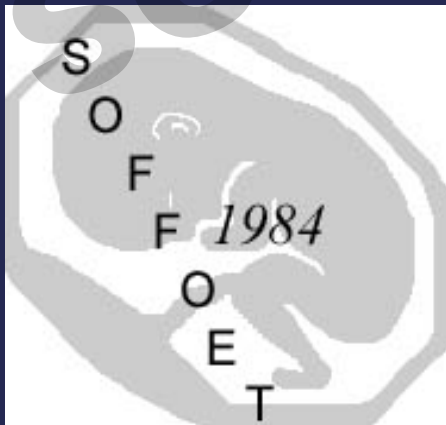




A propos d'un syndrome malformatif foetal

C.Quélin, P.Loget, G.Lebouar, C.Rozel,
S.Le Lez Soquet, C.Dubourg



Contexte

- G1P0
- Échographie T1 : suspicion d'anomalie de fosse postérieure
- Échographie de référence à **12+5 SA**
 - Nuque mesurée à 2 mm
 - Aspect cérébral
 - Supra-tentoriel :
 - Ligne médiane en place
 - Infra-tentoriel :
 - Fosse postérieure occupée par une image anéchogène de 13 x 7 mm
 - Image compatible avec un cervelet de 8mm
 - En coupe sagittale : grande citerne et V4 semblant communiquer



CN à 2mm



Ligne médiane en place



Fosse postérieure : image anéchogène de 13 x 7 mm



Fosse postérieure : grande citerne et V4 semblent communiquer



Fosse postérieure : image anéchogène de 13 x 7mm et probable cerebelle de 8mm

2ème échographie de référence : 15+3 SA

- Profil et face : RAS
- Reins vus, **dilatation pyélique bilatérale**
- Etage cérébral, en infra-tentoriel :
 - Persistance de **l'image kystique** mesurant 14 x 7mm dans le plan axial et 8mm de hauteur.
 - **Ascension de la tente du cervelet** et refoulement vers le haut des structures cérébelleuses.
 - Structures cérébelleuses horizontalisées et V4 ouvert sur le kyste.



Profil semblant normal



Dilatation pyélique bilatérale





Fosse postérieure : persistance de image kystique



Image kystique avec ascension tente cerevelet



Image kystique avec ascension tente cerevelet



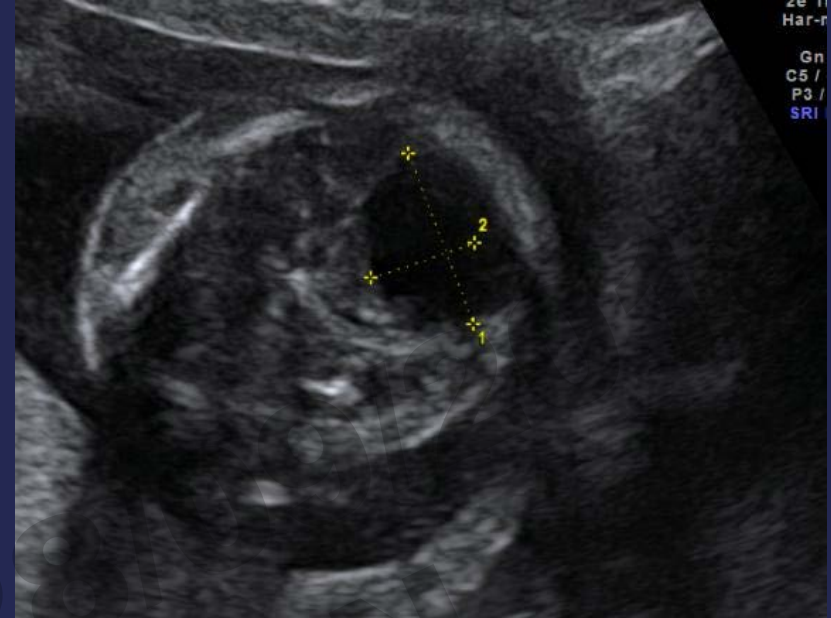
Structures cérébelleuses horizontalisées
V4 ouvert sur le kyste

3ème échographie à 17+3 SA

- Supra-tentoriel : RAS
- Sous-tentoriel :
 - **Persistance du kyste** mesuré à 19 x 11mm dans le plan axial, refoulant le cervelet vers le haut et le tronc cérébral vers l'avant.
 - Hémisphères cérébelleux d'aspect normal et **vermis refoulé vers le haut** mais analyse limitée
- Profil normal, bouche bien dessinée, cristallins vus
- 2 reins en place :
 - **Franche dilatation pyélique et calicielle** et un parenchyme refoulé et hétérogène
 - Reins mesurés à 21,7 et 21,8mm, absence de kyste.
- **Vessie de grande taille** :
 - Récessus sous-vésical bien visible, sans aucune vidange pendant examen



Hémisphères cérébelleux d'aspect normal



Infra-tentorial : persistance du kyste 19 x 11mm, refoulant cervelet vers le haut



Profil d'aspect habituel



Sexe masculin



Vessie de grande taille, pas de vidange pendant examen

Récessus sous-vésical



Reins: franche dilatation pyélo-calicielle, parenchyme refoulé, hyperéchogène

IMG à 18 SA + 4 jours



269 gr (N à 18 - 19 SA). VT = 24.5 cm ; VC = 18 cm ; PC = 16.5 cm ; BIP = 4.6 cm et pieds = 2.7 cm.

→ en accord avec **18-20 SA.**



Syndrome dysmorphique

OBI en rotation postérieure avec hélix peu développés

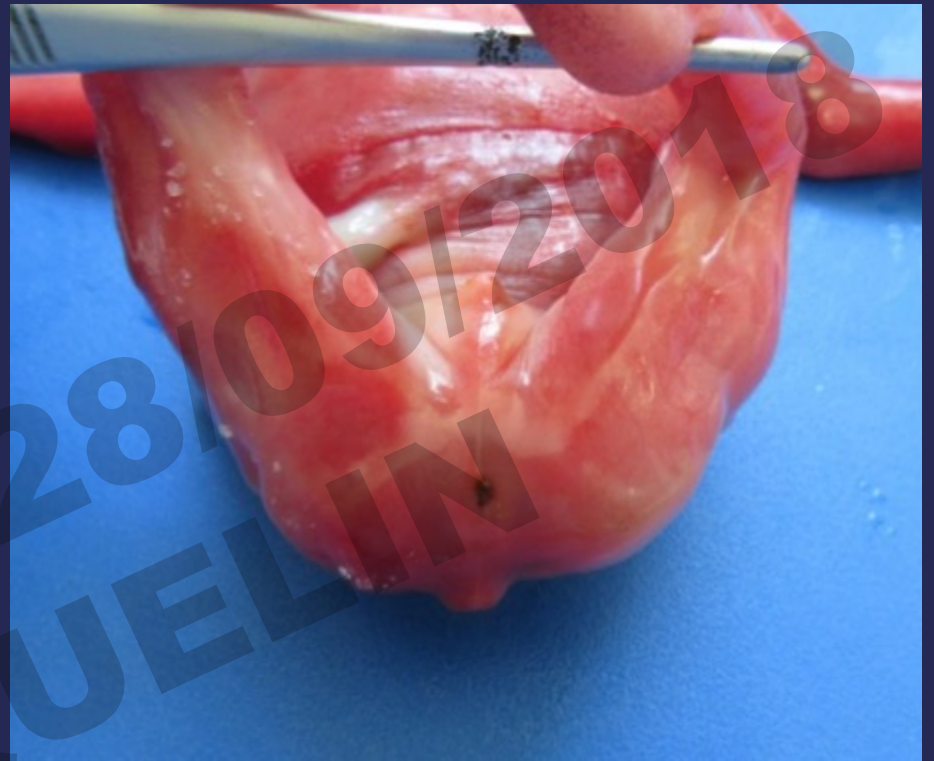
Franc hypertélorisme (DICI 1.9 / FP 0.9)

