Nanismes létaux platyspondyliques

MAD MALADIES OSSEUSES CONSTITUTIONNELLES

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Necker ENFANTS MALADES HÔPITAL UNIVERSITAIRE

PARIS DESCARTES

Classification Internationale : « skeletal disorders »

RESEARCH ARTICLE

AMERICAN JOURNAL OF PART A
medical genetics

Nosology and Classification of Genetic Skeletal Disorders: 2015 Revision

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Am J Med Genet Part A 9999A:1–24.

plus de 400 entités, 40 groupes

-Selon l'anomalie moléculaire	(1-8)
-Selon la radiologie	
-Minéralisation anormale	(22-29)
-Avance staturale	(30)
-Inflammatoire	(31)
-Dysostoses	(32-42

The purpose of the nosology is to serve as a "master" list of the genetic disorders of the skeleton to facilitate diagnosis and to help delineate variant or newly recognized conditions. This is the 9th edition of the nosology and in comparison with its predecessor there are fewer conditions but many new genes. In previous editions, diagnoses that were phenotypically indistinguishable but genetically heterogenous were listed separately but we felt this was an unnecessary distinction. Thus the overall number of disorders has decreased from 456 to 436 but the number of groups has increased to 42 and the number of genes to 364. The nosology may become increasingly important today and tomorrow in the era of big data when the question for the geneticist is often whether a mutation identified by next generation sequencing technology in a particular gene can explain the clinical and radiological phenotype of their patient. This can be particularly difficult to answer conclusively in the prenatal setting. Personalized medicine emphasizes the importance of tailoring diagnosis and therapy to the individual but for our patients with rare skeletal disorders, the importance of tapping into a resource where genetic data can be centralized and made

14. Severe spondylodysplastic dysplasias

Achondrogenesis type 1A (ACG1A)	AR	200600	*TRIP11*	Golgi-microtubule-associated protein, 210-KD; GMAP210	
Schneckenbecken dysplasia	AR	269250	*SLC35D1*	solute carrier family 35 member D1; UDP-glucuronic acid/UDP-N-acetylgalactosamine dual transporter	
Spondylometaphyseal dysplasia, Sedaghatian type	AR	250220	*GPX4*	Glutathione peroxidase 4	
Severe spondylometaphyseal dysplasia (SMD Sedaghatian-like)	AR		*SBDS*	SBDS gene, function still unclear	
Opsismodysplasia	AR	258480	*INPPL1*	Inositol polyphosphate phosphatase-like 1	Includes lethal a
MAGMAS related skeletal dysplasia	AR		*MAGMAS*	Presequence translocase-associated motor 16	
See also: Thanatophoric dysplasia, types 1 and 2 (group 1); ACG2 and Torrance dysplasia (group 2); Fibrochondrogenesis (group 3); Achondrogenesis type 1B (group 4); and Metatropic Dysplasia (group 8)					

Etude rétrospective de 65 cas de nanismes platyspondyliques

Elisa BIAMINO

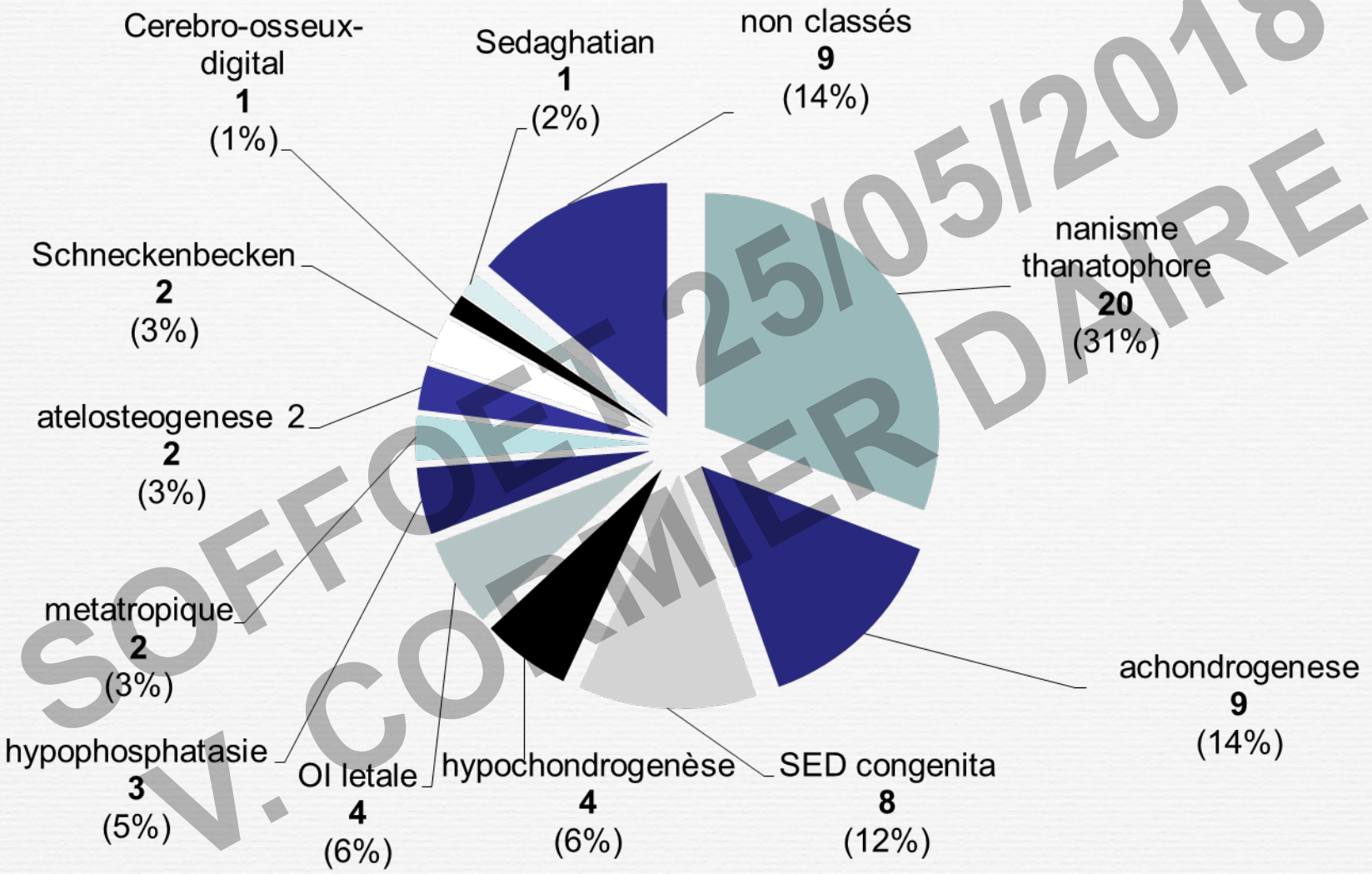
Janvier 2004-décembre 2012
Analyse rétrospective « dysplasies squelettiques létales »
Critères d'Inclusion: **micromélie et platyspondylie**

1) Revue systématique des radiographies
2) Explorations moléculaires :
CGH array, *FGFR3, SLC26A2, COL2A1, ALPL, TRPV4*

- **65 fœtus**
- **26 males/27 females/ 12 ?**
- **Age Fœtal : 23 weeks (13-40W)**

- **Diagnostic : 56/65**
- **Pas de diagnostic : 9/65**

Etude rétrospective de 65 cas de nanismes platyspondyliques



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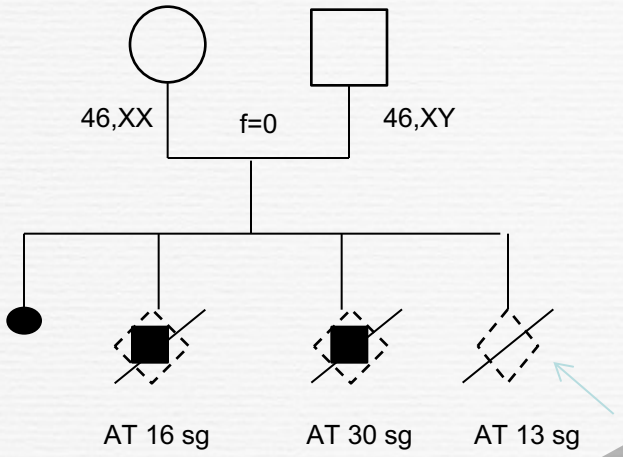
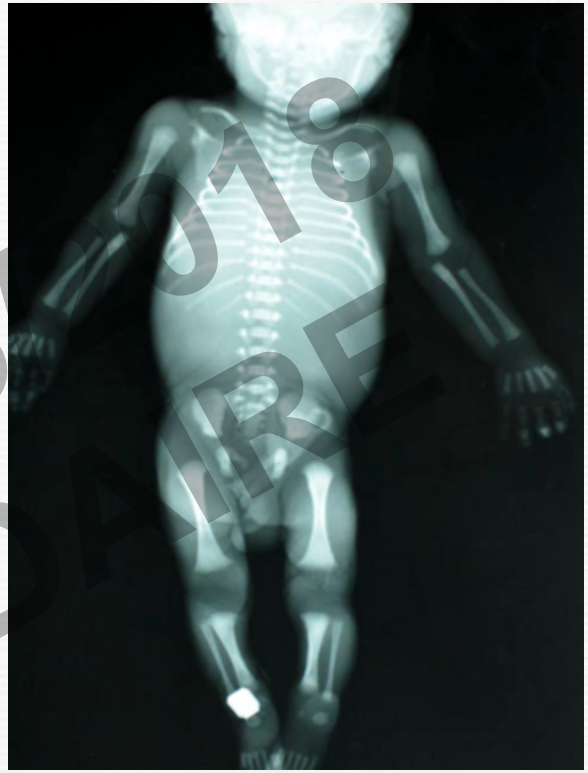


Acondrogenesi tipo 2



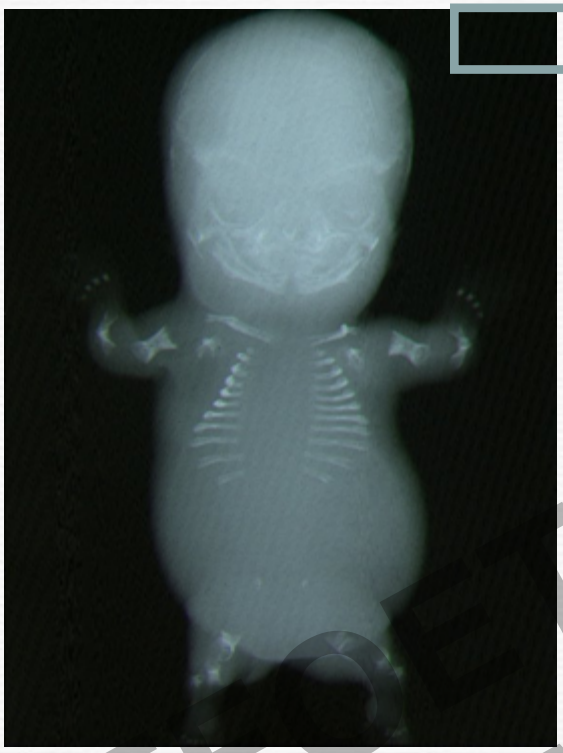
SED congenita

Cariotipo nl, FGFR 3 e DTDST neg

Collagenopatia tipo 2 (AD)
Mosaicismo germinale in 1 genitore

Analisi molecolare *COL2A1* in corso …

Mosaicismo germinale già riportato in qualche caso
→rischio di ricorrenza
Sorveglianza ecografica attentiva nelle gravidanze successive



CSG1001427
14 sg

COL2A1

CSG0800138
26 sg

Acondrogenesi tipo 2

Micromelia eco 1° trimestre
Interruzione 12.5 sg (13-19 sg)
Palatoschisi (3/5 casi)

Micromelia estrema, metafisi cupoliformi con speroni laterali
Vertebre non ossificate

Ipocondrogenesi

Interruzione 23 sg (15-27 sg)
Microretrognazia

Micromelia meno severa, evasamento metafisario
Platispondilia severa, ossificazione assente vertebre C e S

Primo studio sulla classificazione e diagnosi differenziale delle condrodisplasie fetali associate a platispondilia

classificazione possibile in 56/65 casi (86.1%):

nanismo tanatoforo e collagenopatie di tipo 2 (*COL2A1*) sono le cause più frequenti

conferma di osservazioni precedenti (età paterna avanzata ed anomalie SNC in NT, mosaicismo germinale COL2A1, snail-like ilia in Schneckenbecken dysplasia,…)

9/65 non classificabili in nessuna categoria ISDS Nosology 2010

NG/exome sequencing: mutazioni in «nuovi» geni o nuovi fenotipi associati a geni noti?

Nanismes létaux platyspondyliques

- Chondrodysplasie incompatible avec la vie
- Chondrodysplasies de découverte anténatale, de pronostic variable

Place et apport du séquençage ciblé en 2018 ?

MOCOME : 70 gènes dont **10** gènes impliqués dans les nanismes létaux spondylodysplastiques

Importance du diagnostic clinico-radiologique pour interprétation

Délai de rendu >6 mois

Nansimes létaux platyspondyliques

- Chondrodysplasies **incompatibles avec la vie**
  - Nanisme thanatophore
  - Achondrogenèses
  - Autre formes rares

- Chondrodysplasies **de découverte anténatale, de Pronostic variable**
  - Dysplasie métatropique
  - Dysplasies S (E) M ..

Chondrodysplasies **incompatibles** avec la vie

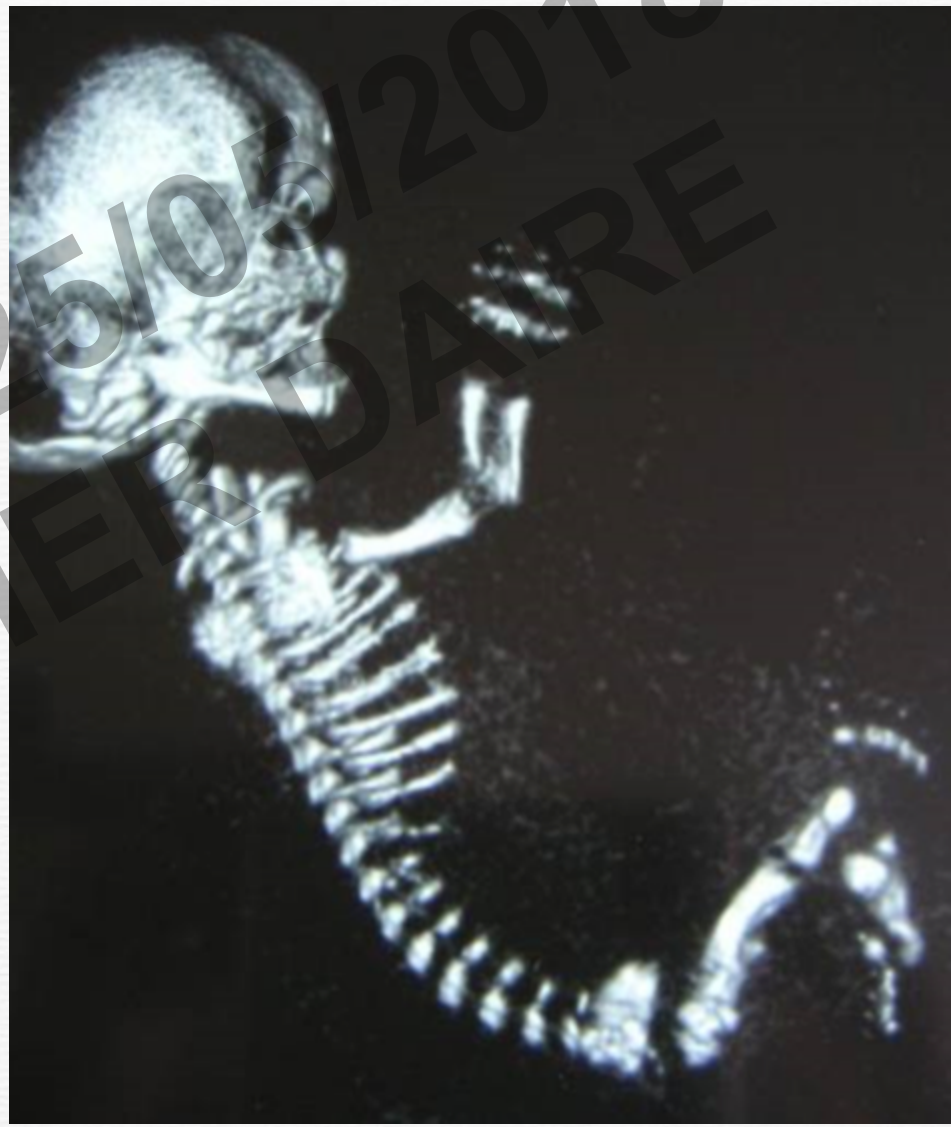
CRITERES

- Micromélie extrême (écho)
- Repérées dès le 2-4ème mois de grossesse (T1)
- Disproportion entre volume du crâne et du corps
- Immobilité/oedème, anasarque, hydramnios
- Signes spécifiques selon le type

