Original Article

Noonan syndrome and Noonan-like syndrome with loose anagen hair: rare phenotypes may emerge during follow-up

Ziqin Liu[1]^, Jianming Lai[2], Fuying Song[1]

[1]Department of Endocrinology, Children's Hospital of Capital Institute of Pediatrics, Beijing, China; [2]Department of Rheumatology, Children's Hospital of Capital Institute of Pediatrics, Beijing, China

Contributions: (I) Conception and design: Z Liu, F Song; (II) Administrative support: J Lai, F Song; (III) Provision of study materials or patients: Z Liu, J Lai; (IV) Collection and assembly of data: Z Liu; (V) Data analysis and interpretation: Z Liu, F Song; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Fuying Song, MD. Department of Endocrinology, Children's Hospital of Capital Institute of Pediatrics, No. 2, Jianguomenwai, Yabo Road, Beijing 100020, China. Email: sfynew@sina.cn.

Background: Noonan syndrome (NS) and Noonan-like syndrome with loose anagen hair (NS/LAH) are neurodevelopmental syndromes resulting from germline mutations in genes that participate in the rat sarcoma/mitogen-activated protein kinases (RAS/MAPK) pathway. The aim of this retrospective study was to describe common and rare manifestations of NS and NS/LAH.

Methods: We collected and analyzed clinical and genetic data from 25 patients with NS and NS/LAH.

Results: The patients' median age was 6.3 years (range, 1–13 years), and the male-to-female ratio was 18:7. In total, 19 patients had NS caused by a mutation in *PTPN11*. Another causative gene was found in six patients, including two patients with a *SHOC2* mutation, one patient with a KRAS mutation, one patient with an *LZTR1* mutation, one patient with a *BRAF* mutation, and one patient with a PPP1CB mutation. Short stature was detected in 100% of the patients. This study provides an overview of the clinical features of NS, including unique facial features, short stature, congenital heart defects, and other manifestations. Notably, systemic lupus erythematosus (SLE) was found in two *SHOC2*-positive patients. One patient had a posterior urethral valve, which is very rare in NS patients.

Conclusions: Our study identified several clinical features that were previously poorly related to NS, including SLE. We concluded that *SHOC2*-related NS is associated with a particularly high risk of SLE, which may have a significant impact on quality of life, and a posterior urethral valve is a novel phenotype. These findings could be helpful in enhancing the understanding of the clinical spectrum of NS.

Keywords: Noonan syndrome (NS); RASopathies; *PTPN11; SHOC2*; systemic lupus erythematosus (SLE)

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Introduction

Background

Noonan syndrome (NS; MIM 163950) and Noonan-like syndrome with loose anagen hair (NS/LAH; MIM 607721, 617506) constitute a group of developmental disorders characterized by unique facial features, short stature, and congenital heart defects (1-3). It was first described by a pediatric cardiologist, Dr. Noonan (4). The incidence of NS is estimated to be between 1/2,000 and 1/2,500 (5). There have been 100 reported cases of NS/LAH (6). Both of these diseases are caused by rat sarcoma/

^ ORCID: 0000-0003-3310-4861.

mitogen-activated protein kinases (RAS/MAPK) signaling pathway hyperactivity. The RAS/MAPK pathway is a highly conserved cascade of phosphorylation. Germline mutations that are activated are responsible for "RASopathies", which are rare autosomal dominant or recessive disorders. NS is a representative RASopathy, a class that includes many developmental disorders. To date, more than 20 genes having germline pathogenic variants that have found to be associated with NS (7). *PTPN11*, *SOS1*, and *RAF1* are the three most common genes; disease-causing variants in these genes account for approximately 65–80% of cases (8,9). The RAS/MAPK pathway represents a signal transduction cascade involved in the processes of cell proliferation, differentiation, survival, and death.

