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 leukemia cases, 5%–10% of all cases of childhood myelodysplastic syndrome, 7% of all cases of B-cell precursor acute lymphoblastic 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).

| 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 FABER LIPOGRANULOMATOSIS; FRBL                                |
| 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 |
| CCB1E| ENST00000439986.4   | *612753| #235510 HENNEKAM LYMPHANGIETASIA-LYMPHEDEMA SYNDROME 1; HKLS1            |
| CLN3 | ENST00000568224.1   | *607042| #204200 CERIOD LIPOFUSCINOSIS, NEURONAL, 3; CLN3                        |
| CLN5 | ENST00000377453.3   | *608102| #256731 CERIOD LIPOFUSCINOSIS, NEURONAL, 5; CLN5                        |
| CLN6 | ENST00000249806.5   | *606725| #601780 CERIOD LIPOFUSCINOSIS, NEURONAL, 6; CLN6                         |
|      |                     |        | #204300 CERIOD LIPOFUSCINOSIS, NEURONAL, 4A, AUTOSOMAL RECESSIVE; CLN4A   |
| CLN8 | ENST00000331222.4   | *607837| #600143 CERIOD LIPOFUSCINOSIS, NEURONAL, 8; CLN8                        |
|      |                     |        | #610003 CERIOD LIPOFUSCINOSIS, NEURONAL, 8, NORTHERN EPILEPSY VARIANT    |
| CTNS | ENST00000246640.3   | *606272| #219800 CYSTINOSIS, NPHIOPATHIC; CTNS;                                 |
| CTSA | ENST00000372484.3   | *613111| #256540 GALACTOSIALIDOSIS; GSL                                          |
| CTSD | ENST00000236671.2   | *116840| #610127. CERIOD LIPOFUSCINOSIS, NEURONAL, 10; CLN10                     |
| CTSK | ENST00000271651.3   | *601105| #265800 PYCNODYSOSTOSIS                                                 |
| DHCRI| ENST00000355527.3   | *602858| #270400 SMITH–LEMLI–OPITZ SYNDROME; SLOS                               |
| DTNBPI| 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)
| 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 LYMPHANGIETASIA–LYMPHEDEMA SYNDROME 2; HKLLS2 |
| FLT4 | ENST00000261937.6 *136352 | #602089 HEMANGIOMA, CAPILLARY INFANTILE; #153100 LYMPHEDEMA, HEREDITARY, IA; LMPH1A |
| FOXC2 | ENST00000320354.4 *602402 | #612222 HENNEKAM LYMPANGIECTASIA–LYMPHEDEMA SYNDROME 2; HKLLS2 |
| FOXP3 | ENST00000376207.4 *300292 | #612411 VAN MALDERGEM SYNDROME 2; VMLDS2; #615546 HENNEKAM LYMPANGIECTASIA–LYMPHEDEMA SYNDROME 2; HKLLS2 |
| FUCA1 | ENST00000374479.3 *606829 | #230200 GAUCHER DISEASE, TYPE I; #230200 GAUCHER DISEASE, TYPE II; #608013 GAUCHER DISEASE, PERINATAL LETHAL |
