

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

Mascha Schönfeld¹  | Mareike Selig² | Alexandra Russo³ | Christine Lindner⁴ |
Christoph Kampmann⁵ | Eva Mildenerberger¹ | Catharina Whybra¹ 

¹Neonatology, University Medical Center of the Johannes Gutenberg University, Mainz, Germany

²Institute of Human Genetics, University Medical Center of the Johannes Gutenberg University, Mainz, Germany

³Hematology, University Medical Center of the Johannes Gutenberg University, Mainz, Germany

⁴Department of Obstetrics and Gynecology, University Medical Center of the Johannes Gutenberg University, Mainz, Germany

⁵Pediatric Cardiology, Department of Pediatrics, University Medical Center of the Johannes Gutenberg University, Mainz, Germany

Correspondence

Catharina Whybra, Neonatology, University Medical Center of the Johannes Gutenberg University Mainz, Germany.
Email: Catharina.whybra@unimedizin-mainz.de

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.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2020 The Authors. *Molecular Genetics & Genomic Medicine* published by Wiley Periodicals, Inc.

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 (auto-inhibition; 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
<i>ALG1</i>	ENST00000262374.5	*605907	#608540 CONGENITAL DISORDER OF GLYCOSYLATION, TYPE Ik; CDG1K
<i>AP3B1</i>	ENST00000255194.6	*603401	#608233 HERMANSKY–PUDLAK SYNDROME 2; HPS2
<i>ARSA</i>	ENST00000216124.5	*607574	#250100. METACHROMATIC LEUKODYSTROPHY; MLD
<i>ARSB</i>	ENST00000264914.4	*611542	#253200 MUCOPOLYSACCHARIDOSIS TYPE VI; MPS6
<i>ASAHI</i>	ENST00000262097.6	*613468	#228000 FARBER LIPOGRANULOMATOSIS; FRBRL
<i>BLOC1S3</i>	ENST00000433642.2	*609762	#614077 HERMANSKY–PUDLAK SYNDROME 8; HPS8
<i>BRAF</i>	ENST00000288602.6	*164757	#613706 Noonan
<i>CALCRL</i>	ENST00000409998.1	*114190	New disease; Duncan <i>et al.</i> J.Exp.Med 2018 Vol.215 No.9
<i>CBL</i>	ENST00000264033.4	*165360	#613563 NOONAN SYNDROME-LIKE DISORDER WITH OR WITHOUT JUVENILE MYELOMONOCYTIC LEUKEMIA; NSLL
<i>CCBE1</i>	ENST00000439986.4	*612753	#235510 HENNEKAM LYMPHANGIECTASIA-LYPHEDEMA SYNDROME 1; HKLLS1
<i>CLN3</i>	ENST00000568224.1	*607042	#204200 CEROID LIPOFUSCINOSIS, NEURONAL, 3; CLN3
<i>CLN5</i>	ENST00000377453.3	*608102	#256731 CEROID LIPOFUSCINOSIS, NEURONAL, 5; CLN5
<i>CLN6</i>	ENST00000249806.5	*606725	#601780 CEROID LIPOFUSCINOSIS, NEURONAL, 6; CLN6 #204300 CEROID LIPOFUSCINOSIS, NEURONAL, 4A, AUTOSOMAL RECESSIVE; CLN4A
<i>CLN8</i>	ENST00000331222.4	*607837	#600143 CEROID LIPOFUSCINOSIS, NEURONAL, 8; CLN8 #610003 CEROID LIPOFUSCINOSIS, NEURONAL, 8, NORTHERN EPILEPSY VARIANT
<i>CTNS</i>	ENST0000046640.3	*606272	#219800 CYSTINOSIS, NEPHROPATHIC; CTNS;
<i>CTSA</i>	ENST00000372484.3	*613111	#256540 GALACTOSIALIDOSIS; GSL
<i>CTSD</i>	ENST00000236671.2	*116840	#610127. CEROID LIPOFUSCINOSIS, NEURONAL, 10; CLN10
<i>CTSK</i>	ENST00000271651.3	*601105	#265800 PYCNODYSTOSIS
<i>DHCR7</i>	ENST00000355527.3	*602858	#270400 SMITH–LEMLI–OPITZ SYNDROME; SLOS
<i>DTNBP1</i>	ENST00000338950.5	*607145	#614076 HERMANSKY–PUDLAK SYNDROME 7; HPS7
<i>EBP</i>	ENST00000495186.1	*300205	#300960 MEND SYNDROME; MEND #302960 CHONDRODYSPLASIA PUNCTATA 2, X-LINKED DOMINANT; CDPX2