Rationale and knowledge gap

NS and NS/LAH are the most common disorders in this group and are characterized by heart defects, short stature, and typical facial features. *PTPN11* has been identified as a major NS gene, and several reports have described *PTPN11* mutations in relation to clinical manifestations in NS patients.

Objective

Here, we performed a retrospective review of all genetically confirmed cases of NS and Noonan-like syndrome in a single center in Beijing. Our primary aim was to dissect the molecular findings associated with NS beyond the most common gene, *PTPN11*. Special attention was given to two patients with mutations in the *SHOC2* gene who developed systemic lupus erythematosus (SLE) at an early age. We present this article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-113/rc).

Highlight box

Key findings

- In this study, we analyzed a small cohort of patients with short stature and Noonan syndrome (NS) caused by sporadic six different genes mutations.
- Patients may present with either common short stature or rare systemic lupus erythematosus (SLE).

What is known and what is new?

- This study provides an overview of the clinical features of NS, including unique facial features, short stature, congenital heart defects and other manifestations. SLE was found in two *SHOC2*-positive patients. One patient had a posterior urethral valve, which is very rare in NS patients.
- We concluded that *SHOC2*-related NS is associated with a particularly high risk of SLE.

What is the implication, and what should change now?

- The most important is to expand the sample size.

Methods

Patient selection

We collected retrospective data from the NS population in the Department of Endocrinology at the Children's Hospital of Capital Institute of Pediatrics from 2017 to 2022. Twenty-five patients had a genetic diagnosis of NS or NS/LAH. All these patients were diagnosed using the NS scoring system developed by van der Burgt *et al.* (10) or with the presence of a causative mutation for NS. In this study, the manifestations of 25 NS patients were analyzed. This group included 18 males (72%) and 7 females (28%). Patients without genetic confirmation of the clinical diagnosis were excluded. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Capital Institute of Pediatrics Ethics Committee (No. SHERLL2023049) and informed consent was taken from their parents.

The patients were identified due to clinical features suggestive of a RASopathy. Variants were detected by routine diagnostic testing for known RASopathy genes using targeted gene panel sequencing or whole-exome sequencing of DNA extracted from venous blood samples (hospital laboratory or qualified gene company).

Statistical analysis

The data were analyzed using SPSS Statistics 24.0. Fisher's test was used to compare the differences between the patients in the two groups. Statistical significance was indicated by a P value of less than 0.05.

Results

Twenty-five patients had genetically confirmed NS or NS/LAH, with a median age of 6.3 years (range, 1–13 years). Data were available for 18 males and 7 females. The clinical findings for 25 individuals are summarized in *Table 1*. Gene mutations (*Figure 1*) associated with NS were detected in

