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OBM Genetics

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Original Research

Clinical Variabilities of *PTPN11* Pathogenic Variant in Indonesian Noonan Syndrome Patients

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Academic Editor: Fabrizio Stasolla

Collection: Rare Genetic Syndromes: From Diagnosis to Treatment

OBM Genetics
2026, volume 10, issue 2
doi:10.21926/obm.genet.2602338

Received: January 08, 2026
Accepted: April 15, 2026
Published: May 06, 2026

Abstract

Noonan syndrome (NS) is an autosomal dominant disorder with a wide spectrum of symptoms and clinical phenotypes, including short stature, congenital heart defects (CHD), and distinctive facial features. A pathogenic variant in the *PTPN11* gene is the major cause of NS. This is a preliminary study in Indonesia involving 29 patients with clinical features of NS. Detailed clinical and echocardiography data were collected. Genomic DNA was extracted from a peripheral blood sample. Exome sequencing or PCR followed by Sanger DNA sequencing was

done. Variant pathogenicity was assessed using the ClinVar database, while the novel variant was analyzed in silico using PolyPhen, Rare Exome Variant Ensemble Learner (REVEL), SIFT, FATHMM Pred, and MutationTaster. Clinical findings in 18 patients showed a typical craniofacial feature of NS, including low-posteriorly rotated ear (83.3%), microcephaly, downslanted palpebral fissures, and a short-webbed neck in 50%, and hypertelorism and a depressed nasal bridge in 44.4%. Other clinical variabilities included CHD (83.3%), thoracic and musculoskeletal deformities (77.8%), short stature (72.2%), and intellectual disability (ID) (50%). A novel variant in exon 3 of *PTPN11* was found in one patient: c.140G>A (p.Arg47Lys), which was predicted to be probably damaging. A variant in exon 8, the c.907G>A (p.Asp303Asn), was found in 11 patients. This variant is not in the ClinVar database yet; however, it was reported in a case report and predicted to be probably damaging. One patient has a variant c.184T>G (p.Tyr62Asp), 1 patient has c.854T>C (p.Phe285Ser), 1 patient has c.922A>G (p.Asn308Asp), 2 patients have c.1510A>G (p.Met504Val), and 1 patient has c.1517A>C (p.Gln506Pro), those variants have been previously reported. Sequencing on the remaining exons of *PTPN11* is still ongoing. NS patients with *PTPN11* variants demonstrate diverse clinical manifestations. Clinicians' awareness of suspecting NS is essential for early diagnosis, particularly in children with short stature, ID, and CHD who have a distinctive facial dysmorphism at any age.

Keywords
PTPN11; Noonan syndrome; clinical variability; short stature; intellectual disability; congenital heart disease

1. Introduction

Noonan syndrome (NS; OMIM#163950) is an autosomal dominant disorder characterized by craniofacial dysmorphism, such as short webbed neck (68.4%), downslanted palpebral fissures (46.6%), low posteriorly rotated ears (43.3%), and microcephaly (32.5%). Other features include congenital heart diseases (CHD) (83.8%), thoracic and musculoskeletal deformities (short stature) (77.4%), intellectual disabilities (ID) (20%) [1-3], and other additional extracardiac features. The incidence of NS is estimated to be 1 in 1000-2500 live births [4, 5].

NS is a heterogeneous condition, with variable phenotypic expression and severity. The syndrome is associated with pathogenic variants in multiple genes in the Ras/Mitogen-Activated Protein Kinase (RAS-MAPK) pathway, which regulates growth and differentiation, leading to dysregulation. More than eight different genes associated with NS, such as *PTPN11* (61%), *SOS1* (12%), *RAF1* (7%), *RIT1* (5%), *LZTR1* (4%), and other implicated genes, including *SOS2*, *BRAF*, *KRAS*, *MAP2K1*, *MRAS*, *NRAS*, *RASA2*, and *RRAS2*, are required to diagnose NS.

Pathogenic variants in the *PTPN11* gene are the major cause of NS, with missense mutations responsible for about 50% of NS cases. This gene encodes the tyrosine protein phosphatase non-receptor (SHP2), which is involved in Extracellular Signal-Regulated Kinase (ERK) activation via the RAS-MAPK pathway [6]. *PTPN11* is located on chromosome 12q24 and contains 15 exons, encoding a total of 593 amino acids. Variants in *PTPN11* are most frequently found in exons 3 and 8 [7]. The

hotspot variant in the *PTPN11* gene associated with NS is c.922A>G (p.Asn308Asp) in exon 8. This variant has been widely studied and reported across a range of populations with prevalence of 16.3% to 43%. The second, c.1510A>G (p.Met504Val) in exon 3, is less prevalent, with a range of 4.2% to 16.3% [1]. Other recurrent variants include c.417G>C (p.Glu139Asp) in exon 8, c.836A>G (p.Tyr279Cys) in exon 7, and c.1403C>T (p.Thr468Met) in exon 13, which are also often found in populations [8].