Ensellure nasale très peu marquée et pointe du nez large

Bouche large avec lèvre inférieure éversée

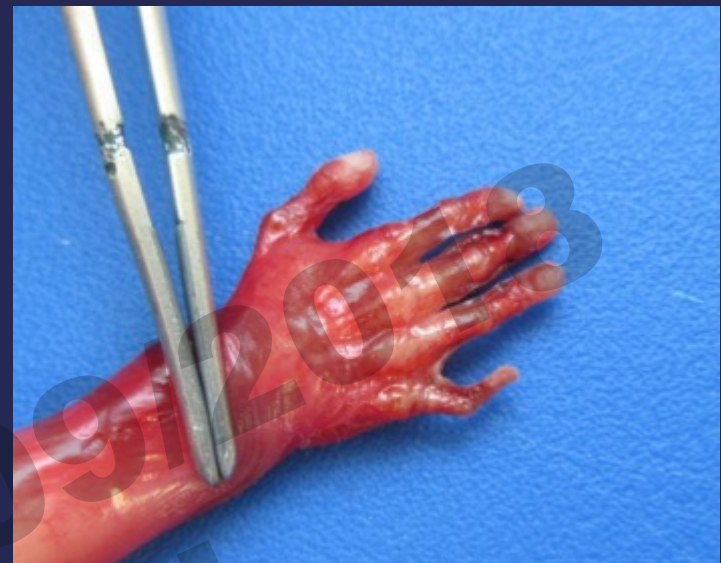
Net micro-rétrognatisme

Glossoptose sans fente palatine



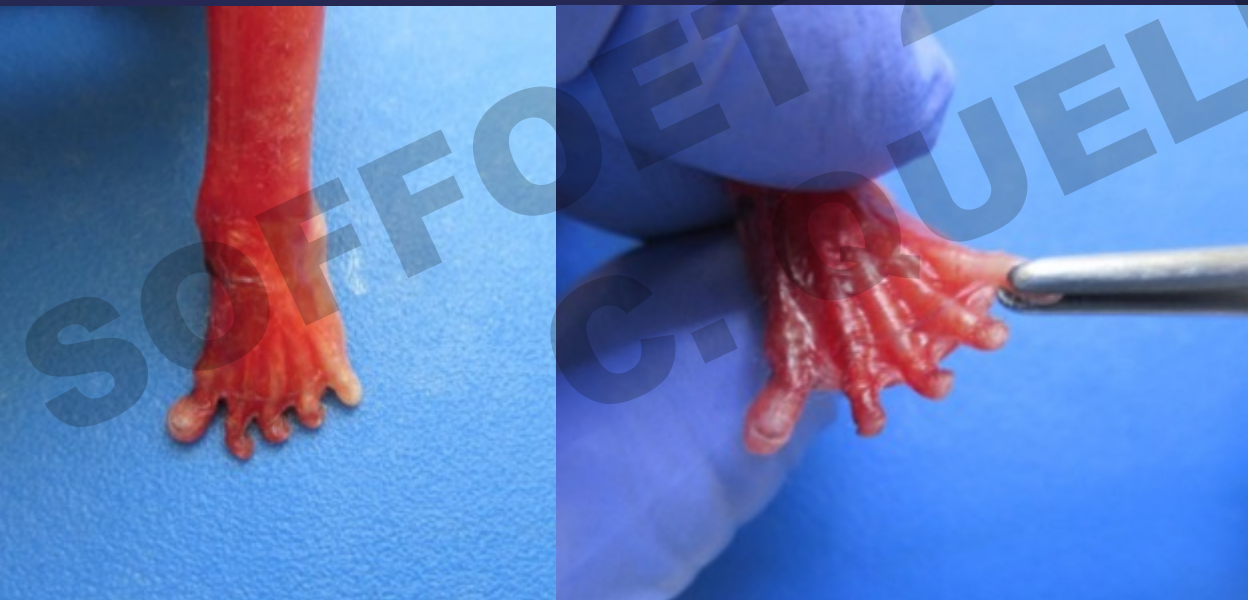
Pénis court (4 mm pour une N à 19 SA de 6 à 13 mm).

Saillie coccygienne.



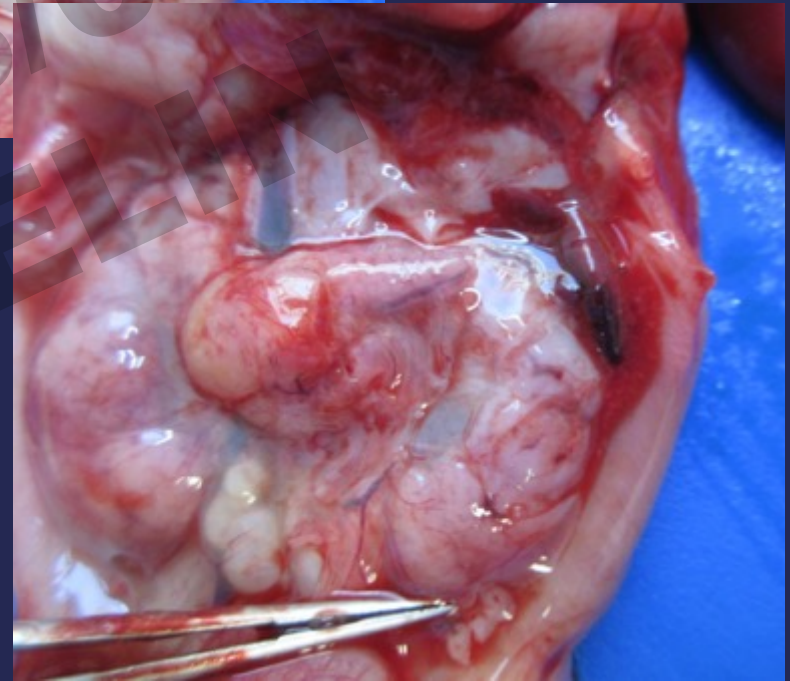
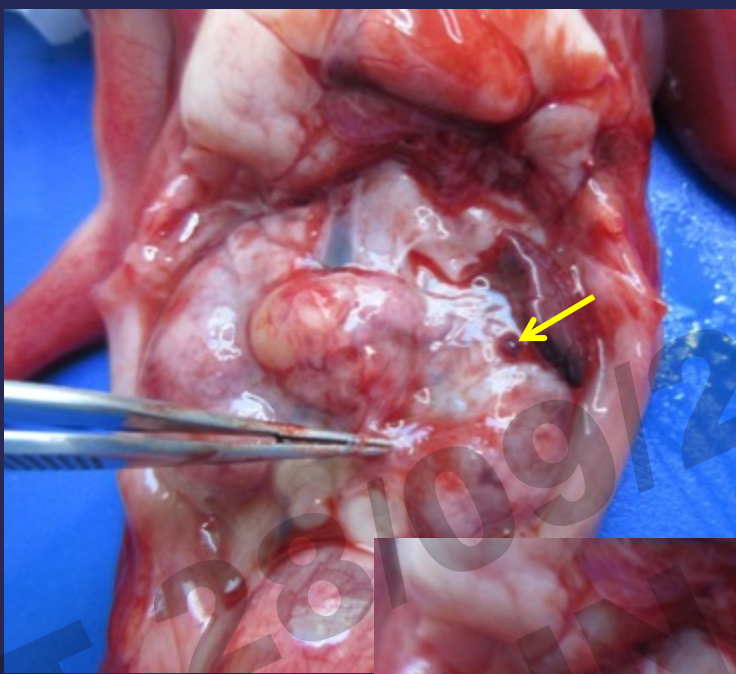
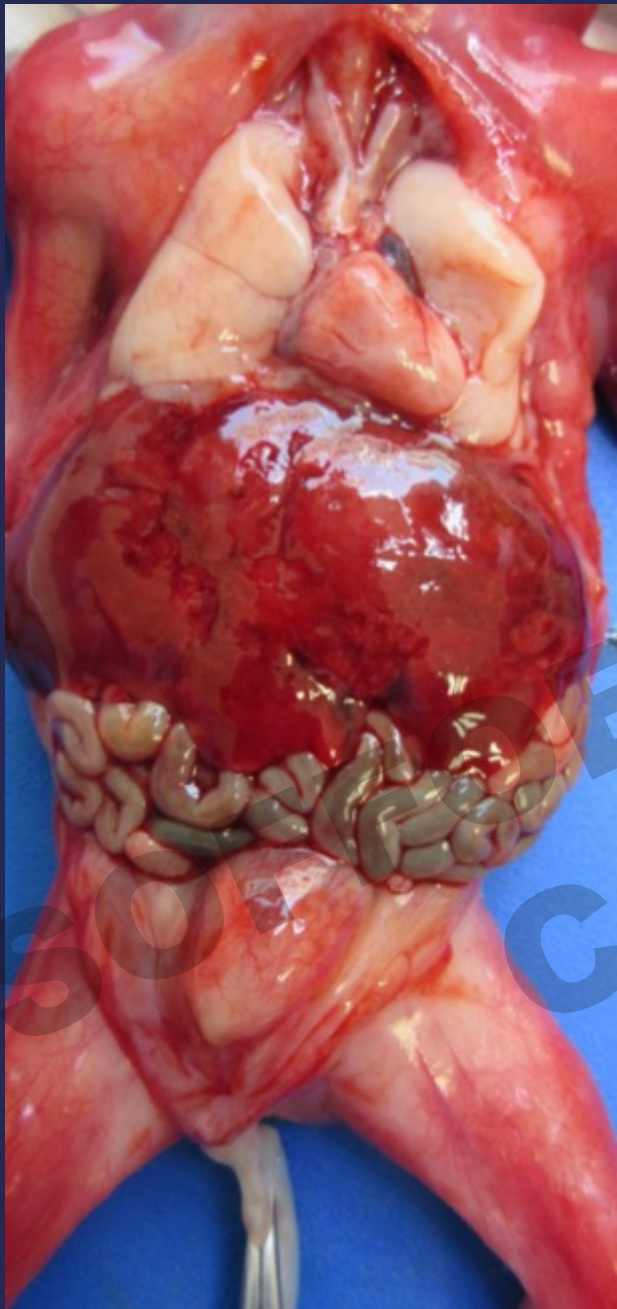
Aspect « **spatulé** » de tous les doigts (phalanges distales élargies)

Clinodactylie du Vème doigt droit.



2 pieds sont malposés, en équins.

Orteils courts, en particulier l'hallux avec syndactylie membraneuse généralisée.