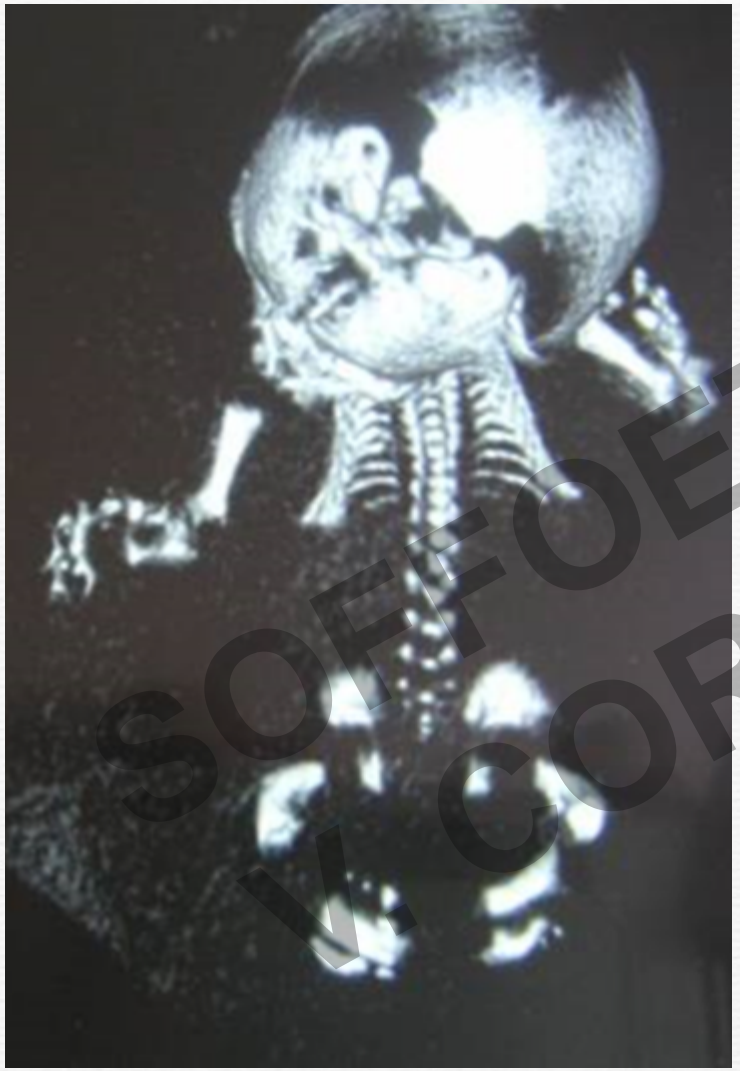
- le diagnostic est souvent précisé après la fin de la grossesse
- **Importance des clichés radiologiques post IMG**

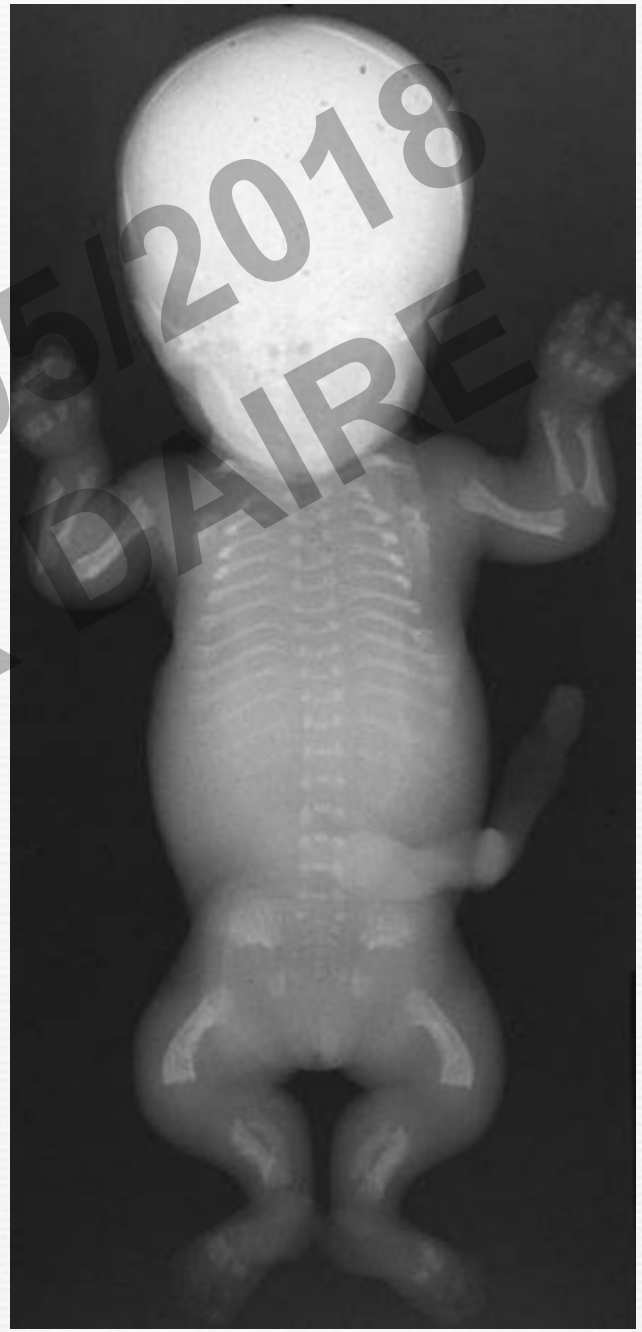
1) Nanisme thanatophore

- 1/40 000
- Platyspondylie sévère,
- Côtes courtes
- Ailes iliaques courtes, toits des cotyles horizontaux
- Brièveté extrême des os longs
- Fémur en « écouteur téléphonique »
- Métaphyses irrégulières et larges
- +/- crâne en trèfle
- Mutation de novo de ***FGFR3***



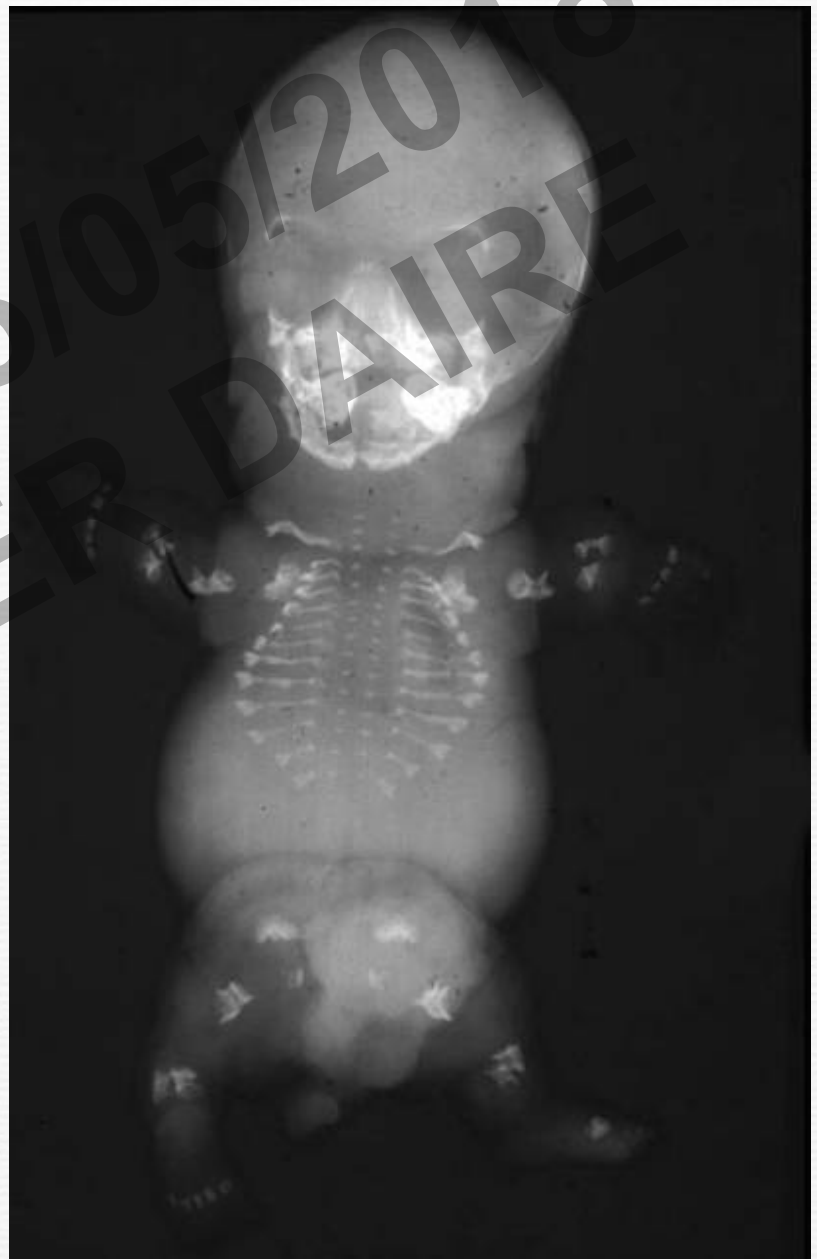
Nanisme thanatophore



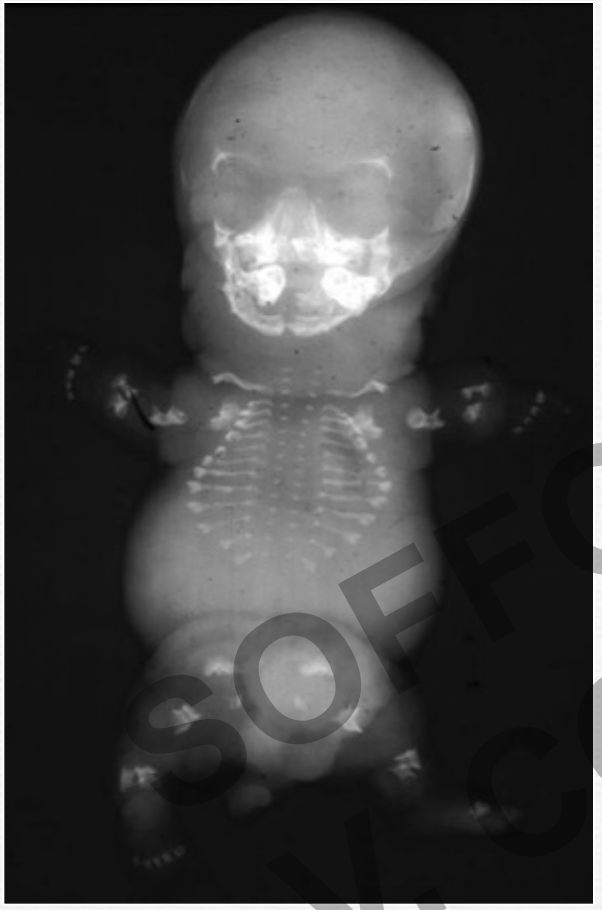


2) Achondrogenèses (Hypo-)

- Micromélie extrême
- Tronc très court
- Défaut majeur d'ossification des corps vertébraux et du crâne
- Métaphyses en cupules
- Ailes iliaques hypoplasiques
- Hygroma kystique, excès de LA
- Type 1A : ***TRIP11*** (AR)
- Type 1B : ***SLC26A2*** (AR)
- Type 2 : ***COL2A1*** (mut dom *de novo*)

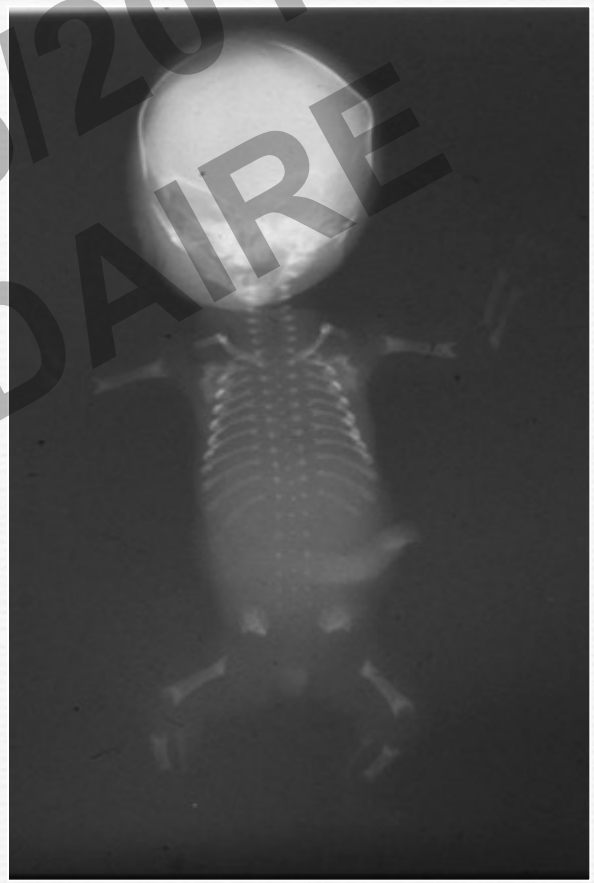


Achondrogenèses (Hypo-)

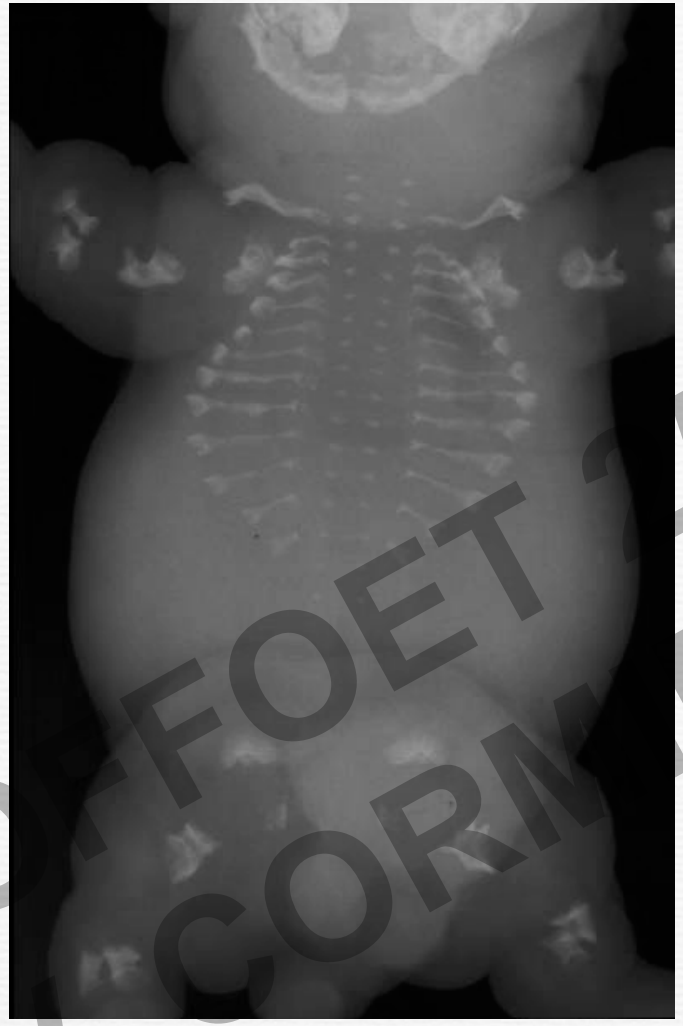


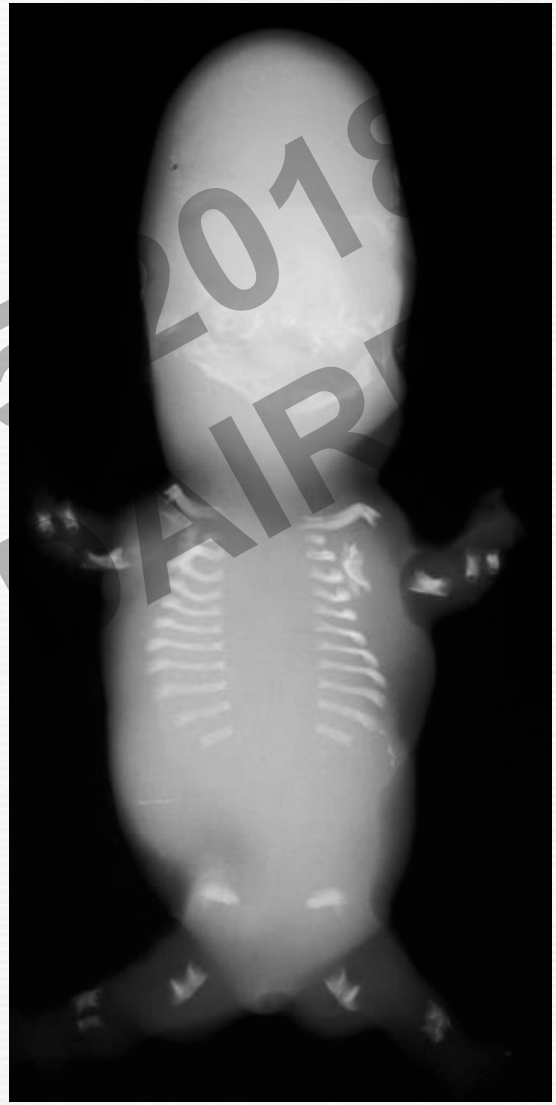
Type Ia (AR, *TRIP11*)

