A *PTPN11* mutation in a woman with Noonan syndrome and protein-losing enteropathy

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**Abstract**

**Background:** Noonan syndrome is an autosomal dominant, variably expressed multisystem disorder characterized by specific facial and cardiac defects, delayed growth, ectodermal abnormalities, and lymphatic dysplasias. Lymphedema and chylous pleural effusions are common in Noonan syndrome, but protein-losing enteropathy (PLE) has only rarely been described in the condition and little is known about its genetic associations.

**Case presentation:** We report the case of a 30-year-old Chinese woman who developed severe recurrent edema and hypoproteinemia. Gastroduodenoscopy showed a “snowflake” appearance of lymphangiectasia in the duodenum, and CT reconstruction of the small intestine showed segmental thickening of the intestinal wall with localized stenosis. Whole exome sequencing revealed that the patient harbored a pathogenic variant of *PTPN11* (c.A922G p.N308D), which was unfortunately inherited by her 2.5-year-old daughter who had short stature and atrial septal defect but no hypoproteinemia.

**Conclusions:** This case of Noonan syndrome with PLE was associated with a *PTPN11* mutation. A comprehensive review of PLE in Noonan syndrome revealed that PLE often presents late in this context but there is no clear genotype-phenotype correlation. Genetic evaluation with next-generation sequencing can be useful for securing the diagnosis and planning early intervention and management.

**Keywords:** Noonan syndrome, Protein-losing enteropathy, *PTPN11*, Hypoproteinemia

**Background**

Noonan syndrome (MIM: 163950) is an autosomal dominant, variably expressed multisystem disorder characterized by specific facies, cardiac defects, delayed growth, auditory deficits, ectodermal abnormalities, and lymphatic dysplasias (< 20%) [1]. While lymphedema and chylous pleural effusions are common in Noonan syndrome [2], protein-losing enteropathy (PLE) has rarely been reported and little is known about its genetic causes or associations in this context [3, 4]. PLE is usually syndromic or associated with non-syndromic primary intestinal lymphangiectasia. On its own, PLE has been reported in association with specific genetic mutations including in *CCEB1*, *FAT4* [5], *PIEZO1* [6], *FOXC2* [7], *CD55* [8], and *DAGT* [9].

Recent high-throughput genetic analyses with genome-wide association studies (GWAS) and whole exome sequencing (WES) have revealed a number of genetic variations that contribute to the susceptibility of Noonan syndrome [1]. All the genes currently implicated in Noonan syndrome encode proteins integral to the RAS–MAPK pathway, an important signal transduction pathway controlling cellular proliferation, differentiation, survival, and metabolism, with specific disease-causing mutations usually determining the Noonan subphenotype. In particular, patients carrying variants of...
PTPN11 (roughly 50%), an upstream member of the MAPK signaling cascade, tend to have pulmonary stenosis, short stature, lower IGF1 concentrations [10], bleeding diatheses, and juvenile myelomonocytic leukemia [11]. Patients harboring RAF1 (roughly 10%) variants in serine 259 and serine 621 have hypertrophic cardiomyopathy [12, 13], and those with KRAS (<2%) variants have delayed cognitive development [14] and intellectual disability [15]. Patients with SOS1 variants (~10%) have a higher prevalence of ectodermal abnormalities [16] and are taller than average [17], and those with NRAS mutations account for < 2% of cases and currently do not have a discernible genotype-phenotype correlation [18]. However, the association between PLE and specific genetic mutations in Noonan syndrome has yet to be determined.

Here we present the case of a 30-year-old Chinese woman presenting with recurrent edema and hypoproteinemia. Using WES and Sanger sequencing, we discovered that the patient carried the common pathogenic PTPN11 variant (c.A922G p.N308D) of Noonan syndrome. Unfortunately, screening of family members revealed the same mutation in her two and a half-year-old daughter. Her daughter had a relatively mild phenotype with facial dysmorphism and short stature. This case provides the opportunity to review the clinical features and genetics of PLE in Noonan syndrome and highlights the importance of mutation testing, genetic counselling, and family member screening to provide early intervention.

**Case presentation**

A 30-year-old woman was admitted to hospital with progressive lower limb edema over 8 months and occasional convulsions. She had initially ignored the bilateral lower limb edema but, as the edema gradually expanded to the abdomen, upper limbs, and even head and face, she was admitted to the local hospital for treatment of hypoproteinemia (albumin 21 g/L; normal range 35–52 g/L) and hypocalcemia (calcium 1.93 mmol/L; 2.13–2.70 mmol/L). However, no diagnosis was made, and she was eventually referred to the tertiary hospital. She reported a past medical history of tetralogy of Fallot at 7 years of age, for which she underwent surgery at age 14. Her menstrual cycle was normal, and she had given birth to a daughter. Her child, who was two and a half years old at presentation, was born normal but had a history of feeding difficulties and atrial septal defect. There was no other family history of note.

