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Clinical and Genetic Characterization of Noonan Syndrome in a Colombian Pediatric Cohort

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ABSTRACT

Objective: Describe the clinical manifestations and genetic variants of Noonan syndrome (NS) in a Colombian pediatric population and to identify the genes most frequently associated with specific phenotypic features.

Methods: A retrospective observational study was conducted on patients under 18 years of age diagnosed with NS between 2013 and 2023. Clinical and molecular data were collected from medical records across several hospitals in Colombia. Molecular confirmation was achieved in all included patients through next generation sequencing-based clinical exome sequencing. However, parental samples were not available for segregation analysis in all cases. Descriptive statistical analyses were performed using R version 4.3.1 to evaluate demographic, clinical, and genetic variables.

Results: Among the 45 patients included (21 females, 24 males; mean age at diagnosis 7.5±5.2 years), pathogenic variants were identified across 13 genes, with *PTPN11* being the most frequent (26/45, 57.8%), followed by *PPP1CB* and several less frequent genes including *SOS1, SOS2, LZTR1, RAF1, MAP2K1, KRAS, NRAS, BRAF, CBL, NF1,* and *SHOC2*. The most common phenotypic features were congenital heart defects (80%, 36/45), predominantly pulmonary stenosis (31.1%, 14/45), short stature (66.7%, 30/45), and learning difficulties (51.1%, 23/45). Seven patients developed neoplasms. Juvenile myelomonocytic leukemia was the most frequent neoplasm and occurred mainly in patients with *PTPN11* variants. Ten patients (22.2%) received growth hormone therapy.

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Conclusion: This study represents the first genetically characterized Colombian cohort for NS. *PTPN11* was the predominant gene identified, particularly the p.(Asn308Asp) variant. These findings reiterate the genetic heterogeneity of NS in Colombian children and the importance of early molecular diagnosis to guide clinical management. Multidisciplinary follow-up is essential due to the risks of growth failure, cardiac anomalies, and malignancies.

Keywords: Noonan syndrome, *PTPN11*, RASopathy

What is already known on this topic?

Noonan syndrome (NS) is a RASopathy characterized by distinctive facial features, short stature, congenital heart defects, particularly pulmonary valve stenosis, and various other anomalies. Complications may include growth retardation, bleeding disorders, lymphatic abnormalities, and an increased risk of malignancies, especially in individuals with variants in the *PTPN11* gene.

What this study adds?

In this Colombian pediatric population, variants in *PTPN11* were the most frequent, with p.(Asn308Asp) variant being the most common. Congenital heart defects were present in 80% (36/45) of patients, most commonly pulmonary valve stenosis. Short stature was observed in 66.7% (30/45) of cases. Pathogenic variants were identified across 13 genes, with *PTPN11* being the most frequent. Less frequent variants involved *PPP1CB, SOS1, SOS2, LZTR1, RAF1, MAP2K1, KRAS, NRAS, BRAF, CBL, NF1,* and *SHOC2,* highlighting the genetic heterogeneity of NS in this cohort.

Introduction

Noonan syndrome (NS) is a common genetic disorder with an estimated incidence of 1 in 2,000 to 2,500 live births (1). It is characterized by three cardinal features: distinctive facial features; postnatal short stature; and congenital heart disease. Additional manifestations may include cryptorchidism, delayed puberty, bleeding disorders, lymphedema, thoracic abnormalities, skin disorders, varying degrees of learning difficulties, and a predisposition to myeloproliferative disorders (2,3), reflecting the marked clinical heterogeneity of the syndrome.

Early descriptions of features now associated with NS date back to 1883, when Koblinski reported a patient with a congenital neck deformity later termed pterygium colli. However, NS was more clearly delineated in 1968, when Jacqueline Noonan described nine patients with shared features, including pulmonary valve stenosis and extracardiac anomalies (4,5), thereby establishing NS as a distinct syndrome affecting both sexes, with normal karyotypes and familial inheritance (3,6,7).

NS belongs to the group of developmental disorders known as RASopathies (8), which result from pathogenic variants affecting components or regulators of the RAS/mitogen-activated protein kinase (MAPK) pathway. This pathway plays a central role in cell proliferation, differentiation, and survival (8,9,10).

