1000genomes.org/), Exome Aggregation Consortium (ExAC) (http://exac.broadinstitute.org/), and Genome Aggregation Database (gnomAD) (http://gnomad.broadinstitute.org/). The impact of the variant on protein structure was evaluated using several *in silico* prediction tools such as SIFT, MutationTaster, and PolyPhen. American College of Medical Genetics (ACMG) guidelines were used for the classification of pathogenicity (9). Segregation analysis was performed using the Sanger Sequencing method.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences, version 21 (IBM Inc., Armonk, NY, USA). Data of each affected patient are presented in Table 1. Descriptive statistics are given in the Results section. Non-parametic data as median (interquartile range 25th-75th percentile).

Results

A total of nine patients from four consanguineous families were included in the study. Four of the patients were male and five were female (Figure 1). There was consanguinity between the parents in all four families. The median (range) age at diagnosis was 11.5 (6.8-13.9) years, and the median follow-up duration was 4.7 (1.0-7.6) years. The most common clinical finding was short stature, present in eight of the patients (88.9%). Dysmorphic manifestations of NS, including broad forehead, ptosis, down-slanting palpebral fissures, and low-set ears, were present in seven (77.8%) of nine patients. Cardiovascular pathologies were not detected in any of the patients. Three (33.3%) of the patients had hearing loss, two (22.2%) had astigmatism and one (11.1%) had a horseshoe kidney. One of the four male patients (25%) had cryptorchidism. The mean psychomotor development performance score of the patients was 84.03 ± 17.09 and the mean verbal score was 82.88 ± 9.42 (90-110). No bleeding disorder was detected in any of the patients. The patients exhibited the stigmata of NS clinically. Variants in the *PTPN11* gene were detected in all patients. Homozygous variants were detected in two patients (one female and one male), and heterozygous variants were detected in the other seven patients.

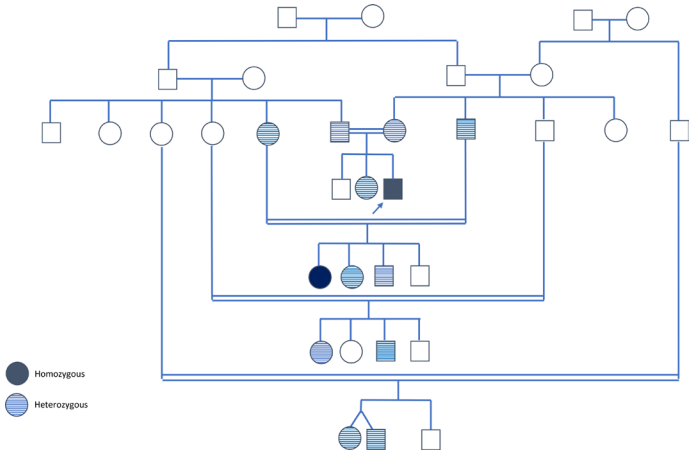

Figure 1. Pedigree of the proband (arrow). Genetic analyses could be performed in the 9 affected children and in the parents of heterozygous cases

The first homozygous case (1a) presented with short stature at the age of 9.4 years. He was born at 39 weeks with a birth weight of 2000 g. The patient did not have any prenatal and pre-school complaints but had school failure. At initial presentation his height was 110 cm (-4.28 SDS) and his weight was 17 kg (-4.16 SDS). Dysmorphology assessment identified bilateral proptosis especially prominent in the right eye, hypertelorism, prominent and wide nasal bridge, low-hanging columella, high-arched palate, dimple on the chin, and low-set ears accompanied by bilateral helical rim deformity. In addition, flaring of the outer one third of both eyebrows, low posterior hairline and mane neck were detected. He had no cardiac, hearing and vision problems, and he had borderline intellectual functioning. He had been operated on for bilateral cryptorchidism at the age of 1.5 years. GH therapy was initiated for severe short stature and poor growth rate. The treatment was terminated at the end of the third year due to a poor response to GH and non-compliance with the treatment. On follow-up, it was found that puberty had not yet started in this male patient with homozygous variant, even though he was 16 years old. We believe this is the first case of NS with homozygous *PTPN11* variant published.

