

Clinical and biological features in *PIEZO1*-hereditary xerocytosis and Gardos channelopathy: a retrospective series of 126 patients

Véronique Picard,^{1,2} Corinne Guitton,³ Isabelle Thuret,⁴ Christian Rose,⁵ Laurence Bendelac,¹ Kaldoun Ghazal,⁶ Patricia Aguilar-Martinez,⁷ Catherine Badens,⁸ Claire Barro,⁹ Claire Bénéteau,¹⁰ Claire Berger,¹¹ Pascal Cathébras,¹² Eric Deconinck,¹³ Jacques Delaunay,¹⁴ Jean-Marc Durand,¹⁵ Nadia Firah,¹⁶ Frédéric Galactéros,¹⁷ Bertrand Godeau,¹⁸ Xavier Jaïs,¹⁹ Jean-Pierre de Jaureguiberry,²⁰ Camille Le Stradic,²¹ François Lifermann,²² Robert Maffre,¹ Gilles Morin,²³ Julien Perin,²⁴ Valérie Proulle,¹ Marc Ruivard,²⁵ Fabienne Toutain,²⁶ Agnès Lahary²⁷ and Loïc Garçon^{1,28}

¹Laboratoire d'Hématologie, Center Hospitalier Universitaire (CHU) Bicêtre, Assistance publique – Hôpitaux de Paris (AP-HP), Le Kremlin-Bicêtre; ²Université Paris Sud Paris Saclay, Faculté de Pharmacie, Chatenay Malabry; ³Service de Pédiatrie Générale, CHU Bicêtre et Filiale MCGRE, AP-HP, Le Kremlin-Bicêtre; ⁴Service de Pédiatrie, Hôpital La Timone, Aix Marseille University, Marseille; ⁵Service d'Oncologie et d'Hématologie, Hôpital Saint Vincent de Paul, Lille; ⁶Laboratoire de Biochimie, CHU Bicêtre, AP-HP, Le Kremlin-Bicêtre; ⁷Laboratoire d'Hématologie Biologique, CHU Saint-Eloi, Montpellier; ⁸Service de Génétique Médicale, Hôpital La Timone, Marseille; ⁹Laboratoire d'Hématologie Biologique, CHU Grenoble, Grenoble; ¹⁰Génétique Médicale, CHU Nantes, Nantes; ¹¹Service d'Hématologie-Oncologie Pédiatrique, CHU, Saint-Etienne; ¹²Service de Médecine Interne, CHU Saint-Etienne; ¹³Service d'Hématologie, CHU Jean Minioz, Besançon; ¹⁴Centre Catherine de Sienne, Nantes; ¹⁵Service de Médecine Interne, Hôpital La Timone, Marseille; ¹⁶Service de Pédiatrie, Centre Hospitalière (CH) Pau; ¹⁷Centre de Référence des Syndromes Drépanocytaires Majeurs, Hôpital Henri-Mondor, AP-HP, Créteil; ¹⁸Service de Médecine Interne, CHU Henri Mondor, AP-HP, Créteil; ¹⁹Service de Pneumologie, CHU Bicêtre, AP-HP, Le Kremlin-Bicêtre; ²⁰Service de Médecine Interne, Sainte Anne, Toulon; ²¹Service de Pédiatrie – Néonatalogie, CH de Bretagne Sud, Lorient; ²²Service de Médecine interne, CH Dax; ²³Génétique Médicale, CHU Amiens; ²⁴Laboratoire d'Hématologie, CHRU Nancy; ²⁵Service de Médecine Interne, CHU Estaing, Clermont-Ferrand; ²⁶Service d'Hémo-Oncologie Pédiatrique, CHU Sud, Rennes; ²⁷Laboratoire d'Hématologie, CHU Rouen and ²⁸Equipe d'Accueil 4666 HEMATIM Université de Picardie Jules Verne and Service d'Hématologie Biologique, CHU Amiens, France