Upon admission, the patient was conscious and her vital signs were within normal limits. She was 150.1 cm tall and weighed 55 kg, and her daughter showed short stature (height 132.5 cm, –3.6SD). They shared the same dysmorphic facies with hypertelorism, low-set ears, and a posterior hairline. Limb circumferences were 24.5 and 25 cm at 10 cm above the upper edge of the patella and 14 and 13.5 cm at 10 cm below the edge of the patella. In addition, early grade 3 diastolic murmurs were audible over the pulmonary and tricuspid valves.

Thorough biochemical screening was performed. Unsurprisingly, many nutritional indices were reduced beyond the lower limit of normal values except for liver function and renal function. The lymphocyte count was 0.29 × 10^9/L (0.80–4.00 × 10^9/L); hemoglobin 108 g/L (110–150 g/L); total protein 31 g/L (60–85 g/L); albumin 19 g/L (35–52 g/L); calcium 1.33 mmol/L (corrected calcium 1.77 mmol/L; 2.13–2.70 mmol/L). All immunoglobulins were decreased.

In view of the definite diagnosis of hypoproteinemia, the digestive, endocrine, and cardiac systems were next screened in detail. For the digestive system, a stool occult blood test was positive and the D-xylose absorption test was 0.9 g/5 h (normal > 1.2). Gastroendoscopy showed a snowflake appearance in the duodenum (Fig. 1a and b), a sign of lymphangiectasia. CT reconstruction of the small intestine showed that the descending duodenum wall was coarsely thickened and the small intestinal wall was sectionally thickened, enhanced, and locally narrowed (Fig. 1c and d). There was no obvious colonic abnormality.

Lymphatic imaging of the lower limbs showed lymphangiectasis and bilateral widening of the venous angle in the mediastinum. Imaging at 1.5 h showed diffuse radioactive uptake in the small intestine, which diminished by 5 hours but at which time showed new areas of radioactive uptake in the ascending colon. Whole body lymphatic imaging indicated widening of the lymphatics in both lower limbs and a flaky radioactive enhancement shadow was seen in the abdominal cavity within 3 h. By 6 h, the hepatic flexure and transverse colon could be visualized.

In the light of paroxysmal tetany, endocrine system screening mainly focused on metabolic indicators. Parathyroid hormone levels were 122.20 pg/ml (12.0–68.0 pg/ml), synchronous blood calcium was 1.55 mmol/L, synchronous albumin was 19 g/L, synchronous 24 h urine calcium was 0.10 mmol/24 h, total 24-hydroxyvitamin D was < 3.00 ng/ml (8.0–50.0 ng/ml), 1,25-dihydroxyvitamin D3 was 24.42 pg/ml (19.6–54.3 pg/ml), blood magnesium was 0.45 mmol/L (0.70–1.10 mmol/L), and β-collagen degradation product was 1.23 ng/ml (0.21–0.44 ng/ml). Echocardiography revealed no abnormality in cardiac structure or function except for changes associated with the previous repair.

The diagnosis remained uncertain, so the patient and family agreed to whole exome sequencing. A pathogenic variant in PTPN11 (c.A922G p.N308D) was detected and confirmed by Sanger sequencing, which also revealed the same mutation in the patient’s daughter.
(Fig. 2a & b). No mutation was detected in the patient’s mother, and the father had died some years before from cardiovascular disease.

The patient was prescribed a medium-chain triglyceride diet. Example dietary changes included the use of 3–4 g/day coconut oil for cooking rather than the intake of long-chain fats; increased intake of high-quality proteins like egg white, skimmed milk, whey protein, and lean meat; and avoidance of crude fiber (e.g., grains, celery) and high-fat food (e.g., cream, fatty pork). In the following 8 months, there were no further episodes of edema or convulsions with periodic infusion of albumin and

Fig. 1 a shows the snowflake appearance of the duodenum and b shows the granuloid changes in the gastric antral mucosa by electronic gastroscopy. Reconstructive CT of the small intestine in (c & d) demonstrate segmental thickening of the intestinal wall with local intestinal stenosis. Arrows highlight the indicated features

Fig. 2 a shows the pedigree of the patient’s family. Patients are represented in black and the arrow represents the proband, which is the patient discussed in this article. b shows the Sanger sequencing of the PTPN11 gene in the family. A missense mutation was found in PTPN11 (c.A922G p.N308D) of the patient (II4), which was inherited by her daughter (III6). The patient’s father died of acute cerebrovascular disease before genetic testing.
oral calcium intake. Her daughter was short and met the
criteria for taking growth hormone replacement. Regular
follow-up of the daughter was also advised.