The *PTPN11* gene is expressed in various tissues and plays a crucial role in regulating eukaryotic cell responses to multiple extracellular signals, such as hormones, cytokines, and growth factors. Mutations in *PTPN11* can be inherited in an autosomal dominant manner or occur de novo. The mutations involved in NS are considered gain-of-function mutations that cause inappropriate prolongation of the RAS/MAPK signaling pathway. The prolonged RAS/MAPK pathway leads to the pleomorphic characteristics in NS [9].

NS is characterized by a broad spectrum of symptoms and physical features that vary greatly in range and severity, and can change with age. The most consistent features are wide-set eyes, low-set ears, short stature, and pulmonary valve stenosis [9, 10]. The diagnosis of NS syndrome depends on the identification of characteristic clinical features [10, 11].

Clinical diagnosis of NS based on the diagnostic criteria for NS. Until recently, diagnosis was made based on clinical features. Molecular genetic testing can confirm approximately 70% of cases [10]. There are major and minor criteria, along with some features, for establishing the diagnosis of NS (Table 1). The features are facial features, cardiac features, height, chest wall shape, family history, and other characteristics such as ID, cryptorchidism, and lymphatic vessel dysplasia [11].

Table 1 Diagnostic Criteria for Noonan syndrome [12].

Feature	**A = Major**	**B = Minor**
Facial	Typical facial dysmorphology (facial features vary with age)	Suggestive facial dysmorphology
Cardiac	Pulmonary valve stenosis, hypertrophic cardiomyopathy, and/or electrocardiographic results typical of Noonan syndrome	Other defect
Height	<3rd percentile	<10th percentile
Chest wall	Pectus carinatum/excavatum	Broad thorax
Family history	First-degree relative with definite Noonan syndrome	First-degree relative with suggestive Noonan syndrome
Other features	All of the following: intellectual disability, cryptorchidism, and lymphatic vessel dysplasia	One of the following: intellectual disability, cryptorchidism, and lymphatic vessel dysplasia

Note: Noonan syndrome is considered present if the patient has typical facial dysmorphology plus one feature from categories 2A through 6A of two categories from features 2B through 6B, or has suggestive facial dysmorphology plus two features from categories 2A through 6A or three features from categories 2B through 6B.

Adapted with permission from van der Burgt et al. [12].

2. Materials and Methods

We included 29 patients who visited the Cytogenetic and Molecular Laboratory, Biomedical Research Center Laboratory (CEBIOR), Faculty of Medicine Universitas Diponegoro, Semarang, Indonesia. The inclusion criteria for subjects are age 0-18 years old who were diagnosed with NS based on Van der Burgt criteria (Table 1) and were clinically confirmed by an experienced pediatrician.

2.1 Clinical Examination

Patients were described according to craniofacial features, cardiac defects, and systemic manifestations. Short stature was defined as a height-for-age z-score (HAZ) below -2 standard deviation (SD) or less than the 3rd percentile. In contrast, severe short stature was defined as HAZ below -3 SD, plotted on World Health Organization (WHO) graphics for subjects below 5 years old, and Centers for Disease Control and Prevention (CDC) for subjects >5 years old. Clinical data were obtained from hospital medical records.

2.2 Molecular Analysis

Genomic DNA was isolated from peripheral blood samples using the QIAamp DNA Mini Kit (QIAGEN, Pune, India) at CEBIOR, Faculty of Medicine, Diponegoro University, Indonesia. The Polymerase Chain Reaction (PCR) has been performed in a 30 µl reaction volume containing 2 µl genomic DNA, 15 µl GoTaq Green Master Mix 2X (Promega Corporation Company, Madison, Wisconsin, United States), 0.5 µl 10 µM forward and 0.5 µl 10 µM reverse primer by Genetika Science Indonesia, Tangerang, Indonesia, and 12 µl nuclease-free water. Cycling parameters were 45 cycles of 95°C for 30 seconds (denaturation); 54-60°C for 30 seconds (annealing); and 68°C for 90 seconds (extension), followed by 68°C for 7 minutes (final extension step). Please refer to Table 2 for the primer sequences, annealing temperatures, and size of PCR products for each primer pair.

Table 2 Primer Sequences, Annealing Temperatures, and Product Lengths to Amplify *PTPN11* [8].