Type Ib (AR, *SLC26A2)*



Type II / hypochondrogenèse (néomutation, *COL2A1*)





Type 1A, AR

TRIP11 (THYROID HORMONE RECEPTOR INTERACTOR 11);

GOLGI-MICROTUBULE-ASSOCIATED PROTEIN

Type 1B, AR

SLC26A2

SOLUTE CARRIER FAMILY 26
(SULFATE TRANSPORTER), MEMBER 2;

Type 2

COL2A1

mut *de novo*

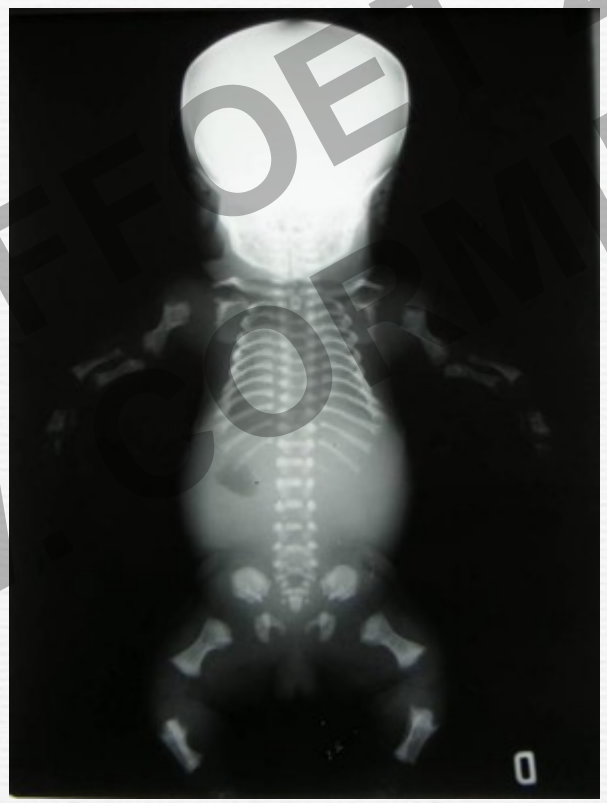
Autres chondrodysplasies létales rares

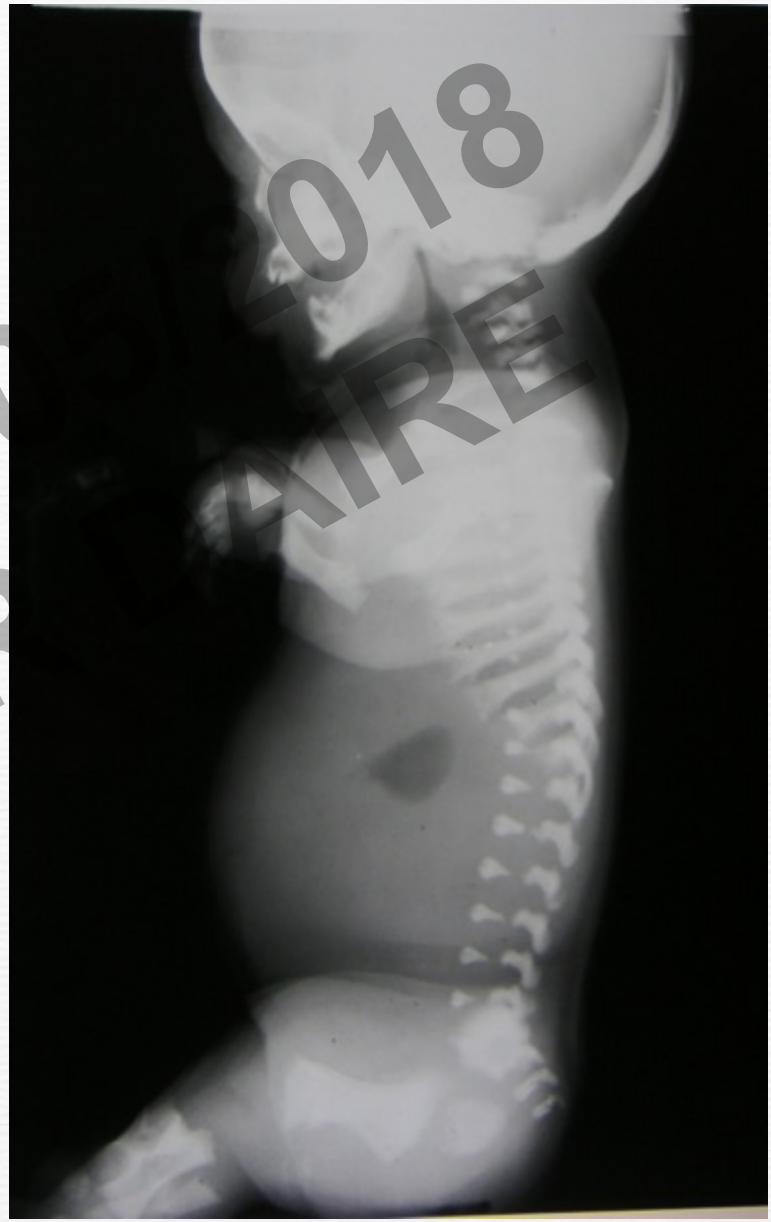
Fibrochondrogénèse létale

- Os denses, corps vertébraux en **poire**
- Histologie +++ : chondrocytes fusilformes dans la zone de réserve

AR , AD ?

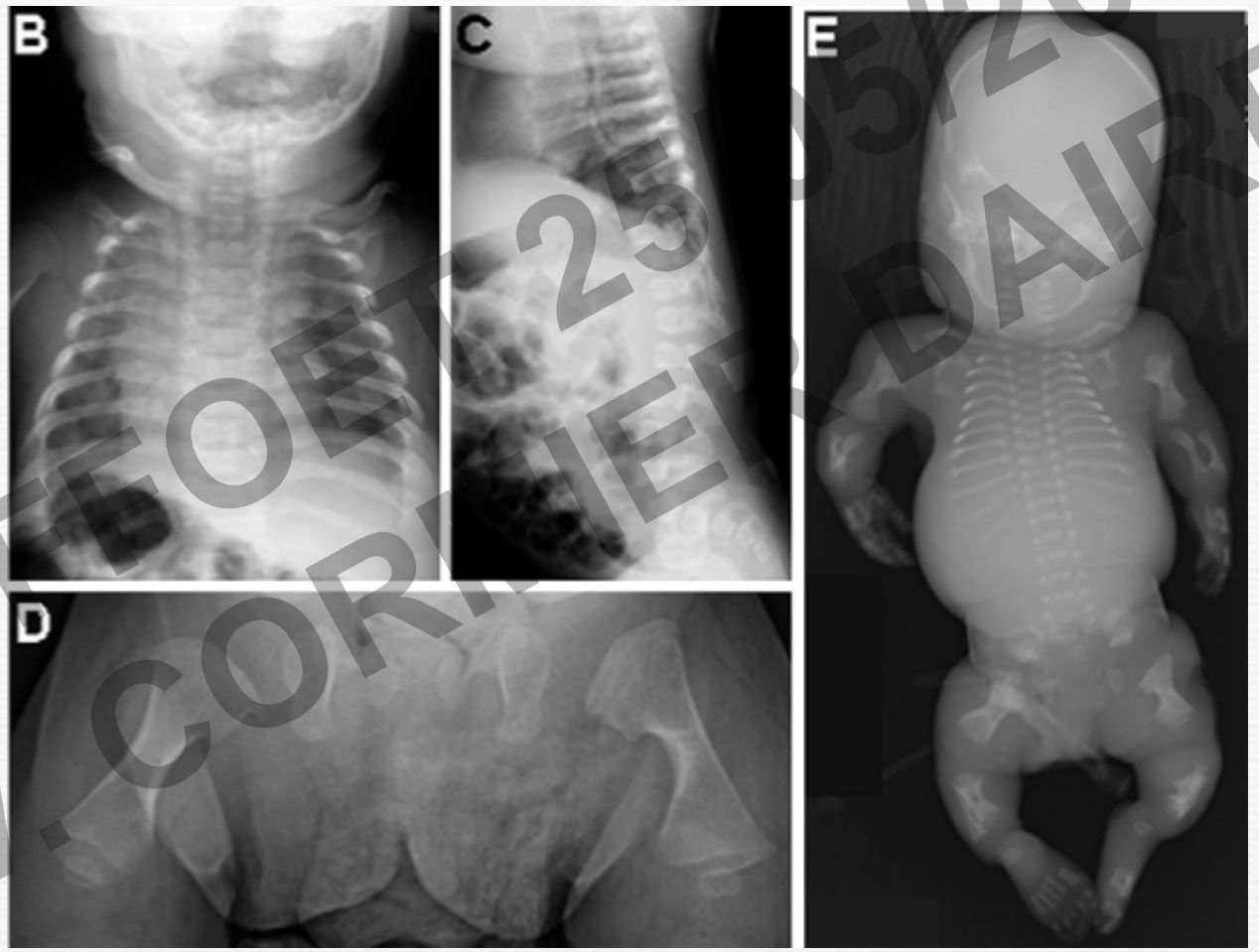
- *COL11A1* et *COL11A2*





***COL11 AI* mutations :**

p.Gly796Arg inherited from the mother (myopia)/
p.Gly315X inherited from the father (hearing loss)



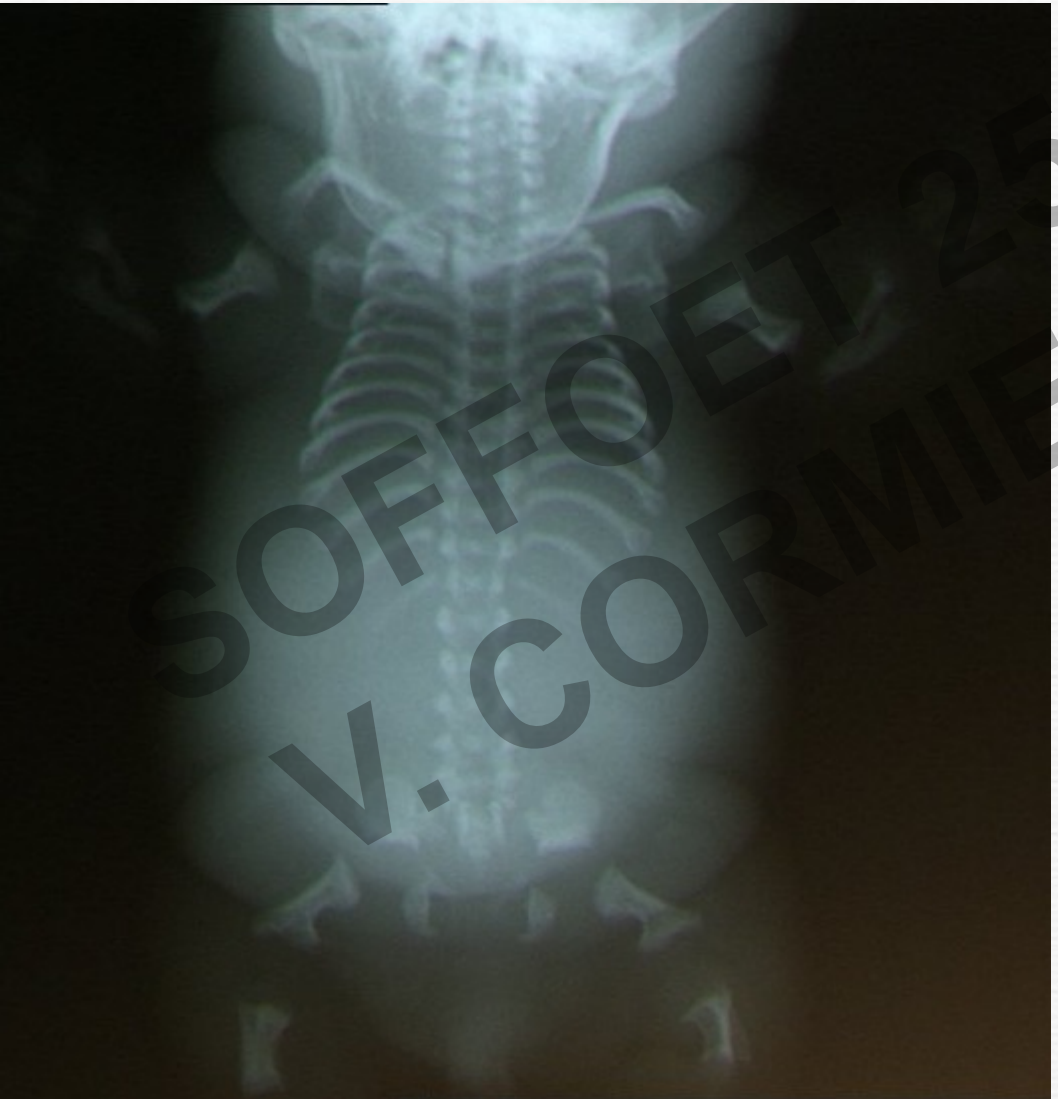
Dominant and recessive forms of fibrochondrogenesis resulting from mutations at a second locus, *COL11A2* (Tomson et al, 2012)

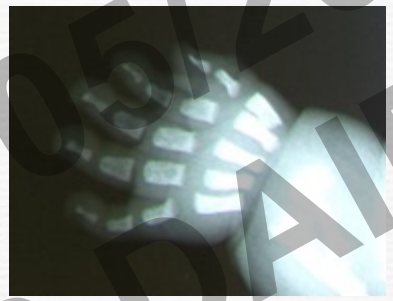
Deafness, autosomal dominant 13	601868	AD
Deafness, autosomal recessive 53	609706	AR
Fibrochondrogenesis 2	614524	AR, AD
Otospondylomegaepiphyseal dysplasia, autosomal dominant	184840	AD
Otospondylomegaepiphyseal dysplasia, autosomal recessive	215150	AR

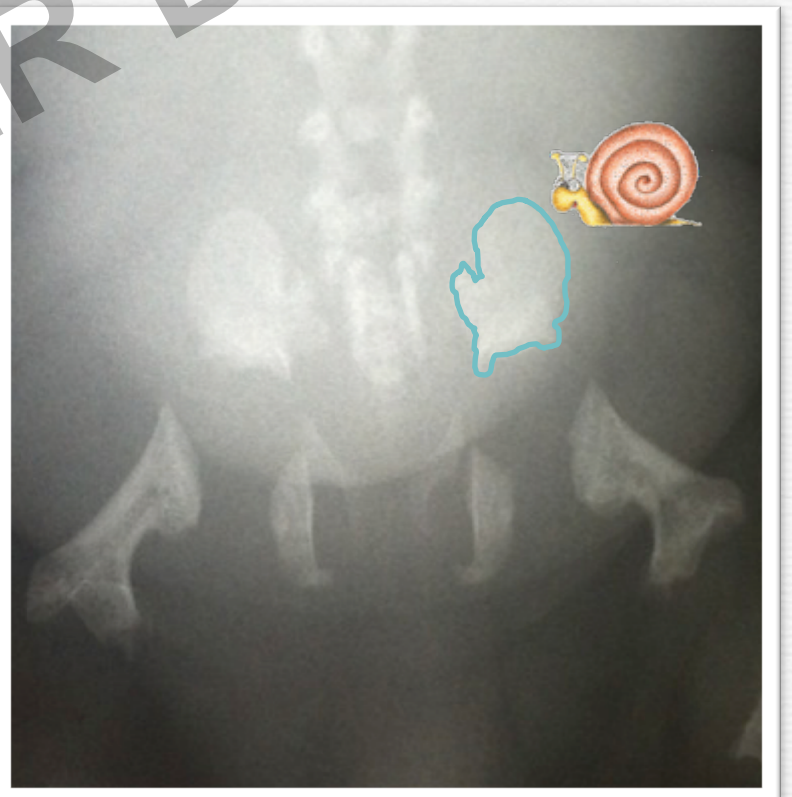
Dysplasie de Schneckenbecken AR

SLC35D1

SOLUTE CARRIER FAMILY 35 (UDP-GLUCURONIC ACID/UDP-N-ACETYLGALACTOSAMINE DUAL TRANSPORTER), MEMBER D1;