NS can be inherited in an autosomal dominant or autosomal recessive manner or occur sporadically. Inherited cases predominantly show maternal transmission, whereas *de novo* cases are more commonly of paternal origin. This paternal predominance reflects the well-established higher mutation rate associated with continuous spermatogonial stem cell divisions, together with positive selection in the male germline, whereby activating variants, particularly those affecting the RAS/MAPK pathway, may undergo clonal expansion with advancing paternal age (4,11,12).

PTPN11 was the first gene identified in association with NS and remains the most frequently affected (4,13,14). Since then, more than 20 genes involved in the RAS/MAPK pathway have been associated with NS and related disorders (2,9,10,14). Pathogenic variants in *PTPN11* account for approximately 50% of cases (14,15), followed by variants in *SOS1, RAF1, RIT1*, and *KRAS*, whereas variants in genes such as *NRAS, BRAF, SHOC2, CBL,* and *LZTR1* are less frequent. *LZTR1* is the only gene associated with both autosomal dominant and autosomal recessive inheritance patterns (9,16), whereas *SPRED2* is the only gene inherited exclusively in an autosomal recessive manner. Overall, a molecular diagnosis can be established in approximately 70% to 80% of patients (17,18).

Studies from different populations have demonstrated considerable phenotypic and genetic heterogeneity in NS. However, data from Latin American pediatric populations, particularly from Colombia, remain scarce. Therefore, the aim of this study was to characterize the clinical manifestations and genetic findings of a Colombian pediatric cohort with NS.

Methods

A retrospective, observational, descriptive study was conducted by screening medical records with ICD-10 codes Q871 (Syndromes of congenital malformations primarily associated

with short stature) and Q878 (Other specified congenital malformation syndromes, not elsewhere classified) from 2013 to 2023. The study was conducted at Research and Ethics Committee of Pablo Tobón Uribe Hospital (HPTU), approved under protocol 2022.088 (date: 08.11.2022); San Vicente Fundación Hospital (HSVF), approved under act number 12-2023 (date: 24.04.2023); and other healthcare centers where pediatric endocrinology consultations are performed. Clinical records were reviewed, and only patients with a molecularly confirmed diagnosis of NS were included. Genetic testing was performed using next-generation sequencing (NGS)-based clinical exome methodology on peripheral blood samples. This approach employed targeted capture to selectively enrich coding regions (exons), which represent approximately 1% of the genome but contain the majority of known disease-causing variants. A total of 7,233 clinically relevant genes were analyzed. Bioinformatic analysis included the detection of single nucleotide variants, small insertions and deletions (indels), and copy number variants. Variant interpretation was performed according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines, integrating molecular findings with the patient's clinical phenotype. Family segregation analysis was not performed because parental samples were unavailable. Authorization was obtained from the ethics committee of the aforementioned institutions. For patients not affiliated with these institutions, informed consent was obtained and signed by their legal representatives.

All patients were clinically diagnosed by geneticists according to the van der Burgt criteria (19), and the diagnosis was molecularly confirmed by NGS-based clinical exome testing. Only patients under 18 years of age were included. Patients with a suggestive phenotype but without confirmatory genetic studies were excluded.

Extracted variables included demographic data, molecular findings, prenatal and postnatal history, auxological measurements, craniofacial features, musculoskeletal abnormalities, learning difficulties, endocrine manifestations, malignancies, and congenital heart disease.

Statistical Analysis

A descriptive analysis was conducted. Absolute and relative frequencies were calculated for qualitative variables, while measures of central tendency and dispersion were obtained for quantitative variables. Clinical characteristics were visualized using a lasagne plot. All data were processed using R statistical software, version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 45 patients were evaluated (21 females, 24 males), with an average age at diagnosis of 7.5±5.2 years. Pathogenic variants were identified in 13 genes. Variants in *PTPN11* were the most frequent, present in 57.8% of cases (26 of 45 patients). The most common variant was c.922A>G; p.(Asn308Asp), identified in 11 of these 26 patients. The second most commonly affected gene was *PPP1CB*, observed in 6.7% of cases, with the variant c.146C>G; p.(Pro49Arg) being the most frequent in this group (Table 1). No novel variants were identified. Segregation analysis was not available; therefore, the *de novo* status of the identified variants could not be determined.