Exon	Primer Sequence (5' → 3')		Annealing Temperatures (°C)	Product Length (bp)
	Forward	Reverse		
1	GCTGACGGGAAGCAGGAAGTGG	CTGGCACCCGTGGTTCCCTC	60	589
2	ACTGAATCCCAGGTCTCTACCAAG	CAGCAAGCTATCCAAGCATGGT	60	405
3	CGACGTGGAAGATGAGATCTGA	CAGTCACAAGCCTTTGGAGTCAG	60	384
4	AGGAGAGCTGACTGTATACAGTAG	CATCTGTAGGTGATAGAGCAAGA	58	447
5	CTGCAGTGAACATGAGAGTGCTTG	GTTGAAGCTGCAATGGGTACATG	60	329
6	TGCATTAACACCGTTTTCTGT	GTCAGTTTCAAGTCTCTCAGGTC	54	282
7	GAACATTTCCTAGGATGAATTCC	GGTACAGAGGTGCTAGGAATCA	56	271
8	GACATCAGGCAGTGTTCACGTTAC	CCTTAAAGTTACTTTCAGGACATG	57	350
9	GTAAGCTTTGCTTTTCACAGTG	CTAAACATGGCCAATCTGACATGTC	56	357
10	GCAAGACTTGAACATTTGTTTGTTGC	GACCCTGAATTCCTACACACCATC	60	284
11	CAAAAGGAGACGAGTTCTGGGAAC	GCAGTTGCTCTATGCCTCAAACAG	60	453
12	GCTCCAAAGAGTAGACATTGTTTC	GACTGTTTTCGTGAGCACTTTC	56	250
13	CAACACTGTAGCCATTGCAACA	CGTATCCAAGAGGCCTAGCAAG	60	356
14	ACCATTGTCCCTCACATGTGC	CAGTGAAAGGCATGTGCTACAAAC	60	259
15	CAGGTCCTAGGCACAGGAACTG	ACATTCCCAAATTGCTTGCCT	60	321

Sanger DNA sequencing was performed at the Integrated Laboratory for Research and Testing (LPPT) Universitas Gadjah Mada, Yogyakarta, Indonesia. The first purification was performed using the Exo-Sap protocol with a mixture of 5 µl of PCR product and 2 µl of ExoSap-IT, then incubated in a thermalcycler at 32°C for 15 minutes and 80°C for the next 15 minutes. Cycle sequencing was performed in 1 µl BigDye Terminator Ready Mix, 2 µl Buffer 5×, 1 µl forward/reverse primer (3.2 pmol), 1 µl template DNA, and 5 µl ddH_2O. Cycling parameters were 25 cycles of 96°C for 10 seconds (denaturation); 50°C for 5 seconds (annealing); 60°C for 4 minutes (extension); and 4°C for hold. The second purification was performed using BigDye X-Terminator Purification kit (BDX) (Applied Biosystems, Foster City, CA, USA) with a mixture of 10 µl of sequencing template result, 45 µl SAM solution, and 10 µl BDX. Electrophoresis was performed in an Applied Biosystem 3500 Genetic Analyzer (Applied Biosystem).

Exome sequencing was performed on five of 29 samples at the Genome Diagnostics Nijmegen, Department of Human Genetics, Radboud University Medical Center, The Netherlands, using Illumina NovaSeq 6000, after exome enrichment with the Twist Exome 2.0 plus Comprehensive Exome Spike-in Kit (Twist Bioscene, South San Francisco, United States).

2.3 Variant Analysis

The Human Gene Mutation Database (HGMD), the National Center for Biotechnology Information (NCBI) database, GnomAD (https://gnomad.broadinstitute.org/), and ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) databases were used to confirm the pathogenicity status of the variant. The novel variant was analyzed for pathogenicity in silico using Polymorphism Phenotyping (PolyPhen) (http://genetics.bwh.harvard.edu/pph2/), Rare Exome Variant Ensemble Learner (REVEL) (https://sites.google.com/site/revelgenomics/), Sorting Intolerant From Tolerant (SIFT) (https://sift.bii.a-star.edu.sg/sift4g/), and Functional Analysis through Hidden Markov Models (FATHMM_pred) (https://fathmm.biocompute.org.uk/), and MutationTaster_pred (https://www.mutationtaster.org/).

2.4 Ethics Statement

This study had been reviewed and approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia [No. 336/EC/KEPK/FK-UNDIP/VII/2024]. Written informed consent to participate in this study, including for the publication of any potentially identifiable images in this paper, was provided by the participants' legal guardian.