(Continues)

TABLE 1 (Continued)

Gen	Transcript	OMIM	DISEASE
<i>EPHB4</i>	ENST00000358173.3	*600011	#617300 LYMPHATIC MALFORMATION 7; LMPHM7
<i>FAT4</i>	ENST00000394329.3	*612411	#615546 VAN MALDERGEM SYNDROME 2; VMLDS2; #616006 HENNEKAM LYMPHANGIECTASIA–LYMPHEDEMA SYNDROME 2; HKLLS2
<i>FLT4</i>	ENST00000261937.6	*136352	#602089 HEMANGIOMA, CAPILLARY INFANTILE; #153100 LYMPHEDEMA, HEREDITARY, IA; LMPH1A
<i>FOXC2</i>	ENST00000320354.4	*602402	#153400 LYMPHEDEMA–DISTICHIASIS SYNDROME; LPHDST
<i>FOXP3</i>	ENST00000376207.4	*300292	#304790 IMMUNODYSREGULATION, POLYENDOCRINOPATHY, AND ENTEROPATHY, X-LINKED; IPEX
<i>FUCA1</i>	ENST00000374479.3	*612280	#230000 FUCOSIDOSIS
<i>GAA</i>	ENST00000302262.3	*606829	#232300 GLYCOGEN STORAGE DISEASE II; GSD2
<i>GALC</i>	ENST00000261304.2	*606890	#245200 KRABBE DISEASE
<i>GALNS</i>	ENST00000268695.5	*612222	#253000 MUCOPOLYSACCHARIDOSIS, TYPE IVA; MPS4A
<i>GBA</i>	ENST00000327247.5	*606463	#230800 GAUCHER DISEASE, TYPE I #230900 GAUCHER DISEASE, TYPE II #608013 GAUCHER DISEASE, PERINATAL LETHAL
<i>GBE1</i>	ENST00000429644.2	*607839	#232500 GLYCOGEN STORAGE DISEASE IV; GSD4;
<i>GLA</i>	ENST00000218516.3	*300644	#301500 FABRY DISEASE
<i>GLB1</i>	ENST00000307363.5	*611458	#230500 GM1-GANGLIOSIDOSIS, TYPE I; #230600 GM1-GANGLIOSIDOSIS, TYPE II; #230650 GM1-GANGLIOSIDOSIS, TYPE III; #253010 MUCOPOLYSACCHARIDOSIS, TYPE IVB; MPS4B
<i>GM2A</i>	ENST00000357164.3	*613109	#272750 GM2-GANGLIOSIDOSIS, AB VARIANT
<i>GNPTAB</i>	ENST00000299314.7	*607840	#252500 MUCOLIPIDOSIS II ALPHA/BETA; #252600 MUCOLIPIDOSIS III ALPHA/BETA
<i>GNPTG</i>	ENST00000204679.4	*607838	#252605 MUCOLIPIDOSIS III GAMMA
<i>GNS</i>	ENST00000258145.3	*607664	#252940 MUCOPOLYSACCHARIDOSIS, TYPE IIID; MPS3D
<i>GUSB</i>	ENST00000304895.4	*611499	#253220 MUCOPOLYSACCHARIDOSIS, TYPE VII; MPS7
<i>HADHA</i>	ENST00000380649.3	*600890	#609015 MITOCHONDRIAL TRIFUNCTIONAL PROTEIN DEFICIENCY; MTPD #609016 LONG-CHAIN 3-HYDROXYACYL-CoA DEHYDROGENASE DEFICIENCY
<i>HBA1</i>	ENST00000320868.5	*141800	#301040 ALPHA-THALASSEMIA/MENTAL RETARDATION SYNDROME, X-LINKED; ATRX
<i>HBA2</i>	ENST00000251595.6	*141850	#236750 HYDROPS FETALIS, NONIMMUNE; NIHF
<i>HEXA</i>	ENST00000566304.5	*606869	#272800 TAY–SACHS DISEASE
<i>HEXB</i>	ENST00000261416.11	*606873	#268800 SANDHOFF DISEASE
<i>HFE</i>	ENST00000357618.9	*613609	#235200 HEMOCHROMATOSIS, TYPE 1
<i>HGSNAT</i>	ENST00000379644.8	*610453	#252930 MPS IIIC; SANFILIPPO SYNDROME C; ACETYL-CoA:ALPHA- GLUCOSAMINIDE N-ACETYLTRANSFERASE DEFICIENCY
<i>HPS1</i>	ENST00000325103.6	*604982	#203300 HERMANSKY–PUDLAK SYNDROME 1; HPS1
<i>HPS3</i>	ENST00000296051.2	*606118	#614072 HERMANSKY–PUDLAK SYNDROME 3; HPS3
<i>HPS4</i>	ENST00000398145.2	*606682	#614073 HERMANSKY–PUDLAK SYNDROME 4; HPS4
<i>HPS5</i>	ENST00000396253.3	*607524	#614074 HERMANSKY–PUDLAK SYNDROME 5; HPS5
<i>HPS6</i>	ENST00000299238.5	*607522	#614075 HERMANSKY–PUDLAK SYNDROME 6; HPS6
<i>HRAS</i>	ENST00000417302.1	*190020	#218040 COSTELLO SYNDROME; CSTLO
<i>HYAL1</i>	ENST00000395144.6	*607071	#601492 MUCOPOLYSACCHARIDOSIS, TYPE IX; MPS9
<i>IDS</i>	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
<i>IDUA</i>	ENST00000247933.8	*252800	#607014 MPS I-H; HURLER SYNDROME
<i>ITGA9</i>	ENST00000264741.5	*603963	Ma G.C. <i>et al.</i> Prenat Diagn. 2008 Nov;28(11):1057–63. https://doi.org/10.1002/pd.2130 .