The second case (IVa) with a homozygous variant also presented due to short stature, at the age of 12.6 years. Patient Ia and this patient were cousins and she also similarly had a history of consanguinity between her parents. She was born at 38 weeks with a birth weight of 2000 g. She had poor school performance. At initial presentation her height was 124 cm (-5.3 SDS) and her weight was 23 kg (-4.33 SDS). Dysmorphology assessment again identified prominent and wide nasal bridge, low-hanging columella and low-set ears, helical rim deformity, hypertelorism, high-arched palate, low posterior hairline, mane neck, and chest deformity. Similar to her cousin, she had mild ptosis in the right eye and a dimple on the chin. She also did not have cardiac and hearing problems, and she had borderline intellectual functioning. Eye examination revealed the presence of astigmatism. Puberty started spontaneously at the age of 13.8 years. On follow-up, GH therapy was initiated for severe short stature and poor growth rate at the age of 13.5 years. The treatment was terminated at the age of 16.1 years when the patient reached the height of 145 cm (-3.07 SDS) due to non-compliance with the treatment and epiphyseal closure.

In cases 1a and 4a, molecular analysis revealed homozygous c.772G>A variants in *PTPN11* (NM_001330437.2) (Figure 2). This missense variant resulted in the substitution of glutamine for lysine at the 258th position of *PTPN11* mRNA. The CADD score at this position was 41. This alteration

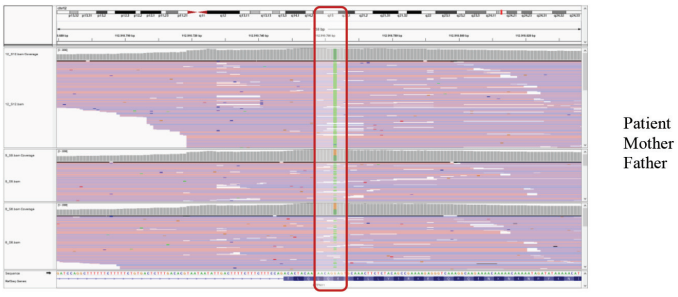

Figure 2. Homozygous *PTPN11* variant [NM_001330437.2; c.772G > A, (p.Glu258Lys)] in proband and heterozygous carrier status in parents visualized on IGV

IGV: integrative genomics viewer

was not found in the GnomAD or in public databases. However, it was submitted to ClinVar as likely pathogenic, and according to ACMG 2015 guidelines, it was pathogenic. However, the impact of this amino acid substitution on the structure and function of the protein was predicted to be benign, according to the Polyphen2 prediction tool. Both parents and other affected family members were found to be heterozygous for the same variant.

Height SDS scores of the two patients with homozygous variants were found to be lower than the other patients (Table 1). Puberty started at the age of 13.8 years in the female patient with a homozygous variant, but did not start in the male patient, even though he was 16 years old. The clinical and laboratory data of all patients were summarized in Table 1.

Discussion

NS is characterized by short stature, hypertelorism, ptosis, mane neck, low-set ears, high-arched palate, chest deformities, cryptorchidism, bleeding disorders, learning disability, and cardiovascular anomalies. Multiple genes are involved in the etiology of NS. Thus, there are 14 different types of NS based on the hereditary traits and genes responsible for the etiology (10). In the present study, nine patients, all diagnosed with NS due to the [c.772G > A(p.Glu258Lys)] variant in the *PTPN11* gene, which has been described previously, are presented (11). Bowling et al. (11) reported that a male patient diagnosed with NS carried variants in *LTZR1* (NM_006767.4: c.742G > A; p.Gly248Arg) and *PTPN11* (NM_002834.5:c.772G > A; p.Glu258Lys) genes, which were shown to be inherited from his parents. However, the *LTZR1* variant was accepted as a causative variant for the disease that had been previously reported as pathogenic. SHP2 is a cytoplasmic protein-tyrosine phosphatase that is essential for vertebrate development. Most of the *PTPN11* biallelic variants show a lethal effect. In animal studies, it was shown that SHP2 has an essential role in early development in the mouse, and homozygous *PTPN11-/-* embryos died pre-implantation (12). We postulate that the biallelic *PTPN11* variant detected in the two affected individuals in this study have a lesser effect on the protein function, as predicted by Polyphen2 (benign protein effect). These cases are the first published human cases of NS with homozygous *PTPN11* variants. We suggest that it is possible to encounter homozygous rare variants in families due to the high rate of consanguineous marriages in Turkey. Of note, short stature was more severe in the two patients with homozygous variants.