**Discussion and conclusions**

Here we describe a patient with severe edema and tetany
developing over a long timeframe. There was no obvious
cause for her diffuse lymphangiectasia, but clinical ob-
servation revealed abnormal facies and she had a history
of congenital heart disease, raising suspicion of a
congenital abnormality. However, next-generation se-
quencing was required to confirm the presence of a
pathogenic *PTPN11* mutation to explain congenital
heart disease and PLE. The genotype-phenotype correl-
ation of Noonan syndrome and PLE has not been estab-
lished. The occurrence or severity of lymphatic
abnormality might differ according to the specific gen-
etic mutation, but data on this hypothesis is lacking.

A comprehensive literature search of the PubMed and
CNKI databases from 1972 to 2019 using the search
terms “Noonan syndrome, protein-losing enteropathy” and
“Noonan syndrome, PTPN11” revealed only nine re-
ported cases (Table 1). Male and female patients with
Noonan syndrome who developed PLE were similarly af-
fected. However, patients usually developed PLE after
Noonan syndrome was diagnosed (16.4 ± 7.9 vs. 7.3 ±
7.1 years; \( p = 0.03 \)), and our patient’s daughter will re-
quire long-term follow-up to anticipate the development
of this complication. All patients had congenital heart
disease, two of whom had tetralogy of Fallot, a rare car-
diac abnormality [4]. Other common manifestations
were edema (6/8, 75%) and hypoalbuminemia (8/8; total
protein 33.6 ± 7.9 g/L; albumin 18.9 ± 3.6 g/L). Other iso-
lated clinical manifestations included hepatomegaly [21],
intratable bleeding from cutaneous lymphatic malfor-
mations [25], drug reactions with eosinophilia and
systemic symptoms (DRESS), and thrombotic microangi-
opathy [26]. Our patient demonstrated occasional tetany
due to hypocalcemia, which was treatable with calcium
supplements. In the published cases, two patients died of
heart failure and another of intractable bleeding from cutaneous lymphatic malfor-
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due to hypocalcemia, which was treatable with calcium
supplements. In the published cases, two patients died of
heart failure and another of hemorrhagic pancreatitis after a valvuloplasty.

**PTPN11** encodes the protein tyrosine phosphatase
SHP-2, which has an amino N-SH2 domain and a phos-
photyrosine phosphatase domain (PTP) to switch the
protein between its inactive and active conformations
[1]. The N-SH2 domain plays a key role in maintaining
inactive SHP-2 [27], with the N-SH2 and PTP domains
sharing a broad interaction surface. Several hydrogen
bonds between the N-SH2/PTP domains form the most
critical catalytic sites. Alterations in these critical amino
acids might disturb the equilibrium between active and
inactive forms of SHP-2 [28]. Indeed, the G > C point
mutation at position 417 (Glu139Asp) is the only
mutation identified which alters an amino acid in the C-
SH2 domain, which contributes to substrate specificity
and binding affinity [28].

An energetics-based structural analysis indicated that
a gain-of-function mutation in *PTPN11* could be respon-
sible for the disease [29]. There are 40 reported *PTPN11*
mutations (UniProt.org; Fig. 3), and several large retro-
spective studies have indicated that different *PTPN11*
mutations are correlated with some sub-phenotypes.
Musante et al. [28] screened for mutations in *PTPN11* in
96 familial and sporadic cases and found that the pheno-
types associated with *PTPN11* mutations included (from
the most to least common) dysmorphic features (hyper-
telorism, low-set ears, down-slanting palpebral fissures),
cryptorchidism, short stature, cardiac defects, and mye-
loydysplasia. In another large retrospective study [29],
the variant was found to be more frequent in familial cases
than sporadic cases. Genotype-phenotype correlation
analysis revealed that pulmonary stenosis was more
prevalent in subjects with Noonan syndrome with
*PTPN11* mutations than those without (70.6% vs. 46.2%;
\( p < 0.01 \)). Furthermore, a pathogenic *PTPN11* mutation
was predicted to confer a 3.5-fold increased risk of de-
veloping cancer compared with the general population
[30]. In a Japanese study of 41 Noonan syndrome pa-
tients, mutations at codons 61, 71, 72, and 76 were fre-
quently identified in patients with leukemia, including
those with JMML, MDS, AML, and ALL [31]. In terms
of other disease associations, three different
*PTPN11* mutations (E69K, T507K, and Y62C) were identified in
89 primary neuroblastomas [32] and, in a case report,
a patient with Noonan syndrome caused by a germline
mutation in exon 13 of *PTPN11* (c1507G > C,
p.Gly503Arg) developed Hodgkin’s lymphoma [33],
which was also associated with congenital refractory
chylothorax and subcutaneous edema [34].