<i>KIF11</i>	ENST00000260731.3	*148760	#152950 MICROCEPHALY WITH OR WITHOUT CHORIORETINOPATHY, LYMPHEDEMA, OR MENTAL RETARDATION; MCLMR
<i>KLF1</i>	ENST00000264834.4	*600599	#613673 ANEMIA, CONGENITAL DYSERYTHROPOIETIC, TYPE IV; CDAN4
<i>KRAS</i>	ENST00000311936.3	*190070	#609942 NOONAN SYNDROME 3; NS3
<i>LAMP2</i>	ENST00000434600.2	*309060	#300257 DANON DISEASE
<i>LAMP3</i>	ENST00000265598.3	*605883	#614075 HERMANSKY–PUDLAK SYNDROME 6; HPS6
<i>LBR</i>	ENST00000338179.6	*600024	#215140 REYNOLDS SYNDROME #613471; GREENBERG DYSPLASIA #169400 PELGER–HUET ANOMALY
<i>LIPA</i>	ENST00000336233.9	*613497	#278000 LYSOSOMAL ACID LIPASE DEFICIENCY
<i>LMOD3</i>	ENST00000420581.2	*616112	#616165 NEMALINE MYOPATHY 10; NEM10
<i>LZTR1</i>	ENST00000215739.8	*600574	#616564 NOONAN SYNDROME 10; NS10
<i>MAN1B1</i>	ENST00000371589.8	*604346	#614202 MENTAL RETARDATION, AUTOSOMAL RECESSIVE 15
<i>MAN2B1</i>	ENST00000456935.6	*609458	#248500 MANNOSIDOSIS, ALPHA B, LYSOSOMAL
<i>MANBA</i>	ENST00000226578.8	*609489	#248510 MANNOSIDOSIS, BETA A, LYSOSOMAL
<i>MAP2K2</i>	ENST00000262948.5	*601263	#115150 CARDIOFACIOCUTANEOUS SYNDROME 1; CFC1
<i>MAP2K1</i>	ENST00000307102.5	*176872	#615279 CARDIOFACIOCUTANEOUS SYNDROME 3; CFC3
<i>MCOLN1</i>	ENST00000264079.10	*605248	#252650 MUCOLIPIDOSIS IV
<i>MFSD8</i>	ENST00000296468.3	*611124	# 610,951. CEROID LIPOFUSCINOSIS, NEURONAL, 7; CLN7
<i>NAGA</i>	ENST00000396398.7	*104170	# 609,241 SCHINDLER DISEASE, TYPE I #609242 KANZAKI DISEASE
<i>NAGLU</i>	ENST00000225927.6	*252920	#609701 MPS IIIB; SANFILIPPO SYNDROME B; N-ACETYL-ALPHA-D-GLUCOSAMINIDASE DEFICIENCY; NAGLU DEFICIENCY
<i>NEU1</i>	ENST00000375631.4	*608272	#256550 NEURAMINIDASE DEFICIENCY
<i>NF1</i>	ENST00000358273.4	*613113	#162200 NEUROFIBROMATOSIS, TYPE I; NF1
<i>NPC1</i>	ENST00000269228.9	*607623	#257220 NIEMANN-PICK DISEASE, TYPE C1
<i>NPC2</i>	ENST00000555619.5	*601015	#607625 NIEMANN-PICK DISEASE, TYPE C2
<i>NRAS</i>	ENST00000369535.4	*164790	# 613,224 NOONAN SYNDROME 6; NS6
<i>PEX1</i>	ENST00000248633.8	*602136	#214100 PEROXISOME BIOGENESIS DISORDER 1A (ZELLWEGER) #234580 PEROXISOME BIOGENESIS DISORDER 1B #601539; HEIMLER SYNDROME 1
<i>PEX10</i>	ENST00000288774.7	*602859	#614870 PEROXISOME BIOGENESIS DISORDER 6A (ZELLWEGER) #614871 PEROXISOME BIOGENESIS DISORDER 6B
<i>PEX11B</i>	ENST00000369306.7	*603867	#614920 PEROXISOME BIOGENESIS DISORDER 14B
<i>PEX12</i>	ENST00000225873	*601758	#614859 PEROXISOME BIOGENESIS DISORDER 3A (ZELLWEGER) #266510 PEROXISOME BIOGENESIS DISORDER 3B
<i>PEX13</i>	ENST00000295030.5	*601789	#614883 PEROXISOME BIOGENESIS DISORDER 11A (ZELLWEGER) #614885 PEROXISOME BIOGENESIS DISORDER 11B
<i>PEX14</i>	ENST00000356607.8	*601791	#614887 PEROXISOME BIOGENESIS DISORDER 13A (ZELLWEGER)
<i>PEX16</i>	ENST00000241041.7	*603360	#614877 PEROXISOME BIOGENESIS DISORDER 8B #614876 PEROXISOME BIOGENESIS DISORDER 8A (ZELLWEGER)
<i>PEX19</i>	ENST00000368072.9	*600279	#614886 PEROXISOME BIOGENESIS DISORDER 12A (ZELLWEGER)
<i>PEX2</i>	ENST00000357039.8	*170993	#614867 PEROXISOME BIOGENESIS DISORDER 5B #614866 PEROXISOME BIOGENESIS DISORDER 5A (ZELLWEGER)
<i>PEX26</i>	ENST00000329627.11	*608666	#614872 PEROXISOME BIOGENESIS DISORDER 7A (ZELLWEGER) #614873 PEROXISOME BIOGENESIS DISORDER 7B