Proportionate short stature is the most common presenting complaint in patients with NS (13). Despite normal birth weight and height, short stature is observed in 50-70% of patients (7). The median age of onset of puberty in patients with NS has been reported as 13.4 (10.8-16.4) years in boys and 13 (10.9-15) years in girls (14). Short stature was present in eight of the nine patients (88.9%) in this study, which was slightly higher than the rates reported in the literature. In previous studies, it has been reported that among patients with NS, short stature is more common in children with *PTPN11* gene variants (6,7). Thus, the higher rate of short stature in the present study was possibly due to all patients harboring variants in the *PTPN11* gene.

GH treatment in NS is thought to be beneficial because the dysmorphic findings are similar to those in Turner syndrome. Therefore, in NS patients with severe short stature, GH has been administered at the same dose used in the treatment of Turner syndrome (15,16). In the multicenter study of MacFarlane et al. (17), recombinant human GH (rhGH) treatment (0.33 mg/kg/week) was administered to 23 NS patients with a mean age of 9.3 years. The mean height SDS of the patients was -2.7 ± 0.4 at the start of treatment, which reached -1.9 ± 0.9 at the end of three years. In the study of Şıklar et al. (18), which was the first multicenter study on NS reported in Turkey, 124 patients with NS were evaluated retrospectively and 47 (37.9%) with a clinical diagnosis (according to the Van Der Burgt Criteria) or genetic diagnosis received rhGH treatment. While the height SDS of the patients was -3.62 ± 1.14 at the start of GH treatment, it reached -2.85 ± 0.96 after three years of treatment. In the present study, GH treatment was initiated at a dose of 0.023 mg/kg/week in six of the nine patients. In patients who received GH treatment, while the initial mean height SDS was -3.68 ± 1.13, it had improved to -3.28 ± 0.94 after one year of treatment. Both the mean height SDS on admission of all patients and the post-treatment height SDS

Table 1. Clinical and laboratory findings of patients with c.772G > A(p.Glu258Lys) mutation in the *PTPN11* gene

