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PTPN11-associated Noonan syndrome presenting with neonatal spontaneous hemorrhagic pleural effusion: a case report

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Case Report

Keywords: Noonan syndrome, PTPN11, Neonate, Hemorrhagic pleural effusion, Lymphatic abnormality, Sirolimus

Posted Date: September 25th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10692071/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Noonan syndrome (NS) is an autosomal dominant disorder caused by pathogenic variants affecting the RAS/MAPK signaling pathway. Lymphatic abnormalities are recognized manifestations of NS and may present during fetal or neonatal life with increased nuchal translucency, cystic hygroma, chylothorax, ascites, or generalized edema. However, spontaneous hemorrhagic pleural effusion as the initial presentation of NS in the neonatal period is extremely rare.

Case presentation

We report a male infant born at 29 weeks and 2 days of gestation with a birth weight of 1950 g who developed severe respiratory distress, generalized edema, and progressive hemorrhagic pleural effusion shortly after birth. Despite repeated drainage and supportive treatment, the pleural effusion persisted. Extensive investigations excluded common causes of hemorrhagic pleural effusion, including infection, malignancy, autoimmune disorders, metabolic diseases, and catheter-related complications. Imaging studies suggested underlying lymphatic abnormalities involving the lungs and chest wall. Whole-exome sequencing identified a heterozygous PTPN11 c.1403C > T (p.T468M) variant inherited from the mother, confirming the diagnosis of Noonan syndrome type 1 (NS1). Treatment with methylprednisolone followed by sirolimus resulted in improvement of pleural effusion and ascites. However, because of pulmonary hypertension, ventricular hypertrophy, and multisystem disease, the family elected to withdraw life-sustaining treatment, and the infant died.

Conclusion

Progressive hemorrhagic pleural effusion may represent a rare neonatal manifestation of NS-associated lymphatic abnormalities. NS should be considered in neonates with unexplained pleural effusion accompanied by characteristic facial features, edema, congenital heart abnormalities, or other suggestive findings. Early genetic evaluation may facilitate diagnosis, and sirolimus may represent a potential therapeutic option for NS-associated lymphatic abnormalities. Further studies are needed to clarify the mechanisms and long-term outcomes of this rare complication.

Background

Noonan syndrome (NS) is an autosomal dominant disorder characterized by substantial clinical and genetic heterogeneity[1]. It is mainly caused by pathogenic variants in genes involved in the RAS/MAPK signaling pathway, among which PTPN11 is the most frequently affected gene[2–3]. The clinical spectrum of NS is broad and includes distinctive facial features, congenital heart defects, short stature,

developmental delay, feeding difficulties, cryptorchidism, renal abnormalities, and abnormalities of the lymphatic system[4–5].

Abnormal lymphatic development is a well-recognized feature of NS, particularly during fetal and early neonatal periods. Reported manifestations include increased nuchal translucency, dilated jugular lymphatic sacs, cystic hygroma, chylothorax, ascites, and generalized edema[6–8]. Although lymphatic abnormalities are relatively common in NS, hemorrhagic pleural effusion presenting in the neonatal period has rarely been reported.

Previous reports of NS-associated hemothorax have mainly involved older children or adults and were usually related to identifiable triggers, such as trauma, central venous catheterization, or thoracic surgery[9]. In contrast, spontaneous and progressive hemorrhagic pleural effusion occurring shortly after birth without an apparent precipitating factor has not been well characterized.

Sirolimus, an inhibitor of the mammalian target of rapamycin (mTOR) pathway, has been increasingly used for complex lymphatic malformations in children[10–11]. However, clinical experience with sirolimus in neonates, particularly extremely preterm infants, remains limited. Here, we report a premature infant with PTPN11-associated Noonan syndrome type 1 presenting with progressive hemorrhagic pleural effusion as the initial manifestation. This case expands the neonatal phenotypic spectrum of NS and provides clinical experience regarding the diagnosis and management of NS-associated lymphatic abnormalities.