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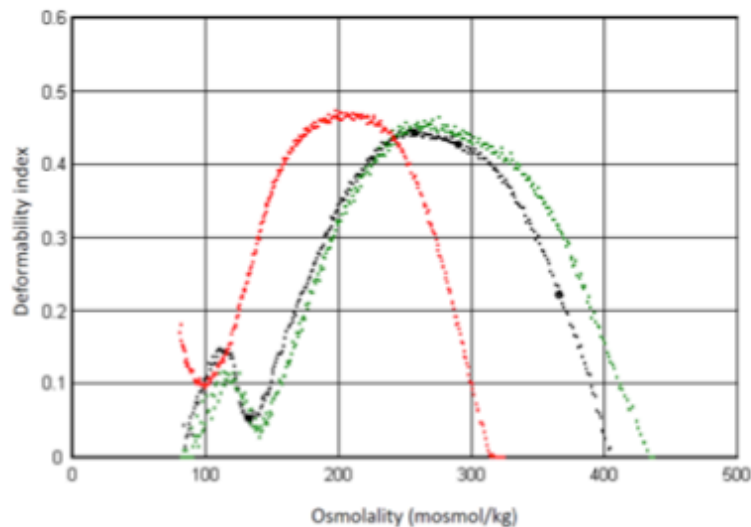
Correspondence: *LOÏC GARÇON* - Garcon.Loic@chu-amiens.fr

Supplemental data

Supplemental Methods: gene sequencing

The *PIEZO1* and *KCNN4* coding exons and exon-intron boundaries were sequenced as follows: PCR-amplification products obtained using reported primers for *PIEZO1*²¹ or designed primers for *KCNN4* (primer sequence available on request) and the GO TAQ G2 Flexi DNA Polymerase (Promega) were purified (Agencourt AMPure XP product, Beckman Coulter, Brea, CA), and sequenced using the same primers and ABI Big Dye Terminator sequencing kits (Applied Biosystems). After purification (Agencourt CleanSEQ Kit, Beckman Coulter), products were separated on a 3130xL DNA sequencer (Applied Biosystems). Data were analyzed by SeqScape 2.5 version software (Applied Biosystems)

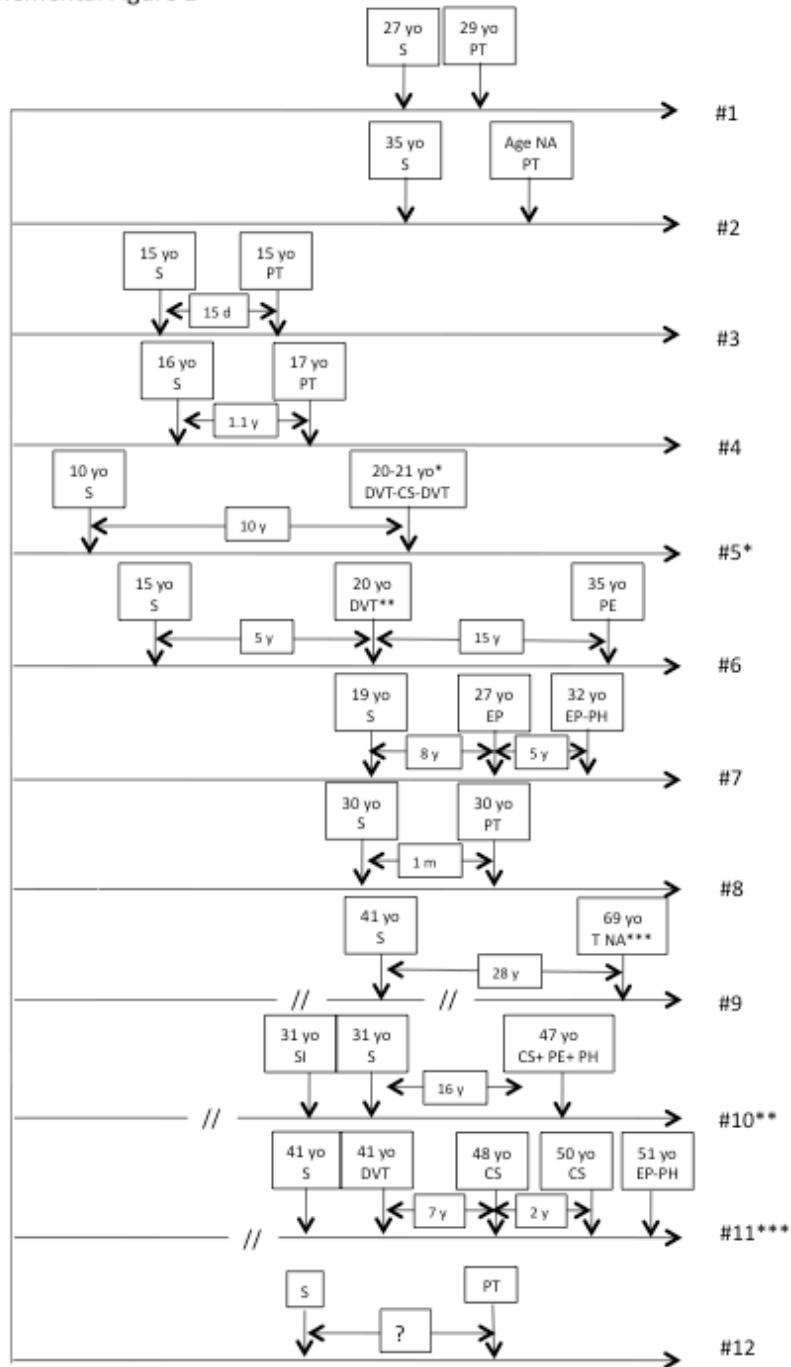
Supplemental Figures:



Supplemental figure 1

Ektacytometric profile is not significantly different from the control (black, O_{hypo} 131 mosmol/kg, DI_{max} 0,44, O_{hyper} 365 mosmol/kg) in *KCNN4*-HX (green, O_{hypo} 135 mosmol/kg, DI_{max} 0,46, O_{hyper} 380 mosmol/kg) and reflects red cell dehydration in *PIEZO1* HX (red, O_{hypo} 97 mosmol/kg, DI_{max} 0,47, O_{hyper} 281mosmol/kg).

Supplemental Figure S 2



Supplemental figure 2: Schematic representation of the thrombotic events in 12 splenectomised patients

#1: *PIEZO1* c.7479-84 dup 6³⁴

#2: *PIEZO1* c.7467C>T

#3: NA

#4: *PIEZO1* c.7367G>A

#5: NA

* Essential thrombocythemia at adult age, under cytoreductive therapy (Anagrelide)

#6: *PIEZO1* c.2152 G>A, 7463 G>A

#7: NA

#8: *PIEZO1* c.6479 C>T

#9: *PIEZO1* c.7479-84 dup 6

#10: NA

**AS trait²⁴

#11: *PIEZO1* c.4556A>C, c.5728 G>A

*** β -thalassemia trait + α -globin gene triplication +HX

#12: *PIEZO1* c.7479-84 dup 6. Age at splenectomy and delay between splenectomy and portal thrombosis were not available.

S: splenectomy; PT: portal thrombosis; DVT: deep venous thrombosis; PE: pulmonary embolism; CS: cerebral stroke; PH: post embolism pulmonary hypertension; SI: spleen infarct; NA: not available.

Supplemental Table 1: Main comorbidities/associated symptoms noticed in the medical reports

Symptoms/comorbidities	Number of patients
Asthma	3
Cramps	3
Osteoporosis	3
High blood pressure	3
Depression	2
Cryptorchidia	2
Bone pain	2
Hepatitis C	2
Ischemic cardiomyopathy	2
Diabetes Mellitus	2
Supraventricular tachycardia	2
Hypogonadism	2
Kidney hypoplasia	1
Essential thrombocytemia JAK2 ^{V617F} neg.	1
Myopathy	1
Parkinson disease	1
Dementia	1
Mitral prolapse	1
Syringomyelia	1
Crohn disease	1
Benign prostatic hypertrophy	1
Hypothyroidism	1
Pancreatitis	1
Hyperparathyroidism	1
Extramedullar hematopoiesis	1
Nephroblastoma	1
Migraine	1
Psoriasis	1
Pneumothorax	1
Little disease	1
Cutaneous porphyria	1
Antiphospholipid syndrom	1
Hepatocarcinoma	1

