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CLINICAL REPORT

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Rapid detection by *hydrops panel* of Noonan syndrome with *PTPN11* mutation (p.Thr73Ile) and persistent thrombocytopenia

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Abstract

Background: Nonimmune hydrops fetalis (NIHF) is still a challenging diagnosis. The differential diagnosis is extensive and the success of identifying a cause depends on the thoroughness of efforts to establish a diagnosis. For the early diagnosis of NIHF, a virtual gene panel diagnostic tool was developed. The female premature baby in question was delivered via emergency cesarean at 30 + 1 weeks of gestational age (GA) due to rapidly developing NIHF to a healthy mother. The family history was noncontributory.

Methods: DNA of the family was extracted and sequenced by the virtual *hydrops panel* with whole-exome sequencing.

Results: The *hydrops panel* revealed Noonan syndrome (NS) with a germline mutation in PTPN11 c.218C>T (p.Thr73Ile).

Conclusion: The diagnosis of our patient was rapidly confirmed by the *hydrops panel*. The variant of c.218C>T (p.Thr73Ile) has not yet been described in literature relating to NIHF. Only a few case reports of this variant are known. This particular mutation is associated with Noonan syndrome, congenital heart defect and persistent thrombocytopenia. Few reveal juvenile myelomonocytic leukemia.

KEYWORDS

hydrops panel, next-generation sequencing, nonimmune hydrops fetalis, Noonan syndrome, rare variant

1 | INTRODUCTION

Noonan syndrome is still a challenging diagnosis as well as the diagnosis of nonimmune hydrops fetalis mainly because of extensive differential diagnosis. The success of identifying a cause depends on the thoroughness of efforts to establish a diagnosis.

Therefore, we developed the so-called *hydrops panel,* a virtual gene panel diagnostic tool for quick diagnosis of NIHF. The panel includes 119 genes which are associated with NIHF (Table 1). In a second step, a complete analysis can be performed by whole-exome sequencing (WES). This facilitates the diagnosis and thus the management of the underlying disease.

Noonan syndrome (NS) is an autosomal dominant disorder with a prevalence of 1:1,000–2,500 live births (Tartaglia, Gelb, & Zenker, 2011). It is characterized by various major and minor anomalies such as congenital heart defects, facial anomalies, and short stature.

PTPN11 (OMIM#176876; Protein–tyrosine phosphatase nonreceptor-type 11) mutations are found in up to 35% of all cases of sporadic juvenile myelomonocytic leukaemia cases, 5%–10% of all cases of childhood myelodysplastic syndrome, 7% of all cases of B-cell precursor acute lymphoblastic leukaemia, in cases of pediatric and adult acute myelogenous leukemia (AML) and some solid tumors (Kratz, Niemeyer, & Castleberry, 2005). Germline mutations in the *PTPN11* gene cause about half of all cases of NS (Araki et al., 2009). The mutation c.218C>T (p.Thr73Ile) revealed in this case is a germline mutation, but it can also be found as a somatic one in sporadic juvenile myelomonocytic leukemia (Kratz et al., 2005).

The *PTPN11* gene encodes for the cytoplasmatic tyrosine phosphatase named Src homology region 2- domain-containing phosphatase-2 (SHP-2) which plays an important role in mesodermal patterning (Tang, Freeman, O'Reilly, Neel, & Sokol, 1995), for example, limb development (Saxton et al., 1997), hematopoietic cell differentiation (Qu et al., 1997), and semilunar valvulogenesis (Chen et al., 2000).

SHP2 contains different domains named N-SH2, C-SH2, and PTP (Keilhack, David, McGregor, Cantley, & Neel, 2005). The mutation noted in this child was in the N-SH2 domain. The N-SH2 domain acts as a molecular switch, activating and deactivating SHP-2. By binding the PTP domain, a stable intermolecular interaction deactivates SHP2 (autoinhibition; Martinelli, 2012). The c.218C>T (p.Thr73Ile) mutation causes a conformational change in the interaction region between the N-SH2 and the PTP domain, leading to a disruption of N-SH2 and PTP with a consecutive persistent activation of SHP2 which acts upstream of RAS (Rat sarcoma, proto–oncogene) as gain of function (Chan & Feng, 2007).