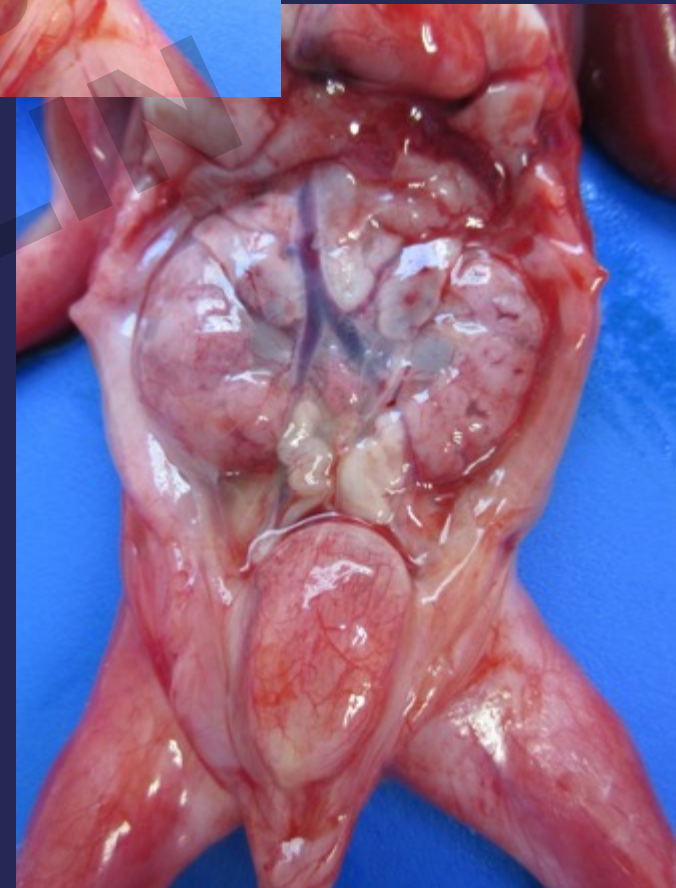
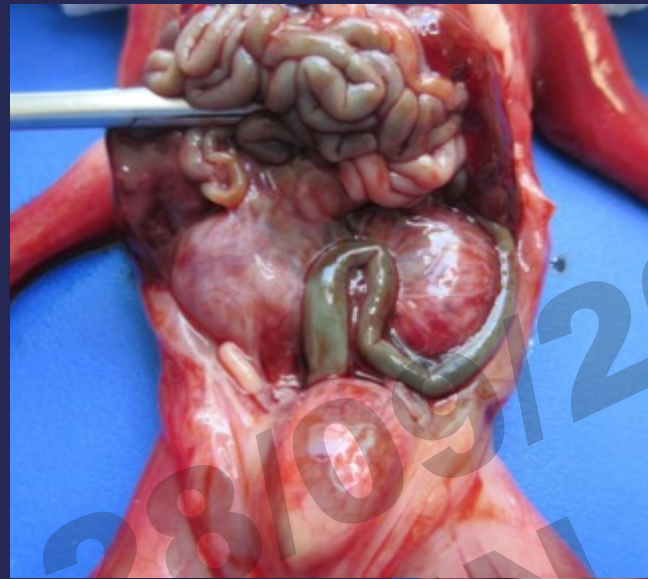
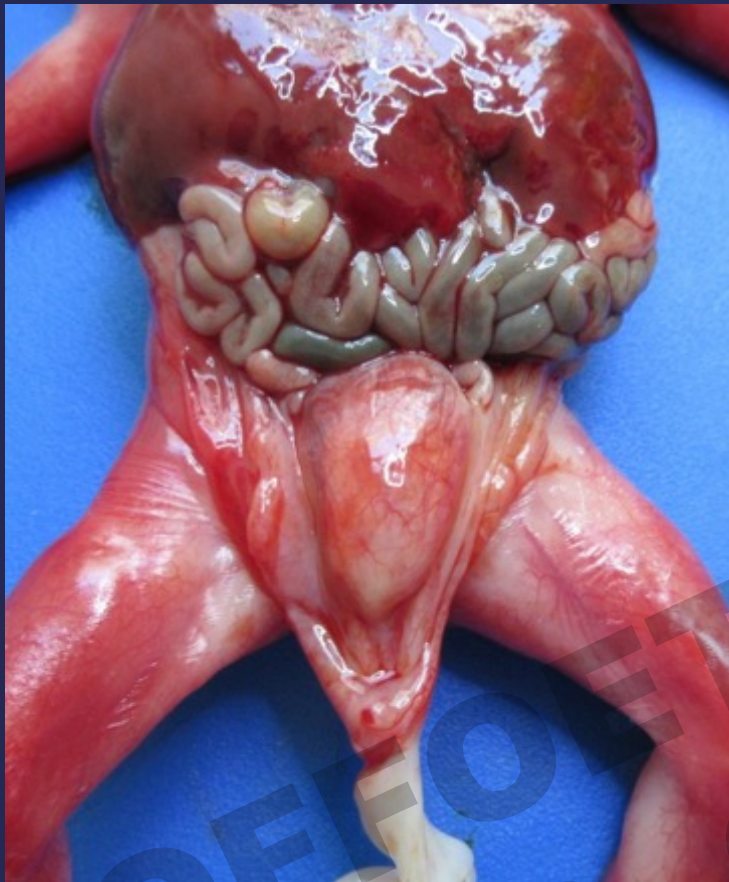


Petite rate surnuméraire.
Queue du pancréas un peu courte (Poids N).



Pas de cardiopathie

Septum membraneux très visible mais sans CIV ni équivalent de CAV.



Vessie de taille augmentée.

Gros reins (5.6 gr pour une N de 2.7 gr).

Uretères tortueux et dilatés.