Supplemental Table 2: genetic data of the 126 patients/64 families

Subject	Family	Typical HX OGE	Gene	Gene variation #1	Gene variation #2	Protein variation#1	Protein variation#2	
1	1	I	yes	<i>PIEZO1</i>	c.7367G>A	p.Arg2456His		
2		mother	yes	<i>PIEZO1</i>	c.7367G>A	p.Arg2456His		
3	2	I	yes	<i>PIEZO1</i>	c.6058G>A	p.Ala2020Thr		
4		mother	yes	<i>PIEZO1</i>	c.6058G>A	p.Ala2020Thr		
5		grandfather	yes	<i>PIEZO1</i>	c.6058G>A	p.Ala2020Thr		
6	3	I	yes		nd	nd		
7	4	I	yes	<i>PIEZO1</i>	c.7367G>A	p.Arg2456His		
8		son	nd	<i>PIEZO1</i>	c.7367G>A	p.Arg2456His		
9		daughter	nd	<i>PIEZO1</i>	c.7367G>A	p.Arg2456His		
10	5	I	yes	<i>PIEZO1</i>	c.7479_84dup	p.Leu2495_Glu2496dup		
11		son	yes	<i>PIEZO1</i>	c.7479_84dup	p.Leu2495_Glu2496dup		
12	6	I	yes	<i>PIEZO1</i>	c.6380C>T	p.Thr2127Met		
13	7	I	yes	<i>PIEZO1</i>	c.7297G>C	c.7529C>T	p.Gly2433Arg	p.Pro2510Leu
14	8	I (βthal)	yes	<i>PIEZO1</i>	c.4556A>C	c.5728G>A	p.Gln1519Pro	p.Glu1910Lys
15	9	I	yes	<i>PIEZO1</i>	c.1815G>A		p.Met605Ile	
16	10	I	yes		nd	nd		
17		father	yes		nd	nd		
18	11	I	yes	<i>PIEZO1</i>	c.2152G>A	c.7463G>A	p.Gly718Ser	p.Arg2488Gln
19		mother	yes	<i>PIEZO1</i>	c.2153G>A	c.7463G>A	p.Gly718Ser	p.Arg2488Gln
20	12	I	yes	<i>PIEZO1</i>	c.7367G>A		p.Arg2456His	
21		son	yes	<i>PIEZO1</i>	c.7367G>A		p.Arg2456His	
22		son	yes	<i>PIEZO1</i>	c.7367G>A		p.Arg2456His	
23		daughter	yes	<i>PIEZO1</i>	c.7367G>A		p.Arg2456His	
24		daughter	yes	<i>PIEZO1</i>	c.7367G>A		p.Arg2456His	
25	13	I	yes	<i>PIEZO1</i>	c.6008C>A		p.Ala2003Asp	
26		brother	yes	<i>PIEZO1</i>	c.6008C>A		p.Ala2003Asp	
27		brother	nd		nd	nd		
28		daughter	nd		nd	nd		
29	14	I	yes	<i>PIEZO1</i>	c.2042T>C		p.Phe681Ser	
30	15	I	yes	<i>PIEZO1</i>	c.7479_84dup		p.Leu2495_Glu2496dup	
31		daughter	yes	<i>PIEZO1</i>	c.7479_84dup		p.Leu2495_Glu2496dup	
32		daughter	yes	<i>PIEZO1</i>	c.7479_84dup		p.Leu2495_Glu2496dup	
33		son	yes	<i>PIEZO1</i>	c.7479_84dup		p.Leu2495_Glu2496dup	
34		grandson	yes	<i>PIEZO1</i>	c.7479_84dup		p.Leu2495_Glu2496dup	
35		granddaughter	yes	<i>PIEZO1</i>	c.7479_84dup		p.Leu2495_Glu2496dup	
36		granddaughter	yes	<i>PIEZO1</i>	c.7479_84dup		p.Leu2495_Glu2496dup	
37	16	I	yes	<i>PIEZO1</i>	c.7479_84dup		p.Leu2495_Glu2496dup	
38		mother	yes	<i>PIEZO1</i>	c.7479_84dup		p.Leu2495_Glu2496dup	
39	17	I	yes	<i>PIEZO1</i>	c.6451T>C		p.Cys2151Arg	
40		mother	yes	<i>PIEZO1</i>	c.6451T>C		p.Cys2151Arg	