3. Results

3.1 PTPN11 Variants

We identified a total of 18 patients (62%) with *PTPN11* variants in 29 patients (Table 3), all of which have been previously reported as pathogenic, and one novel variant. Thirteen patients had missense changes in exon 8: 11 patients have a missense variant in c.907G>A (p.Asp303Asn), this change was the most common variant observed in our study (37.93%), one patient has a variant in c.922A>G (p.Asn308Asp), and another in c.854T>C (p.Phe285Ser). Three patients have variants in exon 13: two patients have a variant in c.1510A>G (p.Met504Val), and one has c.1517A>C (p.Gln506Pro). Two patients have a variant in exon 3 c.184T>G (p.Tyr62Asp) and c.140G>A

(p.Arg47Lys); most of these pathogenic variants have previously been reported, as shown in Table 3 [8, 13, 14]. A novel variant, c.140G>A (p.Arg47Lys), was identified in exon 3 and analyzed for pathogenicity in silico using PolyPhen and REVEL.

Table 3 *PTPN11* variants found in this study.

DNA	Protein	Exon	Number of patients	Reference	Clin Var	GnomAD	PolyPhen	REVEL	SIFT	FATHMM Pred	MutationTaster	Conservation	Classification
c.184T>G	p.Tyr62Asp	3	1	[8, 13, 14]	Pathogenic (ID 13329)	Absent	Probably damaging	0.996	Deleterious (Damaging)	Damaging/ Pathogenic	Deleterious	Conserved	Pathogenic
c.140G>A	p.Arg47Lys	3	1	-	Absent	Absent	Probably damaging	0.869	0.36 Tolerated	Damaging/ Pathogenic	Deleterious	Conserved	Pathogenic
c.854T>C	p.Phe285Ser	8	1	[8, 14]	Pathogenic (ID 13335)	Absent	Probably damaging	1.000	Deleterious (Damaging)	Damaging/ Pathogenic	Deleterious	Conserved	Pathogenic
c.907G>A	p.Asp303Asn	8	11	[15]	Absent	Absent	Probably damaging	0.533	Deleterious (Damaging)	Damaging/ Pathogenic	Deleterious	Conserved	Variant of Unknown Significance
c.922A>G	p.Asn308Asp	8	1	[8, 13, 14]	Pathogenic (ID 13326)	Pathogenic	Probably damaging	0.625	Deleterious (Damaging)	Damaging/ Pathogenic	Deleterious	Conserved	Pathogenic
c.1510A>G	p.Met504Val	13	2	[8, 13]	Pathogenic (ID 40562)	Absent	Pathogenic	0.843	Deleterious (Damaging)	Damaging/ Pathogenic	Deleterious	Conserved	Pathogenic
c.1517A>C	p.Gln506Pro	13	1	[8]	Pathogenic (ID 40563)	Absent	Probably damaging	0.900	Deleterious (Damaging)	Damaging/ Pathogenic	Deleterious	Conserved	Pathogenic

All *PTPN11* variants listed in this table are predicted to cause NS in a dominant form.

3.2 Phenotype Analysis

A wide range of phenotypic variability is observed among NS patients with a *PTPN11* pathogenic variant, demonstrating variable expressivity and penetrance. Of the 18 patients with a *PTPN11* variant, 50% of patients were male. Age at diagnosis ranged from <1 month to 7 years 4 months. The mean HAZ was -3.28 SD, while the weight-for-height z-score (WHZ) mean was -1.66 SD. Nine of 18 patients (50%) came with the chief complaint of weight faltering and experienced feeding difficulties in infancy. Two of 18 patients (11.1%) were short in stature. Other clinical manifestations were described (Table 4) to demonstrate the clinical variabilities in *PTPN11* pathogenic variants in Indonesian NS patients.

Table 4 Phenotypic features in patients with positive *PTPN11* pathogenic variant.

Phenotypic features	**Percentage in *PTPN11*-positive patients in our study (n = 18)**	**Percentage in *PTPN11*-positive patients worldwide** [2, 3, 13, 16-23]
Craniofacial characteristics		
Abnormal head shape	2 (11.1%)	5/31 (16.1%)
Microcephaly	9 (50%)	13/40 (32.5%
Tall forehead with narrow temples	5 (27.8%)	34/107 (31.8%)
Thin and curly scalp hair	5 (27.8%)	9/107 (8.4%)
Prominent eyes	7 (38.9%)	10/38
Hypertelorism	8 (44.4%)	68/135 (50.4%)
Downslanted palpebral fissure	9 (50%)	19/28 (67.9%)
Depressed nasal bridge	8 (44.4%)	17/38 (44.7%)
Bulbous nose	5 (27.8%)	17/38 (44.7%)
Upturned/downturned mouth	4 (22.2%)	-
Short chin	4 (22.2%)	110/124 (88.7%)
Low-set posteriorly-rotated ear	15 (83.3%)	96/137 (70.1%)
Short neck, webbed neck	9 (50%)	65/107 (60.7%)
Systemic manifestations		
Arms deformities	3 (16.7%)	18/71 (25.4%)
Legs deformities	6 (33.3%)	18/71 (25.4%)
Palmar crease	3 (16.7%)	5/41 (12.2%)
Cryptorchidism	4 (22.2%)	27/32 (84.4%)
Lymphatic vessel dysplasia	2 (11.1%)	43/115 (37.4%)
Intellectual disability	9 (50%)	4/17 (23.5%)
Cancer and hematologic disorders	4 (22.2%)	2/18 (11.1%)
Dental and oral disorders	5 (27.8%)	17/29 (58.6%)
Cutaneous manifestations or ectodermal involvement	1 (5.6%)	70/129 (54.3%)
Gastrointestinal manifestations	3 (16.7%)	16/25 (64%)
Genitourinary and renal manifestations	2 (11.1%)	10/35 (28.6%)