There were 21 females and 24 males (Table 2). A maternal history of NS was present in 11.1% (5/45) of cases, occurring more frequently in patients with variants in *PTPN11* and *SOS1*. Regarding prenatal history, chylothorax was identified in 6.7% of cases, predominantly among those with *PTPN11* variants. In terms of postnatal history, prematurity was observed in 15.6 % (7/45) of cases. Being small for gestational age was noted in 11.1% (5/45) of cases, commonly associated with *PTPN11* and *KRAS* variants.

The most common characteristics observed in this cohort included congenital heart disease, low-set ears, short stature, downward-slanting palpebral fissures, short neck, learning difficulties, and hypertelorism, each present in more than 40% (18/45) of cases (Figure 1).

The most common cardiac defect observed was pulmonary stenosis, occurring in 31.1% (14 of 45 patients) of cases, followed by atrial septal defect in 22.2% (10 of 45 patients), and mitral regurgitation in 13.3% (6 of 45 patients) (Table 3).

Seven patients in this cohort developed neoplasms. Among them, three female patients were diagnosed with juvenile myelomonocytic leukemia (JMML). Two unrelated patients carried the same PTPN11 variant, c.1507G>A; p.(Gly503Arg). At the time of diagnosis, all three of these girls were under five years of age.

Two cases involved central nervous system neoplasms (glioma and astrocytoma), both harboring the *PTPN11* variant c.922A>G; p.(Asn308Asp). In addition, two patients with neuroendocrine tumors each carried the *PPP1CB* variant c.146C>G; p.(Pro49Arg).

Discussion

Genetic Findings and Diagnostic Considerations

We report the clinical and molecular characteristics of a cohort of 45 Colombian children and adolescents with NS, molecularly confirmed through clinical exome sequencing. This study represents one of the few pediatric NS cohorts reported from

Table 1. Detected pathogenic and likely pathogenic variants in the cohort

Gene	Frequency n (%)	Variant count	Nucleotide change	Protein change	Transcript (NM)
BRAF	1 (2.2)	1	c.1455G>T	p.(Leu485Phe)	NM_004333.6
CBL	1 (2.2)	1	c.1228-2A>G	p.?	NM_005188.4
KRAS	2 (4.4)	1	c.178G>A	p.(Gly60Ser)	NM_033360.4
		1	c.40G>A	p.(Val14Ile)	NM_004985.5
LZTR1	2 (4.4)	1	c.410C>T	p.(Ala137Val)	NM_006767.4
		1	c.2090G>A	p.(Arg697Gln)	NM_006767.4
MAP2K1	1 (2.2)	1	c.364A>G	p.(Asn122Asp)	NM_002755.4
NF1	1 (2.2)	1	c.4267A>G	p.(Lys1423Glu)	NM_000267.3
NRAS	1 (2.2)	1	c.38G>A	p.(Gly13Asp)	NM_002524.5
PPP1CB	3 (6.7)	2	c.146C>G	p.(Pro49Arg)	NM_002709.3
		1	c.548A>C	p.(Glu183Ala)	NM_002709.3
PTPN11	26 (57.8)	11	c.922A>G	p.(Asn308Asp)	NM_002834.5
		2	c.1507G>A	p.(Gly503Arg)	NM_002834.5
		2	c.124A>G	p.(Thr42Ala)	NM_002834.5
		1	c.1493G>T	p.(Arg498Leu)	NM_002834.5
		1	c.181G>A	p.(Asp61Asn)	NM_002834.5
		1	c.1510A>G	p.(Met504Val)	NM_002834.5
		1	c.218C>T	p.(Thr73Ile)	NM_002834.5
		1	c.417G>C	p.(Glu139Asp)	NM_002834.5
		1	c.781C>T	p.(Leu261Phe)	NM_002834.5
		1	c.1519G>C	p.(Gly507Arg)	NM_002834.5
		2	c.846C>G	p.(Ile282Met)	NM_002834.5
		1	c.188A>G	p.(Tyr63Cys)	NM_002834.5
		1	c.923A>G	p.(Asn308Ser)	NM_002834.5
RAF1	2 (4.4)	1	c.786T>G	p.(Asn262Lys)	NM_002880.4
		1	c.770C>T	p.(Ser257Leu)	NM_002880.4
SHOC2	1 (2.2)	1	c.4A>G	p.(Ser2Gly)	NM_007373.4
SOS1	2 (4.4)	1	c.3145A>T	p.(Thr1049Ser)	NM_005633.4
		1	c.1297G>A	p.(Glu433Lys)	NM_005633.4
SOS2	2 (4.4)	1	c.1532C>T	p.(Ala511Val)	NM_006939.4
		1	c.800T>A	p.(Met267Lys)	NM_006939.4

No novel variants were identified. Segregation analysis was not available; therefore, *de novo* status could not be determined

Colombia and provides valuable data from an underrepresented Latin American population.