| GAA | ENST00000302262.3 *606829 | #232300 GLYCOGEN STORAGE DISEASE II; GSD2 |
| GALC | ENST00000261304.2 *606890 | #230000 FUCOSIDOSIS |
| GALNS | ENST00000394329.3 *606890 | #230000 FUCOSIDOSIS; #232300 GLYCOGEN STORAGE DISEASE II; GSD2 |
| GBA | ENST0000032037247.5 *606463 | #230500 GM1-GANGLIOSIDOSIS, TYPE I; #230500 GM1-GANGLIOSIDOSIS, TYPE II; #230500 GM1-GANGLIOSIDOSIS, TYPE III; #253010 MUCOPOLYSACCHARIDOSIS, TYPE IVB; MPS4B |
| GBE1 | ENST00000429644.2 *607839 | #232500 GLYCOGEN STORAGE DISEASE IV; GSD4; #232500 GLYCOGEN STORAGE DISEASE IV; GSD4; #232500 GLYCOGEN STORAGE DISEASE IV; GSD4; #232500 GLYCOGEN STORAGE DISEASE IV; GSD4; |
| GLA | ENST00000218516.3 *300644 | #301500 FABRY DISEASE |
| GLB1 | ENST00000307363.5 *61458 | #230500 GM1-GANGLIOSIDOSIS, TYPE I; #230600 GM1-GANGLIOSIDOSIS, TYPE II; #230650 GM1-GANGLIOSIDOSIS, TYPE III; #253010 MUCOPOLYSACCHARIDOSIS, TYPE IVB; MPS4B |
| GM2A | ENST000000357164.3 *613109 | #272750 GM2-GANGLIOSIDOSIS, AB VARIANT |
| GNPTAB | ENST00000299314.7 *607840 | #252500 MUCOLIPIDOSIS II ALPHA/BETA; #252600 MUCOLIPIDOSIS III ALPHA/BETA |
| GNPTG | ENST000002004659.4 *607388 | #252500 MUCOLIPIDOSIS III GAMMA |
| GNS | ENST000003025145.3 *607664 | #252940 MUCOPOLYSACCHARIDOSIS, TYPE IIIID; MPS3D |
| GUSB | ENST00000304895.4 *611499 | #253220 MUCOPOLYSACCHARIDOSIS, TYPE VII; MPS7 |
| HADHA | ENST00000380649.3 *600890 | #609015 LONG-CHAIN 3-HYDROXYACYL-CoA DEHYDROGENASE DEFICIENCY; MTPD |
| HBA1 | ENST000003028985.1 *614800 | #301040 ALPHA-THALASSEMA/MENTAL RETARDATION SYNDROME, X-LINKED; ATRX |
| HBA2 | ENST00000125195.6 *141850 | #236750 HYDROPS FETALIS, NONIMMUNE; NIHF |
| HEC | ENST00000566304.5 *606890 | #272800 TAY–SACHS DISEASE |
| HEXP | ENST00000261416.11 *60873 | #268800 SANDHOFF DISEASE |
| HFE | ENST00000357618.9 *613609 | #235200 HEMOCHROMATOSIS, TYPE I |
| HGSNAT | ENST00000379644.8 *610453 | #252930 MPS IIIC; SANFILIPPO SYNDROME C; ACETYLCOA:ALPHA-GLUCOSAMINE N-ACETYLTANSFERASE DEFICIENCY |
| HPS1 | ENST00000325103.6 *604982 | #203300 HERMANSKY–PUDLAK SYNDROME 1; HPS1 |
| HPS3 | ENST00000269051.2 *606118 | #614072 HERMANSKY–PUDLAK SYNDROME 3; HPS3 |
| HPS4 | ENST00000398214.5 *606682 | #614073 HERMANSKY–PUDLAK SYNDROME 4; HPS4 |
| HPS5 | ENST00000396253.3 *607524 | #614074 HERMANSKY–PUDLAK SYNDROME 5; HPS5 |
| HPS6 | ENST00000398214.5 *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 | #309990 MPS II; HUNTER SYNDROME; IDURONATE 2-SULFATASE DEFICIENCY; IDS DEFICIENCY; SULFOIDURONATE SULFATASE DEFICIENCY; SIDS DEFICIENCY |