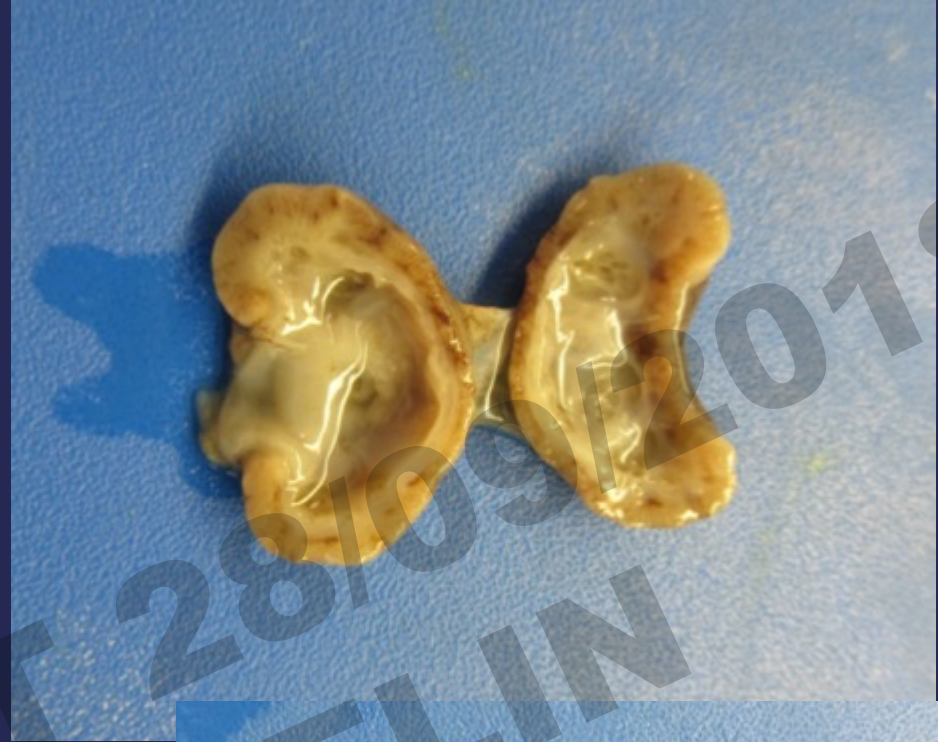


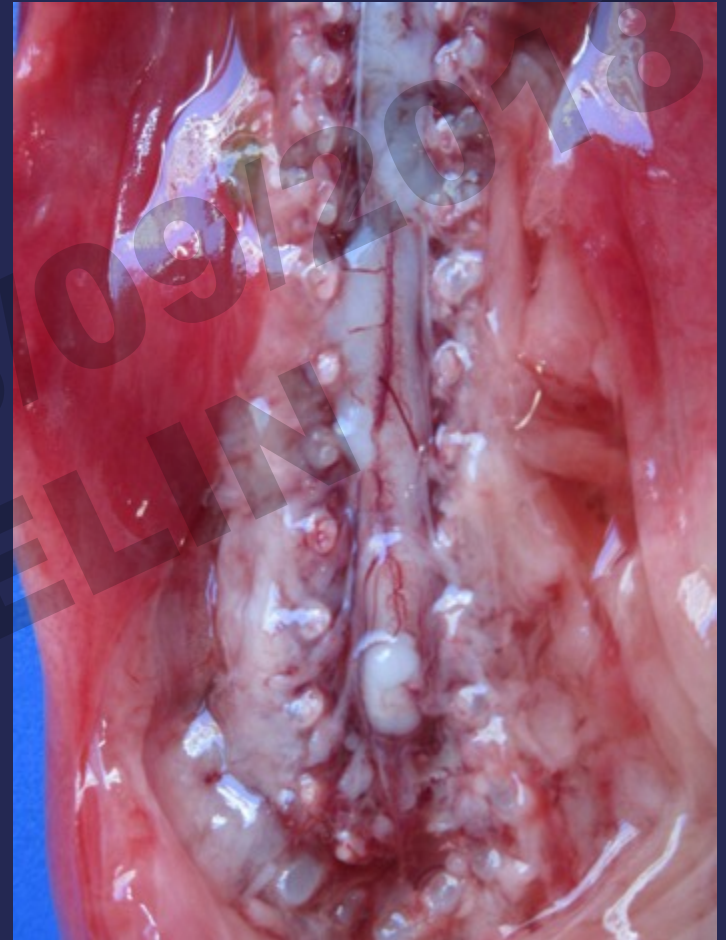
SCIENCE 281021 2018
QUELIN



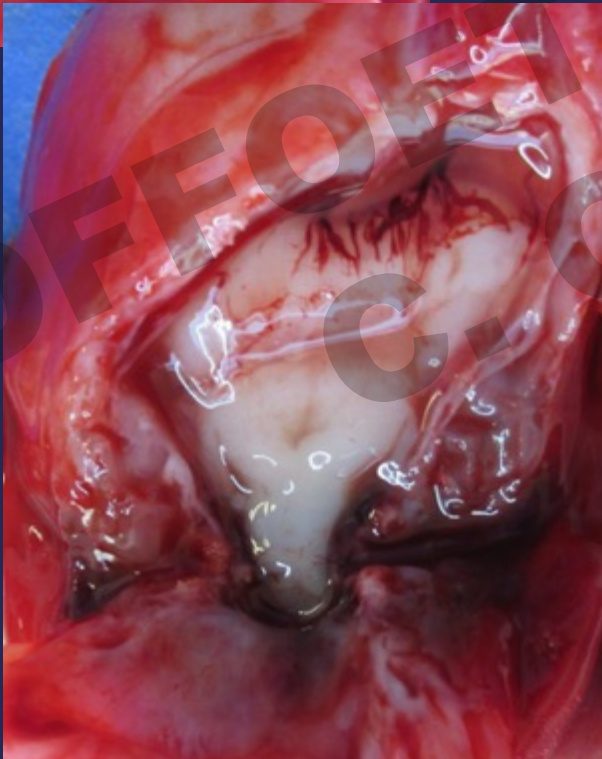
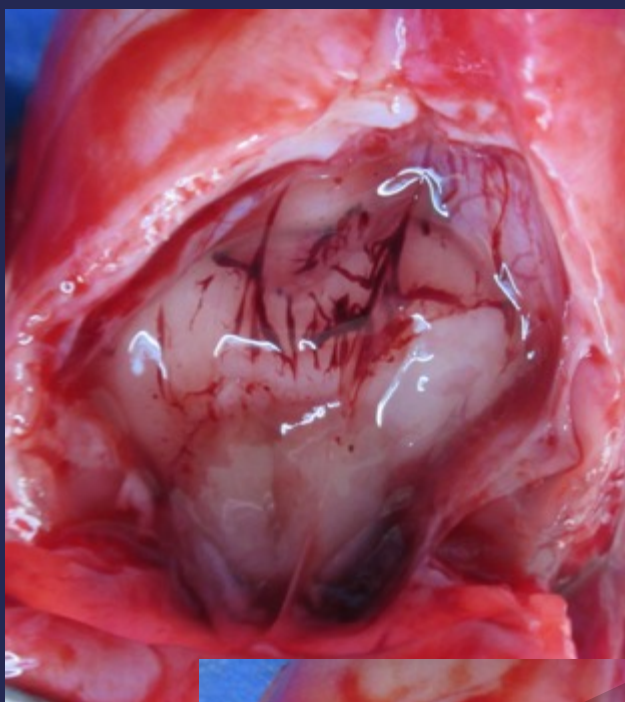
Obstacle urétral.

Importante dilatation des bassinets et amincissement du parenchyme rénal.





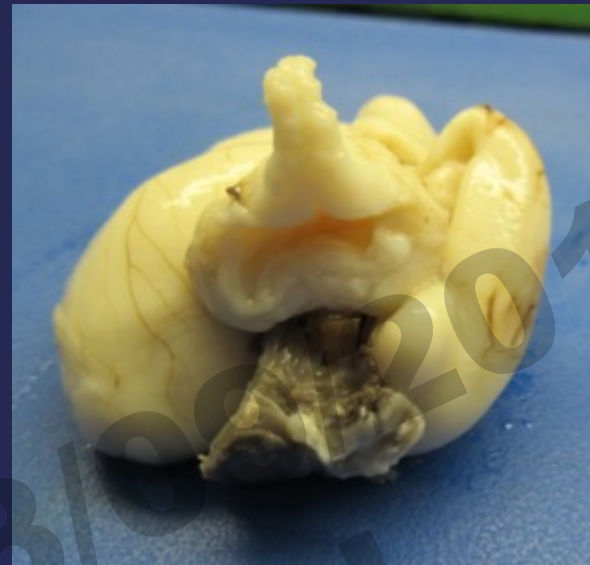
Moelle attachée basse.



4^{ème} ventricule largement ouvert.



Mensurations et aspect des hémisphères en accord avec 20 SA.
Agénésie BO?



4^{ème} ventricule largement ouvert, sans kyste nettement identifiable.
Vermis présent paraissant horizontalisé évoquant un spectre malformatif de type DW.

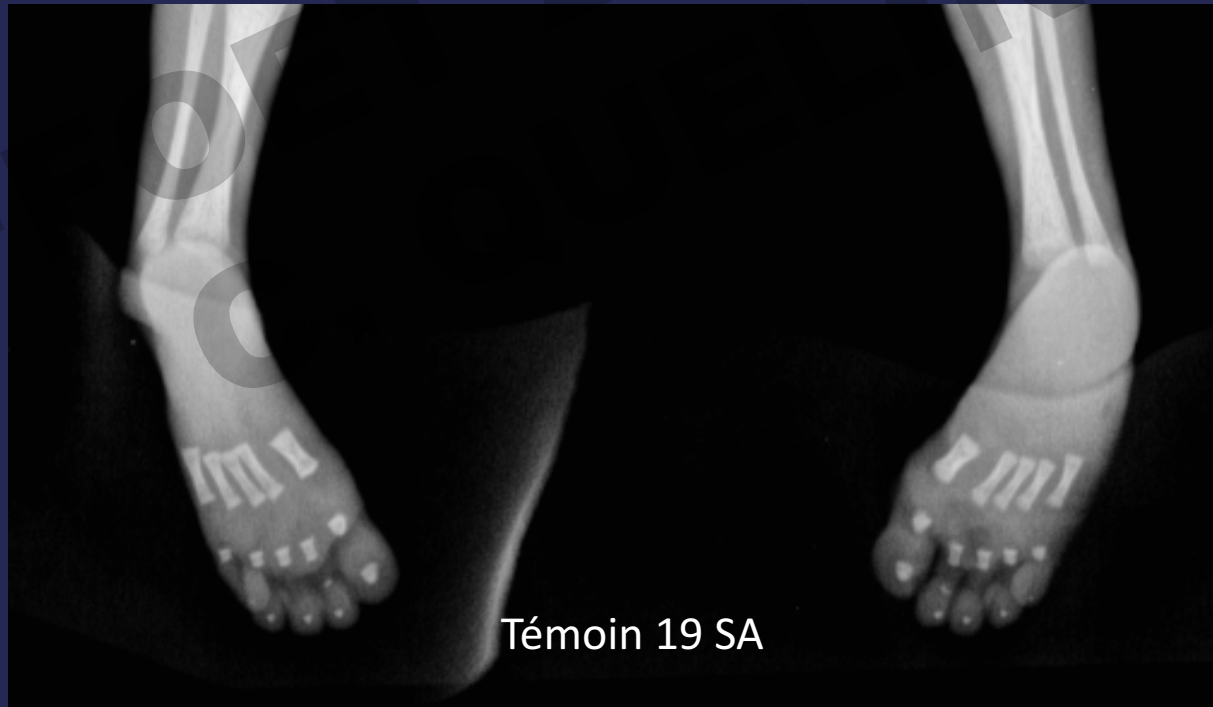


Pas de lésion macroscopique à la coupe des hémisphères.

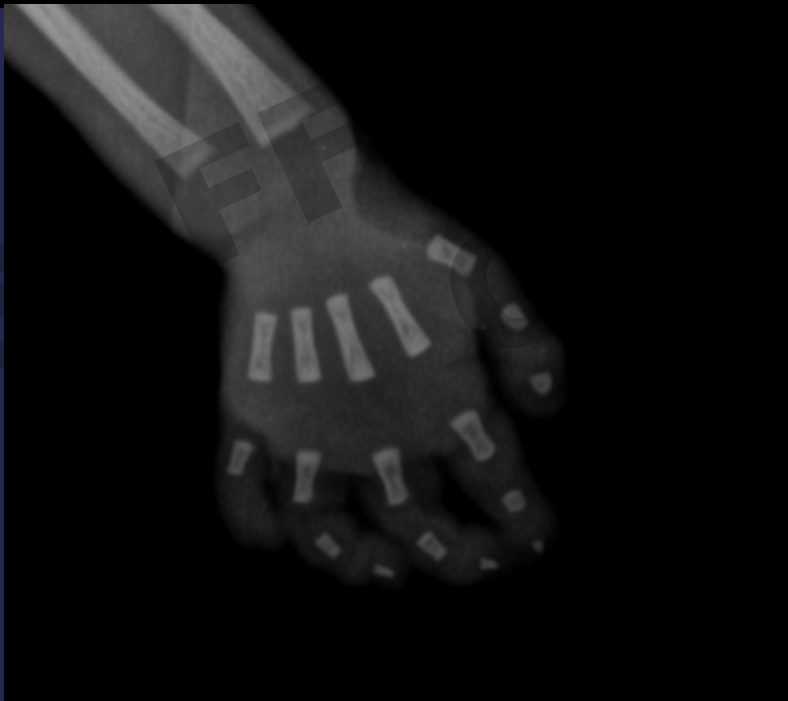
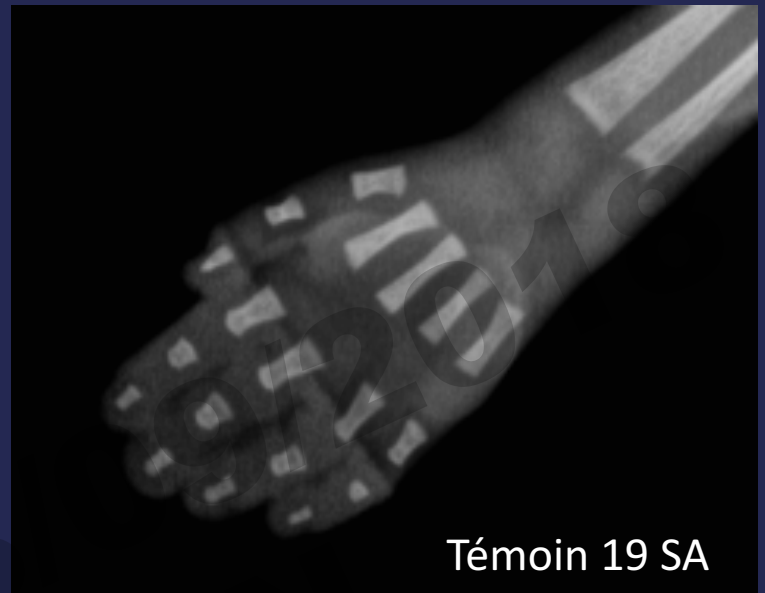


Métatarses courts?