Table 1 Clinical manifestations and variants identified in the study cohort

No.	Gender	Age at evaluation (years)	Typical facial feature	Short stature	Cardiac	Chest wall deformity	Cryptorchidism	Other manifestation	Gene	DNA	Protein	Mode of heritance
1	Female	5	+	+	–	–	–	–	*PTPN11*	c.214G>T	p.Ala72Ser	*De novo*
2	Male	13	–	+	ASD	+	–	Neck webbed	*PTPN11*	c.1510A>G	p.Met504Val	*De novo*
3	Male	3	+	+	ASD	/	–	Neck webbed	*PTPN11*	c.188A>G	p.Tyr63Cys	*De novo*
4	Male	1	+	+	PS	/	–	–	*PTPN11*	c.1507G>C	p.Gly503Arg	Paternal
5	Male	4	+	+	VSD	+	–	–	*PTPN11*	c.1507G>C	p.Gly503Arg	*De novo*
6	Male	2	+	+	ASD	–	+	SLE, PUV, squint, enlarged head circumference, loose hair	*SHOC2*	c.4A>G	p.Ser2Gly	*De novo*
7	Female	1	+	+	PDA	–	–	Hearing impair, iris pigmentation	*PTPN11*	c.1510A>G	p.Met504Val	*De novo*
8	Male	14	–	+	ASD	+	–	Ametropia, splenomegaly	*PTPN11*	c.855T>G	p.Phe285Leu	*De novo*
9	Male	11	+	+	–	+	+	–	*PTPN11*	c.1471C>T	p.Pro491Ser	*De novo*
10	Male	2	+	+	PS	+	+	Enlarged head circumference	*KRAS*	c.173C>T	p.Thr58Ile	*De novo*
11	Male	13	–	+	ASD	–	+	Neck webbed	*LZTR1*	c.651+1G>T, c.1943-256C>T		Paternal, maternal
12	Male	2	+	+	PS	–	–	–	*PTPN11*	c.922A>G	p.Asn308Asp	*De novo*
13	Male	7	+	+	–	–	–	–	*PTPN11*	c.922A>G	p.Asn308Asp	*De novo*
14	Male	2	+	+	–	+	+	Hyperopia and amblyopia	*PTPN11*	c.172A>G	p.Asn58Asp	*De novo*
15	Female	5	+	+	–	–	–	–	*PTPN11*	c.922A>G	p.Asn308Asp	*De novo*
16	Male	5	+	+	ASD	–	–	–	*PTPN11*	c.844A>G	p.Ile28Val	*De novo*
17	Female	7	+	+	–	–	–	–	*PTPN11*	c.844A>G	p.Ile28Val	*De novo*
18	Male	13	+	+	–	–	–	–	*PTPN11*	c.1403C>T	p.Thr468Met	Maternal
19	Female	12	+	+	–	–	+	–	*PTPN11*	c.922A>G	p.Asn308Asp	Paternal
20	Male	2	+	+	ASD	+	–	–	*PTPN11*	c.922A>G	p.Asn308Asp	*De novo*
21	Male	8	+	+	–	/	+	Amblyopia	*PTPN11*	c.236A>G	p.Gln79Arg	*De novo*
22	Female	5	+	+	–	+	–	Squint, hearing loss	*BRAF*	c.1799T>G	p.Val600Gly	*De novo*
23	Male	7	+	+	PDA	+	+	Squint, nystagmus enlarged head circumference, loose hair, hyperactive behavior	*PPP1CB*	c.146C>G	p.Pro49Arg	*De novo*
24	Female	2	+	+	HCM	+	–	SLE, enlarged head circumference, loose hair	*SHOC2*	c.4A>G	p.Ser2Gly	*De novo*
25	Male	11	+	+	–	/	+	–	*PTPN11*	c.188A>G	p.Tyr63Cys	*De novo*

No., number; +, positive; –, negative; /, no data; ASD, atrial septal defect; PS, pulmonic stenosis; VSD, ventricular septal defect; SLE, systemic lupus erythematosus; PUV, posterior urethral valve; PDA, patent ductus arteriosus; HCM, hypertrophic cardiomyopathy.

PTPN11 (n=19, 76%), *SHOC2* (n=2, 8%), *KRAS* (n=1, 4%), *LZTR1* (n=1, 4%), *BRAF* (n=1, 4%), and *PPP1CB* (n=1, 4%). *Table 2* shows the differences between *PTPN11* and the other mutations.

PTPN11 gene

All the subjects were unrelated sporadic patients. Their birthweights and body lengths were usually normal. Short stature manifested in 100% of patients. The most common congenital heart defect was atrial septal defects (ASDs) (26.8%), followed by pulmonary valve stenosis (PVS) (15.3%). Eleven recurrent pathogenic variants of the *PTPN11* gene were identified in 19 patients, with c.922A>G (p.Asn308Asp) being the most common pathogenic variant (5/19, 26.3%), followed by the 1510A>G, 188A>G, 1507G>C and 844A>G mutations in two patients each (10.5% in *PTPN11*, 8% in total). Among all the mutations, 36.8% (7/19) were located in the N-terminal src-homology 2 (N-SH2) domain, and 63.2% (12/19) were located in the protein tyrosine phosphatase (PTP) domain.