Until now a genotype–phenotype correlation in Noonan syndrome could not be established (Zenker et al., 2004).

In Noonan syndrome patients all causative genes encode signaling molecules within the RAS signaling pathway, which is a major contributor to carcinogenesis (Kratz, Rapisuwon, Reed, Hasle, & Rosenberg, 2011).

TABLE 1 Hydrops panel

Gen	Transcript	OMIM	DISEASE
ALG1	ENST00000262374.5	*605907	#608540 CONGENITAL DISORDER OF GLYCOSYLATION, TYPE Ik; CDG1K
AP3B1	ENST00000255194.6	*603401	#608233 HERMANSKY–PUDLAK SYNDROME 2; HPS2
ARSA	ENST00000216124.5	*607574	#250100. METACHROMATIC LEUKODYSTROPHY; MLD
ARSB	ENST00000264914.4	*611542	#253200 MUCOPOLYSACCHARIDOSIS TYPE VI; MPS6
ASAH1	ENST00000262097.6	*613468	#228000 FARBER LIPOGRANULOMATOSIS; FRBRL
BLOC1S3	ENST00000433642.2	*609762	#614077 HERMANSKY–PUDLAK SYNDROME 8; HPS8
BRAF	ENST00000288602.6	*164757	#613706 Noonan
CALCRL	ENST00000409998.1	*114190	New disease; Duncan *et al*. J.Exp.Med 2018 Vol.215 No.9
CBL	ENST00000264033.4	*165360	#613563 NOONAN SYNDROME-LIKE DISORDER WITH OR WITHOUT JUVENILE MYELOMONOCYTIC LEUKEMIA; NSLL
CCBE1	ENST00000439986.4	*612753	#235510 HENNEKAM LYMPHANGIECTASIA-LYMPHEDEMA SYNDROME 1; HKLLS1
CLN3	ENST00000568224.1	*607042	#204200 CEROID LIPOFUSCINOSIS, NEURONAL, 3; CLN3
CLN5	ENST00000377453.3	*608102	#256731 CEROID LIPOFUSCINOSIS, NEURONAL, 5; CLN5
CLN6	ENST00000249806.5	*606725	#601780 CEROID LIPOFUSCINOSIS, NEURONAL, 6; CLN6 #204300 CEROID LIPOFUSCINOSIS, NEURONAL, 4A, AUTOSOMAL RECESSIVE; CLN4A
CLN8	ENST00000331222.4	*607837	#600143 CEROID LIPOFUSCINOSIS, NEURONAL, 8; CLN8 #610003 CEROID LIPOFUSCINOSIS, NEURONAL, 8, NORTHERN EPILEPSY VARIANT
CTNS	ENST00000046640.3	*606272	#219800 CYSTINOSIS, NEPHROPATHIC; CTNS;
CTSA	ENST00000372484.3	*613111	#256540 GALACTOSIALIDOSIS; GSL
CTSD	ENST00000236671.2	*116840	#610127. CEROID LIPOFUSCINOSIS, NEURONAL, 10; CLN10
CTSK	ENST00000271651.3	*601105	#265800 PYCNODYSOSTOSIS
DHCR7	ENST00000355527.3	*602858	#270400 SMITH–LEMLI–OPITZ SYNDROME; SLOS
DTNBP1	ENST00000338950.5	*607145	#614076 HERMANSKY–PUDLAK SYNDROME 7; HPS7
EBP	ENST00000495186.1	*300205	#300960 MEND SYNDROME; MEND #302960 CHONDRODYSPLASIA PUNCTATA 2, X-LINKED DOMINANT; CDPX2

(Continues)