Phalanges globalement courtes : P2 des hallux présentes mais courtes, pas d'ossification des P3.

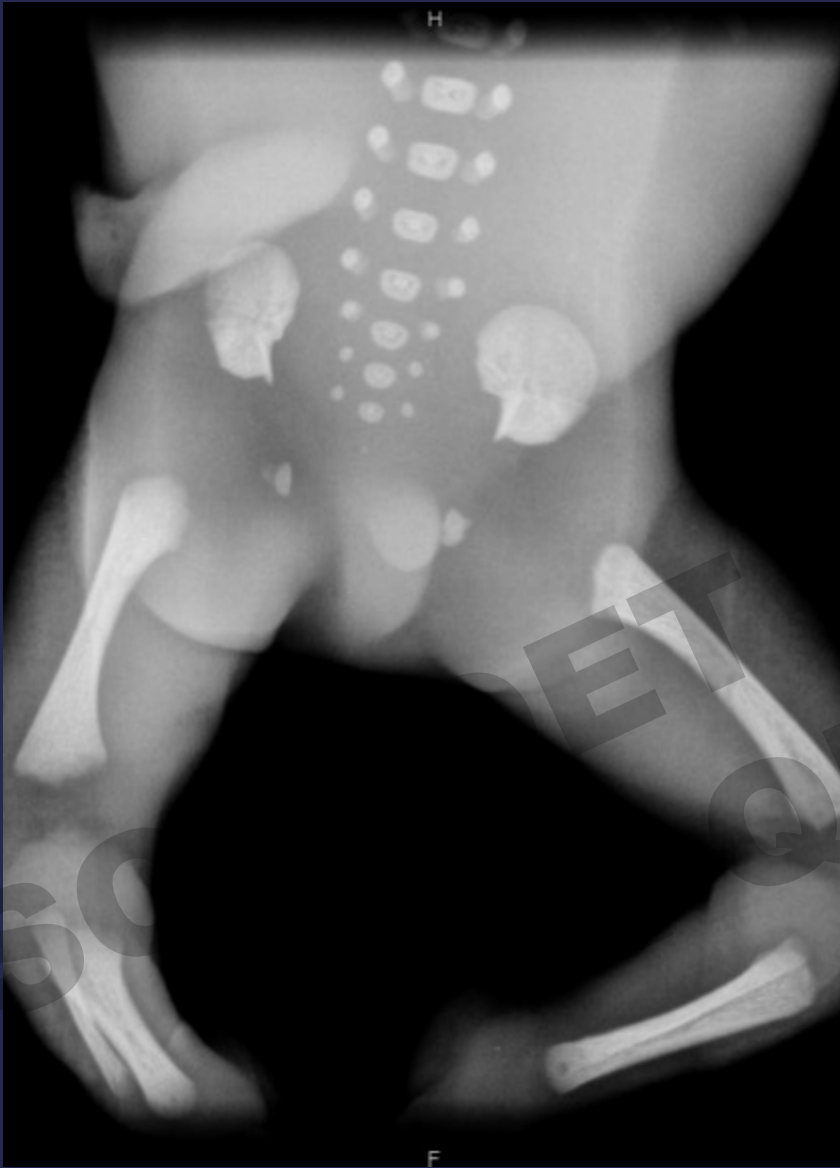


Témoin 19 SA

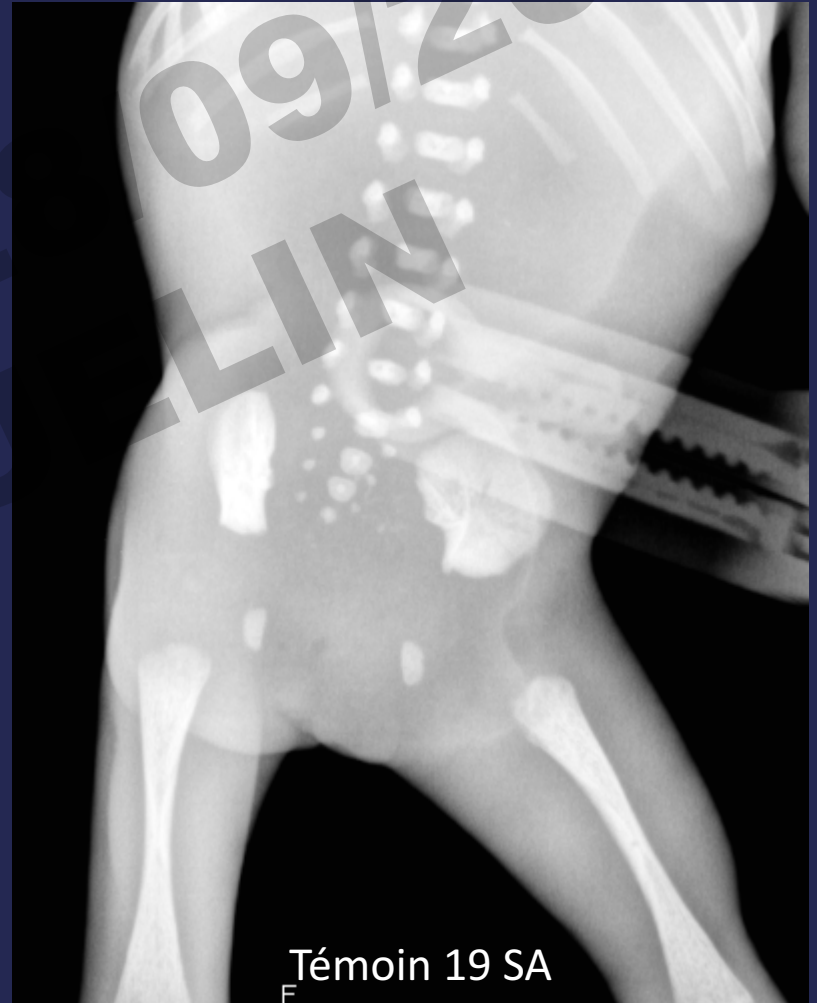


Métacarpes N

Phalanges P1 et P2 légèrement courtes?
Phalanges P3 très courtes (aspect ponctiformes des P3 des index).
Pas d'ossification des P2 et P3 des Vèmes doigts.



Spicule interne au niveau des ailes iliaques?



Témoins 19 SA
F



Témoignage 19 SA

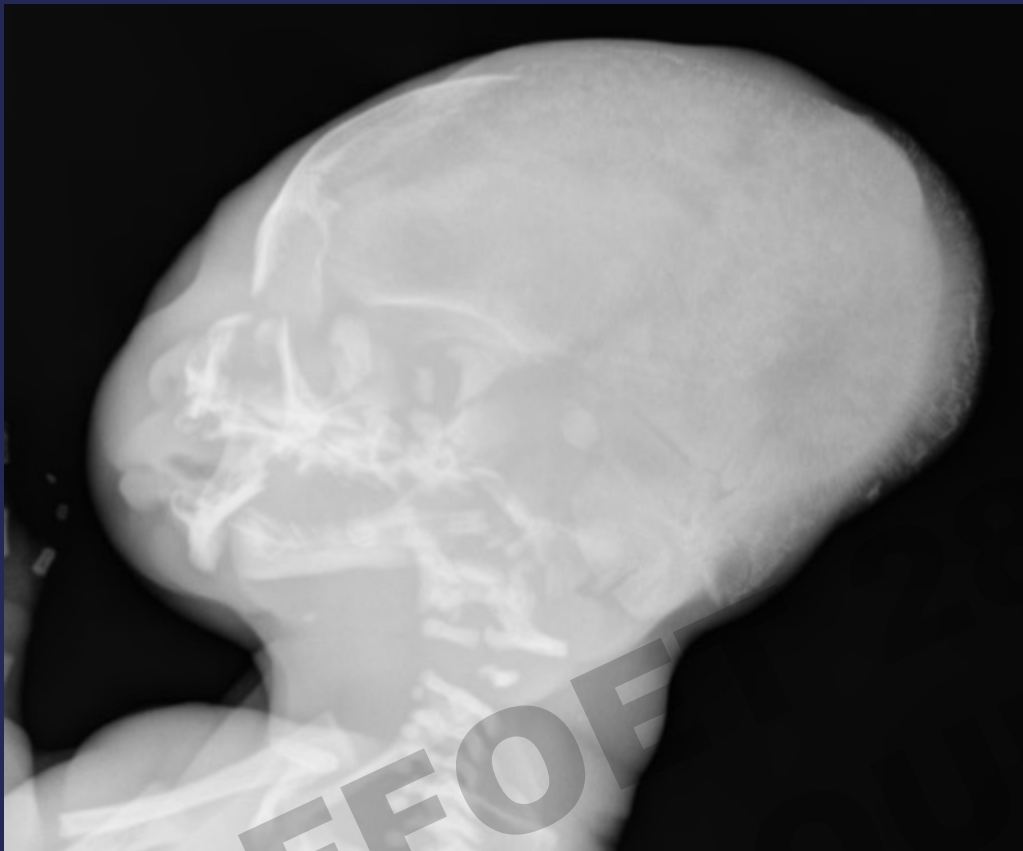
12 paires de côtes paraissant courtes et épaisses.

Clavicules épaissies dans le segment interne.