Hearing loss	3 (16.7%)	2/17 (11.8%)
Short stature	15 (83.3%)	43/107 (40.2%)
Hypothyroidism and autoimmune disorder	7 (38.9%)	6/42 (14.3%)
Thoracic and musculoskeletal deformities	14 (77.8%)	3/18 (16.7%)
Cardiac defects		
Pulmonary valve stenosis	5 (27.8%)	92/181 (50.8%)
Atrial septal defect	4 (22.2%)	70/181 (38.7%)
Pulmonary valve stenosis + atrial septal defect	2 (11.1%)	-
Pulmonary valve stenosis + Patent Foramen Ovale	2 (11.1%)	6/22 (27.3%)
Hypertrophy cardiomyopathy	1 (5.6%)	13/181 (7.2%)
Patent Ductus Arteriosus + Ventricular septal defect + Pulmonary Hypertension	1 (5.6%)	-

A typical craniofacial feature of NS was observed in all patients. Features observed with high frequency in the patients with *PTPN11* pathogenic variants were low-set posteriorly rotated ears found in nearly all patients (83.3%), microcephaly, downslanted palpebral fissure and short-webbed neck found in nine patients (50%), hypertelorism and depressed nasal bridge in eight patients (44.4%), while thin and curly scalp hair, tall forehead with narrow temples, bulbous nose, and upturned/downturned mouth found in five patients (27.8%). CHD diagnosed by echocardiography was present in 15 patients (83.3%), pulmonary valve stenosis was the most common, either isolated (27.8%) or combined with atrial septal defect (ASD) (38.9%). Four of eighteen patients (22.2%) also developed an isolated ASD. CHD was seen most frequently in patients with pathogenic variants in exon 8 (10 out of 12 patients). Severe short stature was observed in 8 patients (44.4%), while short stature was found in 5 patients (27.8%). Other phenotypes observed in most patients (77.8%) include thoracic deformities or musculoskeletal manifestations (sternal deformities and finger-toes deformities). All patients with *PTPN11* pathogenic variants showed mild to moderate ID.

Comorbidities were also observed in this study; one patient reported suffering from juvenile myelomonocytic leukemia. Furthermore, hypothyroidism, cholestasis, multiple caries dentis and cutis marmorata were also found in several patients. Three patients were reported to have hearing loss, which was acquired beyond childhood and was severe enough to require hearing aids. Laryngomalacia was reported in one patient, which was corrected by surgery.

4. Discussion

To the best of our knowledge, this is the first study involving a relatively large NS patient cohort in Indonesia. Missense mutations in *PTPN11* cause NS and involve a gain-of-function mechanism. In the present study, we identified *PTPN11* changes in 18 (62%) out of 29 patients, all of whom had sporadic NS. These findings are limited as we performed only on selected exons, including *PTPN11* exons 3, 4, 8, 11, and 13. The result is consistent with previous studies, which reported that *PTPN11* pathogenic variants were present in 50% of NS cases [24-27]. Other genes responsible for NS, such as *SOS1*, *SOS2*, *BRAF*, *KRAS*, *MAP2K1*, *MRAS*, *NRAS*, *RAF1*, *RASA2*, *RIT1*, *RRAS2*, and *LZTR1*, may still

be found in other patients. Further examination to study these genes and exons will be planned in the future as well.

Six of the 18 pathogenic variants identified in this study were previously reported missense changes. The majority of variants were found in exon 8, as reported in earlier studies, accounting for 72.2% of the *PTPN11* pathogenic variants (Table 3). In this study, 18 (62%) of those with *PTPN11* pathogenic variants had variants in exons 3, 8, and 13; this proportion is consistent with that observed in most studies [13, 28-31].