TABLE 1 (Continued)

Gen	Transcript	OMIM	DISEASE
EPHB4	ENST00000358173.3	*600011	#617300 LYMPHATIC MALFORMATION 7; LMPHM7
FAT4	ENST00000394329.3	*612411	#615546 VAN MALDERGEM SYNDROME 2; VMLDS2; #616006 HENNEKAM LYMPHANGIECTASIA–LYMPHEDEMA SYNDROME 2; HKLLS2
FLT4	ENST00000261937.6	*136352	#602089 HEMANGIOMA, CAPILLARY INFANTILE; #153100 LYMPHEDEMA, HEREDITARY, IA; LMPH1A
FOXC2	ENST00000320354.4	*602402	#153400 LYMPHEDEMA–DISTICHIASIS SYNDROME; LPHDST
FOXP3	ENST00000376207.4	*300292	#304790 IMMUNODYSREGULATION, POLYENDOCRINOPATHY, AND ENTEROPATHY, X-LINKED; IPEX
FUCA1	ENST00000374479.3	*612280	#230000 FUCOSIDOSIS
GAA	ENST00000302262.3	*606829	#232300 GLYCOGEN STORAGE DISEASE II; GSD2
GALC	ENST00000261304.2	*606890	#245200 KRABBE DISEASE
GALNS	ENST00000268695.5	*612222	#253000 MUCOPOLYSACCHARIDOSIS, TYPE IVA; MPS4A
GBA	ENST00000327247.5	*606463	#230800 GAUCHER DISEASE, TYPE I #230900 GAUCHER DISEASE, TYPE II #608013 GAUCHER DISEASE, PERINATAL LETHAL
GBE1	ENST00000429644.2	*607839	#232500 GLYCOGEN STORAGE DISEASE IV; GSD4;
GLA	ENST00000218516.3	*300644	#301500 FABRY DISEASE
GLB1	ENST00000307363.5	*611458	#230500 GM1-GANGLIOSIDOSIS, TYPE I; #230600 GM1-GANGLIOSIDOSIS, TYPE II; #230650 GM1-GANGLIOSIDOSIS, TYPE III; #253010 MUCOPOLYSACCHARIDOSIS, TYPE IVB; MPS4B
GM2A	ENST00000357164.3	*613109	#272750 GM2-GANGLIOSIDOSIS, AB VARIANT
GNPTAB	ENST00000299314.7	*607840	#252500 MUCOLIPIDOSIS II ALPHA/BETA; #252600 MUCOLIPIDOSIS III ALPHA/BETA
GNPTG	ENST00000204679.4	*607838	#252605 MUCOLIPIDOSIS III GAMMA
GNS	ENST00000258145.3	*607664	#252940 MUCOPOLYSACCHARIDOSIS, TYPE IIID; MPS3D
GUSB	ENST00000304895.4	*611499	#253220 MUCOPOLYSACCHARIDOSIS, TYPE VII; MPS7
HADHA	ENST00000380649.3	*600890	#609015 MITOCHONDRIAL TRIFUNCTIONAL PROTEIN DEFICIENCY; MTPD #609016 LONG-CHAIN 3-HYDROXYACYL-CoA DEHYDROGENASE DEFICIENCY
HBA1	ENST00000320868.5	*141800	#301040 ALPHA-THALASSEMIA/MENTAL RETARDATION SYNDROME, X-LINKED; ATRX
HBA2	ENST00000251595.6	*141850	#236750 HYDROPS FETALIS, NONIMMUNE; NIHF
HEXA	ENST00000566304.5	*606869	#272800 TAY–SACHS DISEASE
HEXB	ENST00000261416.11	*606873	#268800 SANDHOFF DISEASE
HFE	ENST00000357618.9	*613609	#235200 HEMOCHROMATOSIS, TYPE 1
HGSNAT	ENST00000379644.8	*610453	#252930 MPS IIIC; SANFILIPPO SYNDROME C; ACETYL-CoA:ALPHA-GLUCOSAMINIDE *N*-ACETYLTRANSFERASE DEFICIENCY
HPS1	ENST00000325103.6	*604982	#203300 HERMANSKY–PUDLAK SYNDROME 1; HPS1
HPS3	ENST00000296051.2	*606118	#614072 HERMANSKY–PUDLAK SYNDROME 3; HPS3
HPS4	ENST00000398145.2	*606682	#614073 HERMANSKY–PUDLAK SYNDROME 4; HPS4
HPS5	ENST00000396253.3	*607524	#614074 HERMANSKY–PUDLAK SYNDROME 5; HPS5
HPS6	ENST00000299238.5	*607522	#614075 HERMANSKY–PUDLAK SYNDROME 6; HPS6
HRAS	ENST00000417302.1	*190020	#218040 COSTELLO SYNDROME; CSTLO
HYAL1	ENST00000395144.6	*607071	#601492 MUCOPOLYSACCHARIDOSIS, TYPE IX; MPS9
IDS	ENST00000340855.10	*300823	#309900 MPS II; HUNTER SYNDROME; IDURONATE 2-SULFATASE DEFICIENCY; IDS DEFICIENCY; SULFOIDURONATE SULFATASE DEFICIENCY; SIDS DEFICIENCY