MOC, démarche diagnostique selon âge de découverte

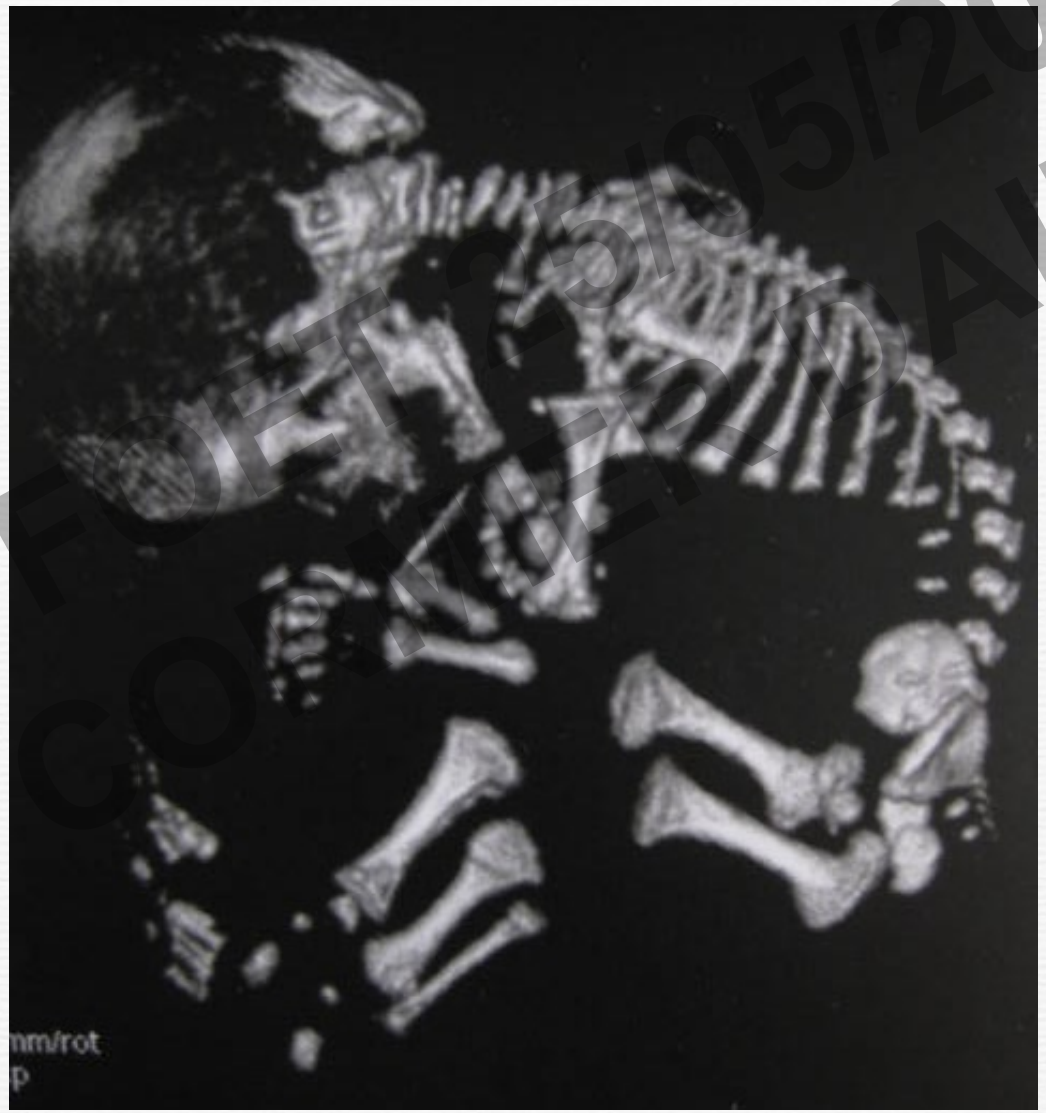
- Chondrodysplasies **incompatibles avec la vie**
  - Nanisme thanatophore
  - Achondrogenèses
  - formes rares

- Chondrodysplasies de découverte anténatale, **de PRONOSTIC variable**

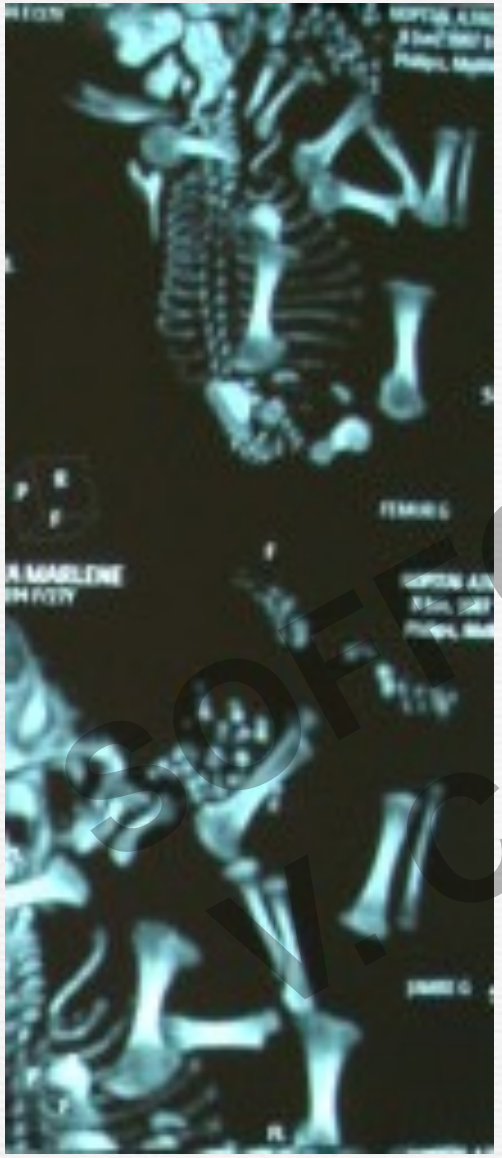
  - Dysplasie métatropique *TRPV4* AD

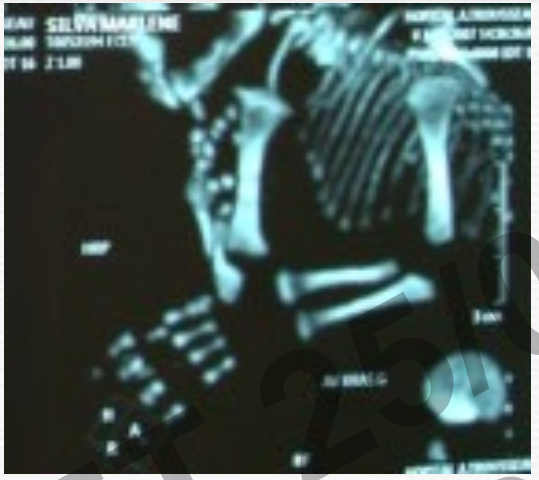
  - Dysplasies S (E)MD ..

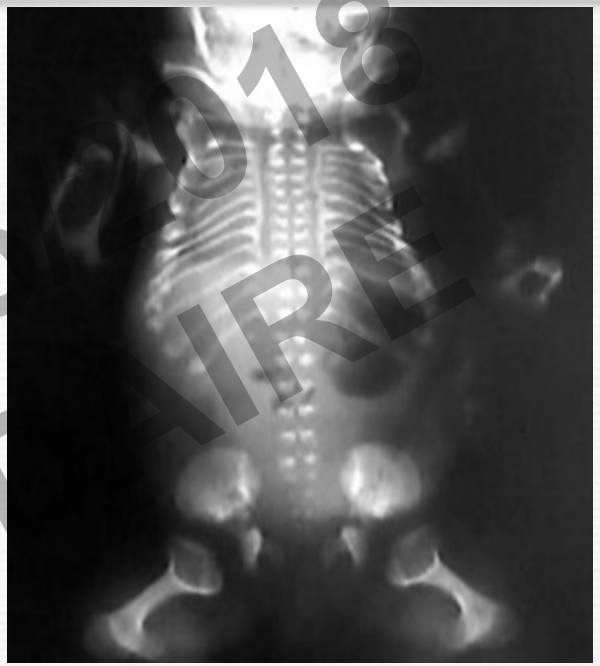
Dysplasie métatropique

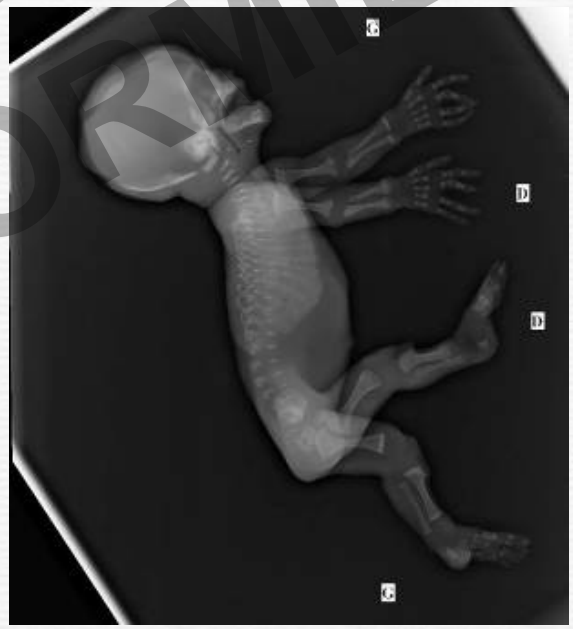


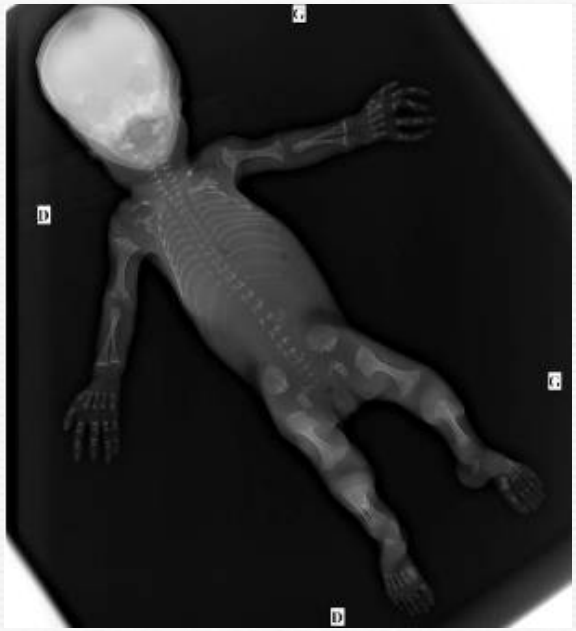
Dysplasie Métatropique



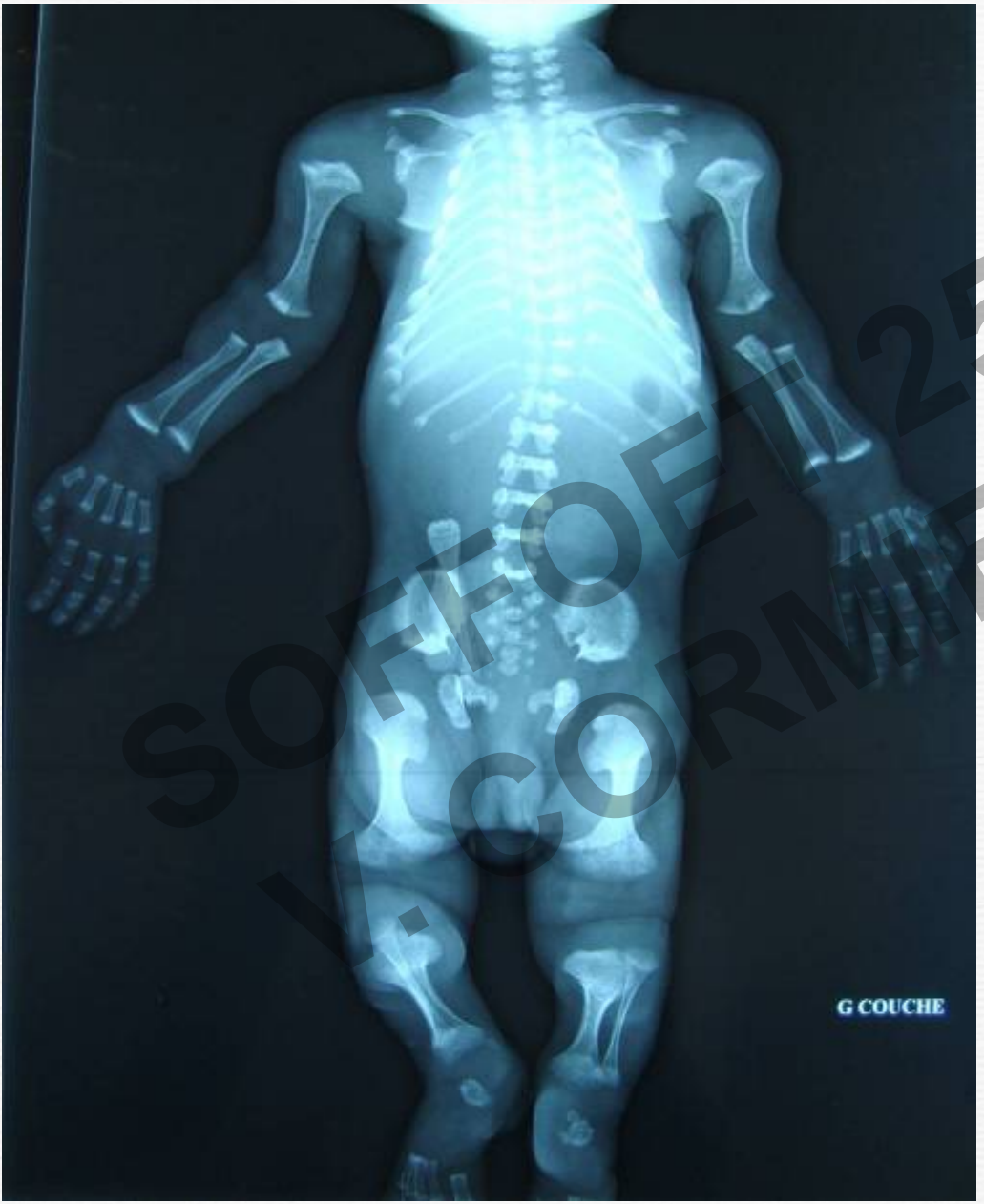








Dysplasie Métatropique



Platyspondylie ++
Déformation des ailes iliaques
Evasement métaphysaire

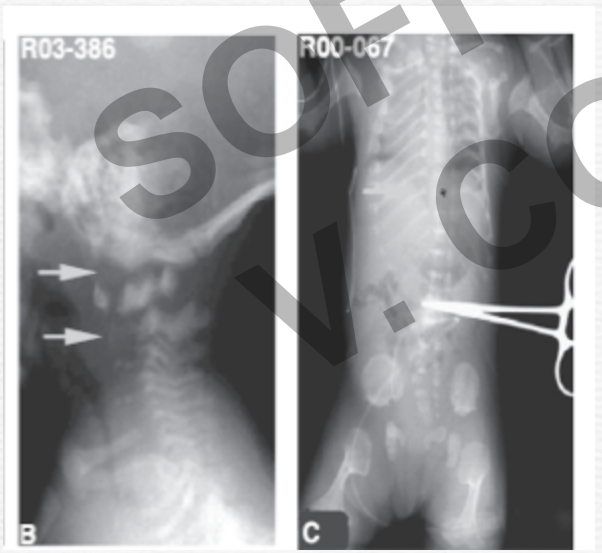
-Scoliose
-Ostéoporose
-Complications articulaires
-Corset, kiné au long cours
-Pronostic cognitif normal