Case Presentation

A male infant of Han Chinese ethnicity was born at 29 weeks and 2 days of gestation (G3P2) with a birth weight of 1,950 g. Cesarean delivery was performed due to maternal scarred uterus and polyhydramnios. The amniotic fluid was clear but excessive in volume. The umbilical cord and placenta were grossly normal. The Apgar scores were 6 at 1 min and 6 at 5 min, respectively. Shortly after birth, the infant developed respiratory distress and required endotracheal intubation, surfactant replacement therapy, and mechanical ventilation. Empirical antibiotic therapy with ceftazidime was initiated because of suspected neonatal infection. Echocardiography revealed pulmonary hypertension, and treatment with sildenafil and inhaled nitric oxide was initiated The infant was transferred to our hospital because he developed anuria accompanied by severe generalized edema. Despite treatment with furosemide, albumin, dopamine, and fluid resuscitation, no significant improvement was observed.

The mother was 42 years old, had a short stature, and had a history of hypothyroidism treated with levothyroxine during pregnancy. No other relevant family history was identified.

Upon admission, the infant's body length was 42 cm (50th percentile), body weight was 2.4 kg (90th–97th percentile), and head circumference was 30 cm (10th–90th percentile). Physical examination revealed generalized edema. Dysmorphic facial features included a broad forehead and hypertelorism.

Two days after admission, the infant developed pulmonary hemorrhage. Chest radiography revealed recurrent pleural effusion (Fig. 1). Multiple thoracenteses were performed, yielding tea-colored to dark-red hemorrhagic pleural fluid (Fig. 2). Routine biochemical analysis of the pleural fluid showed no significant abnormalities. Cytological examination revealed lymphocytes, macrophages, and erythrocytes, without evidence of malignant cells. The infant continued to exhibit generalized edema, and soft, compressible masses were observed on both sides of the chest wall(Fig. 3-a). No pulsation or vascular bruit was detected. Bedside ultrasonography performed on the 29 day of life revealed a hypoechoic lesion in the subcutaneous tissue of the left chest wall, suggesting a possible vascular malformation (Fig. 3-b). A multidisciplinary team (MDT) consultation was conducted that we need further investigations, including genetic testing, metabolic profiling, immune function assessment, and chest magnetic resonance imaging (MRI), were performed to determine the underlying cause of the hemorrhagic pleural effusion. Bedside bronchoscopy demonstrated inflammatory changes in the bronchi. Coagulation studies revealed no significant abnormalities. Tumor marker analysis showed mildly elevated cancer antigen 125 (CA125) and neuron-specific enolase (NSE) levels. Metabolic screening, thyroid function tests, TORCH screening, and antinuclear antibody testing were all within normal limits. Electrocardiography revealed frequent premature atrial contractions. Computed tomography angiography (CTA) revealed an atrial septal defect, bovine aortic arch, left ventricular wall thickening, bilateral pulmonary abnormalities, and bilateral pleural effusions (Fig. 4-a). Ultrasonography of the portal vein, hepatic veins, and inferior vena cava showed no abnormalities. Contrast-enhanced chest magnetic resonance imaging(MRI) demonstrated extensive abnormal signal changes involving both lungs with marked enhancement (Fig. 4-b). Based on the imaging findings and clinical presentation, plastic surgery consultation suggested the possibility of a vascular/lymphatic malformation.

From postnatal day 23 to day 32, intravenous methylprednisolone was administered at a dose of 1.6 mg/kg/day. Sirolimus was initiated on postnatal day 28 at 0.8 mg/m²/day and subsequently reduced by one-third because of hepatic dysfunction. Following treatment, the pleural effusion and ascites gradually improved (Fig. 5). However, despite improvement in fluid accumulation, the infant continued to have severe underlying conditions, including persistent pulmonary involvement, pulmonary hypertension, ventricular wall hypertrophy, and multisystem abnormalities associated with Noonan syndrome.

Whole-exome sequencing identified several genetic variants, including a heterozygous PTPN11 c.1403C > T (p.T468M) variant. This variant was classified as pathogenic and was inherited from the mother. Combined with the clinical manifestations and genetic findings, the patient was diagnosed with Noonan syndrome type 1 (NS1) (next-generation sequencing results are shown in Fig. 6). After comprehensive counseling regarding the overall poor prognosis and the potential long-term complications associated with severe neonatal Noonan syndrome, the family elected to withdraw life-sustaining treatment. The infant died on the 46 day of life.