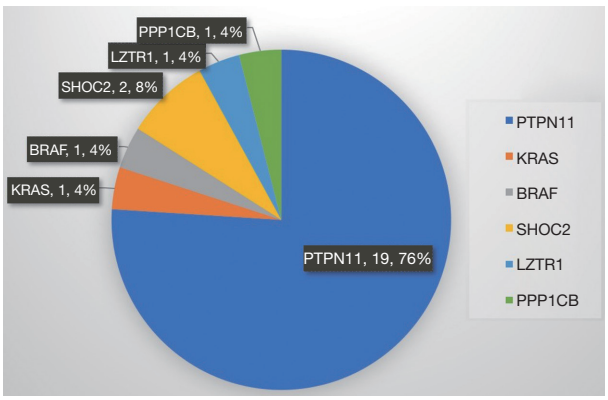

Figure 1 Patients' genetics in our study cohort (n, %).

KRAS and BRAF

We identified a 2-year-old boy harboring a *KRAS* variant (c.173C>T, p.Thr58Ile) (reported by Schubbert *et al.*) (11) and a 5-year-old girl harboring an *NRAS* variant (c.1799T>G, p.Val600Gly). Both kids exhibited slow intellectual development, typical facial features, and short stature. The girl also had hearing loss. There were no ectodermal abnormalities, cutaneous defects, papillomas, or deep palmar or plantar creases.

LZTR1 gene

Two compound heterogeneous variants, c.651+1G>T and c.1943-256C>T, in the *LZTR1* gene were identified in one male patient with the atypical facial appearance of NS, a short stature (–3.0 standard deviation), ASD and cryptorchidism. Family screening for the variants revealed that each parent was a carrier of one of these variants, but neither the mother nor the father was clinically affected. The c.1943-256C>T variant has been previously reported

Table 2 Genotype and phenotype correlations among patients

Clinical feature	With *PTPN11* mutation	Other mutations	P value
Number/total number (%)	19/25 (76.0)	6/25 (24.0)	–
Male:female	14:5 (73.7:26.3)	4:2 (66.7:33.3)	0.56
Height SDS	–2.7±1.85 (–5.90 to 2.35)	–2.0±0.97 (–4.12 to –0.90)	0.49
Distinctive facial feature	17/19 (89.5)	5/6 (83.3)	0.58
Cardiac defect	9/19 (47.4)	5/6 (83.3)	0.14
Cryptorchidism	5/13 (38.5)	4/4 (100.0)	0.13
Thoracic anomalies	6/19 (31.6)	4/6 (66.7)	0.10
Loose anagen hair	0/19 (0.0)	3/6 (50.0)	0.009
Ocular abnormality	4/19 (21.1)	3/6 (50.0)	0.19
SLE	0/19 (0.0)	2/6 (33.3)	0.050

Data are presented as n/total (%), n (%), or mean ± SD (range). Other mutations: *SHOC2/KRAS/LZTR1/BRAF/PPP1CB*. SDS, standard deviation score; SLE, systemic lupus erythematosus; SD, standard deviation.

in NS (12), and the c.651+1G>T variant (13) has been reported to be associated with congenital heart disease and increased cancer risk.

NS/LAH

SHOC2 gene

Two patients harbored the *SHOC2* mutation c.4A>G (p.Ser2Gly) (2,3), and no other variants causing monogenic SLE were found. The first patient was admitted to the hospital because of growth restriction and cognitive impairment at 2 years old. He also urinated frequently. Physical examination revealed the typical facial manifestations of NS, squinting, a head circumference of 50 cm, loose hair and cryptorchidism. Cardiac ultrasound results indicated ASD. Routine urine analysis did not reveal a urinary tract infection, and bladder ultrasound and radiography indicated thickening of the bladder wall, a large bladder diverticulum and dilated lower ureter. Posterior urethral valvulotomy was performed under a cystoscope. During the follow-up, the patient began to receive growth hormone therapy at age 4.5 years, and his height increased by almost 17 cm for 20 months and then stopped. At 7.5 years, he developed thrombocytopenia and recurrent fever. No malar butterfly rash was found. He was diagnosed with SLE based on antinuclear antibody (ANA) positivity (1:1,000+), American College of Rheumatology (ACR) score (5/11), and Systemic Lupus International Collaborating Clinics (SLICC) score (7/11). After high-dose methylprednisolone treatment, hydroxychloroquine and mycophenolate mofetil were used as maintenance therapies.