	I		II		III		IV		
	a	b	a	b	a	b	a	b	c
Genetic mutation	Homozygous	Heterozygous	Heterozygous	Heterozygous	Heterozygous	Heterozygous	Homozygous	Heterozygous	Heterozygous
Birth weight (gr)	2000	2800	3100	3000	1600	1700	2000	2900	3100
Gestational age (week)	39	39	39	38	37	37	38	39	39
Gender	Male	Female	Male	Female	Male	Female	Female	Female	Male
Age at diagnosis (years)	9.4	12	6.8	11	9.3	13.1	12.6	13.9	12.4
Height on admission (SDS) Weight on admission (SDS)	110 (-4.28) 17 (-4.16)	131 (-3.44) 27 (-2.8)	102.4 (-3.39) 14.7 (-2.24)	135.4 (-1.68) 29.4 (-1.33)	121 (-2.06) 23.4 (-1.51)	143.2 (-2.49) 41.5 (-1.31)	124 (-5.3) 23 (-4.33)	136.4 (-3.91) 31.7 (-3.7)	133 (-2.36) 28 (-2.3)
Maternal height (cm) Paternal height (cm) Target height (cm)	140 165 159	140 165 146	158 166 168.5	158 166 155.5	146.5 167 163.3	146.5 167 150.3	152 164 151.5	152 164 151.5	152 164 164.5
Typical facial findings									
- Mane neck	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
- Ptosis	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
- Chest deformity	No	No	Yes	No	No	No	Yes	No	No
Cardiovascular anomalies	No	No	No	No	No	No	No	No	No
GUS anomalies									
- Cryptorchidism	Yes	(-)	No	(-)	No	(-)	(-)	(-)	No
- Renal abnormalities	No	No	No	No	Horseshoe Kidney	No	No	No	No
Abnormal hemostasis	No	No	No	No	No	No	No	No	No
Ocular anomalies	No	No	Yes (astigmatism)	No	No	No	Yes (astigmatism)	No	No
Cutaneous findings	No	No	No	No	No	No	No	No	No
Neurodevelopmental disorders									
- Performance	61	87	81	79	82	76	71	105	117
- Verbal	71	89	90	87	90	71	70	85	93
Hearing loss	No	No	No	Conductive	Conductive	Conductive	No	No	No
IGF-1 (SDS) IGFBP-3 (SDS)	45 (-2.33) 2190 (-1.51)	148 (-1.17) 4200 (-0.69)	103 (0.33) 3700 (0.49)	250 (0.03) 3450 (-1.01)	120 (-0.38) 4200 (0.33)	413 (0.32) 4262 (-0.76)	151 (-1.15) 2110 (-1.98)	241 (-0.88) 4407 (-0.67)	109.5 (-1.49) 2684 (-1.66)
Bone age	6	11.5	5	11	7.5	12.5	10.5	11.5	10.6
Height at growth	Received GH therapy	Did not receive GH therapy	Received GH therapy	Did not receive GH therapy	Received GH therapy	Did not receive GH therapy	Received GH therapy	Received GH therapy	Received GH therapy
Hormone therapy start (SDS) Height after one year of growth hormone therapy (SDS)	115 (-4.31) 122 (-3.96)		113 (-2.9) 119 (-2.57)		137.6 (-2.7) 146.3 (-2.4)		126.2 (-5.52) 133 (-4.77)	137 (-3.97) 142 (-3.39)	133.4 (-2.7) 141 (-2.59)

SDS: standard deviation score, GUS: genitourinary system, IGF-1: insulin-like growth factor-1, IGFBP-3: insulin-like growth factor binding protein-3, GH: growth hormone

of the patients who received GH treatment in the present study were consistent with the literature. In contrast to the literature, the height SDS of the patients with homozygous variants (Ia: -4.28 and IVa: -5.3 SDS) was much lower than the other seven patients with heterozygous variants (mean height SDS: -2.79 ± 0.80).

The most common cardiac abnormalities seen in patients with NS are pulmonary valve stenosis (PVS) and HCM (19,20). In addition to its association with PVS, *PTPN11* variant was reported to be associated with enlargement of the aortic annulus and aortic root (21). In the study of Bell et al. (22), in which 686 pediatric patients diagnosed with PVS between 2009 and 2019 were evaluated retrospectively, NS was detected in 9%. In the present study, cardiac pathology was not detected in any of the patients.

The ophthalmologic findings of NS include a broad spectrum of mainfestations, such as external ocular malformations, refractive errors, mobility abnormalities, and ocular anterior and posterior segment disorders. One of the main criteria for the diagnosis of NS is facial dysmorphology with external ocular features, consisting of hypertelorism, epicanthic folds, ptosis, and/or down-slanting palpebral fissures (23). Marin et al. (24) showed that the most common finding (74%) in patients with identified *PTPN11* variants was down-slanting palpebral fissures. Refractive errors (astigmatism-myopia-hyperopia) have also been reported to be common ocular findings (23). In patients with refractive errors, *PTPN11* variant has usually been detected (10). In the presented kindred, 22.2% had refractive errors and 77.8% had ptosis, which is consistent with previous studies.

In patients with NS, external ear malformations, conductive hearing loss and, less frequently, sensorineural hearing loss may be observed (25). A study by van Trier et al. (25) evaluated 34 patients with NS and hearing loss. They found conductive hearing loss caused by otitis media with effusion that occurred in the past in 20 (58.8%) patients, sensorineural hearing loss in nine (26.5%), permanent conductive hearing loss in two (5.9%), and mixed hearing loss in two (5.9%). Conductive hearing loss was present in three (33.3%) of our patients.