PTPN11 was the most frequently affected gene, identified in 57.8% (26/45) of cases, consistent with previous reports indicating it accounts for approximately 50% of NS cases (20,21,22). Prior studies have shown that up to 86% of pathogenic *PTPN11* variants cluster in exons 3, 8, and 13, as reported in the first Brazilian cohort (13). In our cohort, the most frequent variant was c.922A>G; p.(Asn308Asp). This variant has also been reported as the most prevalent in a cohort of 26 individuals with NS followed at a reference center in southwest Colombia (22,23), as well as in other populations, representing approximately 20% of cases in Europe, the United States, Argentina (15), and Brazil (13), and 11% in southern India (16). These findings suggest a shared distribution of this variant across different populations; however, a recurrent mutational event cannot be excluded.

NS is characterized by significant phenotypic variability (20) ranging from isolated anomalies, such as pulmonary valve stenosis, to subtle facial features, short stature, or multiple congenital anomalies. Due to phenotypic overlap with other conditions and age-related changes in craniofacial characteristics,

Table 2. Family, prenatal, and postnatal history of the patients according to the affected gene

Characteristics	All (n=45)	*KRAS* (n=2)	*LZTR1* (n=2)	*NRAS* (n=1)	*PTPN11* (n=26)	*RAF1* (n=2)	*SOS1* (n=2)	*SOS2* (n=2)
Demographics								
Female:Male	21:24	1:1	1:1	1:0	12:14	2:0	0:2	1:1
Age at diagnosis, years (mean ± SD)	7.5±5.2	4.1±4.2	11.9±4.5	12.0	7.1±5.4	2.7±1.5	3.5±0.47	10.4±10.3
Family history								
Consanguinity, n (%)	3 (6.7)	-	-	-	1 (3.8)	-	-	2 (100)
Mother with Noonan syndrome, n (%)	5 (11.1)	-	-	-	4 (15.4)	-	1 (50)	-
Father with short stature, n (%)	1 (2.2)	-	-	-	1 (3.8)	-	-	-
Mother with short stature, n (%)	5 (11.1)	-	-	-	4 (15.4)	-	1 (50)	-
Prenatal history								
Prenatal chylothorax, n (%)	3 (6.7)	-	-	-	1 (3.8)	-	1 (50)	-
Prenatal pleural effusion, n (%)	1 (2.2)	-	-	-	1 (3.8)	-	-	-
Hydrops fetalis, n (%)	1 (2.2)	-	-	-	1 (3.8)	-	-	-
Prenatal cystic hygroma, n (%)	2 (4.4)	-	-	-	1 (3.8)	1 (50)	-	-
Postnatal history								
Prematurity, n (%)	7 (15.6)	1 (50)	1 (50)	-	3 (11.5)	1 (50)	1 (50)	-
SGA, n (%)	5 (11.1)	1 (50)	-	-	4 (15.4)	-	-	-
Postnatal pleural effusion, n (%)	1 (2.2)	-	-	-	-	1 (50)	-	-
Postnatal chylothorax, n (%)	1 (2.2)	-	-	-	-	1 (50)	-	-

Only genes with more than one clinically relevant observation or selected genes of interest are shown
SD: standard deviation, NS: Noonan syndrome, SGA: small for gestational age

Table 3. Cardiac manifestations according to the affected gene (number of patients)