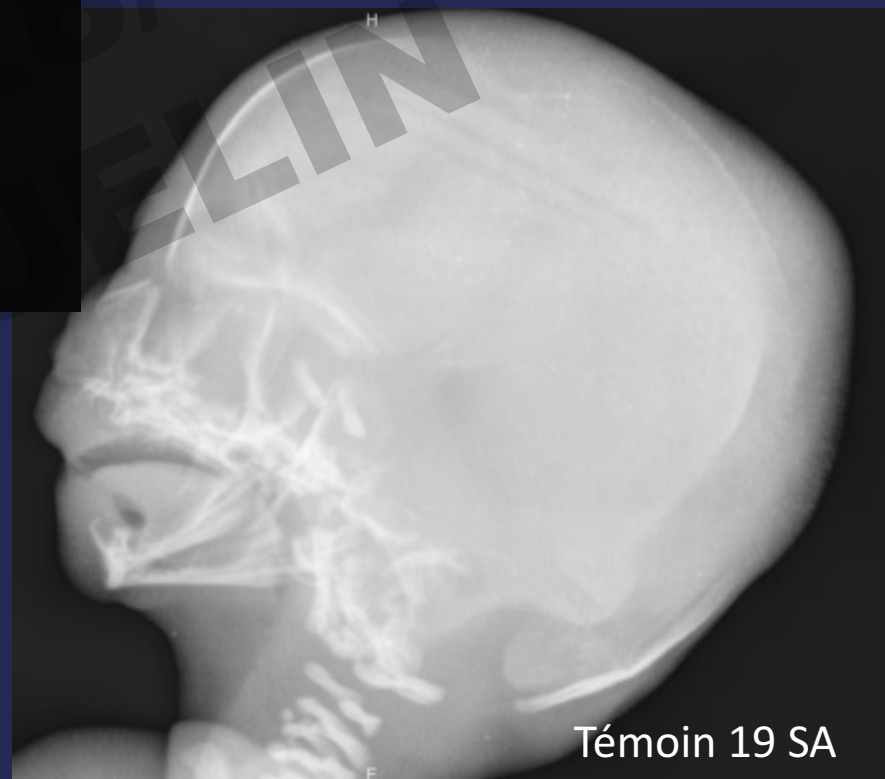


Vertèbres courtes en antéro-postérieur et un peu hautes.

Côtes courtes.



Voûte du crâne insuffisamment ossifiée.



Témoin 19 SA

- **Syndrome dysmorphique.**
- Pieds malposés avec **orteils courts** (en particulier l'hallux) et syndactylie membraneuse.
- **Aspect «spatulé» des doigts** et clinodactylie du 5ème doigt droit.
- Pénis court.
- Petite rate surnuméraire, queue du pancréas un peu courte.
- **Obstacle urétral** avec retentissement d'amont.
- Moëlle attachée basse.
- **Malformation cérébrale** associant probable arhinencéphalie, et anomalie de fosse postérieure (malformation de Dandy-Walker).

- **Anomalies squelettiques** : défaut d'ossification de la voûte crânienne, côtes courtes et épaisses, clavicules épaissies, vertèbres hautes et courtes en antéro-postérieur, métatarses courts, phalanges des orteils courts et absence d'ossification des P3, phalanges des doigts courts (en particulier les P3), absence d'ossification des P2 et P3 des 5èmes doigts.

Syndrome oto-palato-digital de type II ?

Spectre oto-palato-digital

- Pathologies en lien avec des mutation dans le gène *FLNA* (chr X).
- Otopalatodigital syndrome type I (OPD1)
- Otopalatodigital syndrome type II (OPD2)
- Frontometaphyseal dysplasia (FMD)
- Melnick-Needles syndrome (MNS)



Clin Genet 2016; 89: 371–377

Printed in Singapore. All rights reserved

© 2015 John Wiley & Sons A/S.
Published by John Wiley & Sons Ltd

CLINICAL GENETICS

doi: 10.1111/cge.12679

Short Report

Fetal phenotypes in otopalatodigital spectrum disorders

Naudion S., Moutton S., Coupry I., Sole G., Deforges J., Guerineau E., Hubert C., Deves S., Pilliod J., Rooryck C., Abel C., Le Breton F., Collardeau-Frachon S., Cordier M.P., Delezoide A.L., Goldenberg A., Loget P., Melki J., Odent S., Patrier S., Verloes A., Viot G., Blesson S., Bessières B., Lacombe D., Arveiler B., Goizet C., Fergelot P. Fetal phenotypes in otopalatodigital spectrum disorders.

Clin Genet 2016; 89: 371–377. © John Wiley & Sons A/S. Published by John Wiley & Sons Ltd, 2015

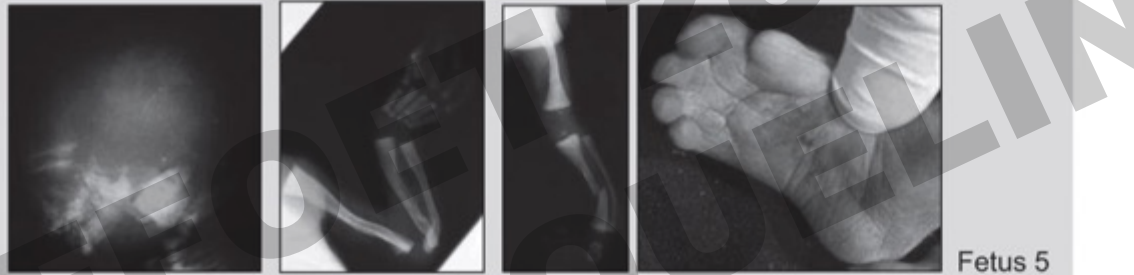
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11
Informative family history		x	x	x					x	x	x
Gender	F	M	M	M	M	M	M	M	M	M	M
Gestational weeks	21	22	15	12	34	Newborn	21	21	13	23	21
Facial dysmorphism											
<u>Flat face</u>	x	x									
Large anterior fontanelle			x	x							
<u>Hypertelorism</u>		x	x			x	x	x	x	x	x
<u>Flat nose</u>	x	x	x		x		x	x			
Anteverted nostril	x		x	x							
Long philtrum	x	x									
Labial cleft	x								x		
Palate cleft		x		x	x			x	x	x	x
<u>Micrognathia</u>	x	x	x	x	x	x	x	x			x
<u>Low implantation of ears</u>		x	x	x							
<u>Posterior rotation of ears</u>	x							x			
Dysplastic ears	x	x						x		x	x
Short neck	x		x								
Hygroma coli/nuchal oedema	x		x								
Macrocephaly			x								
Microcephaly	x	x			x						
Skeletal anomalies											
Narrow thorax	x		x		x						
Bell shaped thorax	x						x				
Vertebral bodies anomalies	x		x								
Short limbs	x		x	x					x	x	x
Bowed limbs			x	x					x	x	x
Broad metaphysis of long bone	x				x		x				
Synostosis	x										
Arthrogryposis	x				x	x					
Camptodactyly	x	x			x			x			
Syndactyly		x	x	x	x		x		x		
<u>Short thumbs/halluces</u>	x	x			x			x			
Long fingers										x	x
<u>Talipes equinovarus</u>	x			x							
Fibula agenesis			x	x					x		
Phalangeal hypo/aplasia	x	x									
Cervical ribs	x					x					
Other malformations											
Omphalocele/umbilical hernia			x		x		x				
<u>Renal/ureteral dilatation</u>		x	x					x		x	x
Renal dysplasia		x			x						
Renal cysts			x	x							
<u>Posterior urethral valves</u>		x			x						
<u>Cerebral anomaly</u>	x	x			x						x
Abnormal genitalia	x	x								x	x
Vascular/cardiac anomalies					x			x			

x, present; F, female; M, male.

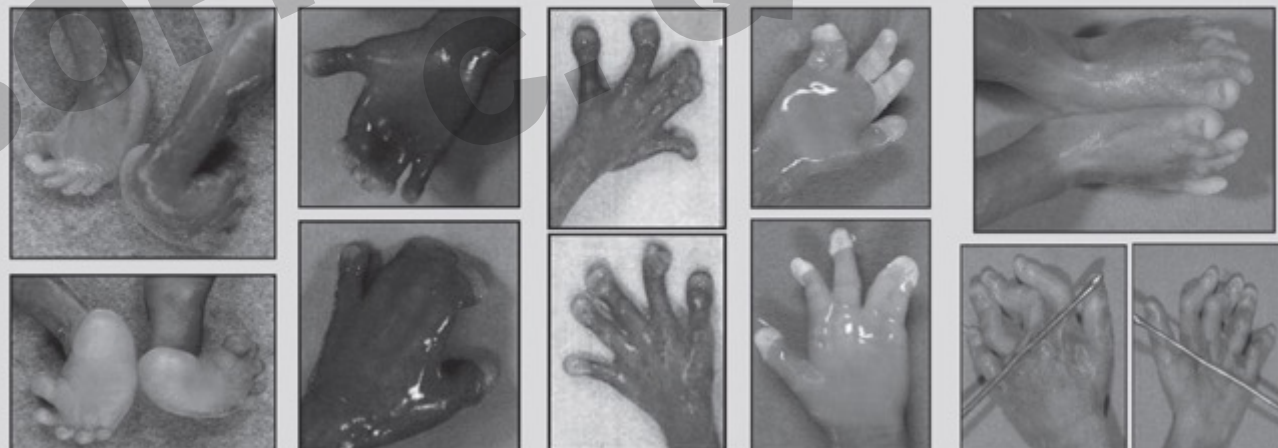


Fetus 2

Patient 6



Fetus 5



Fetus 1

Fetus 3

Fetus 4

Fetus 7

Fetus 8

Etude du gène *FLNA* (Dr Maurin, Bordeaux)

- Séquençage (NGS) + CGH ciblée haute résolution (recherche d'une délétion en mosaïque ou d'un éventuel remaniement restreint au séquences régulatrices) : **normal**.

Exome médical

/ Focused Exome Agilent

- 2 variants à l'état hétérozygote composite dans le gène *PIGV* :
 - ✓ c.1022C>A précédemment décrit comme pathogène, hérité de la mère.
 - ✓ C.1405C>T, prédit comme probablement délétère car générant l'apparition d'un codon STOP prématuré, hérité du père.