Discussion

Noonan syndrome (NS) is an autosomal dominant disorder characterized by substantial clinical and genetic heterogeneity[12]. Pathogenic variants in PTPN11 are the most frequently identified genetic abnormalities, accounting for approximately half of genetically confirmed cases[13–14]. Variants in other genes involved in the RAS/MAPK signaling pathway, including SOS1, RAF1, RIT1, NRAS, and BRAF, have also been associated with NS, contributing to its diverse phenotypic spectrum [15–19].We report a case of PTPN11-associated Noonan syndrome type 1 preterm infant with progressive hemorrhagic pleural effusion as the initial presentation.

In this patient, the predominant clinical manifestation was progressive hemorrhagic pleural effusion during the neonatal period. A broad differential diagnosis was considered, including coagulation disorders, infection, malignancy, autoimmune diseases, metabolic disorders, and catheter-related complications. However, none of these conditions adequately explained the persistent progression of hemothorax. The absence of malignant cells in pleural fluid, lack of significant abnormalities on thoracic imaging, negative infectious evaluations, normal autoimmune screening, and exclusion of catheter-related complications supported the possibility of an underlying developmental abnormality rather than an acquired disorder.

The combination of generalized edema, bilateral compressible chest wall masses, imaging findings suggestive of a vascular/lymphatic malformation, and improvement of pleural and abdominal effusions after sirolimus treatment raised suspicion of a lymphatic abnormality associated with NS. Furthermore, whole-exome sequencing identified a heterozygous PTPN11 c.1403C > T (p.T468M) variant inherited from the mother, which was classified as pathogenic and confirmed the diagnosis of Noonan syndrome type 1 (NS1). Therefore, the progressive hemorrhagic pleural effusion in this infant was considered to be associated with NS-related lymphatic developmental abnormalities.

The PTPN11 gene encodes the non-receptor protein tyrosine phosphatase SHP-2, a critical regulator of the RAS/MAPK signaling pathway[20–21]. Most pathogenic PTPN11 variants associated with NS are gain-of-function mutations that result in excessive activation of this pathway. The p.T468M variant identified in this infant has been reported as a pathogenic variant and may contribute to abnormal developmental signaling. Although a direct genotype–phenotype correlation remains incompletely established, the severe neonatal presentation in this case suggests that this variant may be associated with a more aggressive clinical phenotype involving lymphatic and cardiovascular systems.

In fetal NS, abnormalities of lymphatic development may present as increased nuchal translucency, abnormal venous development, chylothorax, ascites, or generalized edema, with hydrops fetalis being the most frequently recognized manifestation. However, clinically significant lymphatic dysplasia is considered relatively uncommon, occurring in fewer than one-fifth of affected individuals. In contrast, lymphatic abnormalities appear to be more prevalent among neonates with pathogenic PTPN11 variants, with some studies reporting involvement in more than half of affected infants.

Progressive spontaneous hemothorax as the initial presentation of neonatal NS is extremely rare. Previous reports of NS-associated lymphatic malformations (LMs) have mainly described chylothorax, cystic hygroma, or generalized edema. Hemothorax has seldom been reported and is more commonly associated with trauma, invasive procedures, or central venous catheterization in older patients. In contrast, our patient developed spontaneous hemorrhagic pleural effusion at 29 weeks and 2 days of gestation without identifiable precipitating factors. The progressive nature of the effusion and exclusion of alternative causes suggest that NS-associated lymphatic abnormalities may occasionally present with hemorrhagic rather than chylous effusions.

The mechanism underlying hemorrhagic effusion in NS remains unclear. In this infant, routine coagulation tests did not demonstrate a specific coagulation factor deficiency, including factor VII deficiency or abnormalities of vitamin K-dependent factors. Previous studies have reported abnormalities in platelet function, aggregation, and secretion among patients with NS, which may not be detected by conventional coagulation screening[22]. Therefore, subtle hemostatic dysfunction cannot be completely excluded. The hemorrhagic nature of the pleural effusion may result from increased fragility of abnormal lymphatic vessels, possibly combined with impaired hemostatic function. Further studies are required to clarify the mechanisms responsible for bleeding complications in NS-associated lymphatic abnormalities.