Cardiac manifestation	All (n=45)	*BRAF* (n=1)	*CBL* (n=1)	*KRAS* (n=2)	*LZTR1* (n=2)	*MAP2K1* (n=1)	*PPP1CB* (n=3)	*PTPN11* (n=26)	*RAF1* (n=2)	*SHOC2* (n=1)	*SOS1* (n=2)	*SOS2* (n=2)
Pulmonary stenosis	14	-	-	-	-	-	-	12	-	-	1	-
Atrial septal defect	10	-	-	1	-	-	-	8	-	1	-	-
Mitral regurgitation	6	1	1	-	-	-	2	-	1	-	1	-
Hypertrophic cardiomyopathy	5	-	-	-	-	-	-	2	2	1	-	1
Ventricular septal defect	5	-	-	-	-	-	-	2	1	-	-	1
Arrhythmia	2	-	-	1	-	-	-	-	1	-	-	-
Ventricular extrasystole	2	-	-	1	-	-	-	-	1	-	-	-
Bicuspid aortic valve	2	-	-	-	-	-	-	2	-	-	-	-
Tricuspid regurgitation	2	-	-	-	-	-	2	-	-	-	-	-
Patent ductus arteriosus	1	-	-	-	-	-	1	-	-	-	-	-
Cardiomyopathy (unspecified)	1	-	-	-	-	-	-	1	-	-	-	-
Tetralogy of Fallot	1	-	-	-	1	-	-	-	-	-	-	-

establishing a definitive diagnosis based solely on clinical criteria is often challenging (15). In this context, genetic analysis plays an important role in confirming the diagnosis and may guide clinical follow-up and therapeutic decisions.

Facial Features

Distinctive facial features are more common in patients with *PTPN11* variants and typically include an inverted triangular facial shape (9,10), low-set ears with posterior rotation and a thickened helix, downward-slanting palpebral fissures (9,24),

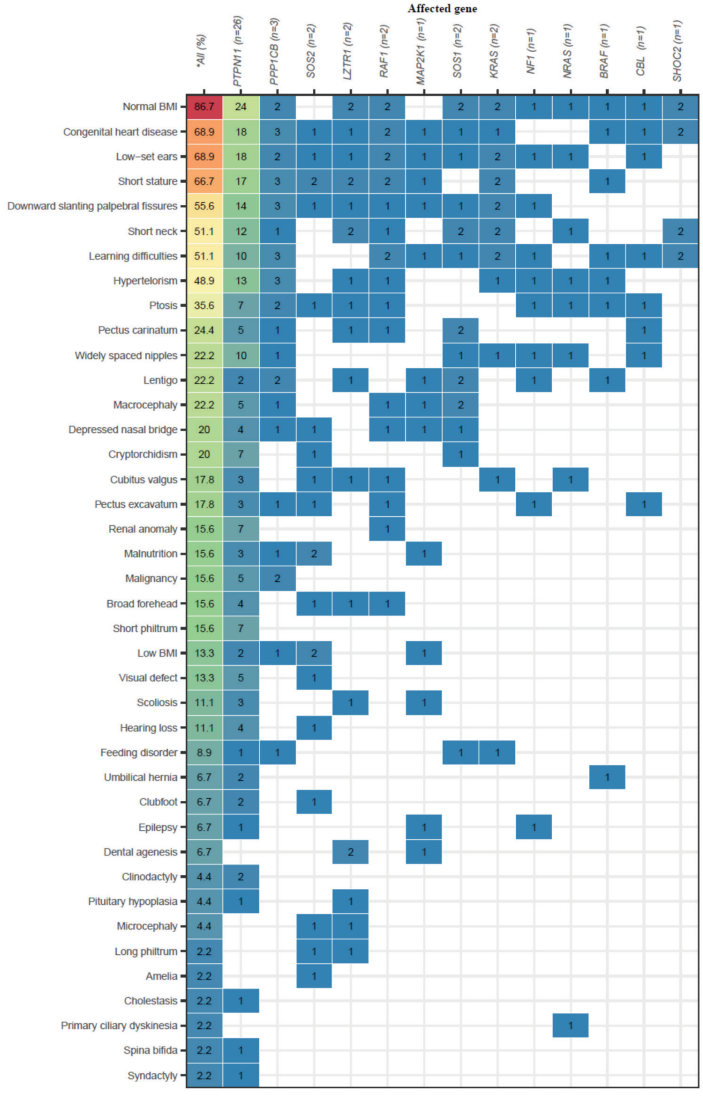

Figure 1. Clinical characteristics of the studied patients according to the affected gene
BMI: body mass index

hypertelorism (10), ptosis, arched eyebrows, a depressed nasal bridge with a bulbous nasal tip, a long and deep philtrum, high peaks of the upper lip, a low anterior hairline in a "W" shape, a high-arched palate, malar hypoplasia, and a short or webbed neck (4,25). These facial characteristics may vary with age, becoming more evident during puberty and less pronounced in adulthood (26,27,28).