(Continues)

TABLE 1 (Continued)

Gen	Transcript	OMIM	DISEASE
IDUA	ENST00000247933.8	*252800	#607014 MPS1-H; HURLER SYNDROME
ITGA9	ENST00000264741.5	*603963	Ma G.C. *et al.* Prenat Diagn. 2008 Nov;28(11):1057–63. https://doi.org/10.1002/pd.2130.
KIF11	ENST00000260731.3	*148760	#152950 MICROCEPHALY WITH OR WITHOUT CHORIORETINOPATHY, LYMPHEDEMA, OR MENTAL RETARDATION; MCLMR
KLF1	ENST00000264834.4	*600599	#613673 ANEMIA, CONGENITAL DYSERYTHROPOIETIC, TYPE IV; CDAN4
KRAS	ENST00000311936.3	*190070	#609942 NOONAN SYNDROME 3; NS3
LAMP2	ENST00000434600.2	*309060	#300257 DANON DISEASE
LAMP3	ENST00000265598.3	*605883	#614075 HERMANSKY–PUDLAK SYNDROME 6; HPS6
LBR	ENST00000338179.6	*600024	#215140 REYNOLDS SYNDROME #613471; GREENBERG DYSPLASIA #169400 PELGER–HUET ANOMALY
LIPA	ENST00000336233.9	*613497	#278000 LYSOSOMAL ACID LIPASE DEFICIENCY
LMOD3	ENST00000420581.2	*616112	#616165 NEMALINE MYOPATHY 10; NEM10
LZTR1	ENST00000215739.8	*600574	#616564 NOONAN SYNDROME 10; NS10
MAN1B1	ENST00000371589.8	*604346	#614202 MENTAL RETARDATION, AUTOSOMAL RECESSIVE 15
MAN2B1	ENST00000456935.6	*609458	#248500 MANNOSIDOSIS, ALPHA B, LYSOSOMAL
MANBA	ENST00000226578.8	*609489	#248510 MANNOSIDOSIS, BETA A, LYSOSOMAL
MAP2K2	ENST00000262948.5	*601263	#115150 CARDIOFACIOCUTANEOUS SYNDROME 1; CFC1
MAP2K1	ENST00000307102.5	*176872	#615279 CARDIOFACIOCUTANEOUS SYNDROME 3; CFC3
MCOLN1	ENST00000264079.10	*605248	#252650 MUCOLIPIDOSIS IV
MFSD8	ENST00000296468.3	*611124	# 610,951. CEROID LIPOFUSCINOSIS, NEURONAL, 7; CLN7
NAGA	ENST00000396398.7	*104170	# 609,241 SCHINDLER DISEASE, TYPE I #609242 KANZAKI DISEASE