The second patient was a 2-year-old girl with growth restriction. She was diagnosed with hypertrophic cardiomyopathy (HCM) (interventricular septum: 6 mm; left ventricular posterior wall: 6.6 mm). An electrocardiogram indicated changes in the T wave. Despite her typical facial features, loose hair, and large head circumference, no further etiological examination was conducted. When she was 6 years old, she was found to have hemolytic anemia, thrombocytopenia, pericardial effusion, pleural effusion, and albuminuria. Her height was –3.8 standard deviation, and her head circumference was 54 cm. Examination showed clubbing of her fingers and heart murmur in the auscultation area of the pulmonary valve (interventricular septum: 8.9 mm). She was also diagnosed with SLE based on ANA positivity (1:1,000+), ACR score (5/11), and SLICC score (7/11). After high-dose methylprednisolone treatment, the dosage was gradually reduced for maintenance.

PPP1CB gene

One boy had a *de novo* mutation in *PPP1CB* and presented with nystagmus, squinting, and a tall forehead. He had short stature, absolute macrocephaly, and loose anagen hair. Cardiac ultrasound revealed a patent ductus arteriosus (PDA). The patient was very hyperactive and excited. He carried a mutation in *PPP1CB*, c.146C>G; p.Pro49Arg. This variant has been previously reported (14).

Discussion

Key findings

In this study, we analyzed a small cohort of patients with short stature and NS caused by sporadic gene mutations. *PTPN11* (76%) and *SHOC2* (8%) were the most common mutations in NS, whereas the *RAF1*, *KRAS*, *BRAF*, *LZTR1*, and *PPP1CB* mutations were less common. We found, though very rare, *SHOC2*-related NS is associated with a particularly risk of SLE.

Strengths and limitations

Amino acid substitutions at p.Ser2Gly have been shown to lead to a gain of function in *SHOC2* and increase RAS/MAPK pathway activation (15). The almost invariant occurrence of the c.4A>G missense change in *SHOC2* is mirrored by the relatively homogeneous clinical phenotype of NS/LAH 1 (15,16). In this study, the two patients with *SHOC2* mutations presented with SLE at 6 years and 7.5 years old. Autoimmune diseases and autoantibodies are frequently present in patients with RASopathies; subclinical thyroiditis occurs more often, but SLE combined with NS is very rare (17-21). Three other patients with comorbid SLE have been reported, with ages of 13, 13, and 24 years (19-21) (*Table 3*). The C.4A>G variant in the *SHOC2* gene may be a hotspot and a male dominant variant (male:female =4:1). However, this could be coincidental because of the small sample size. Interestingly, all five patients had serositis, but only one patient had classical malar rash. All these findings suggest that SLE caused by mutations in the *SHOC2* gene is different from classical SLE. We reported the two youngest patients with the *SHOC2* variant who developed SLE. Other cases reported the age of onset of SLE from adolescence to adulthood. Patients with *SHOC2* gene variants are more prone to SLE than those with

Table 3 Literature review of the patients with RASopathies with genetic variants and SLE-like syndrome (21)

