American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2020; 21: e922468
DOI: 10.12659/AJCR.922468

Received: 2019.12.29
Accepted: 2020.03.28
Available online: 2020.06.08
Published: 2020.07.31

The Fetal Phenotype of Noonan Syndrome Caused by Severe, Cancer-Related *PTPN11* Variants

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared
Source of support: Riga Stradiņš University Internal grants

Case series
Patients: Female, 37-year-old • Female, 31-year-old
Final Diagnosis: Noonan syndrome
Symptoms: Fetal nuchal fold thickening
Medication: —
Clinical Procedure: Chorionic villi sampling
Specialty: Genetics • Obstetrics and Gynecology

Objective: Rare disease

Background: The nuchal translucency measurement is the major focus of an early fetal ultrasound scan, with the goal to identify various inherited conditions, such as chromosomal aberrations and others. The diagnostic strategy for fetuses with increased nuchal translucency and normal karyotype is not clearly defined and may vary between countries.

Case Reports: We describe 2 cases of Noonan syndrome diagnosed prenatally by ultrasound scanning and genetic testing. The prenatal ultrasound scans showed abnormal nuchal translucencies, cystic lymphangioma/cystic hygroma, and other findings. Both fetuses had normal karyotype; however, after additional analysis, pathogenic variants of the *PTPN11* gene (encoding SH2 domain-containing protein tyrosine phosphatase) were found, previously frequently described as somatic variants in hematological malignancies in postnatal life, but not previously described with severe prenatal phenotype of Noonan syndrome.

Conclusions: Our case reports confirm the hypothesis that severe, cancer related *PTPN11* variants cause severe Noonan syndrome prenatal phenotype, when inherited in the germline.
Analysis of pathogenic variants associated with Noonan syndrome should be included in the prenatal diagnostics for fetuses with increased nuchal translucency and normal karyotype.

MeSH Keywords: Lymphangioma, Cystic • Noonan Syndrome • Nuchal Translucency Measurement • SH2 Domain-Containing Protein Tyrosine Phosphatases

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/922468

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Background

In approximately 3% of all pregnancies, fetal structural abnormalities can be visualized in an ultrasound scan, which can range from a single minor defect to severe and fatal multisystem anomalies [1].

Nuchal translucency (NT) is defined as the collection of fluid behind the neck of the fetus [2]. The definitions for increased NT vary in the literature, although any value ≥3.5 mm is ≥99th percentile for any gestational age between 11–13^{+6} weeks and is considered to be abnormal [2]. The causes of increased NT can vary greatly, chromosomal aneuploidies and aberrations being responsible for more than 50% of cases [3]. Therefore, NT measurement is the major focus of an early fetal scan to uncover possible inherited conditions [4–6]. Increased NT requires fetal karyotyping as well as detailed anatomic examination with fetal echocardiography in the second trimester [7]. In cases of increased NT and normal karyotype as well as chromosomal analysis results, the successive strategy is not clearly defined and may vary between countries and even hospitals.

In this report we describe the phenotype, genotype, and diagnostic strategies of 2 cases of Noonan syndrome, with increased NT and normal karyotype to emphasize the importance of prenatal diagnostics of Noonan syndrome and highlight the phenotypic features of severe, cancer-related *PTPN11* variants. In both cases, the parents signed informed consent and agreed to manuscript publication; genetic analysis was done as part of the diagnostic workflow.

Case Reports

Case 1

A 37-year-old Caucasian female was referred to our department from the local health center due to an increased fetal nuchal translucency found during the first-trimester screening ultrasound scan. From anamnesis data, it was known that the patient had autosomal dominant polycystic kidney syndrome and 3 years prior she had had one normal delivery resulting in a healthy child. The patient did not have a history of smoking or of alcohol or substance abuse during pregnancy.