NAGLU	ENST00000225927.6	*252920	#609701 MPS IIIB; SANFILIPPO SYNDROME B; *N*-ACETYL-ALPHA-D-GLUCOSAMINIDASE DEFICIENCY; NAGLU DEFICIENCY
NEU1	ENST00000375631.4	*608272	#256550 NEURAMINIDASE DEFICIENCY
NF1	ENST00000358273.4	*613113	#162200 NEUROFIBROMATOSIS, TYPE I; NF1
NPC1	ENST00000269228.9	*607623	#257220 NIEMANN-PICK DISEASE, TYPE C1
NPC2	ENST00000555619.5	*601015	#607625 NIEMANN-PICK DISEASE, TYPE C2
NRAS	ENST00000369535.4	*164790	# 613,224 NOONAN SYNDROME 6; NS6
PEX1	ENST00000248633.8	*602136	#214100 PEROXISOME BIOGENESIS DISORDER 1A (ZELLWEGER) #234580 PEROXISOME BIOGENESIS DISORDER 1B #601539; HEIMLER SYNDROME 1
PEX10	ENST00000288774.7	*602859	#614870 PEROXISOME BIOGENESIS DISORDER 6A (ZELLWEGER) #614871 PEROXISOME BIOGENESIS DISORDER 6B
PEX11B	ENST00000369306.7	*603867	#614920 PEROXISOME BIOGENESIS DISORDER 14B
PEX12	ENST00000225873	*601758	#614859 PEROXISOME BIOGENESIS DISORDER 3A (ZELLWEGER) #266510 PEROXISOME BIOGENESIS DISORDER 3B
PEX13	ENST00000295030.5	*601789	#614883 PEROXISOME BIOGENESIS DISORDER 11A (ZELLWEGER) #614885 PEROXISOME BIOGENESIS DISORDER 11B
PEX14	ENST00000356607.8	*601791	#614887 PEROXISOME BIOGENESIS DISORDER 13A (ZELLWEGER)
PEX16	ENST00000241041.7	*603360	#614877 PEROXISOME BIOGENESIS DISORDER 8B #614876 PEROXISOME BIOGENESIS DISORDER 8A (ZELLWEGER)
PEX19	ENST00000368072.9	*600279	#614886 PEROXISOME BIOGENESIS DISORDER 12A (ZELLWEGER)
PEX2	ENST00000357039.8	*170993	#614867 PEROXISOME BIOGENESIS DISORDER 5B #614866 PEROXISOME BIOGENESIS DISORDER 5A (ZELLWEGER)
PEX26	ENST00000329627.11	*608666	#614872 PEROXISOME BIOGENESIS DISORDER 7A (ZELLWEGER) #614873 PEROXISOME BIOGENESIS DISORDER 7B

(Continues)

TABLE 1 (Continued)