Nat Genet. 2010 Oct;42(10):827-9. doi: 10.1038/ng.653. Epub 2010 Aug 29.

Identity-by-descent filtering of exome sequence data identifies PIGV mutations in hyperphosphatasia mental retardation syndrome.

Krawitz PM¹, Schweiger MR, Rödelsperger C, Marcelis C, Kölsch U, Meisel C, Stephani F, Kinoshita T, Murakami Y, Bauer S, Isau M, Fischer A, Dahl A, Kerick M, Hecht J, Köhler S, Jäger M, Grünhagen J, de Condor BJ, Doelken S, Brunner HG, Meinecke P, Passarge E, Thompson MD, Cole DE, Horn D, Roscioli T, Mundlos S, Robinson PN.

⊕ Author information

Abstract

Hyperphosphatasia mental retardation (HPMR) syndrome is an autosomal recessive form of mental retardation with distinct facial features and elevated serum alkaline phosphatase. We performed whole-exome sequencing in three siblings of a nonconsanguineous union with HPMR and performed computational inference of regions identical by descent in all siblings to establish PIGV, encoding a member of the GPI-anchor biosynthesis pathway, as the gene mutated in HPMR. We identified homozygous or compound heterozygous mutations in PIGV in three additional families.

with mental retardation, brachytelephalangy, and a d
eation of a recognizable syndrome

Schottmann^b, Peter Meinecke^c

^bUniversitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany
^cCharité-Universitätsmedizin Berlin, Berlin, Germany
rankenhaus, Hamburg, Germany

A B S T R A C T

The association of mental retardation and persistent hyperphosphatasia has been desc
instances. Because of parental consanguinity and sib recurrences autosomal recessive in
been proposed. We report three sibs with a syndrome consisting of severe mental retard
erably elevated serum levels of alkaline phosphatase, hypoplastic terminal phalanges, and



Syndrome HPMR décrit depuis début 2010 (DI, élévation PAL, dysmorphie, brachytéléphalangie)

AR

Actuellement, mutations de différents gènes *PIG* (*PIGV*, *PIGO*, *PGAP2* ...) impliqués dans le syndrome HPMR.

Codent pour des protéines impliqués dans la biosynthèse du glycosylphosphatidylinositol (GPI).

ARTICLE

Delineation of *PIGV* mutation spectrum and associated phenotypes in hyperphosphatasia with mental retardation syndrome

Denise Horn^{*1}, Dagmar Wieczorek², Kay Metcalfe³, Ivo Barić^{4,5}, Lidija Paležac⁵, Mario Ćuk^{4,5}, Danijela Petković Ramadža⁴, Ulrike Krüger¹, Stephanie Demuth⁶, Wolfram Heinritz⁷, Tobias Linden⁸, Jens Koenig⁸, Peter N Robinson¹ and Peter Krawitz¹

Three different genes of the glycosylphosphatidylinositol anchor synthesis pathway, *PIGV*, *PIGO*, and *PGAP2*, have recently been implicated in hyperphosphatasia-mental retardation syndrome (HPMRS), also known as Mabry syndrome, a rare autosomal recessive form of intellectual disability. The aim of this study was to delineate the *PIGV* mutation spectrum as well as the associated phenotypic spectrum in a cohort of 16 individuals diagnosed with HPMRS on the basis of intellectual disability and elevated serum alkaline phosphatase as minimal diagnostic criteria. All *PIGV* exons and intronic boundaries were sequenced in 16 individuals. Biallelic *PIGV* mutations were identified in 8 of 16 unrelated families with HPMRS. The most frequent mutation detected in about 80% of affected families including the cases reported here is the c.1022C>A *PIGV* mutation, which was found in both the homozygous as well as the heterozygous state. Four further mutations found in this study (c. 176T>G, c.53G>A, c.905T>C, and c.1405C>T) are novel. Our findings in the largest reported cohort to date significantly extend the range of reported manifestations associated with *PIGV* mutations and demonstrate that the severe end of the clinical spectrum presents as a multiple congenital malformation syndrome with a high frequency of Hirschsprung disease, vesicoureteral, and renal anomalies as well as anorectal malformations. *PIGV* mutations are the major cause of HPMRS, which displays a broad clinical variability regarding associated malformations and growth patterns. Severe developmental delays, particular facial anomalies, brachytelephalangy, and hyperphosphatasia are consistently found in *PIGV*-positive individuals.

European Journal of Human Genetics (2014) 22, 762–767; doi:10.1038/ejhg.2013.241; published online 16 October 2013

Keywords: Hyperphosphatasia; intellectual disability; alkaline phosphatase; brachytelephalangy; seizures

Table 1 Summary of molecular and clinical findings in patients carrying *PIGV* mutations (transcript NM_017837.3)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
PIGV mutations	c.905T>C (p.Leu302-Pro), homozygous	c.1022C>A (p.Ala341Glu), homozygous	c.1022C>A (p.Ala341Glu), homozygous	c.1022C>A (p.Ala341Glu), homozygous	c.1022C>A (p.Ala341-Glu), homozygous	c.1022C>A, c.176T>G (p.Ala341-Glu; p.Leu59Arg)	c.1022C>A (p.Ala341Glu), homozygous	c.1022C>A, c.530>A (p.Ala341-Glu; p.Oys187Yr)	c.1022C>A, c.1405C>T (p.Ala341Glu; p.Arg469*)
Sex	Female	Male	Female	Male	Male	Male	Female	Male	Female
Age of last assessment	First day of life	4 5/12 years	21 months	19 years	3.5 years	13 years	2.5 years	4 8/12 years	First day of life
Origin	Pakistan	German	German	Croatian	Croatian	German	German	German	German
Consanguinity	Yes	No	No	No	No	No	No	No	No
Gestation (weeks)	33	37	40	41	40	40	39	40	36
Birth length (SD)	45cm (+0.3)	49cm (-0.5)	50cm (-0.8)	52 cm (-0.5)	53 cm (+0.2)	53cm (+0.2)	52 cm (+0.4)	55cm (+1.5)	46 cm (-0.9)
Birth weight (SD)	2310g (+0.8)	3170g (+0.2)	3220g (-0.6)	3850g (+0.25)	3870g (+0.5)	3770g (+0.3)	4170g (+1.9)	4550g (+2.1)	2975g (+0.5)
OFC at birth (SD)	36.8cm (+3.2)	32.5 cm (-1.3)	35cm (+0.1)	n.a.	35.5cm(-0.1)	n.d.	36cm(+1.1)	35cm (+0.3)	33.5cm (+0.1)
Height (SD)	-	109 cm (-0.2)	82cm (-0.5)	174cm(-0.5)	104cm(+1.1)	150cm(-0.85)	94cm(+1.0)	111cm (+0.5)	-
Weight (SD)	-	16 kg (-0.9)	12kg (-0.1)	83kg (+2.0)	19 kg (+1.7)	n.d.	14.6kg (+0.5)	20.5 kg (+1.1)	-
OFC (SD)	-	48.5 cm (-2.3)	47.5 cm (-0.3)	59.5 cm (+2.0)	n.a.	53.5 cm (-0.3)	46 cm (-2.3)	50.5cm(-0.9)	-
Hyper-phosatasia	777-1211U/l	981 U/l	973U/l	850-8600 U/l	1100-3600 U/l	2730U/l	1224 U/l	750-1400U/l	738 U/l
Normal age-adjusted range of AP	50-240	40-129	35-104	25-500	25-500	<832	108-316	<269	<479
Global developmental delay	n.a.	+	+	+	+	+	+	+	na.
Age at walking	n.a.	24 Months	-	17 months	11 months	5 years	21 months	-	na.
Delayed speech and language development	n.a.	+(Single words)	+(No words)	+(no speech development)	+(No words at 2.5 years)	+(no speech)	+(no words)	+(no words)	na.
Muscular hypotonia	-	+	+	-	-	Axial hypotonia/hypertonia of legs	+	-	-
Seizures	Neonatal seizures	+	+	Myoclonic seizures	Myoclonic seizures	+	+	+	+
Facial gestalt	+	+	+	+	+	(+)	+	+	+
Apparent hypertelorism	+	+	+	+	+	(+)	+	-	+
Long palpebral fissures	+	+	+	+	+	+	+	+	+
Broad nasal bridge	+	+	+	+	+	+	+	+	+
Broad nasal tip	+	+	+	+	+	+	+	+	+
Tented upper lip vermillion	+	+	+	+	+	+	+	+	+
Brachytelephalangy	Absent distal phalanges V, very hypoplastic distal phalanges II, bulbous distal thumbs	Hypoplastic distal phalanges II, V, broad finger nails	+	Hypoplastic nails of fingers, hypoplastic metacarpal bone V	Hypo- plastic nails of fingers and toes, hypoplastic terminal phalanges	Hypo- plastic distal phalanges	Broad distal phalanges I	Hypoplastic fingernails, broad halluces	Hypoplastic fingernails, broad thumbnails
Aganglionic megacolon	-	+	+	-	-	+	+	+	-
Anal stenosis/anal atresia	+(Anal atresia, recto-vestibular fistula)	-	-	-	-	-	+	+	-
Vesicoureteral/renal anomalies	Congenital hydro-nephrosis	-	+	-	-	Bilateral duplication of kidneys	Congenital hydro-nephrosis	Congenital hydro-nephrosis, megacystis-megoureter, vesicoureteral reflux	Congenital hydro-nephrosis, megaureter
Heart defect	VSD	-	-	-	-	-	PFO	-	VSD
Cleft palate	+	-	-	-	-	-	+	-	+
Further anomalies	Poorly formed cerebellar vermis, absent cilia, contractures of large joints, prominent ear lobes	-	-	Pectus excavatum	-	-	Singular umbilical artery	-	-