41		cousin	yes	PIEZO1	c.6451T>C		p.Cys2151Arg	
42	18	I	yes		nd		nd	
43		son	yes		nd		nd	
44	19	I*	nd		nd		nd	
45		sister	yes		nd		nd	
46	20	I (A/S)	yes		nd		nd	
47	21	I**	nd		nd		nd	
48		father	yes	PIEZO1	c.1792G>A		p.Val598Met	
49	22	I	yes	PIEZO1	c.7420G>A	c.7479_84dup	p.Val2474Met	p.Leu2495_Glu2496dup
50		daughter	yes	PIEZO1	c.7479_84 dup		p.Leu2495_Glu2496dup	
51		cousin	nd		nd		nd	
52	23	I	yes		nd		nd	
53	24	I	yes	PIEZO1	c.6007G>A	c.7471C>T	p.Ala2003Thr	p.Arg2491Tyr
54	25	I	yes	PIEZO1	c.7479_84 dup		p.Leu2495_Glu2496dup	
55		father	nd		nd		nd	
56	26	I	yes	PIEZO1	c.7391A>C		p.His2464Pro	
57		daughter	yes	PIEZO1	7391A>C		p.His2464Pro	
58	27	I	yes	PIEZO1	c.2005G>T		p.Asp669Tyr	
59		brother	yes	PIEZO1	c.2005G>T		p.Asp669Tyr	
60		brother	yes	PIEZO1	c.2005G>T		p.Asp669Tyr	
61	28	I	yes	PIEZO1	c.6601G>T		p.Val2201Phe	
62		brother	yes	PIEZO1	c.6601G>T		p.Val2201Phe	
63		father	nd		nd		nd	
64	29	I	yes	PIEZO1	c.7479_84dup		p.Leu2495_Glu2496dup	
65	30	I	yes		nd		nd	
66	31	I	yes	PIEZO1	c.7463G>A		p.Arg2488Gln	
67		brother	yes	PIEZO1	c.7463G>A		p.Arg2488Gln	
68		mother	yes	PIEZO1	c.7463G>A		p.Arg2488Gln	
69	32	I	yes	PIEZO1	c.1792G>C	c.7529C>T	p.Val598Leu	p.Pro2510Leu
70	33	I	yes	PIEZO1	c.7367G>A		p.Arg2456His	
71	34	I	yes	PIEZO1	c.2815C>A	c.7374C>G	p.Phe2458Leu	p.Leu939Met
72	35	I	yes		nd		nd	
73	36	I	yes	PIEZO1	c.7479_84dup		p.Leu2495_Glu2496dup	
74		daughter	yes	PIEZO1	c.7479_84 dup		p.Leu2495_Glu2496dup	
75	37	I	yes	PIEZO1	c.4073G>C		p.Arg1358Pro	
76	38	I	yes	PIEZO1	c.4069A>G		p.Ile1357Val	
77		son	yes	PIEZO1	c.4069A>G		p.Ile1357Val	
78	39	I	yes	PIEZO1	c.5981C>T		p.Ser1994Phe	
79	40	I	yes	PIEZO1	c.7367G>A		p.Arg2456His	
80		mother	yes	PIEZO1	c.7367G>A		p.Arg2456His	
81		cousin	yes	PIEZO1	c.7367G>A		p.Arg2456His	
82	41	I	yes	PIEZO1	c.6329G>A hnz		p.Arg2110Gln	
83	42	I	yes	PIEZO1	c.6016G>A		p.Val2006Ile	
84	43	I	yes	PIEZO1	c.1013C>A		p.Ser338Tyr	
85		son	nd		nd		nd	
86		son	yes	PIEZO1	c.1013C>A		p.Ser338Tyr	