Gen	Transcript	OMIM	DISEASE
PEX3	ENST00000367591.4	*603164	#614882 PEROXISOME BIOGENESIS DISORDER 10A (ZELLWEGER) #617370 PEROXISOME BIOGENESIS DISORDER 10B
PEX5	ENST00000412720.6	*600414	#616716 RHIZOMELIC CHONDRODYSPLASIA PUNCTATA, TYPE 5 #202370 PEROXISOME BIOGENESIS DISORDER 2B #214110 PEROXISOME BIOGENESIS DISORDER 2A (ZELLWEGER)
PEX6	ENST00000304611.12	*601498	#614863 PEROXISOME BIOGENESIS DISORDER 4B #614862 PEROXISOME BIOGENESIS DISORDER 4A (ZELLWEGER)
PEX7	ENST00000318471.4	*601757	#215100 RHIZOMELIC CHONDRODYSPLASIA PUNCTATA, TYPE 1; #614879 PEROXISOME BIOGENESIS DISORDER 9B
PIEZO1	ENST00000301015.9	*611184	#194380 DEHYDRATED HEREDITARY STOMATOCYTOSIS 1 WITH OR WITHOUT PSEUDOHYPERKALEMIA AND/OR PERINATAL EDEMA; DHS1 #616843 LYMPHEDEMA, HEREDITARY, III; LMPH3
PIK3CA	ENST00000263967.3	*171834	#602501 MEGALENCEPHALY-CAPILLARY MALFORMATION-POLYMICROGYRIA SYNDROME; MCAP
PMM2	ENST00000268261.4	*601785	#212065 CONGENITAL DISORDER OF GLYCOSYLATION, TYPE Ia; CDG1A
PPT1	ENST00000433473.3	*600722	#256730 CEROID LIPOFUSCINOSIS, NEURONAL, 1
PSAP	ENST00000394936.7	*176801	#610539 GAUCHER DISEASE, ATYPICAL, DUE TO SAPOSIN C DEFICIENCY #249900 METACHROMATIC LEUKODYSTROPHY DUE TO SAPOSIN B DEFICIENCY #611721 COMBINED SAPOSIN DEFICIENCY
PTPN11	ENST00000351677.2	*176876	#163950 NOONAN SYNDROME 1; NS1; # 151,100. LEOPARD SYNDROME 1; LPRD1
RAF1	ENST00000251849.4	*164760	#611553 NOONAN SYNDROME 5; NS5
RASA1	ENST00000456692.2	*139150	#608354. CAPILLARY MALFORMATION-ARTERIOVENOUS MALFORMATION; CMAVM # 608,355 PARKES WEBER SYNDROME; PKWS
RIT1	ENST00000368323.3	*609591	#615355 NOONAN SYNDROME 8; NS8
RPL15	ENST00000307839.5	*604174	#615550 DIAMOND-BLACKFAN ANEMIA 12; DBA12
RYR1	ENST00000359596.3	*180901	Lethal multiple pterygium syndrome; Kariminejad *et al*. BMC Musculoskeletal Disorders (2016) 17:109
SGSH	ENST00000326317.10	*605270	#252900 MPS IIIA; SANFILIPPO SYNDROME A; HEPARAN SULFATE SULFATASE DEFICIENCY; SULFAMIDASE DEFICIENCY
SHOC2	ENST00000369452.4	*602775	#607721 NOONAN SYNDROME-LIKE DISORDER WITH LOOSE ANAGEN HAIR 1; NSLH1
SLC17A5	ENST00000355773.5	*604322	#604369 SALLA DISEASE #269920 INFANTILE SIALIC ACID STORAGE DISEASE
SLC22A5	ENST00000435065.6	*603377	#212140 CARNITINE DEFICIENCY, SYSTEMIC PRIMARY
SMPD1	ENST00000342245.8	*607608	#257200 NIEMANN-PICK DISEASE, TYPE A #607616 NIEMANN-PICK DISEASE, TYPE B
SOS1	ENST00000426016.1	*182530	#610733 NOONAN SYNDROME 4; NS4
SOS2	ENST00000216373.5	*601247	#616559 NOONAN SYNDROME 9; NS9
SOX18	ENST00000340356.7	*601618	#607823 HYPOTRICHOSIS-LYMPHEDEMA-TELANGIECTASIA SYNDROME; HLTS #137940 HYPOTRICHOSIS-LYMPHEDEMA-TELANGIECTASIA-RENAL DEFECT SYNDROME; HLTRS
SPRED1	ENST00000299084.4	*609291	#611431 LEGIUS SYNDROME; LGSS
SUMF1	ENST00000272902.9	*607939	#272200 MULTIPLE SULFATASE DEFICIENCY
TALDO	ENST00000319006.3	*602063	#606003 TRANSALDOLASE DEFICIENCY
THSD1	ENST00000349258.4	*616821	#236750 HYDROPS FETALIS, NONIMMUNE; NIHF
TPP1	ENST00000299427.10	*607998	#204500 CEROID LIPOFUSCINOSIS, NEURONAL, 2
UROS	ENST00000368797.8	*606938	#263700 PORPHYRIA, CONGENITAL ERYTHROPOIETIC
VEGFC	ENST00000280193.2	*601528	#615907 LYMPHEDEMA, HEREDITARY, ID; LMPH1D