No.	Gene	Gender	Age at onset SLE (years)	Malar rash	Serositis	ANA	ACR	SLICC	GH	Ref.
1	*KRAS* (p.N26I)	Female	18	–	–	1:>40	5/11	7/11	NA	(17)
2	*PTPN11* (p.F285S)	Female	32	–	–	1:320	5/11	7/11	NA	(18)
3	*SHOC2* (p.S2G)	Male	13	–	Pericarditis	1:800	4/11	4/17	NA	(19)
4	*SHOC2* (p.S2G)	Male	13	–	Pericarditis	1:640	3/11	5/17	NA	(20)
5	*SHOC2* (p.S2G)	Male	24	+	Pleuritis	1:2,560	5/11	7/17	+	(21)
Case 1	*SHOC2* (p.S2G)	Male	7.5	–	Pleuritis	1:1,000	5/11	7/11	+	–
Case 2	*SHOC2* (p.S2G)	Female	6	–	Pleuritis	1:1,000	5/11	7/11	–	–

SLE, systemic lupus erythematosus; No., number; ANA, antinuclear antibody; ACR, American College of Rheumatology; SLICC, Systemic Lupus International Collaborating Clinics; GH, growth hormone; Ref., reference; –, negative; +, positive; NA, not available.

pathogenic variants in other RASopathies. Therefore, attention should be given to monitoring for SLE during long-term follow-up. However, the etiology of this disease remains to be determined.

Comparison with similar researches

A host of studies have shown that RAS/MAPK signaling may affect the peripheral tolerance to prevent autoimmune destruction by self-reactive T cells (22-25). RAS-guanosine triphosphate (GTP) activates several effectors, and increased activation of extracellular-signal-regulated kinase (ERK) and/or PI3K in lymphoid cells could explain this disease (26). Although monogenic SLE is very rare, 3–10% of early-onset SLE cases are caused by recognized damaging variants (27,28), Our two patients suffered very early-onset SLE and typical NS/LAH, and genetic tests confirmed our suspicions of monogenic SLE. Continuing surveillance is of paramount importance in NS patients. The male patient also had a posterior urethral valve; this deformity has not been previously reported in NS/LAH patients, and our findings have enriched the spectrum of manifestations of NS/LAH.

Explanations of findings

Gain-of-function mutations in *PTPN11* account for approximately 40–50% of all cases of NS (29,30). In our cohort, 76% of all NS cases were caused by *PTPN11* mutations, which is a relatively high percentage compared with that in previous studies. This may be because all of our patients were genetically diagnosed rather than clinically diagnosed. These mutations affect residues located within or close to the interacting surfaces of the PTP and N-SH2 domains. *SOS1* (10–20%) and *RAF1* (3–17%) (31,32), which are commonly reported mutations, were not found in our cohort.

Implications and actions needed

Genotype-phenotype analysis revealed that congenital heart defects, cryptorchidism, ocular abnormalities, and thoracic anomalies were more prevalent among the group of patients with other mutations than among those with *PTPN11* mutations, although these differences were not significant. We observed a significantly greater incidence of other complicating diseases among patients with other mutations than among patients with NS with the *PTPN11* mutation. Some features that are considered very suggestive of NS, such as lymphatic abnormalities (33), were not frequently found in our population. The non-*PTPN11* mutations tend to affect the backbone of the RAS/MAPK cascade, and this tendency for mutations to affect the central or lower part of the cascade may lead to more severe conditions (6). However, our analyses of genotype-phenotype correlations were underpowered due to the small sample size.

Conclusions

We confirmed the previously observed *PTPN11* mutation 922A>G (Asn308Asp), a hotspot mutation in Chinese patients with NS. The development of second-generation sequencing technology has enabled the identification of common and rare genes that cause NS. We conclude that

SHOC2 variants are a rare cause of NS combined with SLE. The role of the *SHOC2* gene in SLE occurrence needs to be further explored. Larger cohorts are needed to obtain a more accurate clinical definition of each mutation.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-113/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-113/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-113/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Capital Institute of Pediatrics Ethics Committee (No. SHERLL2023049) and informed consent was taken from their parents.

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