With respect to *PTPN11* mutations in Noonan syn-
drome, Joyce et al. [24] identified *PTPN11* (c.181G > A,
p.Asp61Asn) and *PTPN11* (c.188A > G, p.Tyr63Cys) mu-
tations in two Noonan syndrome patients with PLE.
Interestingly, Noonan syndrome and cardiofaciocuta-
neous syndrome (CFC) are both RASopathies that share
some similarities including the same genetic variants
[35]. Joyce et al. [24] also reported three patients with
CFC-PLE carrying *KRAS* (c.178G > C, p.Gly60Arg),
*BRAF* (c.770A > G, p.Gln257Arg), and *RIT1* (c.246 T > G,
p.Phe82Leu) mutations. Whether the *PTPN11* mutation
or the N308D variant is causal for PLE remains to be
determined, but other lymphatic disorders have been re-
ported in association with *PTPN11* mutations, including
jugular lymphatic obstruction with a heterozygous T > C
change in exon 8 [36] and lymphatic dysplasia in the
lung and mesentery with a heterozygous mutation at
G503R [37]. Interestingly, the N308D mutation is
Table 1 Summary of all patients with Noonan syndrome-associated PLE identified in the literature (1972–2019)

| Cases | Sex | The onset of NS (yr) | The onset of PLE (yr) | Symptoms | Cardiac disorder | TP (g/L) | Alb (g/L) | Transnodal lymphangiography | Treatments | Follow-up |
|-------|-----|----------------------|-----------------------|----------|------------------|----------|-----------|-----------------------------|------------|-----------|
| Matsumoto et al. [19] | F | 17 | 17 | No obvious clinical symptoms | HCM | 31 | 15 | Absent thoracic duct abdominal collateral lymphatics and bilateral iliac lymphangiectasia | Steroid therapy (1 mg/kg/d) Low-fat, protein-rich diet supplemented with medium-chain triglycerides | Relieved |
| Mizuochi et al. [20] | F | 1.5 | 8 | Edema, abdominal pain, diarrhea | ASD PVS | 32 | 18 | | Spironolactone (2.5 mg/kg/d) Furosemide (2.0 mg/kg/d) | Relieved |
| Keberle et al. [4] | M | 6 | 13 | Edema of abdomen and hydrocele testis | ASD PVS | 32 | 18 | Protein loss from the small intestine | Albumin (2.5 g) Growth hormone | Relieved |
| Keberle et al. [4] | M | 19 | 21 | Tibial edema Clubbing | Fallot’s tetralogy | 41 | 26 | Intestinal protein loss predominantly in the ileum | Low-fat, protein-rich diet, medium-chain triglycerides | Relieved |
| O’Sullivan et al. [21] | M | 7 | 22 | Diarrhea | PVS | < 20 | | | Anti-heart failure | Died a |
| Herzog et al. [22] | F | 0.9 | 15 | Ankle swelling | ASD PVS | 45 | | Hypoplasia of the lymphatics of the extremity and multiple ectatic lymph vessels in the mediastinal area and right supracavicular area | Medium-chain triglyceride diet | Relieved |
| Vallet et al. [23] | M | 0.3 | 6 | Diarrhea Anasarca, chylorrhea from the inguinal skin | PVS | 38 | 20 | | Medium-chain triglycerides and a low-fat diet | Died b |
| Joyce et al. [24] | F | Unavailable | 27 | Bilateral lower limb and genital swelling | PVS | Unavailable | Unavailable | Lymph reflux/rerouting R: popliteal LN present. Contrast in vulva and multiple channels in both legs | Low-fat MCT diet | Relieved |
| Joyce et al. [24] | M | Unavailable | 55 | Bilateral lower limb and suprapubic swelling | ASD | Unavailable | Unavailable | | Unavailable | Unavailable |
| Our case | F | 7 | 30 | Extrimitis edema | Fallot’s tetralogy | 31 | 19 | Lymphangiectasis and bilateral widening of the venous angle in the mediastinum and small intestine | Low-fat, medium-chain triglycerides | Relieved |

Abbreviations: PLE Protein-losing enteropathy, HCM Hypertrophic cardiomyopathy, ASD Atrial septal defect, PVS Pulmonary valve stenosis, TP Total protein, Alb Albumin; a means the patient died of heart failure; b, the autopsy revealed the immediate cause of death to be hemorrhagic pancreatitis after a valvuloplasty for PVS. The normal range for TP and Alb is 60-85 g/L and 35-52 g/L, respectively.