2 | CASE REPORT

This female premature infant was delivered via emergency cesarean at 30 + 1 weeks GA (weight 1,400 g (P50), first measured on day 3 of life, length 40 cm (P50), head circumference 28.5 cm (P58), as the result of rapidly developing NIHF (first diagnosed at 30 + 0 weeks GA) to a healthy mother with no consanguinity in the family history. In former prenatal screenings, there had been the suspicion of a congenital cardiac defect but no signs of increased nuchal translucency, polyhydramnios or short femur, otherwise typical of Noonan syndrome.

The Apgar score was 1/3/4, umbilical artery pH was 7.33. The patient was born with NIHF, hypovolemic shock, severe anemia (hemoglobin 7.7 g/dl), severe thrombocytopenia (8/nl), and disseminated intravascular coagulation. At immediate drainage of both pleural and the peritoneal cavities, bloody effusions were observed. After stabilization with fluid and catecholamine rescue, the patient was transferred to our NICU. Physical examination revealed muscular hypotonia and a distinct short and webbed neck. Unilateral infarction and bilateral intraventricular hemorrhage grade II was detected on ultrasound. Echocardiography confirmed a double–outlet right ventricle in combination with an atrial septum defect with left-right shunt. During the first few weeks the infant was mechanically ventilated and had bilateral chest tube drainage for chylothoraces. We excluded bacterial or viral infection, coagulation disorders and alloimmune, and familial thrombocytopenia, respectively. Genetic testing by the *hydrops panel* especially developed for NIHF detected a de novo gain of function mutation in exon 3 of the *PTPN11* gene (c.218C>T; (p.Thr73Ile)). A mutation was not detected in parental blood. Research of literature revealed only few cases of the same mutation – our case is the only one presenting as NIHF (Table 2).

3 | CLINICAL COURSE

The infant was mechanically ventilated until the day of life 22. Because of a hypertrophic cardiomyopathy, propranolol therapy was started. A persistent ductus arteriosus was stented to keep it open.

Due to recurrent pleural effusions chest tubes were placed repeatedly until the age of 197 days. The infant developed a (sub-) ileus. A laparoscopy revealed a giant Meckel's diverticulum, but no stenosis.

Since birth, the infant showed persistent severe thrombocytopenia requiring weekly platelet transfusions up to the present (Figure 1). So far no blasts that suggest a transient myeloproliferation syndrome or juvenile myelomonocytic leukemia (JMML) have been detected in peripheral blood smear. Bone marrow aspiration was declined by the parents as well as further therapy for example 6-mercaptopurine mentioned by Strullu et al. (2014). The monocyte population is currently 18% in the blood count, slightly progressive over the course, but has notably declined compared to a maximum of 37% at birth.

The infant was discharged on day 264 after birth without additional oxygen supply.

4 | CONCLUSION

Although a variety of prenatal presentations of Noonan syndrome and NIHF have been reported in literature, this is the first description of NIHF due to the mutation identified in our patient with the c.218C>T (p.Thr73Ile) variant.