Sirolimus, an inhibitor of the mammalian target of rapamycin (mTOR) pathway, has increasingly been used for the treatment of complex vascular anomalies, particularly lymphatic malformations. Activation of the PI3K/AKT/mTOR pathway plays an important role in abnormal lymphatic and vascular proliferation[23]. By binding to FKBP12 and inhibiting mTOR complex 1 (mTORC1), sirolimus suppresses lymphangiogenesis and angiogenesis, regulates cellular proliferation, and promotes lesion stabilization.

In this patient, treatment with sirolimus was associated with improvement of pleural effusion and ascites, suggesting a potential therapeutic effect on NS-associated lymphatic abnormalities. However, the efficacy of sirolimus may vary depending on lesion location and disease severity[24–25]. Previous reports have suggested better responses in head and neck lymphatic lesions, whereas thoracic and visceral involvement may be more difficult to treat[26]. In addition, experience with sirolimus use in critically ill neonates remains limited, and long-term safety, particularly regarding neurodevelopmental outcomes, requires further investigation.

For macrocystic or mixed-type lymphatic malformations, image-guided aspiration combined with sclerotherapy remains an important treatment option[27]. Surgical intervention may be considered for localized lesions that are completely resectable without compromising vital structures or for lesions causing severe compression symptoms. However, in patients with diffuse lymphatic involvement, systemic therapy and multidisciplinary management are often required.

Early recognition of NS-associated lymphatic abnormalities is essential in neonates presenting with unexplained pleural effusion or hemorrhagic effusion. Management requires close collaboration among

neonatologists, geneticists, radiologists, surgeons, and other specialists. A comprehensive strategy focusing on stabilization of vital functions, control of effusion and bleeding, targeted treatment of lymphatic abnormalities, and management of associated systemic complications may improve clinical outcomes in these challenging cases.

Abbreviations

NS Noonan syndrome

NS1 Noonan syndrome type 1

mTOR the mammalian target of rapamycin

MDT multidisciplinary team

CA125 cancer antigen 125

NSE neuron-specific enolase

CTA Computed tomography angiography

MRI magnetic resonance imaging

LMs lymphatic malformations

mTOR the mammalian target of rapamycin

mTORC1 mTOR complex 1

Declarations

Ethics approval and consent to participate

This case report was conducted in accordance with the principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board of the Children's Hospital, Zhejiang University School of Medicine (Approval No. 2026-IRB-0139-P-01). Written informed consent for participation in this study was obtained from the patient's parents.

This study is not a clinical trial; therefore, trial registration is not applicable.

Consent for publication

Written informed consent for publication of this case report, including the use of clinical information and images, was obtained from the patient's parents. A copy of the signed consent form is available for review by the Editor-in-Chief of the journal upon request.

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due to patient privacy and ethical restrictions but are available from the corresponding author upon reasonable request. The PTPN11 variant identified in this case, NM_002834.5:c.1403C>T (p.Thr468Met), has an existing public record in the ClinVar database (ClinVar Variation ID: 13331), which is accessible at https://www.ncbi.nlm.nih.gov/clinvar/variation/13331/.

Competing interests

The authors declare that they have no competing interests.

Funding

This study received no external funding.

Authors' contributions

Minjie Pan conceived and designed the study. Xinning Wang collected and analyzed the clinical data . Minjie Pan drafted the manuscript. Chenhong Wang performed the genetic analysis. Xiujing Wu contributed to manuscript revision. Yanping Xu supervised clinical management and critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

Acknowledgements

We sincerely thank the patient's family for their cooperation and consent to participate in this study. We also appreciate the dedicated care provided by the medical and nursing staff of the Department of Neonatology. In addition, we thank the genetic testing center for technical support during the molecular analysis.