Fig. 3 Distribution of the missense mutations identified in PTPN11, as provided by the UniProt database (uniprot.org). The mutation detected in our patient is marked with an asterisk. The different colored rectangles represent the protein domains and the purple spheres represent amino acid changes at different mutation sites.
Noonan syndrome may be confused with other genetic diseases late in patients with Noonan syndrome. Noonan syndrome has no clear genotype-phenotype correlation, there are certainly several cases suggesting that these mutations may be pathogenic; further work is needed in larger cohorts.

In our case, the patient carried the PTPN11 variant, which was inherited by her daughter. It was unclear whether this variant was inherited or sporadic (Fig. 3), although her father, who had died of acute cerebrovascular disease aged 55 years and could therefore not be tested, showed no clinical manifestations of Noonan syndrome.

There is no standard treatment for PLE in Noonan syndrome. Most patients reported in the literature recovered after treatment, which included periodic supplemental albumin and long-term medium-chain triglycerides. Moreover, glucocorticoids and diuretics achieved long-term symptomatic relief in some patients with Noonan syndrome [19, 20]. Systemic corticosteroids such as prednisone have been used for their anti-inflammatory effects [39]. Diuretics may decrease the CVP, which promotes lymphangiogenesis and lymphangiectasia [40]. Early growth hormone replacement in children can result in near adult heights later in life [41].

PTE is often congenital in etiology and associated with Hennekam syndrome (HS), Turner syndrome (TS), and Noonan syndrome (Table 2). HS is a recessive disorder that can have disordered small intestinal lymphangiogenesis associated with mutations in CCEB1 and FAT4 [42, 43]. TS is an allosomal disorder in which infants with the 45,X karyotype are most likely to have congenital lymphedema [44].

In conclusion, here we report a case of Noonan syndrome with PLE carrying a PTPN11 variant. PLE occurs late in patients with Noonan syndrome. Noonan syndrome may be confused with other genetic diseases clinically, and genetic evaluation with next-generation sequencing to identify the genetic basis can be helpful. Finally, screening family members, especially children, may provide the definitive diagnosis to guide early intervention.

Abbreviations
CT: Computed tomography; DRESS: Drug reactions with eosinophilia and systemic symptoms; GWAS: Genome-wide association studies; HS: Hennekam syndrome; MAPK: Mitogen activated protein kinase; PLE: Protein-losing enteropathy; TS: Turner syndrome; WES: Whole exome sequencing

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Authors’ contributions
All authors were involved in the care of the patients. NW wrote the initial draft of the manuscript. WS and YJ critically appraised and revised the overall content of the manuscript. All authors read and approved the final manuscript.

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Ethics approval and consent to participate
Not applicable.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests
The authors declare that they have no competing interests.

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Table 2 Differential characteristics of three congenital diseases associated with PLE

| Disease            | Genetic property | Causative genes | Morbidity                  | Pattern                          | Height (cm) |
|--------------------|------------------|-----------------|----------------------------|---------------------------------|-------------|
| Hennekam syndrome | Recessive inheritance | CCEB1, FAT4, ADAMTS3 | Rare < 50 cases/worldwide | Lymphangiogenesis can occur in many areas, the most common being the small intestine but also the kidney, chest, pericardium, thyroid gland and skin [39]. | 156.3 ± 11.3 155.3 ± 4.7 |
| Turner syndrome   | Allosomal inheritance | 46, X, 46, X (Xq) Mosaicism | 1/1500–2500 | Infants with a 45,X karyotype are the most likely to have congenital lymphedema [40]. | 141.3 ± 5.6 |
| Noonan syndrome   | Autosomal dominant | PTPN11, SOS1, RAF1, KRAS, SHOC2, NRAS | 1/1000–1/2500 | Lymphangiogenesis restricted to pterygium and limbal lymphedema and often combined with cardiac disease. | 157.3 ± 7.4 146.8 ± 6.9 |

Abbreviation: PLE Protein-losing enteropathy
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