However, one pathogenic variant (c.140G>A p.(Arg47Lys)) represents a novel finding within the N-terminal SH2 domain (N-SH2). N-SH2 plays a critical regulatory role as a key regulatory domain of the protein. This variant has not been previously reported in major population databases and literature [6]. Variants affecting the N-SH2 domain of *PTPN11* are associated with NS due to a gain-of-function that destabilizes the autoinhibitory interaction between the N-SH2 and Protein Tyrosine Phosphatase (PTP) domains. Thus, SHP2 becomes excessively active, leading to hyperactivation of the RAS-MAPK pathway and dysregulated developmental signaling [32]. In silico predictive tools suggest that the variant is probably damaging, and conservation analysis demonstrates it is highly conserved across species, indicating potential functional importance [33].

The missense variant in c.907G>A p.(Asp303Asn) was the most common pathogenic variant we identified. This variant was previously reported in a case of Kawasaki disease in NS by Takai et al. In silico analysis predicted that it was “probably damaging” by Poplyphen2 with a prediction score of 0.533, adding further evidence of the occurrence of this variant in another NS patient [15]. A missense variant, c.922A>G (p.Asn308Asp), found in one patient, is consistent with earlier studies on PTPN11 pathogenic variants, which identified c.922A>G as a mutation hotspot for NS-causing missense changes [8, 13, 14].

Sequence variant c.907G>A p.(Asp303Asn) is likely to represent a non-synonymous single-nucleotide polymorphism (nsSNP) that causes NS in Javanese, Southeast Asian, and Indonesian populations. In our case, we have collected data on family trees; however, we have not found evidence of familial segregation. Therefore, functional studies are needed for this variant. The pathogenic nsSNPs of *PTPN11* c.907G>A p.(Asp303Asn) were analyzed by five in-silico pathogenicity tools, such as PolyPhen, REVEL, SIFT, FATHMM Pred, and MutationTaster. The results support a deleterious effect on protein function in some predictors, but with the REVEL score of 0.533, it is not convincing enough to categorize it as likely pathogenic. With only one previous case report of a Noonan Syndrome patient with this variant [15], we classified it as a variant of unknown significance (VUS), which will need further evidence to reclassify it, according to the American College of Medical Genetics and Genomics (ACMG) guidelines [34]. Considering that about 30% of nsSNPs may influence clinical phenotypes by altering post-translational modifications (PTMs), protein stability, and protein-protein interactions, functional studies and clinical correlation are recommended for definitive pathogenicity confirmation [35, 36].

The SNPs in the coding region of human genes were associated with genetic disorders. A large number of SNPs have been reported in the database, making it difficult to screen them all for a particular phenotype. Computational analysis tools help narrow down and examine pathogenic SNPs for specific genetic disorders, thereby minimizing risk [37, 38].

In many previous studies, genotype-phenotype correlations have been widely investigated. However, the result obtained is that within the same pathogenic variant location, a wide range of

clinical variability is observed [24]. Several studies describe the role of SHP2 in regulating various developmental processes and the possible causes of this variation [39-41].

Variability in craniofacial features may vary due to subjective assessment. Low-set posteriorly rotated ears (83.3%) are the most commonly observed in our study, followed by microcephaly, downslanted palpebral fissure, and short-webbed neck (50%). Hypertelorism and depressed nasal bridge are present in eight (44.4%) patients, while prominent eyes are present in seven (38.9%) of the 18 cases. The mean age is 1 year 11 months, with children being the majority of cases, consistent with the literature on craniofacial features in childhood with NS. In the childhood category, the head is relatively abnormal in shape, with low-set, posteriorly rotated ears, downslanted palpebral fissures, a wide forehead, epicanthal folds, a short-webbed neck, and sternal deformities (pectus carinatum or excavatum). Hypertelorism, ptosis, or thick, hooded eyelids are characteristics. The nose is short and wide with a depressed root [42]. Thereafter, due to age changes, the craniofacial features become less noticeable in adulthood.

Severe short stature (HAZ below -3 SD) and short stature (HAZ below -2 SD or at the 3rd percentile) were seen in 13 (72.2%) of 18 patients with *PTPN11* pathogenic variants. Proportionate short stature is present in more than 50% of cases. The molecular mechanism by which NS-causing SHP2 mutants induce growth retardation had been reported previously [43]. SHP2 mutations in NS by a postreceptor signaling defect cause mild Growth Hormone (GH) resistance, which is partially compensated by increased GH secretion. In children with SHP2 mutations who have a poor response to rhGH, this defect may contribute to the short stature phenotype [44]. Growth delay was associated with low Insulin-like Growth Factor 1 (IGF-1) levels during the early postweaning growth phase. Impaired IGF-1 production contributes to growth retardation in NS. This is in agreement with clinical data showing that NS patients, notably those carrying a *PTPN11* mutation, display low IGF-1 levels [39]. GH treatment in NS is thought to be beneficial because the dysmorphic findings are similar to those in Turner syndrome. Therefore, GH has been administered at the same dose used in the treatment of Turner syndrome [45, 46].