At the time of the fetal ultrasound scan, the fetus was 11 weeks and 1 day old with increased NT of 12.0 mm and increased ductus venosus pulsatility index of 1.8. On a detailed ultrasound scan, lymphatic dysgenesis with large multilocular fluid-filled cavities around the fetal neck was found and is shown in Figure 1. These findings were consistent with cystic lymphangioma/cystic hygroma. Chorionic villus sampling (CVS) was performed and the obtained material was referred

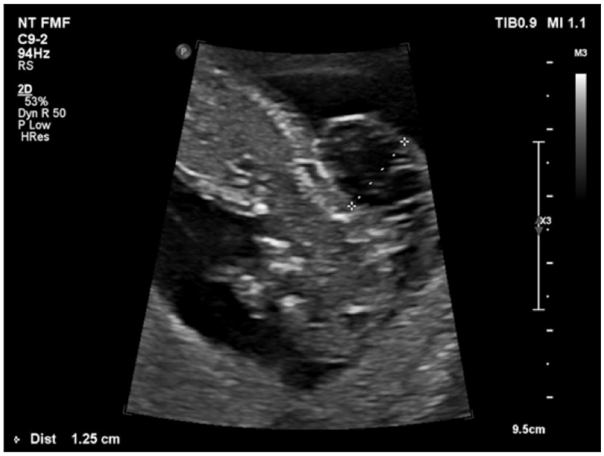

Figure 1. Ultrasound scan for first fetus at 12^{+3} weeks with cystic hygroma.

for fluorescence *in situ* hybridization (FISH) testing, karyotyping, and *PTPN11* gene (reference sequence: NG_007445911) mutation hotspot testing by Sanger sequencing.

During the follow-up visit, at the 16th week scan, the cystic hygroma was still present and the NT was significantly increased; in addition, kidney pyelectasis was diagnosed (Table 1). At this point the results of genetic testing were available, showing that the fetus had normal karyotype (46, XX), and no abnormalities were found by FISH (22q11.2). However, pathogenic *de novo* variant c.211T>C, p.Phe71Leu (rs397507512, Clinvar allele ID: 48969) of the *PTPN11* gene was found, which confirmed the diagnosis of Noonan syndrome (shown in Figure 2). After a genetic consultation, the family decided to continue the pregnancy. An echocardiography scan was performed at the 22nd week, with no pathologic findings. During successive follow-up visits, we provided regular check-ups and ultrasound scans to evaluate the fetus. On the 35th week, during the last antenatal care visit, polyhydramnios and new phenotypic features were diagnosed, such as fetal hydrothorax (chylothorax) and subcutaneous generalized edema (nonimmune hydrops) (Table 1). At 35 weeks, a decision to perform partial amniotomy was made, because of polyhydramnios. After this procedure, partial placental abruption had started, therefore a cesarean section was performed. The newborn girl weighted 3080 g, with length of 46 cm and Apgar scores of 1 and 4 points at first and fifth minutes, respectively.

The newborn had a facial phenotype typical of Noonan syndrome: proptosis, epicanthal folds, ptosis, broad nasal bridge, hypertelorism, short neck, low-set ears, and abnormal auricles (similar to features seen in prenatal 3-dimensional ultrasound scan, Figure 3). The newborn had a lifespan of 25 days and passed away due to heart failure caused by ventricular and atrial septal defects, which had not been recognized prenatally.

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Table 1. USS findings in the first fetus.

	12+3 weeks	16th week	22nd week	29th week	33rd week	35th week
NT	12.0 mm	5.8 mm	4.6 mm			
PI	1.8					
Cystic hygroma	+	11×8 mm 16×8 mm	6×3.7 mm 5.4×3.6 mm 4.9×5.3 mm			
Right kidney pyelectasia		AP=5.6 mm	AP=16.0 mm	AP=26.0 mm	AP=33.0 mm	
Polyhydramnios				AFI=27.1 cm	AFI=32.9 cm	AFI=32.9 cm
Additional features	CRL=52.4 mm					Hydrothorax (chylothorax)
						Subcutaneous generalized edema

USS – ultrasound scan; NT – nuchal translucency; PI – ductus venosus pulsatility; AP – anterior-posterior; AFI – amniotic fluid index; CRL – crown-rump length.