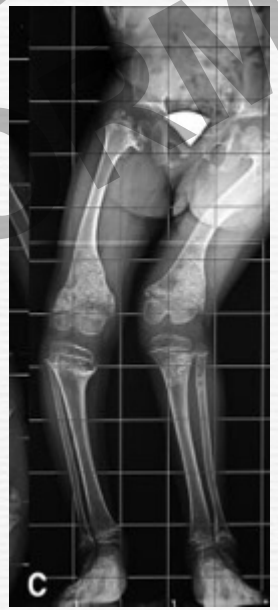
TRPV4 (AD)

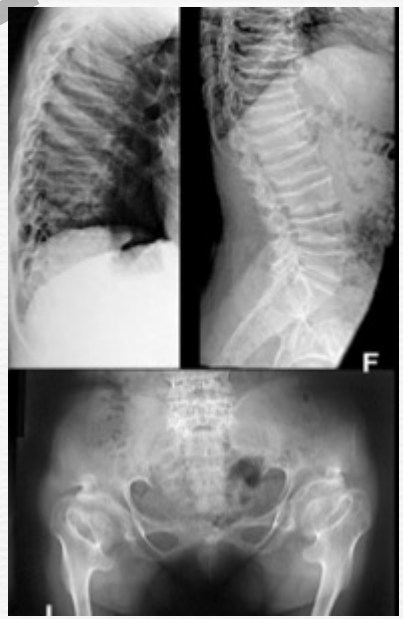
TRANSIENT RECEPTOR POTENTIAL CATION CHANNEL, SUBFAMILY V, MEMBER 4;

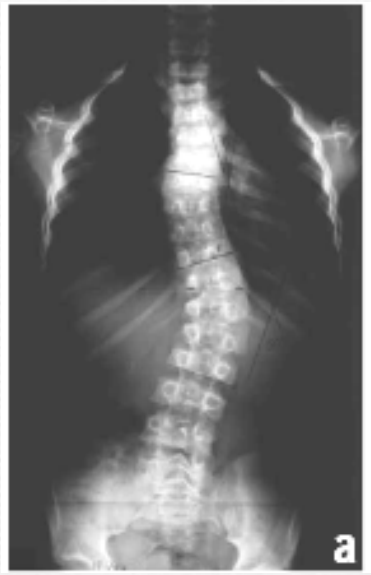
Anomalie de TRPV4

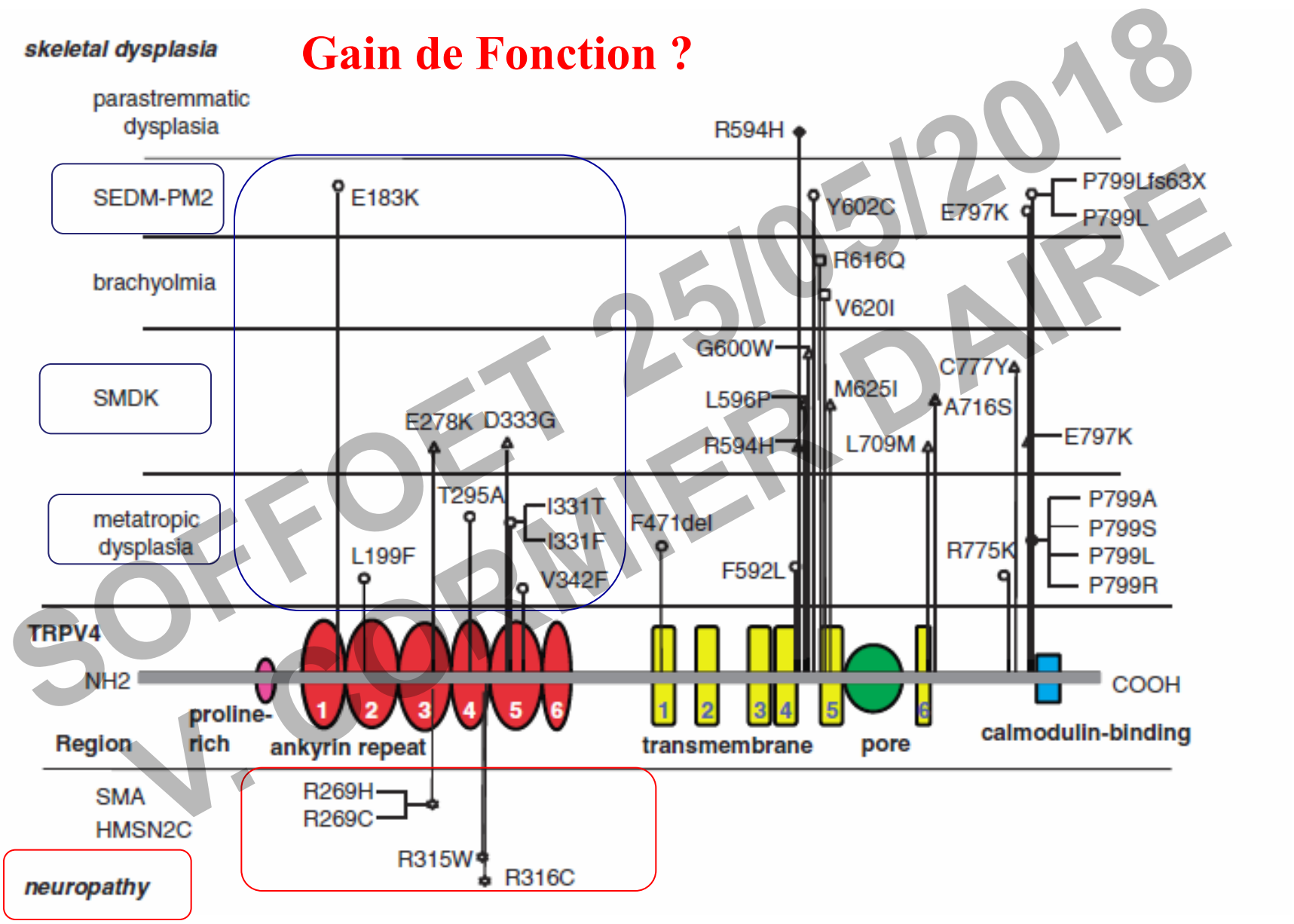
1. Dysplasie métatropique
2. Dysplasie spondylo-métaphysaire type Kozlowski: pas de BD
3. Dysplasie parastrematique: atteinte majeure des MI, enchondromes
4. Dysplasie spondylo-épi-métaphysaire type Maroteaux, Pseudomorquio type 2: pas de scoliose/ni de cyphose
5. Brachyolmie











Perte de fonction? domaine ANK,

MOC, démarche diagnostique selon âge de découverte

- Chondrodysplasies **incompatibles avec la vie**
  - Nanisme thanatophore
  - Achondrogenèses
  - formes rares

- Chondrodysplasies de découverte anténatale, **de PRONOSTIC variable**

  - Dysplasie métatropique *TRPV4* AD

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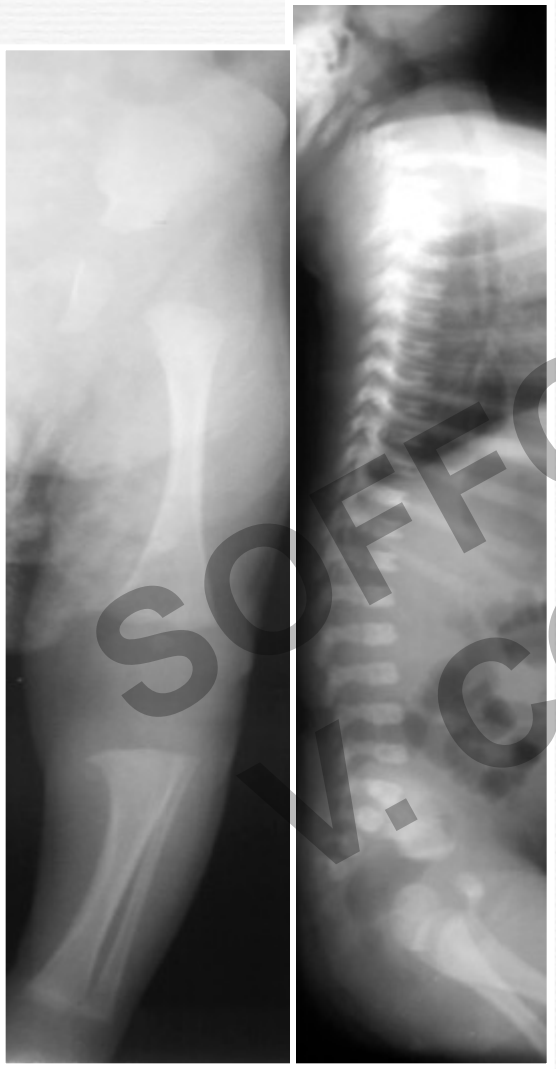
Dysplasies spondylo-epi-métaphysaires

• SEMD Strudwick type	Col2A1	AD
• Schwartz-Jampel type 1/ Dysegmentaire	Perlecan(HSPG2)	AR
• SEMD Pakistani type	ATPSK2	AR
• Dyggve-Melchior-Clausen syndrome	Dym/RAB	AR
• SEMD avec hyperlaxité, type1	B3GALT6	AR
• SEMD avec hyperlaxité, type 2	KIF22	AD
• Opsismodysplasie	INPPL1	AR
• SMD sedhagatian	SBDS/GXP4	AR
• MAGMAS		AR

…..

Syndrome de Dyggve-Melchior-Clausen

Naissance

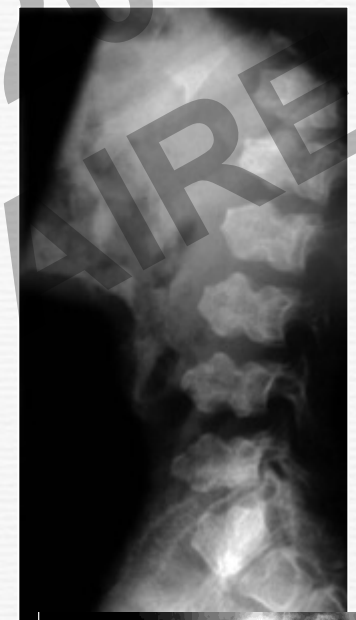


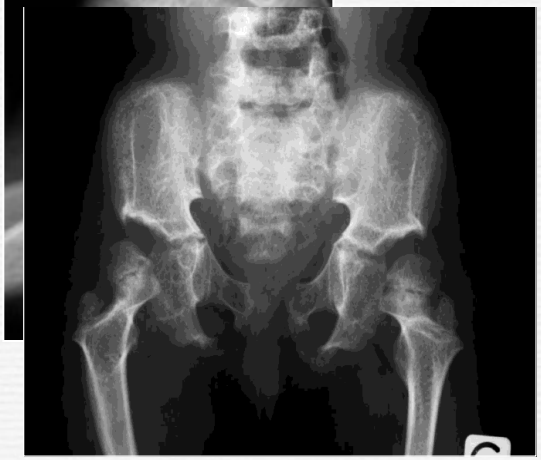
-DSEM
-**Vertèbres ondulées**
-Aspect **festonné** des ailes iliaque
-Microcéphalie
-Retard mental
-Transmission autosomique récessive

Gènes responsables :
Dymeclin (18q21) , trafic cellulaire

RAB33B (4q) régulateur du transport rétrograde GOLGI

6 ans





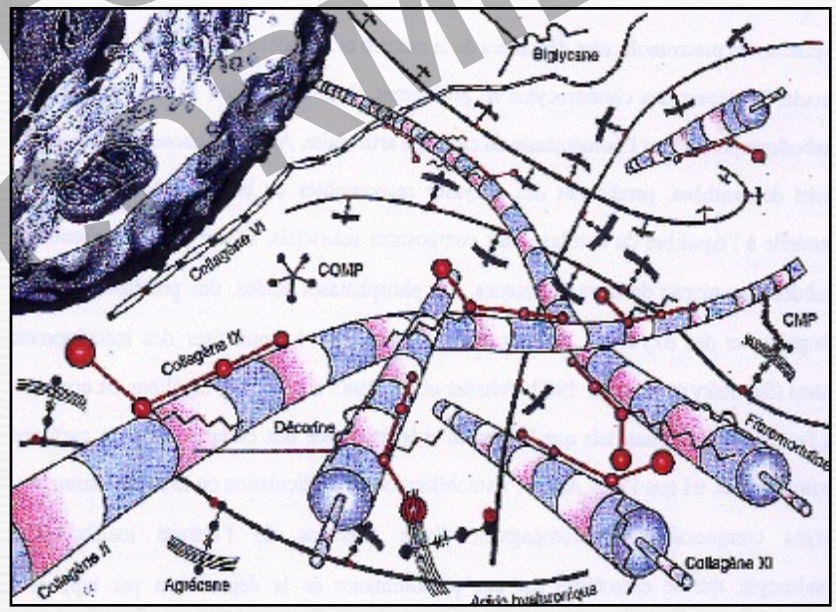
Dysplasies spondylo-epi-métaphysaires

Pas de mécanismes physiopathologiques commun

Protéines de la matrice extracellulaire

Métabolique : Lysosomes/ Golgi/RE/…

Voies de signalisation: INPPL1; GXP4;



Dysplasies spondylo-epi-métaphysaires

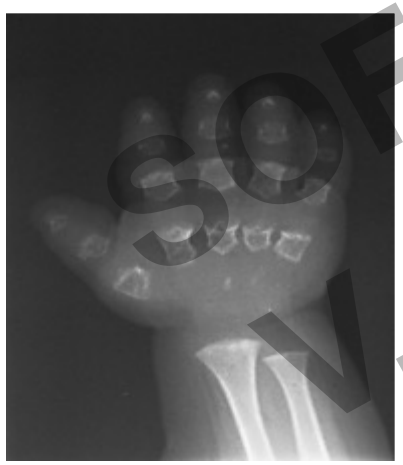
• SEMD Strudwick type	Col2A1	AD
• Schwartz-Jampel type 1/ Dysegmentaire	Perlecan(HSPG2)	AR
• SEMD Pakistani type	ATPSK2	AR
• Dyggve-Melchior-Clausen syndrome	Dym/RAB	AR
• SEMD avec hyperlaxité, type1	B3GALT6	AR
• SEMD avec hyperlaxité, type 2	KIF22	AD
• **Opsismodysplasie**	**INPPL1**	**AR**
• **SMD sedhagatian**	**SBDS/GPX4**	**AR**
• **MAGMAS**		**AR**

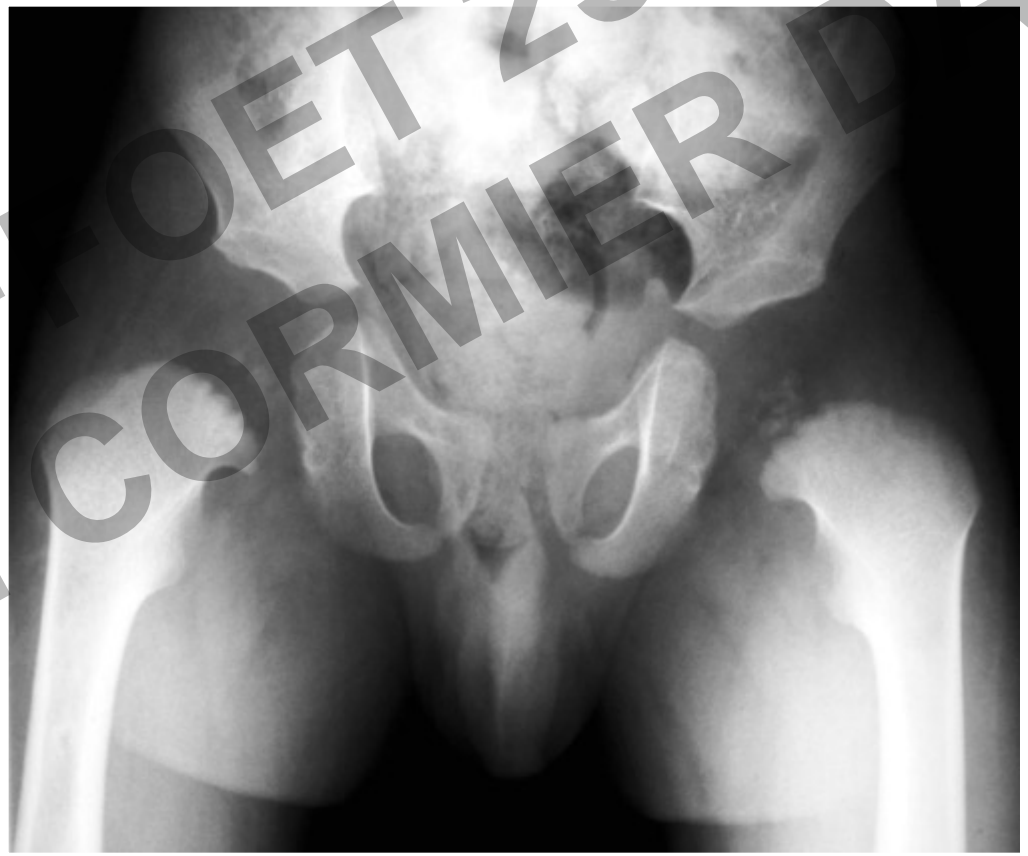
…..