87	44	I	yes	PIEZO1	c.7479_84 dup		p.Leu2495_Glu2496dup	
88	45	I	yes	PIEZO1	c.6479C>T		p.Pro2160Leu	
89		daughter	nd		nd		nd	
90	46	I	yes	PIEZO1	c.7467C>T		p.Glu2489Asp	
91		mother	yes		nd		nd	
92		son	yes	PIEZO1	c.7467C>T		p.Glu2489Asp	
93		daughter	yes	PIEZO1	c.7467C>T		p.Glu2489Asp	
94	47	I	yes	PIEZO1	c.2423G>A	c.2344G>A	p.Gly782Ser	p.Arg808Gln
98		brother **	nd		nd		nd	
99		brother *	nd		nd		nd	
95		mother	yes	PIEZO1	c.2423G>A	c.2344G>A	p.Gly782Ser	p.Arg808Gln
96		son	yes	PIEZO1	c.2423G>A	c.2344G>A	p.Gly782Ser	p.Arg808Gln
97		daughter	yes	PIEZO1	c.2423G>A	c.2344G>A	p.Gly782Ser	p.Arg808Gln
100	48	I	yes		nd		nd	
101	49	I	yes	PIEZO1	c.6922C>G		p.Gln2308Glu	
102	50	I	yes	PIEZO1	c.7479_84 dup		p.Leu2495_Glu2496dup	
103	51	I	yes	PIEZO1	c.7479_84 dup		p.Leu2495_Glu2496dup	
104	52	I	yes	PIEZO1	c.2005G>T		p.Asp669Tyr	
105	53	I	yes	PIEZO1	c.6574C>A		p.Leu2192Ile	
106	54	I	yes	PIEZO1	c.6019A>C		p.Met2007Leu	
107		mother	yes	PIEZO1	c.6019A>C		p.Met2007Leu	
108		aunt	yes	PIEZO1	c.6019A>C		p.Met2007Leu	
109	55	I	yes	PIEZO1	c.1813A>G	c.6829C>A	p.Met605Val	p.Leu2277Met
110		father	yes	PIEZO1	c.1813A>G	c.6829C>A	p.Met605Val	p.Leu2277Met
111		sister	yes	PIEZO1	c.1813A>G	c.6829C>A	p.Met605Val	p.Leu2277Met
112	56	I	yes	PIEZO1	c.7367G>A		p.Arg2456His	
113	57	I	yes	PIEZO1	c.5773C>T	c.7463 G>A	p.Arg1925Trp	p.Arg2488Gln
114	58	I	yes	PIEZO1	c.4071C>G		p.Ile1357Met	
115	59	I	no	KCNN4	c.1109_1119+17del		nd***	
116		brother	no	KCNN4	c.1109_1119+17del		p.Val369_Lys373del	
117		father	no	KCNN4	c.1109_1119+17del		p.Val369_Lys373del	
118	60	I	no	KCNN4	c.1055G>A		p.Arg352His	
119		sister	no	KCNN4	c.1055G>A		p.Arg352His	
120		son	no	KCNN4	c.1055G>A		p.Arg352His	
121	61	I	no	KCNN4	c.1055G>A		p.Arg352His	
122		daughter	no	KCNN4	c.1055G>A		p.Arg352His	
123	62	I	no	KCNN4	c.1055G>A		p.Arg352His	
124		son	no	KCNN4	c.1055G>A		p.Arg352His	
125	63	I	no	KCNN4	c.1055G>A		p.Arg352His	
126	64	I	no	KCNN4	c.1055G>A		p.Arg352His	

* deceased neonate

** deceased foetus

*** includes p.Val369_Lys373del.

NB : c.7479_84dup (p.Leu2495_Glu2496dup) is also reported as c.7473_7478dup (p.Glu2492_Leu2493dup)

Supplemental table 3 (4 parts) : Perinatal edema (PNE) in 19 patients/11 families