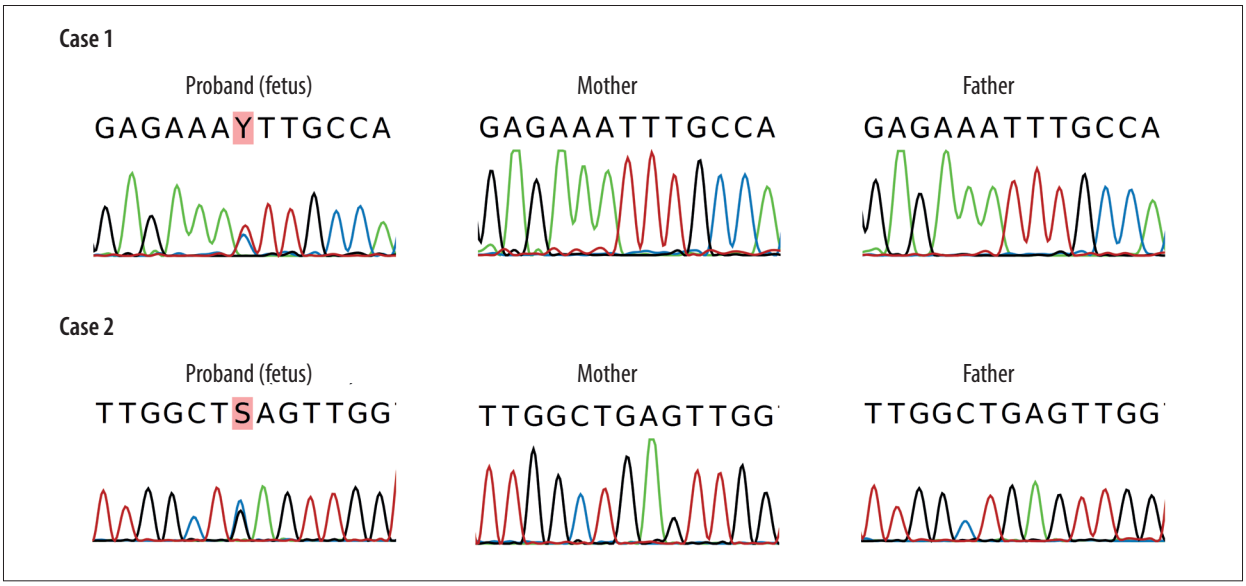

Figure 2. The DNA sequence electropherogram of the *PTPN11* variants of the described probands and their parents. Case 1: *PTPN11*: c.211T>C, p.Phe71Leu *de novo* variant. Case 2: *PTPN11*: c.226G>C, p.Glu76Gln *de novo* variant.

Case 2

A 31-year-old Caucasian female presented to our department for the first-trimester screening of her second pregnancy. It was known that she was healthy, without chronic diseases or known risk factors such as smoking or alcohol abuse. Her first pregnancy was without complications and resulted in the delivery of a healthy child.

At the time of the fetal ultrasound scan, the fetus was 13 weeks and 6 days old, with increased NT of 17.2 mm and an increased ductus venosus pulsatility index (Table 2). Detailed ultrasound showed additional findings: cystic hygroma, subcutaneous edema, hydrothorax/chylothorax, and echogenic bowel (Figure 4, Table 2). Therefore, CVS was performed, and the obtained material was referred for genetic testing similar to what was described for Case 1.

During the follow-up ultrasound scan (14^{+6}), subcutaneous edema and initial ascites were additionally diagnosed; furthermore, hydrothorax/chylothorax had increased, and hepatomegaly was suspected (Table 2).

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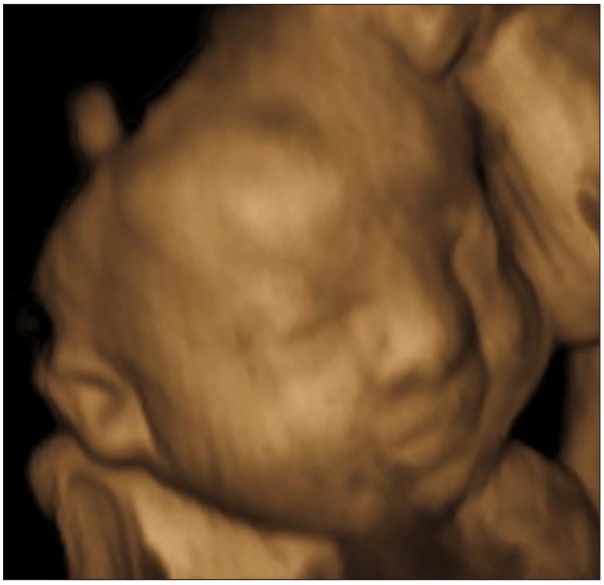

Figure 3. Fetal facial dysmorphism at 33^{+0} weeks of gestation: prominent forehead, broad nasal bridge, hypertelorism, and low set, posteriorly rotated ears.