In this Colombian cohort, low-set ears were observed in 68.9% (31/45) of patients, a short neck in 51% (23/45), hypertelorism in 48.9% (22/45), ptosis in 35.6% (16/45), macrocephaly in 22.2% (10/45), a depressed nasal bridge in 20% (9/45), and a wide forehead with a short nasolabial fold in 15.6% (7/45). This phenotype has been more frequently associated with *PTPN11* variants and is consistent with findings reported in other NS populations, showing similar frequencies (10).

Cardiac Findings

Congenital heart defects occur in up to 80% of individuals with NS, with pulmonary valve stenosis being the most common anomaly, reported in 25% to 71% of cases, followed by atrial septal defects in 4% to 57% of cases (29). Hypertrophic cardiomyopathy, often presenting as asymmetric septal hypertrophy, is observed in approximately 20% of patients (29). Electrocardiographic abnormalities have been reported in up to 87% of cases, including wide QRS complexes with a predominant negative pattern in the left precordial leads, left-axis deviation, and giant Q waves (26,29,30)

PTPN11 and *SOS1* variants are more frequently associated with pulmonary valve stenosis, whereas *RAF1* and *RIT1* variants are more commonly linked to hypertrophic cardiomyopathy. In our cohort, pulmonary valve stenosis was the most common cardiac defect, occurring in 31.1% of patients (14/45), of whom 12 carried *PTPN11* variants. Atrial septal defects were identified in 22.2% of patients (10/45), with *PTPN11* variants present in 8 of the 10 affected individuals (29). These findings are consistent with other NS cohorts, in which pulmonary valve stenosis is the most frequently reported congenital heart defect (10,31).

Short Stature and Growth Hormone Therapy

Short stature occurs in up to 80% of individuals with NS, typically presenting with normal prenatal growth (25). Its pathophysiology is multifactorial and may involve growth hormone deficiency, growth plate abnormalities, and mild growth hormone resistance (28,32,33). This resistance is believed to occur at the post-receptor level, primarily through impaired STAT5B signaling, and is more pronounced in individuals with *PTPN11* variants due to alterations in the SHP-2 protein, which plays a key role in growth hormone signaling (29,34).

Genes in the RAS-MAPK pathway also play a role in the development of the hypothalamic-pituitary axis, which may result in structural and functional alterations in RASopathies (29,35). A higher prevalence of short stature has been reported in patients with NS carrying *PTPN11*, *RAF1*, and *KRAS* variants compared to those harboring *SOS1* variants (28,36). In our cohort, short stature was observed in 66.7% of patients and was noted mainly among patients carrying variants in *PTPN11, PPP1CB, SOS2, LZTR1, RAF1,* and *MAP2K1*, whereas variants in *SOS1, NF1, NRAS, CBL,* and *SHOC2* were not linked to this feature.

Somatropin therapy was administered to 10 patients in this cohort, nine of whom received treatment due to a confirmed diagnosis of growth hormone deficiency. Growth hormone therapy has been approved by the U.S. Food and Drug Administration for use in patients with NS since 2007, at a dose of 0.066 mg/kg/day (37). However, it has not been approved by the European Medicines Agency (37,38,39).

In our cohort, none of the patients receiving somatropin therapy harbored variants typically associated with hypertrophic cardiomyopathy, such as *RAF1* or *RIT1,* and no cardiac complications related to the treatment were observed during follow-up. Although growth hormone therapy remains controversial in NS, particularly in patients with variants linked to hypertrophic cardiomyopathy or high-risk *PTPN11*-related neoplasms (37,38,40), our findings align with previous reports suggesting that treatment may be considered after five years of age, when the risk of hypertrophic cardiomyopathy and lymphoproliferative neoplasms is lower.

Skeletal and Other Systemic Findings

Skeletal deformities, such as pectus carinatum and pectus excavatum, are reported in up to 95% of patients with NS. Valgus deformity of the elbow occurs in approximately 50% of cases, clinodactyly in 30%, and thoracic scoliosis in 13% (31).