By mapping out the genetic lesion that occurs in this patient, a hematological risk stratification in NS can be performed. The c.218C>T (p.Thr73Ile) is already described in the literature with comparable hematological neonatal processes but so far without hydrops (Kratz et al., 2005). Strullu

TABLE 2 Cases in literature with gain of function in exon 3 of the *PTPN11* gene (c.218C>T; Thr73Ile)

Author	Gestational age	Heart defect	Thrombocytopenia	NIHF	Outcome	Myeloproliferative disorder	Year
Christensen, Yaish, Leon, Sola-Visner, and Agrawal (2013)	38	None	Yes	None	Alive	None	2013
Nunes et al. (2012)	39	Yes	Yes	None	Alive	None	2012
Bufalino, Carrera, Carlos, and Coletta (2010)	n.d.	Yes	n.d.	None	Alive	n.d.	2010
Kratz et al. (2005)	n.d.	n.d.	n.d.	n.d.	n.d.	MPD (2), JMML none	2005
Kosaki, Suzuki, and Muroya (2002)	39	None	n.d.	None	Alive	n.d.	2002
Musante et al. (2003)	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2002
Tartaglia et al. (2002)	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2002
Our case	30 + 1	Yes	Yes	Yes	Alive	None	2018

Abbreviations: JMML, Juvenile Myelomonocytic Leukemia; MPD, Myeloproliferative Disorder; n.d., not denoted.

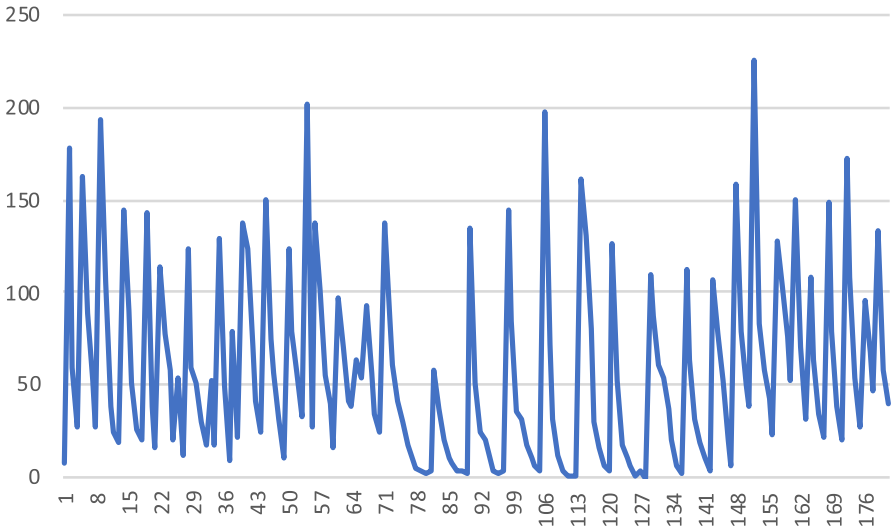

FIGURE 1 Platelets/nl (*y*-axis) and day of life (*x*-axis); peaks after transfusion

et al. published four comparable patients, ranging in age from birth to the 90th day of life. The follow-up time is given as 3.4 years. The c.218C>T (p.Thr73Ile) is thereby associated with solid tumors (e.g., neuroblastoma) and amegakaryocytosis (Strullu et al., 2014).

In the literature, a case reported by Shenoy et al. with myelodysplastic syndrome and transformation into AML with consecutive stem cell transplantation can also be found (Shenoy et al., 2019).

Patients reporting with this germline mutation partly have a heart defect; all show persistent severe thrombocytopenia and a few juvenile myelomonocytic leukemia. Patients with a c.218C>T (p.Thr73Ile) mutation are at higher risk of developing myeloproliferative diseases/JMML during the first 5 years of life (Ganapathi, Schafernak, & Rao, 2015). The clinical course in this early state is milder and more often associated with spontaneous remission than in later years of age (Strullu et al., 2014).

The mechanism by which thrombocytopenia develops in patients with Noonan Syndrome is not entirely understood (Zenker et al., 2004).

In patients with severe congenital hemorrhagic disorder, persistent thrombocytopenia and congenital heart defect, the medical history and a careful clinical examination can lead to the diagnosis of NS. RASopathies are probably overlooked in cases of early lethality or in patients hospitalized in neonatal or pediatric intensive care units (Jhang, 2016).

The diagnosis of our patient was rapidly confirmed by the *hydrops panel*.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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