(Continues)

TABLE 1 (Continued)

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

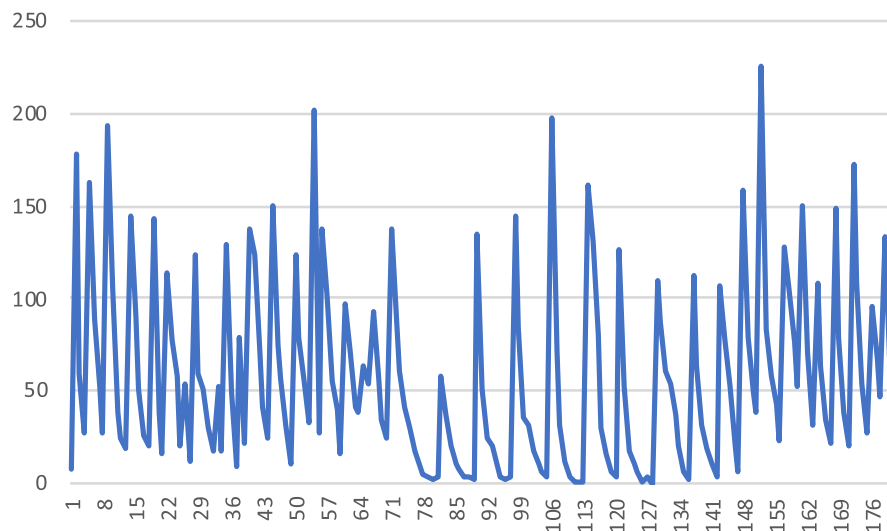
By mapping out the genetic lesion that occurs in this patient, a hematological risk stratification in NS can be performed. The c.218C>T (p.Thr73Ile) is already described in the literature with comparable hematological neonatal processes but so far without hydrops (Kratz et al., 2005). Strullu

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.