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Figures

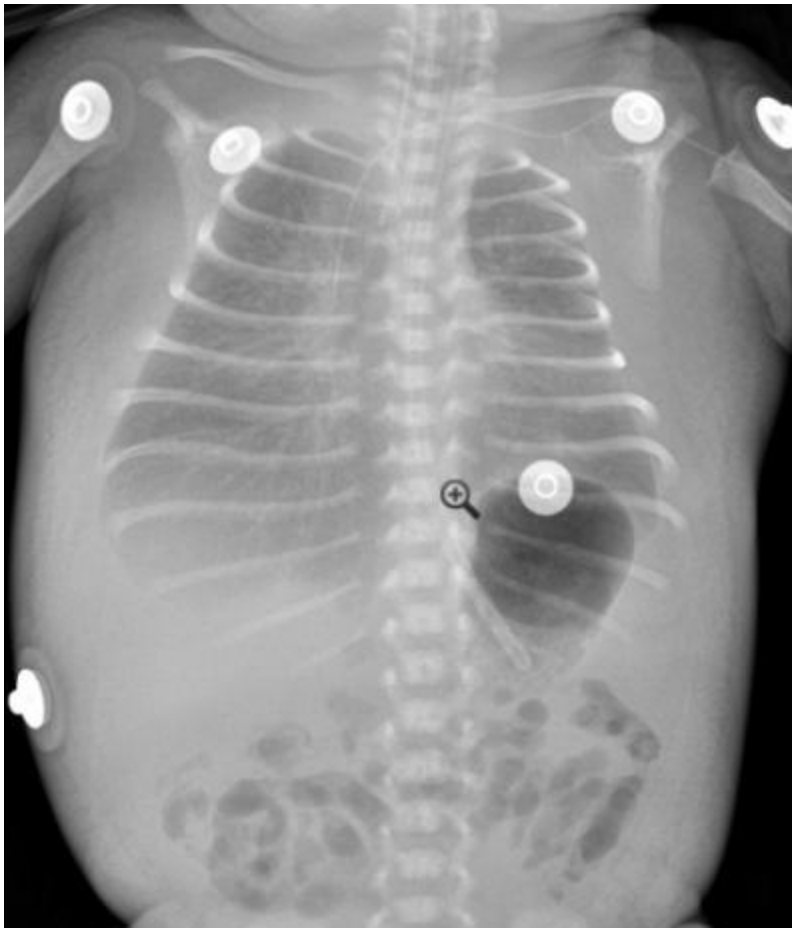


Figure 1

Chest radiograph showing pleural effusion



Figure 2

Hemorrhagic pleural effusion from thoracentesis