Table 2. USS findings in the second fetus.

	13^{+6} weeks	14^{+6} weeks
NT	17.2 mm	
PI	1.5	
Cystic hygroma	+	+
Additional features	CRL=52.4 mm	
	Subcutaneous edema	Subcutaneous edema
	Hydrothorax/ chylothorax	Hydrothorax/ chylothorax (up to 5.1 mm)
	Echogenic bowel	Initial ascites
		Hepatomegaly (20×17×16 mm)

NT – nuchal translucency; PI – ductus venosus pulsatility; CRL – crown–rump length.

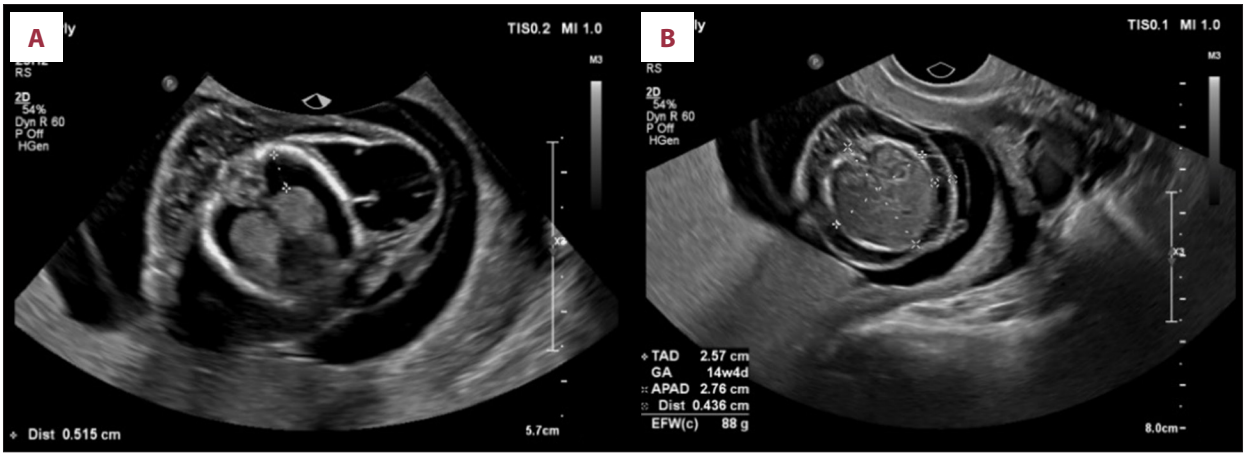

Figure 4. Ultrasound scan results for second fetus. (**A**) Cystic hygroma at 13^{+6} weeks; hydrothorax/chylothorax. (**B**) Subcutaneous generalized edema (abdominal circumference plane).

Genetic testing showed that the fetus had a normal karyotype (46, XX) and no abnormalities were found by FISH (22q11.2), but the pathogenic *de novo* variant c.226G>C, p.Glu76Gln (rs121918464, ClinVar allele ID: 179445) of the *PTPN11* gene was found, thus conforming the diagnosis of Noonan syndrome (Figure 2). After a genetic consultation, the family decided to terminate the pregnancy.

Discussion

This report presents 2 severe cases of Noonan syndrome that were diagnosed prenatally, presenting with increased NT in an ultrasound scan. Furthermore, it emphasizes the importance of Noonan syndrome testing in prenatal settings, as well as highlights the phenotype-genotype link in severe Noonan syndrome cases.