	Family 1/ Case 1	Family 1/ Case 2	Family 2/ Case 1	Family 3/ Case 1	Family 3/ Case 2
Mutation (ref§)	PIEZO1: p.Glu2489Asp (6,11,18)		PIEZO1: p.Gln2308Glu	PIEZO1: p.L2495_E2496dup	
Familial HX history at PE occurrence	Y (mother)	Y (mother)	N	Y	N (index case)
Age at diagnosis	Birth	Birth (brother of case 1)	Birth	Birth	19 yo (retrospectively)
PNE intensity (+, ++, +++)	+++	+++	+++	++	+++
PNE type	Hydrops-Hydramnios	Ascites	Hydrops	Ascites and pleural effusion	Hydrops
PNE diagnosis (trimester)	2 nd (22 WA)		2 nd		
In utero drain	Y*	Y	N	N	Y*
Neo/postnatal edema	Y	Y	Y	N	Y
Neo/postnatal drain	N	N			Y
ICU	Y**	Y*	Y*	N	NA
Outcome	F in 3 days	F	F	F	F in 1 month
In utero anemia	Y		Y		
In utero transfusion	Y (EST at 23 WA)		Y (24, 27 and 31 WA)		N
Term at birth (WA)	29+5	36+5	33+4	41+2	35
Birth weight (g)	1850	3200	2360	2850	NA
Neonatal jaundice	N	N	Y	Y	
Max indirect bili NN (µmol/L)				197 at D3)	
Exsanguino-transfusion	N	N	N	N	
Phototherapy	N	N	Y	Y	
Splenomegaly	N	N	N	N	
Postnatal anemia	Y	Y	Y	N	
Hemoglobin (g/L)	71	127	117	NA	
Neonatal Transfusion	Y**	N	Y**	N	

(ref §) : references for families previously reported

Family 1/ Case 1

* Ascites drain 70 mL, reconstitution of ascites and pleural effusion 2 days later; second ascites drain of 300 mL at birth

** Hyaline membrane disease, mechanical ventilation, parenteral nutrition

*** Hemoglobin level at Day 16: 71g/L

Family 1/ Case 2

* ICU 2 Mechanical ventilation (5 days)

Family 2/ Case 1

* Mechanical ventilation (6 days), parenteral nutrition (2 months)

** 4 in the first three months of life

Family 3/ Case 2

* Ascites drain 3 days

	Family 4/ Case 1	Family 4/ Case 2	Family 4/ Case 3	Family 4/ Case 4	Family 4/ Case 5
PIEZO1 mutation	p.Gly782Ser p.Arg808Gln (Case 2 not tested genetically) (6,11,18)				
Familial HX history at PNE occurrence	N	N	N	Y (father)	Y (father)
Age at diagnosis	34 yo (retrospectively) mother of case 3	In utero (retrospectively) case 1 first pregnancy	Birth (index case, son of case 1)	Birth (son of case 3)	Birth (son of case 3)
PNE intensity (+, ++, +++)	+++	+++	+++	++	+++
PNE type	Ascite, subcutaneous edema	Hydrops	Hydrops	Ascite, pleural effusion, subcutaneous edema	
PNE diagnosis (trimester)	NA	2 nd			
In utero puncture	N		N	N	Y*
Neo/postnatal edema	Y		Y	Y	Y
Neo/postnatal puncture	Y*		Y	N	N
ICU	ND		Y*	N	Y**
Outcome	F	Death at 27 WA*	F but persistence of discreet lymphedema at adult age	F in one month	F in two months
In utero anemia					
In utero transfusion	N		N	N	N
Term at birth (WA)		27	31+4	38+6	38+1***
Birth weight (g)			2500	3380	4400
Neonatal jaundice	NA		Y	Y	N
Unconjugated bili NN ($\mu\text{mol/L}$)			356	228	
Exsanguinotransfusion			Y	N	N
Phototherapy				Y	N
Splenomegaly	NA		Y	N	N
Postnatal anemia	NA		Y	N	N
Hemoglobin (g/L)			90		
Transfusion	NA		Y**	N	N

Family 4/ Case 2

* Monochorionic twins pregnancy, the other twin died at birth at 27 WA

Family 4/ Case 3

* Mechanical ventilation (2 months), parenteral nutrition (6 months)