NS is the second most common syndromic cause of congenital heart disease, exceeded in prevalence only by trisomy 21 [23]. Clinical manifestations of CHD problems are the most common reasons that prompt patients to see a doctor. In this study, CHD was found in 15 patients (83.3%) with *PTPN11* pathogenic variants. Pulmonary valve stenosis, seen in 9 patients (50%), was the most common finding in the present study, followed by atrial septal defects in 6 patients (33.3%), either isolated or combined with other types. Compared to the data from the previous study, NS patients with the *PTPN11* pathogenic variant are more likely to be associated with pulmonary valve stenosis or ASD [47]. *PTPN11* encodes the Src homology-2 domain-containing protein tyrosine phosphatase and is reported to be associated with enlargement of the aortic annulus and aortic root [48, 49].

Thoracic and musculoskeletal deformities of NS consist of insufficient and/or delayed growth, causing short stature, and axial skeletal deformities, including sternal deformities, vertebral anomalies, cubitus valgus, and finger-toes abnormalities. Sternal deformities, such as pectus carinatum and/or excavatum, were presented in 10 (55.6%) of the 18 cases with *PTPN11* pathogenic variants. Four patients (27.8%) had widely-spaced nipples, and the chest circumference was measured across the internipple line. The internipple index was calculated according to the formula: internipple distance (cm) multiplied by 100 and divided by chest circumference (cm). The internipple distance and chest circumference increased with age. The internipple index in the neonatal period was the highest among all ages (26.4 ± 1.6 for males and 26.3 ± 2 for females), and will gradually

decrease until the age of four years (23.8 ± 1.2 for males and 23.8 ± 1.4 for females), thereafter it would be relatively constant through the age of 18 years in males and the age of 11 years in females [48].

Neurological manifestations and cognitive and behavioral changes in individuals with NS are highly variable. Heterogeneity in cognitive abilities within RAS-MAPK signaling pathway syndromes has been observed, which depends on the affected gene and the variant type. IQ tests were not examined; instead, the cognitive & behavioural changes were assessed by a Social Pediatric Consultant using the Denver II as a screening tool to identify potential ID. This assessment evaluated four developmental areas: personal-social, fine-motor-adaptive, language, and gross-motor skills. Eight patients (44.4%) were found to have global developmental delay, as their screening test results did not align with their actual age. In these patients, neurodevelopmental and hearing function evaluations should be performed [50].

Cryptorchidism may be present in males with NS and have an increased risk of infertility. While females with NS generally have normal puberty and fertility, males may experience delayed puberty and reduced fertility due to cryptorchidism and other potential gonadal issues. Male gonadal dysfunction has also been reported and is suggested to be caused by primary Sertoli cell dysfunction rather than cryptorchidism [51]. Among the nine male patients in this study, four have cryptorchidism, although all the patients have undergone orchidopexy as corrective surgery.

Lymphatic vessel dysplasia with a clinical lymphatic abnormality is a major feature of NS. Six NS patients (33.3%) with *PTPN11* pathogenic variants had lower limb lymphedema. Lower limb lymphedema and genital lymphedema are the two most reported types of lymphedema that develop after birth [52]. The presentation of lymphedema in NS may vary, including differences in timing and resolution of edema at different ages. Haque et al. [53] reported prenatal and postnatal onset of lymphatic abnormalities in NS, whereas postnatal onset might result in a milder phenotype.

A broad spectrum of ophthalmologic features is found in NS, with downslanted palpebral fissures (50%) being the most common finding in *PTPN11* pathogenic variants, followed by depressed nasal bridge, hypertelorism (44.4%), and prominent eyes (38.9%). Marin et al. [54] reported that the most common ophthalmologic feature finding (74%) in patients with *PTPN11* pathogenic variants was downslanted palpebral fissures. Refractive errors are not examined. Based on the literature, refractive errors and ptosis are often detected and reported in patients with *PTPN11* pathogenic variants [55].

Several hematological disorders are predisposed to occur in NS, including transient monocytosis, thrombocytopenia, and myeloproliferative disorder [56]. The most common haematologic disorders are coagulation defects, manifested as bleeding abnormalities [57]. In this study, one NS patient with a *PTPN11* pathogenic variant had severe anemia, while other patients had haemangioma and juvenile myelomonocytic leukemia. Several hematological cancers have been reported in patients with NS during childhood, including juvenile myelomonocytic leukemia, acute myelogenous leukemia, and B-cell acute lymphoblastic leukemia [57].