Musculoskeletal manifestations of NS consist of insufficient and/or delayed growth causing short stature, and axial skeletal deformities including spine and rib cage abnormalities such as kyphosis, scoliosis, vertebral anomalies, and pectus deformities, together with micrognathia, cubitus valgus, brachydactyly, syndactyly and osteopenia (26). Chest deformities were present in two (22.2%) of our patients.

Neurological, cognitive and behavioral problems of individuals with NS are highly variable. Patients with NS usually have normal intelligence, but 10% to 40% require special education. The IQ score of the patients is reported to vary between 70 and 120 (27). Affected individuals have been shown to have 10 points less IQ than unaffected family members or 1 SD below the general population (28). The heterogeneity observed in cognitive abilities in RAS-MAPK signaling pathway syndromes, including NS, may vary depending on the genes affected and the type of variant. For example, patients with *PTPN11* and *SOS1* variants show mild cognitive delay (27). Speech disorders are more common compared to the general population. In these patients, hearing and neurodevelopmental evaluations should be performed. Similarly, IQ scores of our patients were between 61-117. While the performance score of patients with heterozygous variants was 89.6 ± 15.4 and the verbal score was 86.4 ± 7.25, the performance scores of the two homozygous cases were 61 and 71, respectively, their verbal scores were calculated as 71 and 70. Studies have shown that the *PTPN11* gene plays a role in brain development (29). Similarly, in our study, the majority of our cases had learning disabilities.

Renal abnormalities in NS are usually mild with a reported frequency of 11% (30). The prevalence of cryptorchidism in boys with NS is 60-80% (31). In the present study, cryptorchidism was present in one (25%) of the four male patients and horseshoe kidney pathology was present in one of the nine patients (11.1%). Given the reported frequencies of these two anomalies, all children diagnosed with NS should be evaluated in terms of cryptorchidism and renal pathology.

In different studies on the prevalence of bleeding disorders in NS, the rate has varied from 30-72% (32). In addition, the prevalence of hemostatic laboratory derangements has been reported to vary between 30-74% (32). The prevalence of bleeding disorders has been reported to be 14-60% in patients with *PTPN11* variant (31). Despite all patients in the present study having *PTPN11* variants, and contrary to the literature, no bleeding disorder was found in any of them. Functional studies could not be performed in the patients.

Study Limitations

The follow-up period was short in patients who were started on GH treatment. Due to time constraints and limited resources, functional studies on the effect on the protein could not be conducted, but we hope to investigate this issue in future studies.

Conclusion

NS is a variable syndrome that may affect many systems. All patients diagnosed with NS should be followed up with a multidisciplinary approach. In the present study, a variant that had been described before in the literature was detected in the *PTPN11* gene and, notably, this variant was homozygous in two patients. To the best of our understanding, these are the first human homozygous *PTPN11* case reports published and they come from two related, consanguineous families. It should be kept in mind that in regions where the prevalence of consanguineous marriages is high, rare variants may cluster among members of the same family.

Ethics

Ethics Committee Approval: The study was performed in accordance with the rules of Declaration of Helsinki and approved by the Institutional Ethics Committee of University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital (no: 69, date: 21.04.2022).

Informed Consent: Informed consent was obtained from all patients included in the study.

Authorship Contributions

Concept: Ruken Yıldırım, Şervan Özalkak, Ayça Aykut, Nevzat Yılmaz, Design: Ruken Yıldırım, Edip Ünal, Şervan Özalkak, Ayça Aykut, Data Collection or Processing: Ruken Yıldırım, Edip Ünal, Şervan Özalkak, Analysis or Interpretation: Ruken Yıldırım, Literature Search: Ruken Yıldırım, Şervan Özalkak, Nevzat Yılmaz, Writing: Ruken Yıldırım, Edip Ünal, Şervan Özalkak.

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