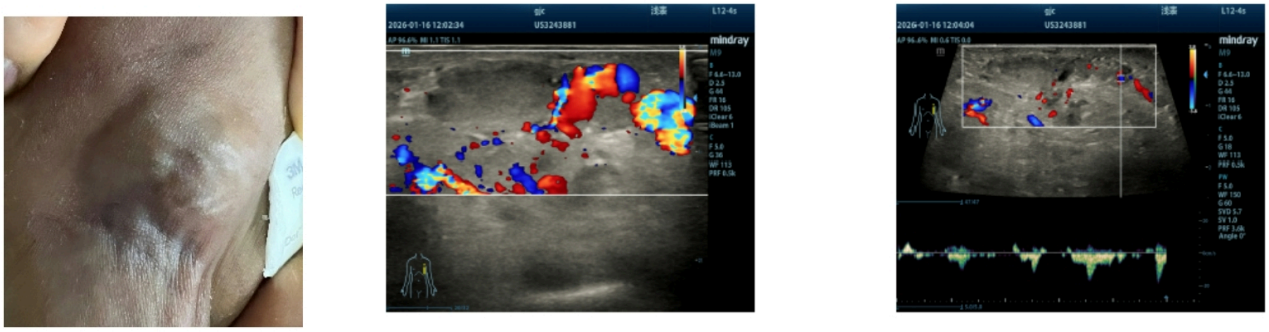


Figure 3

Chest wall bag piece and bedside ultrasound examination

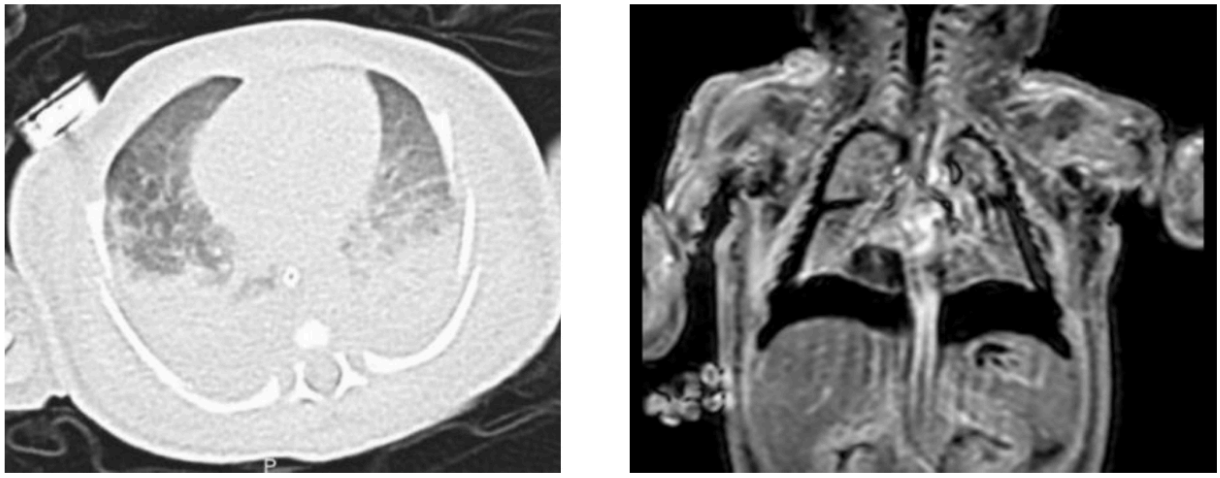
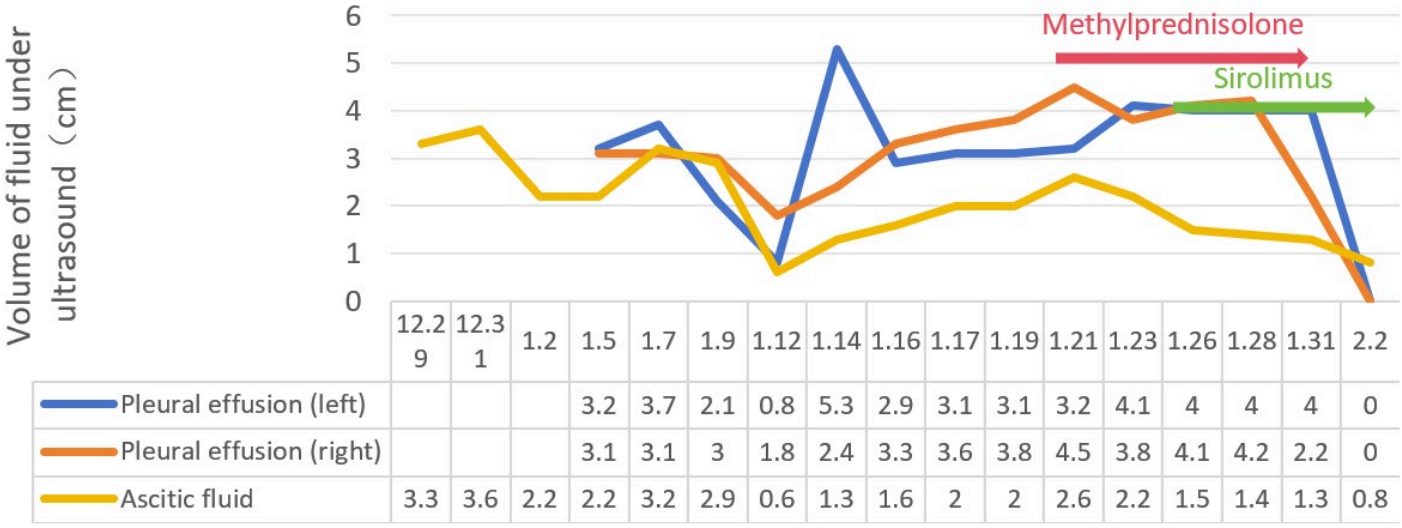