** Six during the first 6 months

Family 4/ Case 5

* Amniotic liquid drain and ascites drain at 31 and 35.5 WA

** Non invasive respiratory assistance, parenteral nutrition (2 days)

	Family 5/ Case 1	Family 6/ Case 1	Family 7/ Case 1	Family 8/ Case 1
Mutation (aa)	PIEZO1: p.Val598Leu	PIEZO1: p.Val598Met	PIEZO1: p.Arg2456His	PIEZO1: p.L2495_E2496dup (42)
Familial HX history at PNE occurrence	N	N	N	Y (mother)
Age at diagnosis	First month	In utero	21yo (retrospectively)	Birth
PNE intensity	++	+++	++	+++
PE type	Ascites, pleural and pericardic effusion	Ascites, pleural effusion, pericardic effusion, subcutaneous edema	Ascites	Hydrops, persistant hygroma, severe ascites and jugular cyst at 30 WA
PNE diagnosis (trimester)				1 st *
In utero drain	N	N	N	Y**
Neo/postnatal edema	N		Y	Y***
Neo/postnatal drain			N	
ICU			N	Y****
Outcome	F	Medical termination at 28 WA	F	Death at D15
In utero anemia	Y*			N
In utero transfusion	Y		N	N
Term at birth (WA)	41			37+1
Birth weight (g)	3320			3750
Neonatal jaundice	N			Y
Max indirect bili NN (µmol/L)				316
exsanguino-transfusion	N			N
phototherapy	N			Y
Splenomegaly	N			Y
Postnatal anemia	Y		N	Y
Hemoglobin (g/L)	99 at birth, 71 at lowest during the first 2 months			67
Neonatal Transfusion	Y**		N	Y

Family 5/ Case 1

* Ultrasonographic signs of anemia

** Two transfusions during the first two months, EPO treatment during 7 months

Family 8/ Case 1

* Nuchal clarity at 17 WA; Amniocentesis : normal karyotype

** Ascites drain 620mL at 30WA then 650mL at 32 WA and 1000mL before caesarean; jugular cyst drain : 810mL at 32 WA then second drain before caesarean

*** Iterative Hygroma and ascites drains during the first days, no efficiency; last drain at day13 (Hygroma :160mL, ascite: 260mL)

**** Hyaline membrane disease prevention using steroids at 33SA1/2. Caesarean.

Mechanical ventilation at Day 2 ; pulmonary hypoplasia, APH, capillar leak syndrome with anasarque, hypoproteinemia and metabolic acidosis and hyponatremia, cytolysis, cholestasis, kidney failure

	Family 9/ Case 1	Family 10/ Case1	Family 10/ Case2	Family 11/ Case1	Family 11/ Case2
Mutation (aa)	NA	PIEZO1: p.Arg2456His (19)		PIEZO1: p.Arg2456His (19)	
Familial HX history at PNE occurrence	N	N	N (diagnosis on mother during pregnancy)	N	N
Age at diagnosis	Birth	3y (retrospectively)	Birth (brother of case 1)	2,5yo (retrospectively)	0,4 Brother of c.1
PNE intensity (+, ++, +++)	+	+	+++	NA	NA
PNE type	Transient ascites	Transient ascites	Ascites, pleural effusion, hydramnios	Ascites	Hydrops
PNE diagnosis (trimester)	NA	NA	1 ST*	NA	NA
In utero drain	N	N	N	NA	NA
Neo/postnatal edema	N	N	Y	NA	NA
Neo/postnatal drain			Y**	NA	NA
ICU	N	N	Y	NA	NA
Outcome	F	F	F	F	F
In utero anemia	N	N	N		
In utero transfusion	N	N	N	N	N
Term at birth (WA)			33+1***		
Birth weight (g)	3280	3300			
Neonatal jaundice	Y	N			
Max bili libre NN (µmol/L)	NA				
Exsanguino-transfusion	N				
Phototherapy					
Splenomegaly	N				
Postnatal anemia	N	N	N		
Hemoglobin (g/L)					
Neonatal Transfusion	N	N	N		

Family 10/ Case2

* First US: nuchal clarity 2mm; 2nd US: ascites + bilateral pleural effusion; 3rd US: ascites + hydramnios

** Ascites drain

*** Maternal liver cytolysis at 31 WA; caesarean; newborn: normal karyotype