Other associated manifestations include hemorrhagic diathesis (65%) (3), altered spermatogenesis (60-80%), renal anomalies (10%), cryptorchidism (80% of males) (3), peripheral lymphedema (<20%), hearing deficits (10-25%), and delayed puberty (approximately two years) (6). In our cohort, these complications were observed at lower frequencies. Learning difficulties, reported in up to 50% of NS patients (25), were present in 51.1% of our cohort and were most commonly associated with variants in *PTPN11, PPP1CB, RAF1,* and *KRAS*.

Neoplasms

Individuals with NS have an increased risk of malignancy, estimated to be 3.5 times higher than that of the general population (40). Some studies report an 8.1-fold increased risk for JMML and solid tumors, including brain tumors, neuroblastoma, and rhabdomyosarcoma (39). Specific variants, such as *PTPN11*, c.218C>T; p.(Thr73Ile), *PTPN11* codon 61 variants, and *KRAS* p.(Thr58Ile), have been associated with predisposition to myeloproliferative disorders (13).

In addition to JMML, two patients in our cohort developed central nervous system tumors, one glioma and one astrocytoma, both harboring the PTPN11 c.922A>G; p.(Asn308Asp) variant. Brain tumors have been reported in patients with NS, particularly in association with PTPN11 variants, although they remain uncommon. Previous reports have described glial and glioneuronal tumors, including low-grade gliomas, dysembryoplastic neuroepithelial tumors, and astrocytomas, in patients with PTPN11-related NS. Notably, the p.(Asn308Asp) variant identified in our two patients has also been reported in patients with NS and different types of brain tumors. However, given the small number of affected patients in our cohort, no causal or genotype-specific association can be established (11).

In addition, two patients in our cohort with the PPP1CB c.146C>G; p.(Pro49Arg) variant developed neuroendocrine tumors. PPP1CB is a recognized RASopathy-associated gene; however, the relationship between germline PPP1CB variants and neuroendocrine tumors has not been clearly established. Therefore, although this finding is noteworthy, the small number of affected patients and the retrospective nature of our study preclude establishing a causal or genotype-specific association. Further studies are required to determine whether neuroendocrine tumors represent part of the neoplastic spectrum associated with PPP1CB-related NS.

In our cohort, seven patients developed neoplasms, three of whom were diagnosed with JMML. Two shared the *PTPN11* c.1507G>A; p.(Gly503Arg) variant, while the third carried the *PTPN11* c.218C>T; p.(Thr73Ile) variant. None of the three patients with JMML received growth hormone therapy prior to the diagnosis of JMML. All were under five years of age at diagnosis of JMML and were monitored through regular clinical evaluations and complete blood counts, in accordance with published surveillance recommendations (40).

Diagnostic Implications

The diagnosis of NS is primarily based on clinical features, most commonly using the van der Burgt scoring system to identify patients for molecular testing (19). Confirmation requires molecular testing, which may include targeted RASopathy panels, clinical exome sequencing, or broader approaches, such as whole-exome or whole-genome sequencing, depending on clinical suspicion and test availability (27). Overall, our findings reinforce the importance of an integrated clinical and molecular approach for accurate diagnosis, risk stratification, and individualized management of patients with NS.

Study Limitations

This study has several limitations. Its retrospective design and the relatively small sample size may limit the generalizability of the findings. In addition, as patients were recruited from tertiary referral centers, a referral bias cannot be excluded. Nevertheless, the availability of comprehensive clinical records and molecular confirmation by clinical exome sequencing strengthens the reliability and internal consistency of the data.

Conclusion

This study provides the first genetically characterized pediatric cohort of NS from Colombia, highlighting its marked genetic and phenotypic heterogeneity. *PTPN11* was the most frequently affected gene, and congenital heart disease, short stature, and learning difficulties were the predominant clinical features. These findings emphasize the importance of early molecular diagnosis and multidisciplinary follow-up for optimal clinical management.

Ethics

Ethics Committee Approval: The study was conducted at Research and Ethics Committee of Pablo Tobón Uribe Hospital (HPTU), approved under protocol 2022.088 (date: 08.11.2022); San Vicente Fundación Hospital (HSVF), approved under act number 12-2023 (date: 24.04.2023).

Informed Consent: Authorization was obtained from the ethics committee of the aforementioned institutions. For patients not affiliated with these institutions, informed consent was obtained and signed by their legal representatives.

Footnotes

Authorship Contributions

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