ORCID

Mascha Schönfeld  <https://orcid.org/0000-0003-1985-4818>

Catharina Whybra  <https://orcid.org/0000-0003-1679-9112>

REFERENCES

- Araki, T., Chan, G., Newbigging, S., Morikawa, L., Bronson, R. T., & Neel, B. G. (2009). Noonan syndrome cardiac defects are caused by PTPN11 acting in endocardium to enhance endocardial-mesenchymal transformation. *Proceedings of the National Academy of Sciences of the United States of America*, 106(12), 4736–4741. <https://doi.org/10.1073/pnas.0810053106>
- Bufalino, A., Carrera, M., Carlos, R., & Coletta, R. D. (2010). Giant cell lesions in Noonan syndrome: Case report and review of the literature. *Head and Neck Pathology*, 4(2), 174–177. <https://doi.org/10.1007/s12105-010-0178-2>
- Chan, R., & Feng, G.-S. (2007). *PTPN11* is the first identified proto-oncogene that encodes a tyrosine phosphatase. *Blood*, 109(3), 862–867.
- Chen, B., Bronson, R. T., Klamann, L. D., Hampton, T. G., Wang, J.-F., Green, P. J., ... Neel, B. G. (2000). Mice mutant for *Egfr* and *Shp2* have defective cardiac semilunar valvulogenesis. *Nature Genetics*, 24(3), 296–299. <https://doi.org/10.1038/73528>
- Christensen, R. D., Yaish, H. M., Leon, E. L., Sola-Visner, M. C., & Agrawal, P. B. (2013). A de novo T73I mutation in *PTPN11* in a neonate with severe and prolonged congenital thrombocytopenia and Noonan syndrome. *Neonatology*, 104(1), 1–5. <https://doi.org/10.1159/000346375>
- Ganapathi, K. A., Schafernak, K. T., Rao, V. K., & Calvo, K. R. (2015). Pediatric myelodysplastic/myeloproliferative neoplasms and related diseases. *Journal of Hematopathology*, 8, 159. <https://doi.org/10.1007/s12308-015-0250-7>
- Jhang, W. K., Choi, J.-H., Lee, B.-H., Kim, G.-H., & Yoo, H.-W. (2016). Cardiac manifestations and associations with gene mutations in patients diagnosed with RASopathies. *Pediatric Cardiology*, 37(8), 1539–1547. <https://doi.org/10.1007/s00246-016-1468-6>
- Keilhack, H., David, F. S., McGregor, M., Cantley, L. C., & Neel, B. G. (2005). Diverse biochemical properties of *Shp2* mutants. Implications for disease phenotypes. *Journal of Biological Chemistry*, 280(35), 30984–30993. <https://doi.org/10.1074/jbc.M504699200>
- Kosaki, K., Suzuki, T., Muroya, K., Hasegawa, T., Sato, S., Matsuo, N., ... Ogata, T. (2002). *PTPN11* (protein-tyrosine phosphatase, nonreceptor-type 11) mutations in seven Japanese patients with Noonan syndrome. *Journal of Clinical Endocrinology and Metabolism*, 87(8), 3529–3533. <https://doi.org/10.1210/jcem.87.8.8694>