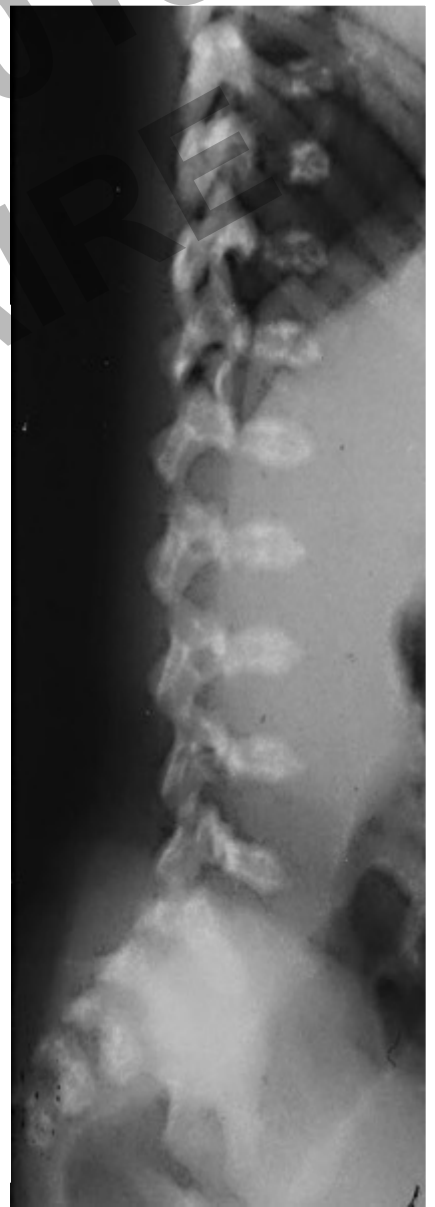
Opsismodysplasie

- décrit en 1982 , “retard” en grec
- retard **majeur** de maturation osseuse
- briéveté des extrémités

2ans





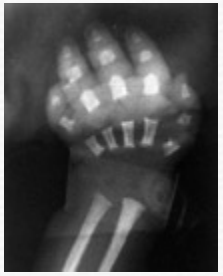
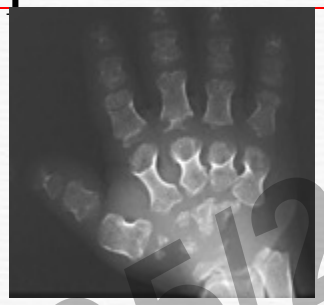


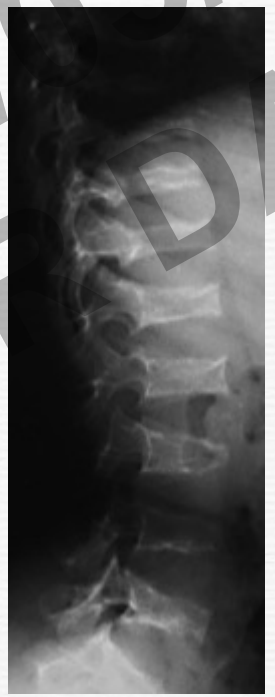
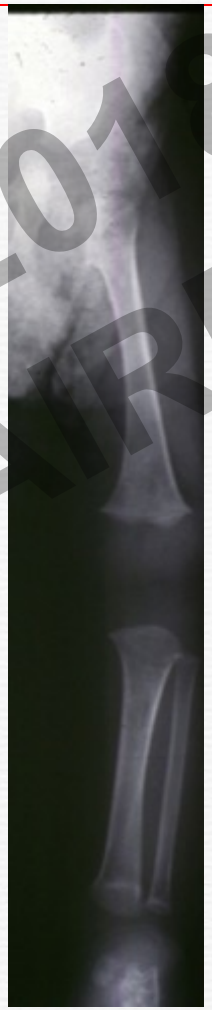
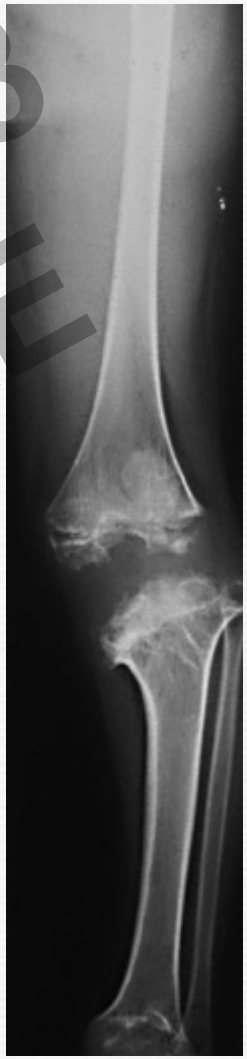
Opsismodysplasie

- Décrit en 1982 “retard” en grec
- Retard **majeur** de maturation osseuse
- Briéveté des extrémités
- DSEM
- Transmission autosomique récessive

Total de 19 cas

IMG	10
DC d’insuff respiratoire	4
période neonatale	6
2- 4	2
Survivants	5

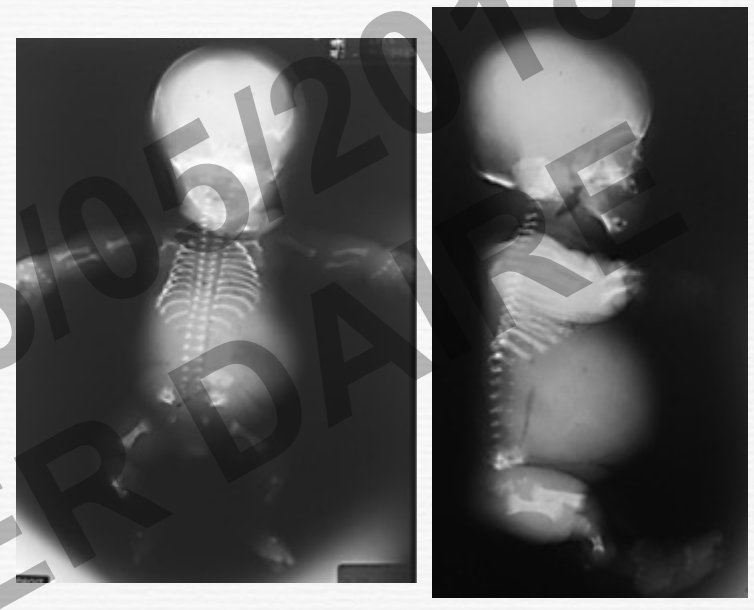




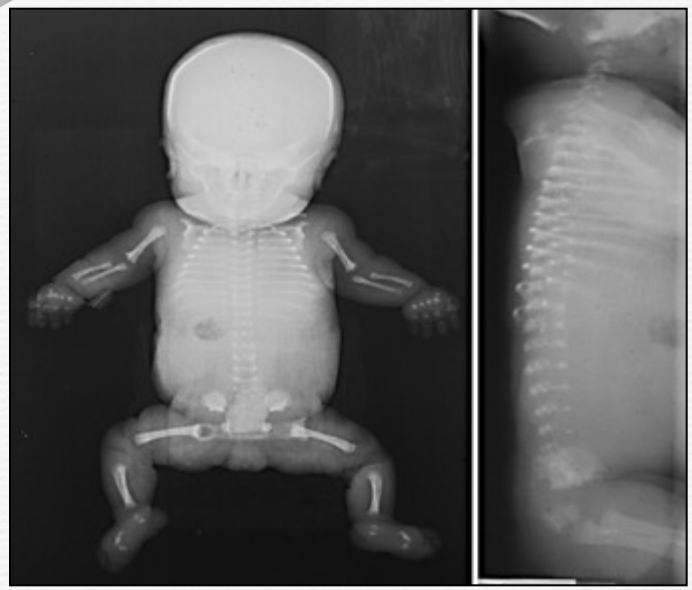
Opsismodysplasie

10 terminated pregnancies

(14 – 29 WG)

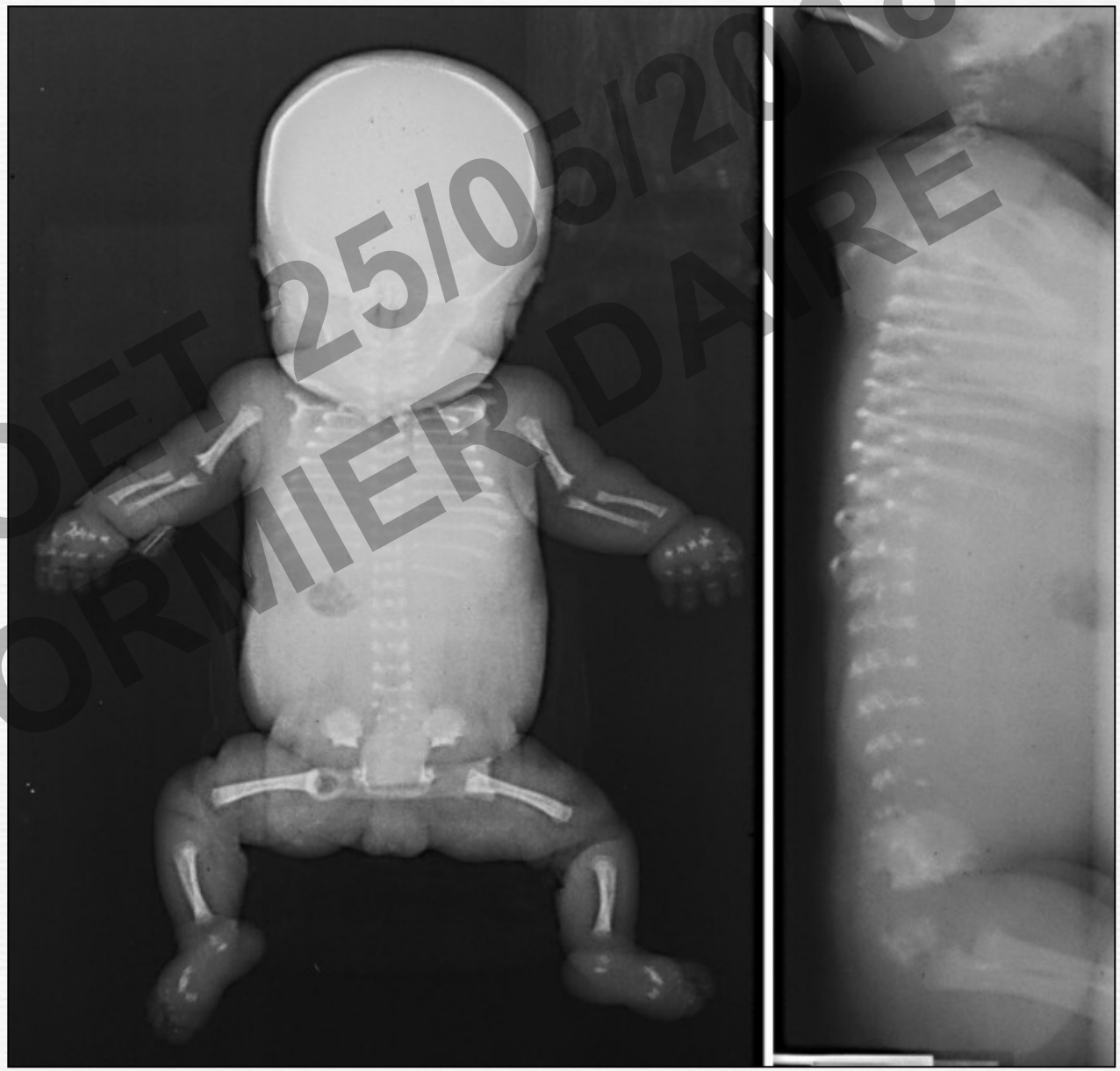
- Hygroma
- Short long bones
- Short extremities
- Narrow thorax





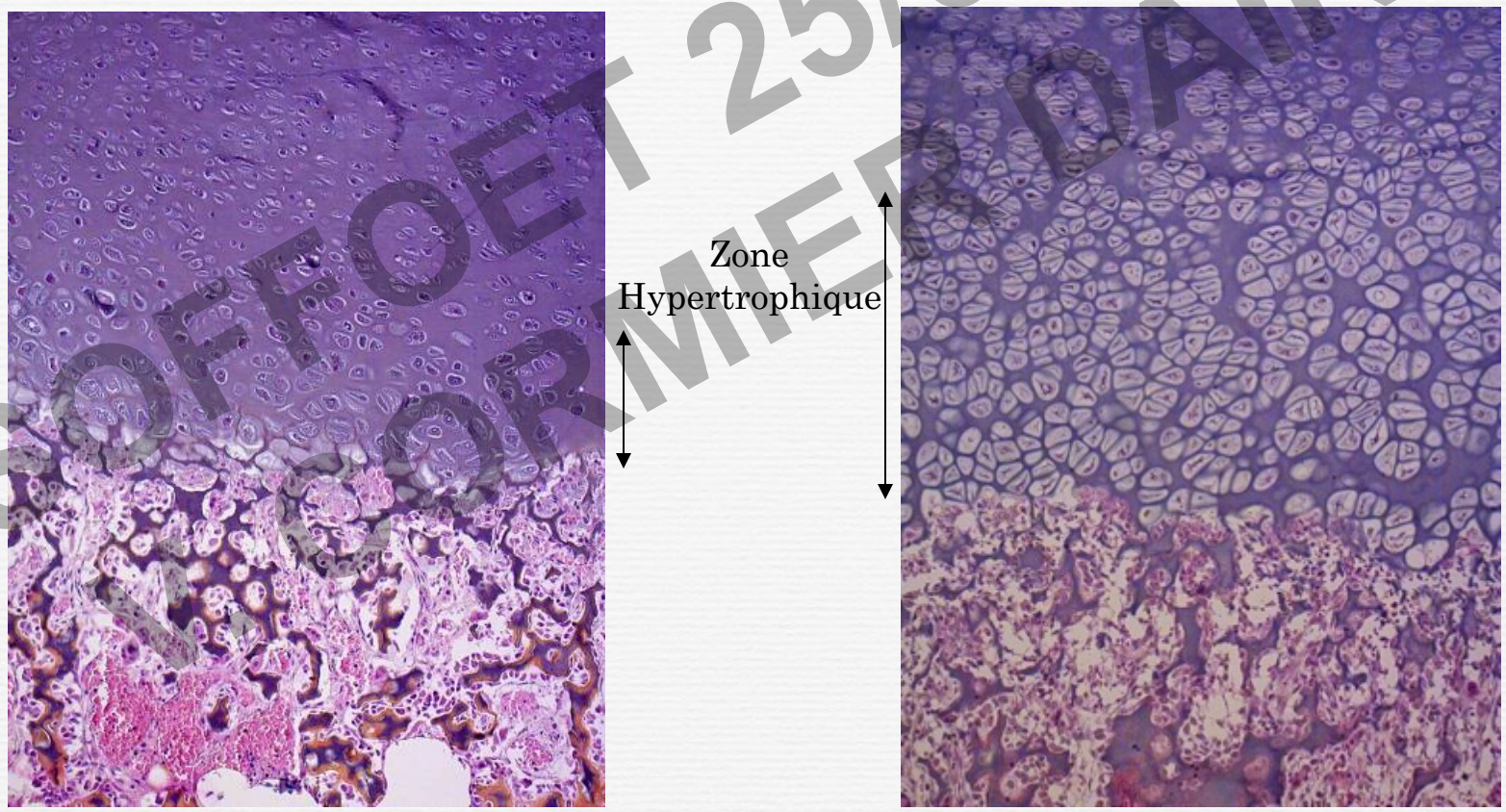
Opsismodysplasie

(Diagnostic Antenatal, 29 SA)