Figure 4

Results of CTA and MRI of the chest



	12.29	12.31	1.2	1.5	1.7	1.9	1.12	1.14	1.16	1.17	1.19	1.21	1.23	1.26	1.28	1.31	2.2
Pleural effusion (left)				3.2	3.7	2.1	0.8	5.3	2.9	3.1	3.1	3.2	4.1	4	4	4	0
Pleural effusion (right)				3.1	3.1	3	1.8	2.4	3.3	3.6	3.8	4.5	3.8	4.1	4.2	2.2	0
Ascitic fluid	3.3	3.6	2.2	2.2	3.2	2.9	0.6	1.3	1.6	2	2	2.6	2.2	1.5	1.4	1.3	0.8

Figure 5

Pleural effusion and peritoneal effusion conditions of the child patient

Thoracentesis was performed on January 3 (22 mL), January 5 (26 mL), January 15 (7 mL), January 17 (15 mL), and January 24 (25 mL), each yielding hemorrhagic pleural effusion.

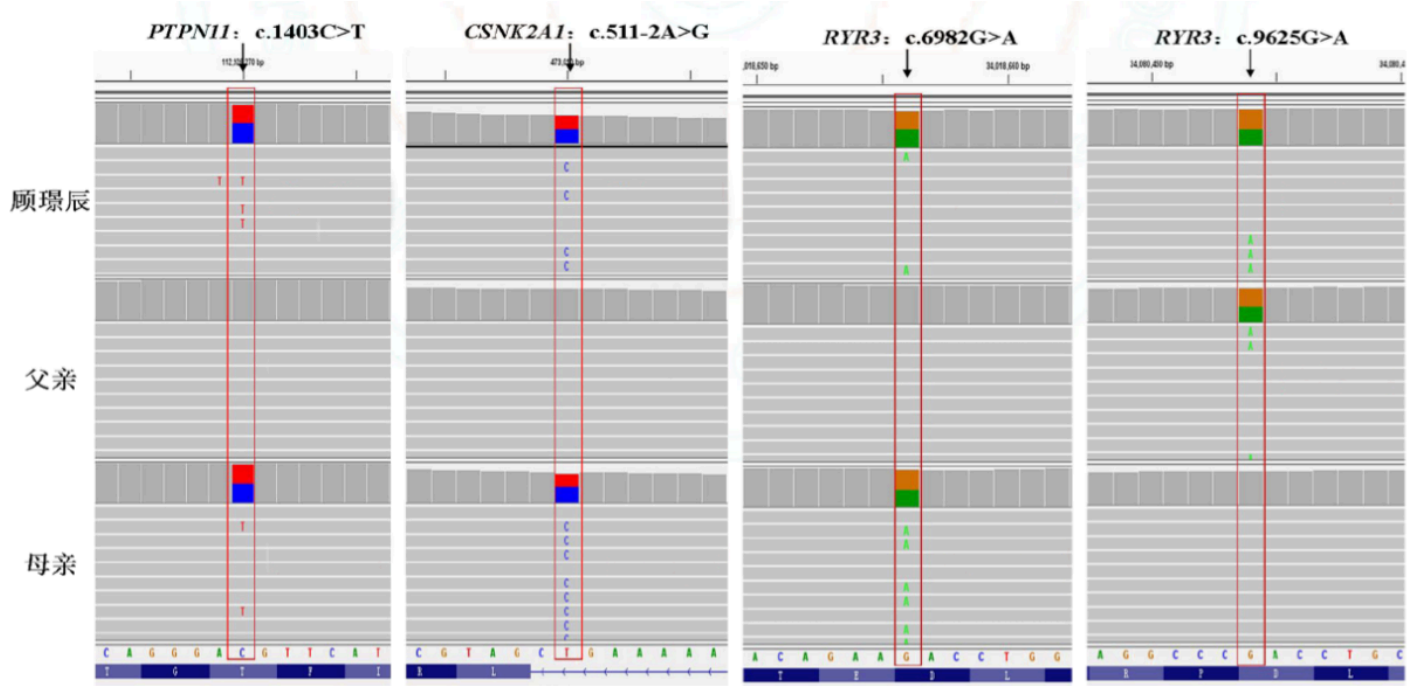


Figure 6

Second generation sequencing results (IGV diagram)