- Kratz, C. P., Niemeyer, C. M., Castleberry, R. P., Cetin, M., Bergsträsser, E., Emanuel, P. D. ... Stary, J. (2005). The mutational spectrum of PTPN11 in juvenile myelomonocytic leukemia and Noonan syndrome/myeloproliferative disease. *Blood*, 106(6), 2183–2185. <https://doi.org/10.1182/blood-2005-02-0531>
- Kratz, C. P., Rapisuwon, S., Reed, H., Hasle, H., & Rosenberg, P. S. (2011). Cancer in Noonan, Costello, Cardiofaciocutaneous and LEOPARD syndromes. *The American Journal of Medical Genetics*, 157(2), 83–89. <https://doi.org/10.1002/ajmg.c.30300>
- Martinelli, S., Nardoza, A. P., Delle Vigne, S., Sabetta, G., Torreri, P., Bocchinfuso, G., ... Tartaglia, M. (2012). Counteracting effects operating on Src homology 2 domain-containing protein-tyrosine phosphatase 2 (SHP2) function drive selection of the recurrent Y62D and Y63C substitutions in Noonan syndrome. *Journal of Biological Chemistry*, 287(32), 27066–27077. <https://doi.org/10.1074/jbc.M112.350231>
- Musante, L., Kehl, H. G., Majewski, F., Meinecke, P., Schweiger, S., Gillissen-Kaesbach, G., ... Kalscheuer, V. M. (2003). Spectrum of mutations in PTPN11 and genotype–phenotype correlation in 96 patients with Noonan syndrome and five patients with cardio-facio-cutaneous syndrome. *European Journal of Human Genetics*, 11(2), 201–206. <https://doi.org/10.1038/sj.ejhg.5200935>
- Nunes, P., Aguilar, S., Prado, S. N., Palaré, M. J., Ferrão, A., & Morais, A. (2012). Severe congenital thrombocytopaenia – First clinical manifestation of Noonan syndrome. *BMJ Case Reports*, <https://doi.org/10.1136/bcr.10.2011.4940>
- Qu, C. K., Shi, Z. Q., Shen, R., Tsai, F. Y., Orkin, S. H., & Feng, G. S. (1997). A deletion mutation in the SH2-N domain of Shp-2 severely suppresses hematopoietic cell development. *Molecular and Cellular Biology*, 17(9), 5499–5507. <https://doi.org/10.1128/MCB.17.9.5499>
- Saxton, T. M., Henkemeyer, M., Gasca, S., Shen, R., Rossi, D. J., Shalaby, F., ... Pawson, T. (1997). Abnormal mesoderm patterning in mouse embryos mutant for the SH2 tyrosine phosphatase Shp-2. *The EMBO Journal*, 16(9), 2352–2364. <https://doi.org/10.1093/emboj/16.9.2352>
- Shenoy, R. D., Yeshvanth, S. K., Prasada, L. H., Shenoy, V., & Shetty, V. (2019). Myelodysplastic syndrome with multilineage dysplasia evolving to acute myeloid leukemia: Noonan syndrome with c.218C>T mutation in PTPN11 gene. *Pediatric Blood & Cancer*, 66(2), e27527. <https://doi.org/10.1002/pbc.27527>
- Strullu, M., Caye, A., Lachenaud, J., Cassinat, B., Gazal, S., Fenneteau, O., ... Cavé, H. (2014). Juvenile myelomonocytic leukaemia and Noonan syndrome. *Journal of Medical Genetics*, 51(10), 689–697. <https://doi.org/10.1136/jmedgenet-2014-102611>
- Tang, T. L., Freeman, R. M., O'Reilly, A. M., Neel, B. G., & Sokol, S. Y. (1995). The SH2-containing protein-tyrosine phosphatase SH-PTP2 is required upstream of MAP kinase for early xenopus development. *Cell*, 80(3), 473–483. [https://doi.org/10.1016/0092-8674\(95\)90498-0](https://doi.org/10.1016/0092-8674(95)90498-0)
- Tartaglia, M., Gelb, B. D., & Zenker, M. (2011). Noonan syndrome and clinically related disorders. *Best Practice & Research Clinical Endocrinology & Metabolism*, 25(1), 161–179. <https://doi.org/10.1016/j.beem.2010.09.002>
- Tartaglia, M., Kalidas, K., Shaw, A., Song, X., Musat, D. L., van der Burgt, I., ... Gelb, B. D. (2002). PTPN11 mutations in Noonan syndrome: Molecular spectrum, genotype-phenotype correlation, and phenotypic heterogeneity. *American Journal of Human Genetics*, 70(6), 1555–1563. <https://doi.org/10.1086/340847>
- Zenker, M., Buheitel, G., Rauch, R., Koenig, R., Bosse, K., Kress, W., ... Rauch, A. (2004). Genotype-phenotype correlations in Noonan syndrome. *Journal of Pediatrics*, 144(3), 368–374. <https://doi.org/10.1016/j.jpeds.2003.11.032>

How to cite this article: Schönfeld M, Selig M, Russo A, et al. Rapid detection by *hydrops panel* of Noonan syndrome with *PTPN11* mutation (p.Thr73Ile) and persistent thrombocytopenia. *Mol Genet Genomic Med*. 2020;00:e1174. <https://doi.org/10.1002/mgg3.1174>