Seizures
 Facial gestalt
 Apparent hypertelorism
 Long palpebral fissures
 Broad nasal bridge
 Broad nasal tip
 Tented upper lip vermillion
 Brachytelephalangy

Aganglionic megacolon
 Anal stenosis/anal atresia
 Vesicoureteral/renal anomalies

Heart defect
 Cleft palate
 Further anomalies

RESEARCH

Open Access



Characterization of glycosylphosphatidylinositol biosynthesis defects by clinical features, flow cytometry, and automated image analysis

Alexej Knaus^{1,2,3,4}, Jean Tori Pantel¹, Manuela Pendziwiat⁵, Nurulhuda Hajjir¹, Max Zhao¹, Tzung-Chien Hsieh^{1,4}, Max Schubach^{1,6}, Yaron Gurovich⁷, Nicole Fleischer⁷, Marten Jäger^{1,6}, Sebastian Köhler¹, Hiltrud Muhle⁵, Christian Korff⁸, Rikke S. Møller^{9,10}, Allan Bayat¹¹, Patrick Calvas¹², Nicolas Chassaing¹², Hannah Warren¹³, Steven Skinner¹³, Raymond Louie¹³, Christina Evers¹⁴, Marc Bohn¹⁵, Hans-Jürgen Christen¹⁶, Myrthe van den Born¹⁷, Ewa Obersztyn¹⁸, Agnieszka Charzewska¹⁸, Milda Endziniene¹⁹, Fanny Kortüm²⁰, Natasha Brown^{21,22}, Peter N. Robinson²³, Helenius J. Schelhaas²⁴, Yvonne Weber²⁵, Ingo Helbig^{4,26}, Stefan Mundlos^{1,2}, Denise Horn^{1**} and Peter M. Krawitz^{1,2,4**}

Table 1 Summary of clinical findings in patients carrying *PGIV*, *PIGD*, *PGAP2*, *PGAP3*, *PIGW*, and *PIGY* mutations

	HPMRS1 <i>PIGV</i> (n = 26, excluding 2 fetus)	HPMRS2 <i>PIGD</i> (n = 16)	HPMRS3 <i>PGAP2</i> (n = 12)	HPMRS4 <i>PGAP3</i> (n = 26)	HPMRS5 <i>PIGW</i> (n = 3)	HPMRS6 <i>PIGY</i> (n = 4)
Hyperphosphatasia	26/26	14/14, ND in 2	6/6, ND in 6	25/26	1/3	4/4
Malformations						
Cleft palate	8/26	4/16	1/12	15/26	-	0/4
Megacolon	8/26	5/16	1/12	0/26	-	0/4
Anorectal malformations	9/26	3/16	1/12	0/26	-	0/4
<u>Vesicoureteral/renal malformations</u>	6/10	2/16	ND	0/26	-	1/4
Heart defect	5/26	2/16	2/12	2/26	-	0/4
Facial gestalt						
Apparent hypertelorism	26/26	6/6, ND in 10	1/12	12/13, ND in 13	ND	1/4
Up-slanting palpebral fissure	26/26	10/11, ND in 5	ND in 12	2/26	ND	0/4
<u>Broad nasal bridge</u>	26/26	5/6, ND in 10	2/12	13/13, ND in 13	1/3 ND in 2	1/4
<u>Broad nasal tip</u>	26/26	5/6, ND in 10	1/12	4/14, ND in 12	ND	1/4
<u>Short nose</u>	26/26	5/6, ND in 10	1/12	14/24, ND in 2	ND	ND
Tented upper lip vermilion	26/26	7/8, ND in 8	2/12	17/24, ND in 21	3/3	ND
Large, fleshy ear lobes	-	1/16		18/24, ND in 21	ND	4/4
<u>Brachytelephalangy</u>	26/26	10/10, ND in 6	0/12 (broad nails in 1/12)	0/26 (broad nails in 6/26)	-	1/4
Further anomalies (rare)	Gastroesophageal reflux, optic atrophy bilateral, scoliosis, hip subluxation (right), thin corpus callosum, gingiva hyperplasia	Coronal synostosis, keratoderma, micrognathia, auricular malformations		Thin corpus callosum (9/26), ventriculomegaly (3/26), <u>vermis hypoplasia</u> (4/26)	Inguinal hernia (1/3)	Cataracts (2/4) Rhizomelic shortness of limbs (2/4)

Syndrome HPRM (syndrome de Mabry)

- RPM, retard de langage, DI ++
- Epilepsie (âge de début et sévérité variables)
- Dysmorphie (hypertélorisme, pointe et racine du nez élargies, macrostomie, lèvre supérieure en chapeau de gendarme, micro-rétrognatisme, anomalies des oreilles, ± fente palatine)
- Brachytéléphalangie
- Malformations viscérales : Hirschsprung, fistule/atrésie anale, hydronéphrose, hernie diaphragmatique, cardiopathies...
- Anomalies cérébrales : CC fin, anomalies du vermis ...



Horn D et al. Delineation of PIGV mutation spectrum and associated phenotypes in hyperphosphatasia with mental retardation syndrome. *Eur J Hum Genet.* 2014 Jun;22(6):762-7.



SOFFOET 28/09/2018
C. QUELIN

NB

- Malformations viscérales : Hirschsprung, fistule/atrésie anale, hydronéphrose, **hernie diaphragmatique**, cardiopathies...
- **Brachytéléphalangie**

→ Fryns?

Hum Mutat. 2016 Jul;37(7):695-702. doi: 10.1002/humu.22994. Epub 2016 May 6.

Fryns Syndrome Associated with Recessive Mutations in PIGN in two Separate Families.

McInerney-Leo AM^{1,2}, Harris JE^{1,2}, Gattas M³, Peach EE⁴, Sinnott S⁴, Dudding-Byth T⁵, Rajaopalan S⁶, Barnett CP^{7,8}, Anderson LK², Wheeler L^{1,2}, Brown MA², Leo PJ^{1,2}, Wicking C⁹, Duncan EL^{1,2,10,11}.

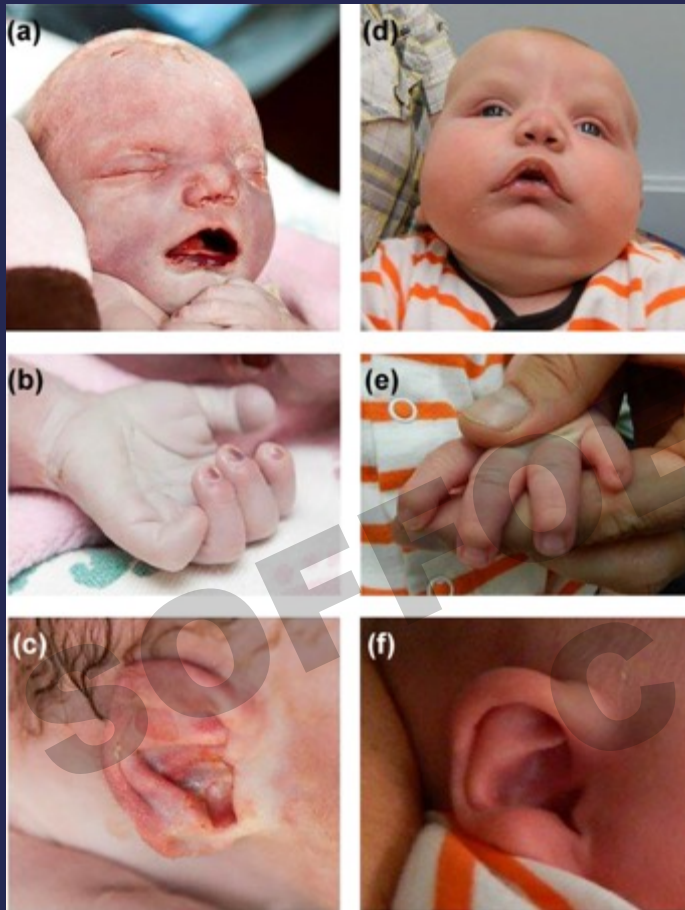
Eur J Hum Genet. 2018 Mar;28(3):340-349. doi: 10.1038/s41431-017-0087-x. Epub 2018 Jan 12.

Recessive loss of function PIGN alleles, including an intragenic deletion with founder effect in La Réunion Island, in patients with Fryns syndrome.

Alessandri JL¹, Gordon CT^{2,3}, Jacquemont ML⁴, Gruchy N⁵, Aieawung NF⁶, Benoist G⁵, Oufadem M^{2,3}, Chebil A⁷, Duffourd Y^{8,9}, Dumont C¹⁰, Gérard M⁵, Kuentz P⁸, Jouan T^{8,9}, Filippini F^{2,3}, Nguyen TTM⁶, Alibeu O^{3,11}, Bole-Feysot C^{3,11}, Nitschké P^{3,12}, Omarjee A¹⁰, Ramful D¹³, Randrianaivo H⁴, Doray B¹⁴, Faivre L^{8,9}, Amiel J^{2,3,15}, Campeau PM⁶, Thevenon J^{8,9,16}.

Prenatal presentation of Mabry syndrome with congenital diaphragmatic hernia and phenotypic overlap with Fryns syndrome.

Reynolds KK¹, Juusola J², Rice GM¹, Giampietro PF³.



1^{er} enfant

MIU à 38 SA. Hernie diaphragmatique gauche ,
dysmorphie, hypoplasie P3 des V.

Refus d'autopsie.

→ Fryns évoqué

2^{ème} enfant

Echo : hydramnios, hydronéphrose bilatérale,
mégavessie, micrognathie, pieds malposés

Naissance : FP, micrognathie, hypoplasie des V, CIA,
imperforation anale, malrotation intestinale,
Hirschsprung, élévation PAL, RVU, épilepsie, Chiari I

→ HPMRS / Mabry

2 variants dans le gène *PIGV* chez le 2^{ème} enfant.