Despite a few studies reporting an autoimmune thyroiditis in NS, an earlier study showed an association between hypothyroidism and NS. In a patient with NS, primary hypothyroidism is an uncommon condition that may develop either separately or in conjunction with NS. Although the precise etiology of this condition is unknown, age, excessive iodine intake, and heredity can make an individual more susceptible. One NS patient in this study was found to have hypothyroidism and

undertreatment with Euthyrax. A multidisciplinary approach is required for these individuals with comorbidities or related conditions to NS [58].

Gastrointestinal manifestations such as liver problems, including elevated liver enzymes, autoimmune hepatitis, and even human hepatocellular carcinoma (HCC), can occur in NS due to its genetic basis affecting the RAS-MAPK pathway, which is commonly seen in other RASopathies like progressive familial intrahepatic cholestasis (PFIC) [59]. We reported one NS patient with a pathogenic *PTPN11* variant with cholestasis. Liver problems in NS are less frequent; a previous study by Rippert [60] revealed a strong association between NS and neonatal liver disease, particularly neonatal hyperbilirubinemia and cholestatic disease. Since the pathogenesis of these conditions has not been definitively linked to NS, understanding the spectrum of liver phenotypes in NS remains a subject of ongoing investigation.

NS is linked to various orodental manifestations reported in several studies. High-arched palate, micrognathia, and macrodontia, which can result in malocclusion and misalignment of teeth, have been reported repeatedly in case reports and retrospective studies [61]. High arched palate and caries dentis are common dental problems in NS.

Cutis marmorata teleangiectatica congenita (CMTC), a cutaneous or ectodermal manifestation of NS, was found in one patient in this study. CMTC is a possible associated anomaly in NS, even though it is not a primary feature. Cutaneous findings are common in NS with *BRAF*, *KRAS*, and *SHOC2* variants [62].

The study's retrospective design had some limitations. We tried to combine the correlations between genotypes and phenotypes based on follow-up results in the medical records from the last examination. Due to the high cost and the fact that genetic testing is not covered by national health insurance, genetic testing has only been performed on selected exons, those frequently reported to cause NS mutations, which were evaluated. Moreover, the relatively small cohort may not adequately represent the broader population variability and may have biased the results. However, this study is, to the best of our knowledge, the first to explore genotype-phenotype correlations of NS. in the Indonesian population, which might be a basis for further study in NS.

5. Conclusions

NS has broad clinical manifestations, and each patient presents with mixed clinical features. Clinicians need to raise awareness of suspecting NS, since the incidence rate is relatively high, and be concerned about comorbidities. Early diagnosis can be achieved by maintaining a high index of suspicion in children with short stature, ID, CHD, and musculoskeletal deformities that have a distinctive facial dysmorphism at any age. Whole exome sequencing or gene panel is the gold standard for NS and other RASopathies. However, in this developing country, Indonesia, where most of the cases come from families with low economic backgrounds, genetic testing is very expensive and not covered by government health insurance. In these situations, based on the results of our study, we might suggest molecular testing, such as Sanger sequencing, for patients clinically suspected of having NS, performed only at several mutation hotspots, such as exons 3, 8, and 13.

Acknowledgments

The authors thank the subjects and their families for participating in this study. We thank Radboud University Medical Center for invaluable technical assistance with exome sequencing and

a multiple gene panel for Noonan syndrome. Also, the authors would like to thank the patient and his parents for their willingness to participate in this study.

Author Contributions

All authors contributed to the study's design, data analysis, and manuscript preparation. Nisa Ayu Thayalisha Hadi led data collection, interpretation, and statistical analysis, while Agustini Utari and Nydia Rena Benita Sihombing assisted in manuscript writing. Tri Indah Winarni and Nani Maharani provided critical revisions to the manuscript and supervised the research project.

Funding

The study was fully supported by RPI grant from LPPM Universitas Diponegoro (Undip) number 609-46/UN7-D2/PP/VIII/2023. LPPM Undip had no direct role in study design, sample collection, data interpretation or manuscript preparation. The study was also supported by the Center for Biomedical Research (CEBIOR) Faculty of Medicine Undip.

Competing Interests

The authors have declared that no competing interests exist.

Data Availability Statement

A list of genes involved in the Table 3 is available on the Human GRCh3/hg19 database on the UCSC Human Genome Browser website.

AI-Assisted Technologies Statement

Artificial intelligence (AI) tools were used solely for basic grammar correction and language refinement in the preparation of the manuscript. Specifically, Grammarly was employed to improve the readability and linguistic clarity of the English text. All scientific content, data interpretation, and conclusion were developed independently by the author. The authors have thoroughly reviewed and edited the AI-assisted text to ensure its accuracy and accept full responsibility for the content of the manuscript.

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