Prenatal screening with ultrasound allows the evaluation of gross fetal abnormalities and nuchal translucency thickness [8]. At present, NT measurement is primarily used to detect chromosomal aneuploidies [8], although there are many reasons for increased NT, including various genetic syndromes, cardiac anomalies, and other structural anomalies [9].

Cystic hygroma is associated with extremely increased NT. In approximately 50% of cases with cystic hygroma, it is caused by a chromosomal aneuploidy, while 30% of cases have an

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additional structural anomaly associated with other conditions, and 20% of fetuses develop normally [4]. Importantly, testing for Noonan syndrome is not currently included in guidelines for prenatal testing [4–6], although it could additionally solve up to 20% of cases with increased NT and even up to 30% in cases with cystic hygroma [10].

Some published studies suggest that Noonan syndrome can be suspected prenatally in cases with large NT in addition to one or more of the following characteristics: cystic hygroma, pleural effusion, hydrops fetalis, cardiac anomalies, or specific facial features [11].

Noonan syndrome is a genetically heterogeneous and pathogenic variants of more than 10 genes are known to be implicated in its development [12]. Approximately 50% of Noonan syndrome cases have a pathogenic variant of the *PTPN11* gene, which encodes the SH2 domain-containing protein tyrosine phosphatase (SHP2) protein [10]. Testing for Noonan syndrome could be performed either by next-generation sequencing (NGS) or by Sanger sequencing. NGS, including whole exome sequencing (WES), has limited availability in prenatal settings, a high price, long turn-around times, and substantial risk of incidental findings. Therefore, WES is not currently recommended by guidelines for routine use in prenatal settings [5].

In Latvia, we have implemented the strategy of performing karyotype and FISH analysis for the most common aberrations in case of increased NT. Euploid fetuses are also tested for Noonan syndrome by Sanger sequencing for mutation hotspots in the genes most commonly involved in Noonan syndrome – *PTPN11, SOS1,* and *RAF1* – which covers 60–70% of Noonan syndrome cases [13].

The SHP2 is a Src homology 2 (SH2) domain-containing protein-tyrosine phosphatase that positively modulates Ras function. Ras proteins are known to be signaling molecules that regulate a variety of cellular processes, including cell growth, differentiation, the mitotic cycle, and oncogenic transformation [14]. It is interesting to note that both *PTPN11* pathogenic variants that are described in this paper (p.Phe71Leu and p.Glu76Gln), are class I variants located within an autoinhibitory region of the SHP2 protein, which disrupt the interaction of the N-SH2 domain with the PTP domain, leading to affected switching between active and inactive state and result in hyperactive phosphatase activity [15]. Variants leading to an extreme activation of the protein are mostly identified in malignancies, while germline variants found in Noonan syndrome patients have less severe consequences on the protein activation [16]. In fact, Noonan syndrome-causing variants inherited in the germline are not only 2–5× less active, but also commonly have another activation mechanism, e.g., 85% of the cancer-related variants and only 42% of the germline Noonan syndrome cases are class I variants. Therefore, it was hypothesized that if a cancer-associated variant is inherited in the germline, it would cause severe fetus malformations that would not be compatible with long-term survival [16]. Since 2005, there have been only a handful of reports available describing such cases [17]. Variant p.Glu76Gln has previously been reported only in association with leukemia and other cancers, but it has not been reported to be inherited in the germline [18]. Variant p.Phe71Leu has been reported as a Noonan syndrome-causing allele in literature, and it has also been identified in various cancers [18].

Our report emphasizes the role of testing for Noonan syndrome in cases with increased NT/cystic hygroma and suggests testing primarily for mutation hotspots of Noonan syndrome-causing genes. This report also highlights the features of mutations observed in severe prenatal cases of Noonan syndrome.

Conclusions

Our case reports confirm the hypothesis that severe, cancer related *PTPN11* variants cause severe Noonan syndrome prenatal phenotype, when inherited in the germline. Noonan syndrome mutation testing should be included in prenatal diagnostic guidelines for fetuses with increased nuchal translucency and normal karyotype.

Acknowledgments

We thank the parents for consenting to the publication of these case reports.

Department and Institution where work was done

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Conflicts of interest

None.

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