(Continues)
| Gen   | Transcript   | OMIM  | DISEASE                                                                 |
|-------|---------------|-------|-------------------------------------------------------------------------|
| IDUA  | ENST0000024793.8 | *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             |
| KIT   | ENST0000031936.3 | *190070 | #609942 NOONAN SYNDROME 3; NS3                                           |
| LIPA  | ENST00000336233.9 | *613497 | #278000 LYSOSOMAL ACID LIPASE DEFICIENCY                                |
| LMOD3 | ENST00000420581.2 | *616112 | #616165 NOONAN SYNDROME 10; NEM10                                       |
| LZTR1 | ENST00000371939.8 | *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                                                |
| MFS6  | ENST00000296468.3 | *611124 | #169400 PELGER–HUET ANOMALY                                              |
| NAGA  | ENST00000396398.7 | *104170 | #609241 SCHINDLER DISEASE, TYPE I                                       |
| NAGLU | ENST00000225927.6 | *252920 | #609701 MPS IIIB; SANFILIPPO SYNDROME B; N-ACETYL-ALPHA-D-GLUCOSAMINIDASE DEFICIENCY; NAGLU DEFICIENCY |
| NEU1  | ENST00000375631.4 | *608272 | #256550 NEUROMUSCULAR DYSTROPHY                                          |
| NF1   | ENST00000358273.4 | *613113 | #162200 NEUROFIBROMATOSIS, TYPE I; NF1                                   |
| NPC1  | ENST00000269228.9 | *607623 | #257220 NIEMANN-PICK DISEASE, TYPE C                                     |
| NPC2  | ENST00000555619.5 | *601015 | #607625 NIEMANN-PICK DISEASE, TYPE C                                     |
| NRAS  | ENST00000365935.4 | *164790 | #613,224 NOONAN SYNDROME 6; NS6                                         |
| PEX1  | ENST00000248633.8 | *602136 | #214100 PEROXISOME BIOGENESIS DISORDER 1A (ZELLWEGER)                   |
| PEX10 | ENST00000288774.7 | *602859 | #614870 PEROXISOME BIOGENESIS DISORDER 6A (ZELLWEGER)                   |
| PEX11B| ENST00000369306.7 | *603867 | #614871 PEROXISOME BIOGENESIS DISORDER 6B                                 |
| PEX12 | ENST00000225873 | *601789 | #614883 PEROXISOME BIOGENESIS DISORDER 11A (ZELLWEGER)                  |
| PEX13 | ENST00000295030.5 | *601791 | #614885 PEROXISOME BIOGENESIS DISORDER 11B                                 |
| PEX14 | ENST00000356607.8 | *601791 | #614886 PEROXISOME BIOGENESIS DISORDER 12A (ZELLWEGER)                   |
| PEX16 | ENST00000241041.7 | *603360 | #614887 PEROXISOME BIOGENESIS DISORDER 12B (ZELLWEGER)                   |
| PEX19 | ENST00000368072.9 | *602797 | #614888 PEROXISOME BIOGENESIS DISORDER 13A (ZELLWEGER)                   |
| PEX2  | ENST00000357039.9 | *170993 | #614889 PEROXISOME BIOGENESIS DISORDER 13B (ZELLWEGER)                   |
| PEX26 | ENST00000329627.11 | *608666 | #614890 PEROXISOME BIOGENESIS DISORDER 14A (ZELLWEGER)                   |
| Gen | Transcript | OMIM   | DISEASE                                                                 |
|-----|------------|--------|-------------------------------------------------------------------------|
| PEX3 | ENST00000367591.4 | *603164 | #614882 PEROXISOME BIOGENESIS DISORDER 10A (ZELLWEGGER) #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 (ZELLWEGGER) |
| PEX6 | ENST00000304611.12 | *601498 | #614863 PEROXISOME BIOGENESIS DISORDER 4B #614862 PEROXISOME BIOGENESIS DISORDER 4A (ZELLWEGGER) |
| 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 | ENST00000272964.9 | *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 |
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. 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).

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.

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

| 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 | Alive | None | 2018 |

Abbreviations: JMML, Juvenile Myelomonocytic Leukemia; MPD, Myeloproliferative Disorder; n.d., not denoted.
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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FIGURE 1 Platelets/nl (y-axis) and day of life (x-axis); peaks after transfusion
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