Opsismodysplasie

Etude histologique



15 SA

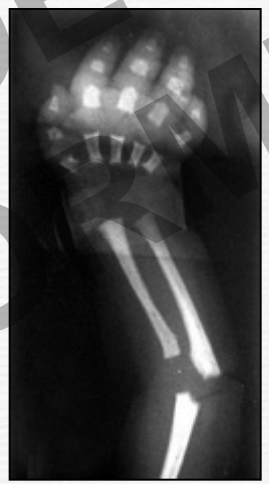
Contrôle

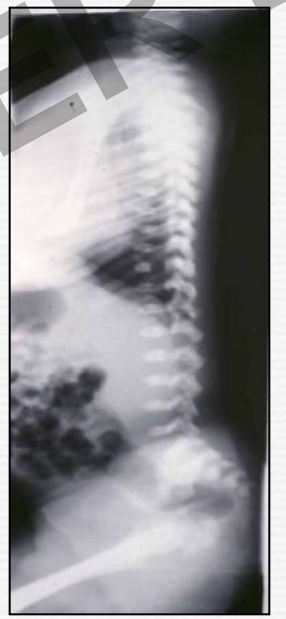
Opsismodysplasie

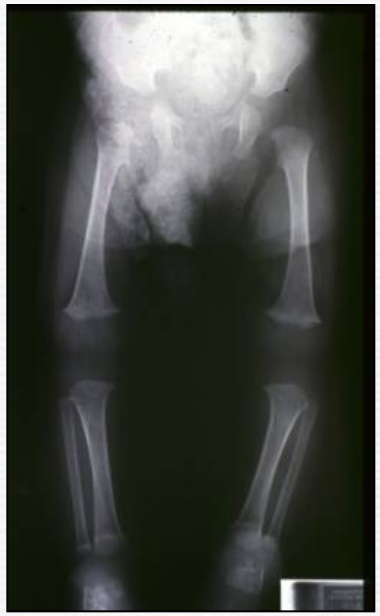
postnatal cases

4/9 : Early death of respiratory distress

D1-15 months







Opsismodysplasie

9 postnatal cases

5 survivors: **age range 4-19 years**

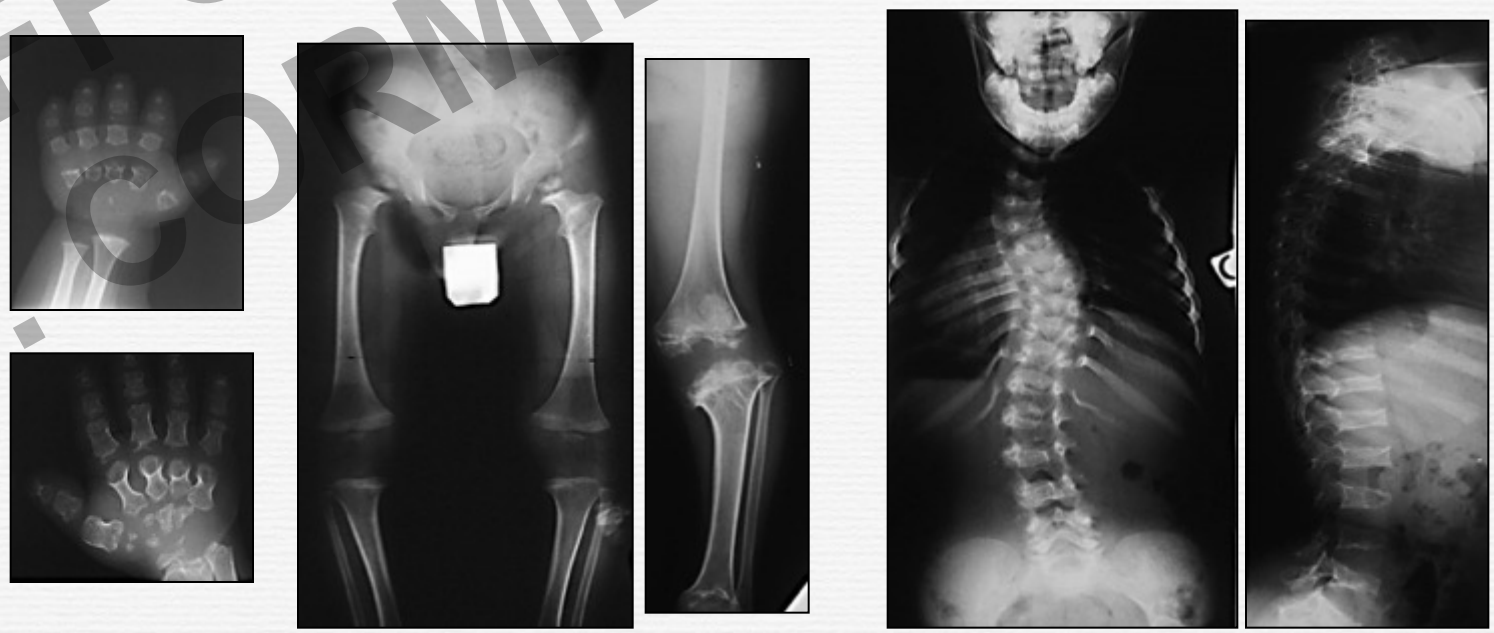
-Normal cognitive development

-Severe short stature < – 4 SD

-Lower limb deformity

-Scoliosis

-Atlantoaxial instability at least in 1



Opsismodysplasie

10 familles (16 cas)

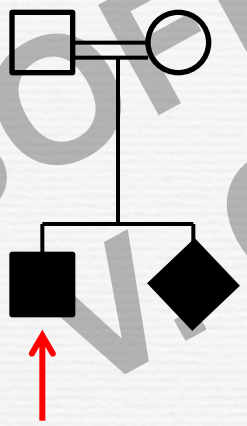
7 IMG
(14 – 29 SA)

9 cas post nataux
(décès précoce – 19 ans)

- Retard statural sévère – 4DS
- Développement cognitif normal
- Déformation des membres inférieurs
- Scoliose sévère

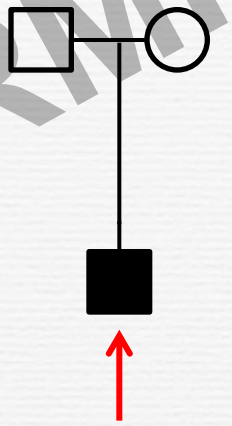
Exome : ***INPPL1***

Famille 1



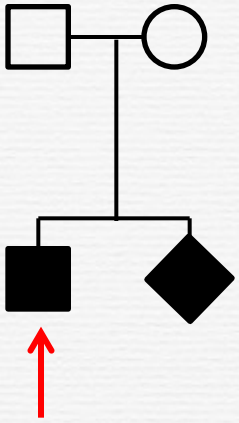
p.Arg949*

Famille 2



p.Gln93Profs*3
p.Pro659Ser

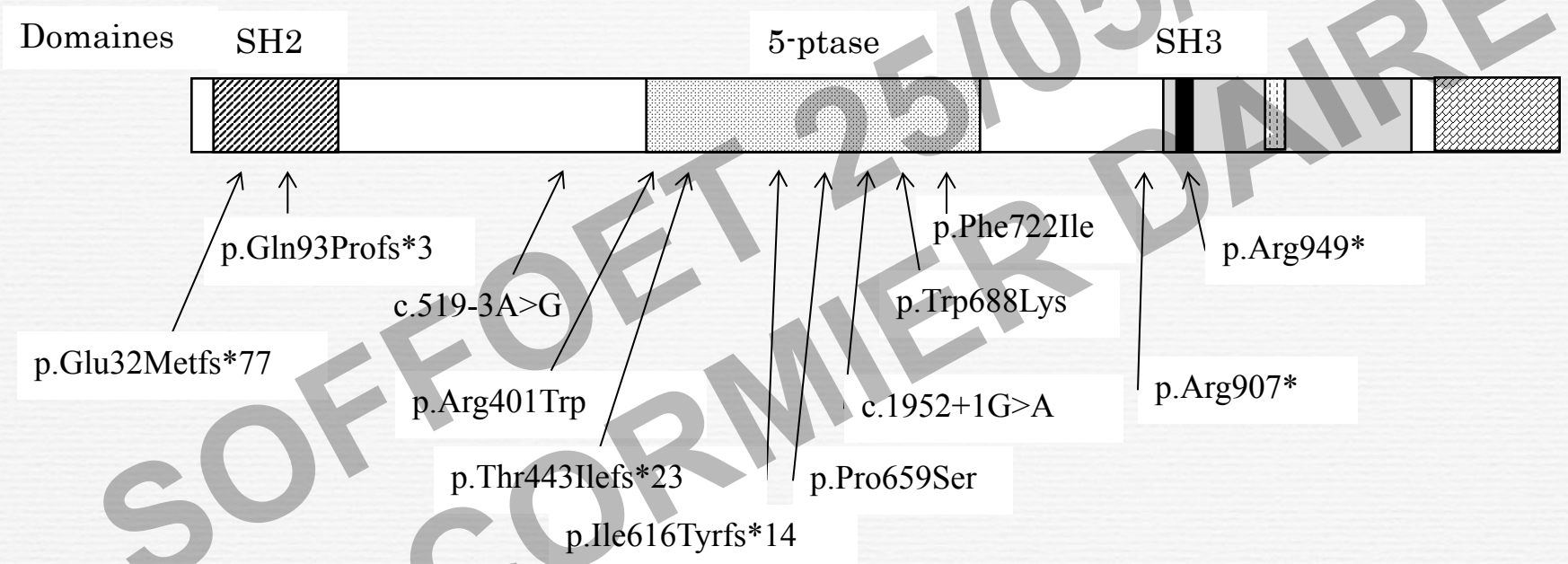
Famille 3



p.Arg401Trp
p.Phe722Ile

Opsismodysplasie

Séquençage de *INPPL1* (inositole polyphosphate 5-phosphatase)



Domaine riche en proline

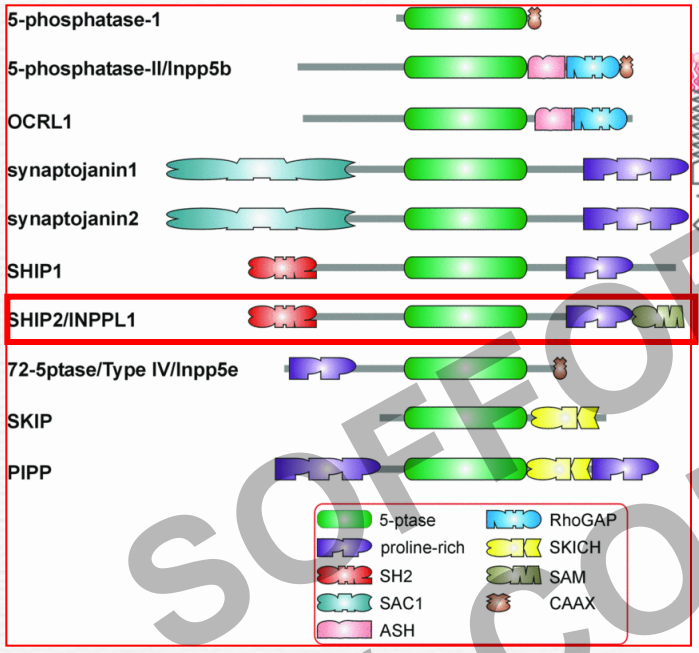
Motif NPXY

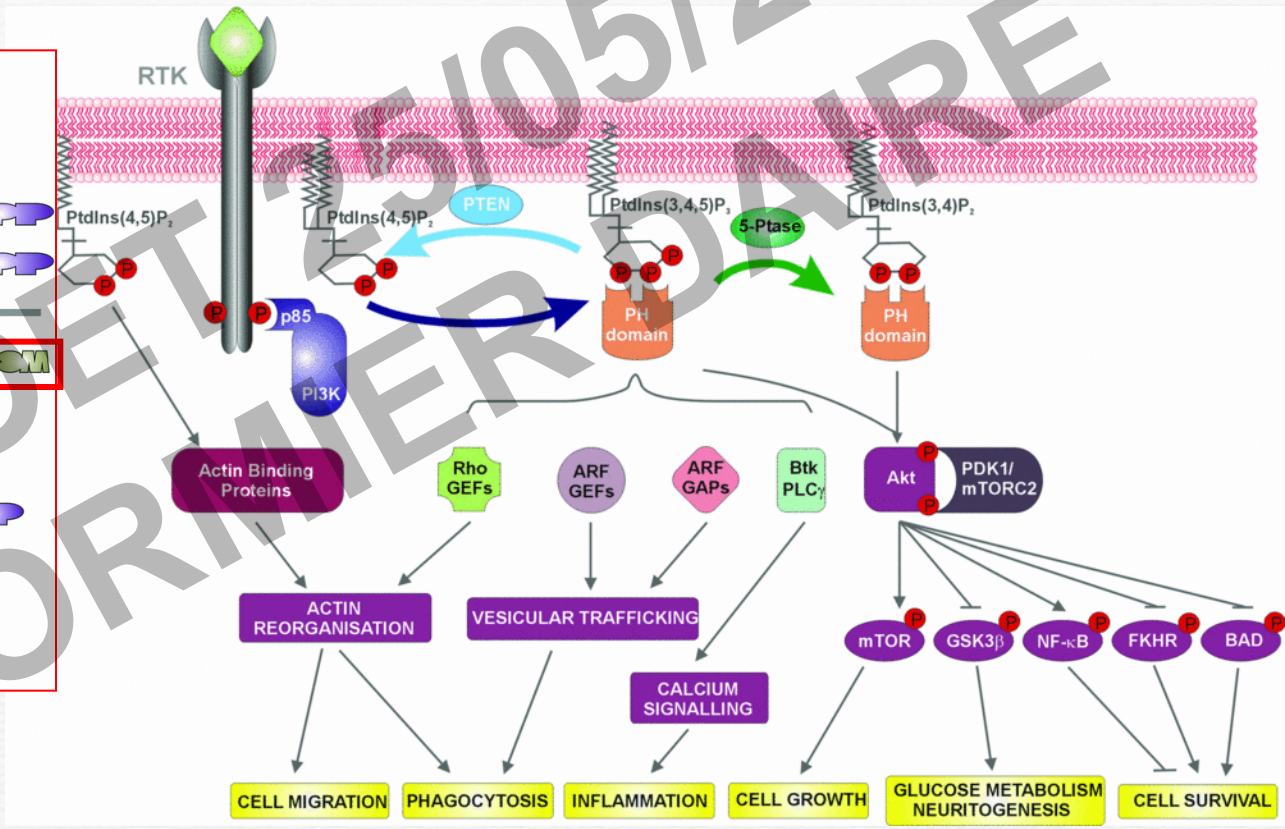
Domaine SAM

2 mutations stop
4 del, ins, dup
2 mutations d'épissage
4 mutations faux sens

Opsismodysplasie

Structure des inositole polyphosphate 5-phosphatases





Biochemical Journal (2009) 419, 29-49 - Lisa M. Ooms et al.

negative regulation of insulin signalling and glucose homeostasis

Opsismodysplasia

SNP analysis in the japanese population

- *INPPL1* polymorphisms associated with predisposition to insulin resistance

***Inppl1*-/- mice**

- viable and half size of wild type
- normal glucose and insulin levels
- high resistant to weight gain

→ **Obesity resistance**

Eléonore Dubois et al.
Cell ular Signalling (2012)

5 survivors in our series:

- no insulin resistance reported
- height and weight both < -4 SD

Huber C et al,2012 Am J Hum Genet

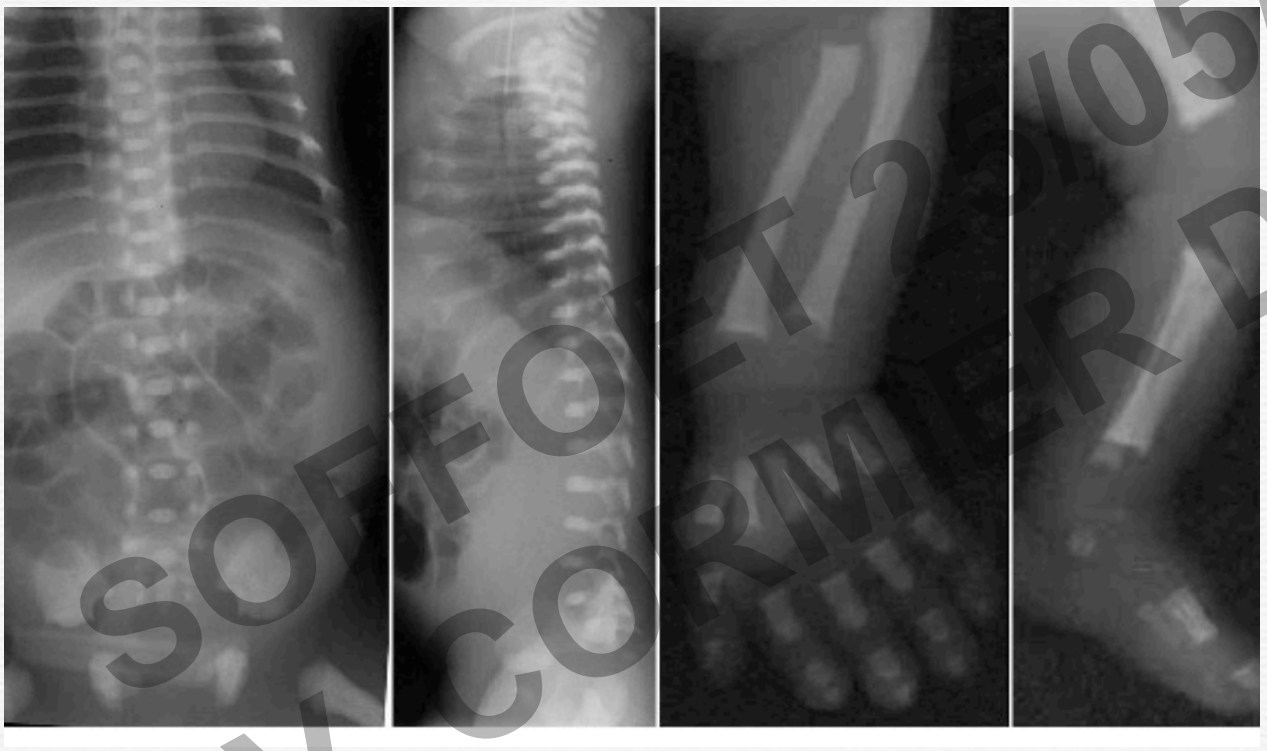
Dysplasie spondylo-metaphysaire, type Sedhagatian

(MIM 25020)

- **Rare lethal disorder** : 17 infants from 12 families reported so far, first described in 1980, in an Iranian family
- **Severe metaphyseal chondrodysplasia** with mild limb shortening, platyspondyly, delayed epiphyseal ossification, irregular iliac crests and pulmonary heamorrage
- Hypotonia and cardiorespiratory problems: longest survivor 161 days
- **Complex cardiac anomalies** : conduction defects, complete heart block
- **CNS malformations** : agenesis of CC, pachygyria, lissencephaly, cerebellar hypoplasisa

Dysplasie spondylo-métaphysaire, type Sedhagatian

SBDS (Schwachman-Bodian-diamond)



TN -5 DS/ W -3.1 SD,/HC -0.3 DS
Narrow thorax
Hypotonia
Seizures

Neutropenia in infancy

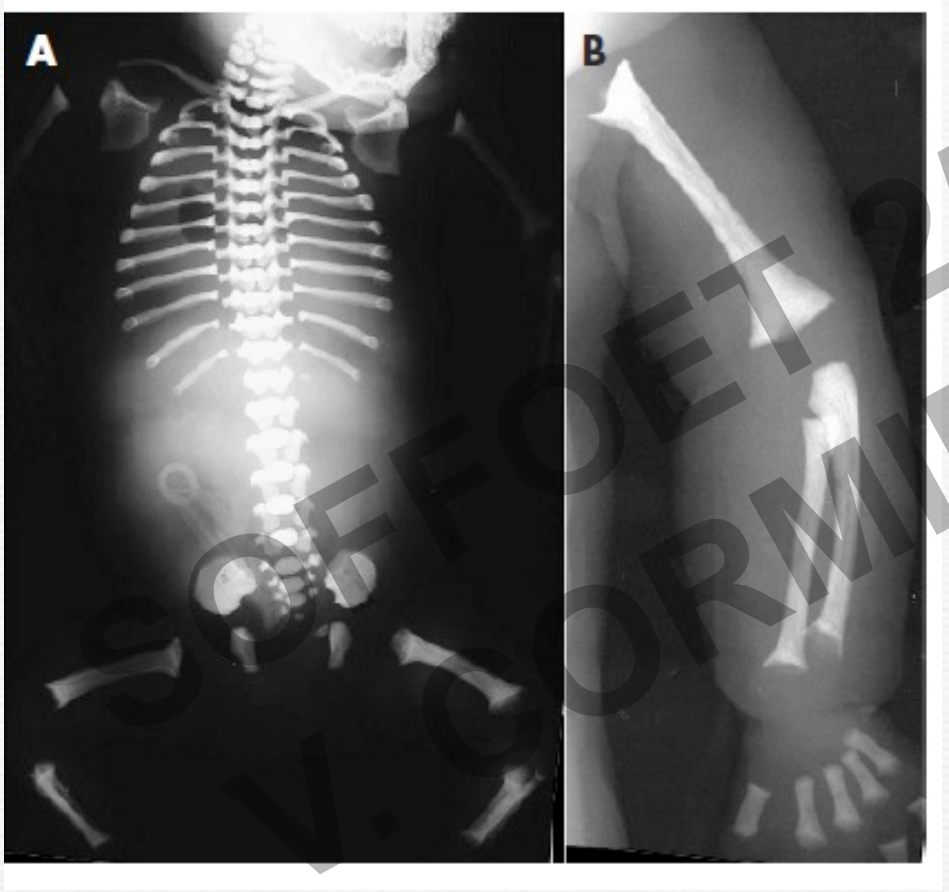
-7.5 DS at 11 years

***SBDS* :**
79T>C/ 183TA> CT

Nishimura et al, J Med Genet 2007

Dysplasie spondylo-metaphysaire, type Sedhagatian

SBDS (Schwachman-Bodian-diamond)

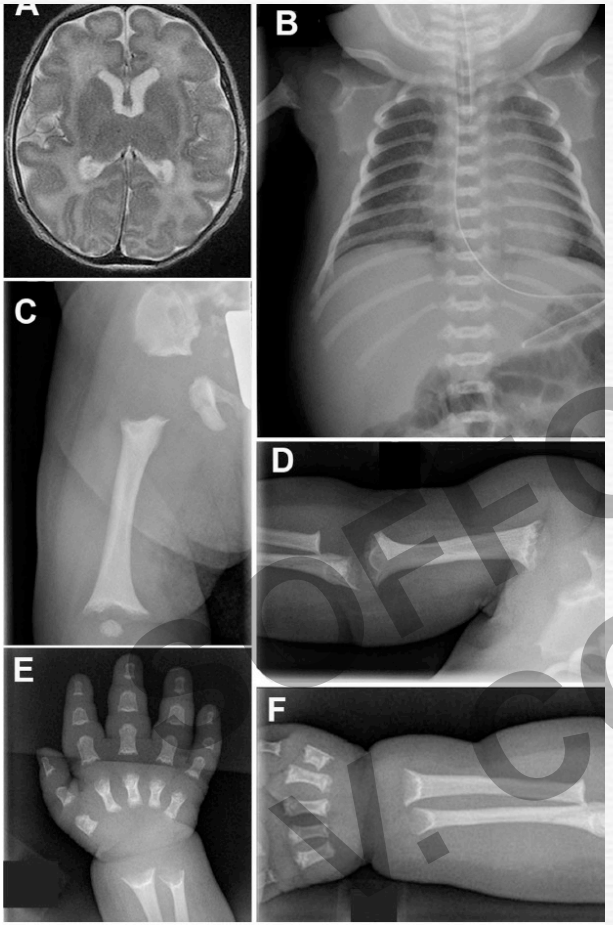


- ***SBDS* : 183TA>CT/258+2T>C**
- **Stillbirth at full term**
- Narrow thorax
- Cupped methhyses
- Irregular iliac crest
- Platyspondyly
- Pulmonary hypoplasia
- Hepatic fibrosis

Nishimura et al, J Med Genet 2007

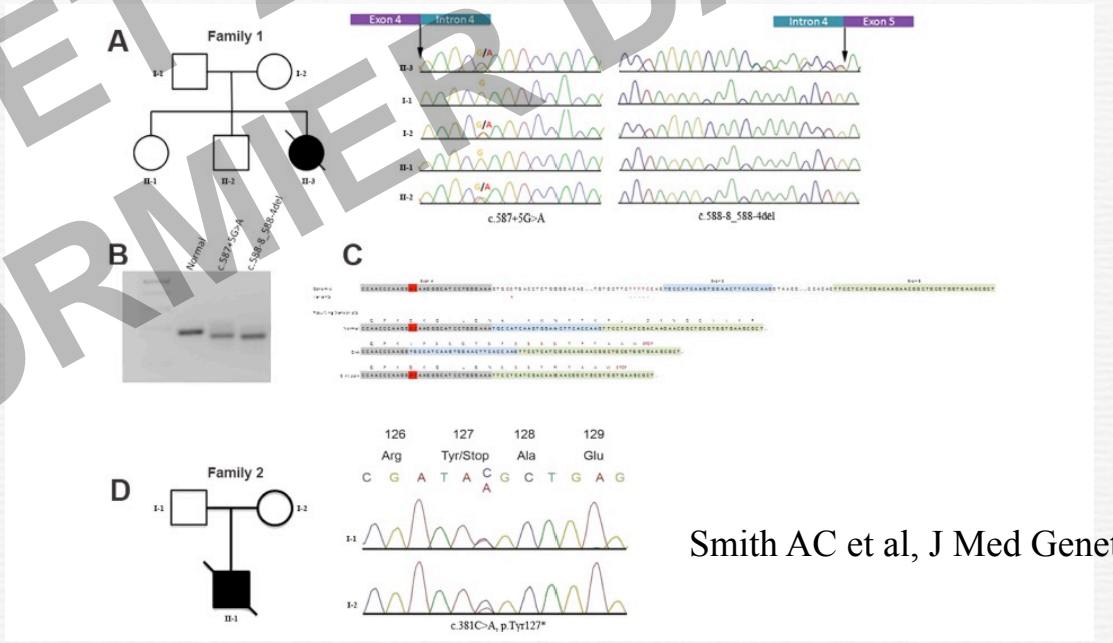
Dysplasie spondylo-metaphysaire, type Sedhagatian

GPX4 (glutathione peroxidase*)*



IUGR
Apnoiec episodes
cardiac arythmias
simplified gyral pattern
Death at D18

IUGR
Hypotonia
Congenital AV block
Simplified gyral pattern
Death 4 months of age



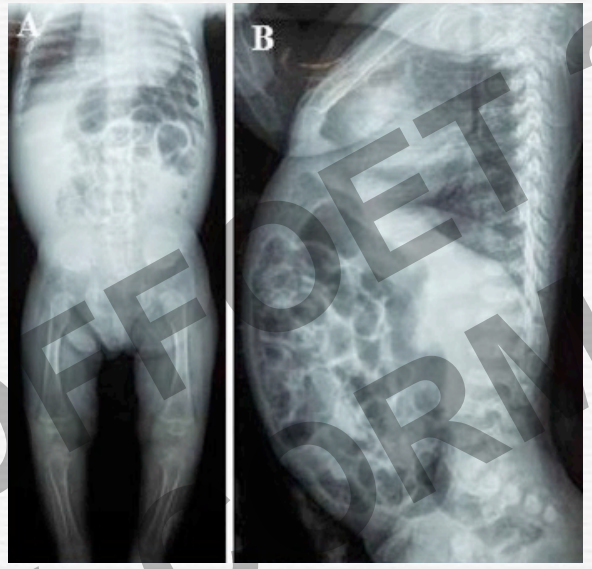
Smith AC et al, J Med Genet 2014

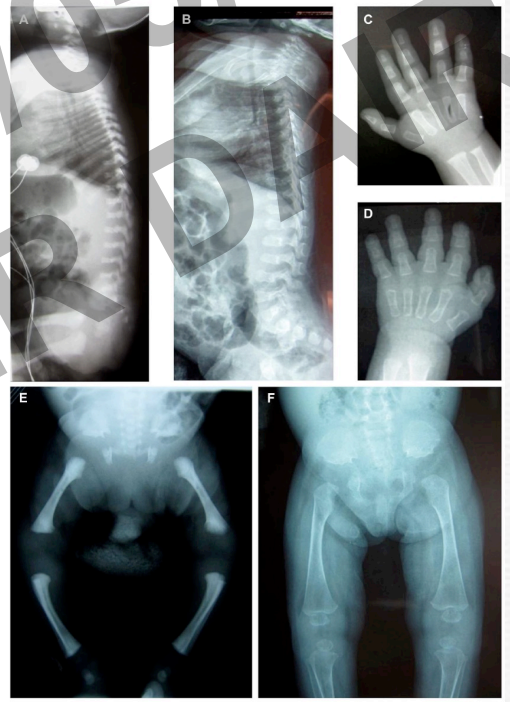
GPX4 essential for early embryonic development
regulating anti oxidative and anti apoptotic activities

MAGMA

Mitochondria-associated granulocyte
macrophage colony stimulating factor signaling molecule macrophage

deux familles consanguines libanaises
nanisme spondylodysplastique et insuffisance cardiaque
DC > 2 ans





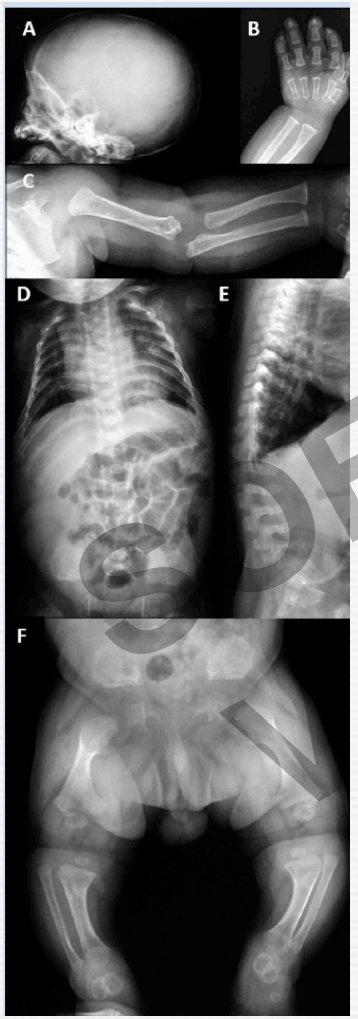
mutation homozygote: c.226 A>G, p.Asn76Asp
protéine mitochondriale (PAM: presequence translocase associated priotein import motor)
regulates preprotein translocation into the mitochondrial matrix

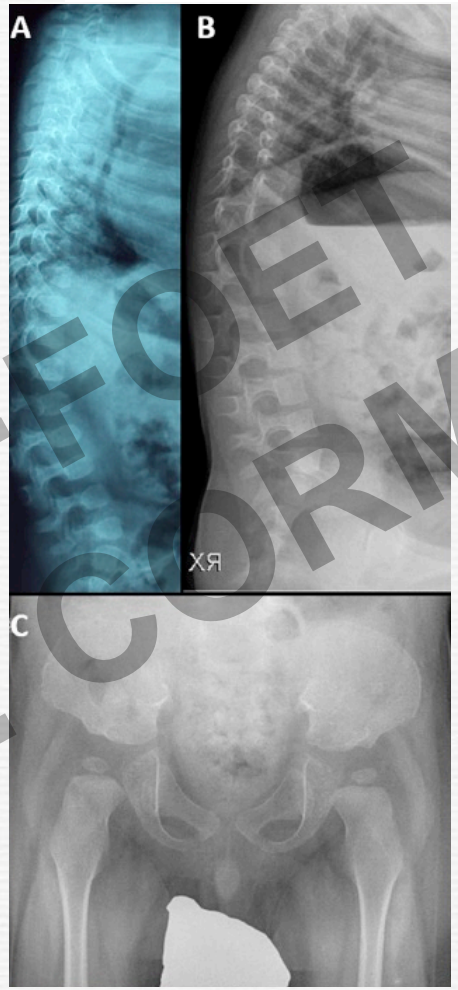
Mehawej C et al, PLOS Genet 2014

A Novel Homozygous *PAM16* Mutation in a Patient with a Milder Phenotype and Longer Survival

Shahida Moosa,[1] Virginia Fano,[2] Maria Gabriela Obregon,[3] Janine Altmüller,[4,5] Holger Thiele,[5] Peter Nürnberg,[5,6] Gen Nishimura,[7] and Bernd Wollnik[1]*

PAM16: c. 221A>C (p.Q74P)





TN 40 cm
5 ans : -5 DS poids et taille, retard de developpement, pas d'atteinte cardiaque
Amélioration de la platyspondylie

Nanismes létaux palysopndyliques

- **Grande hétérogénéité génétique**
- **Pas de mécanismes physiopathologiques commun**

  Protéines de la matrice extracellulaire

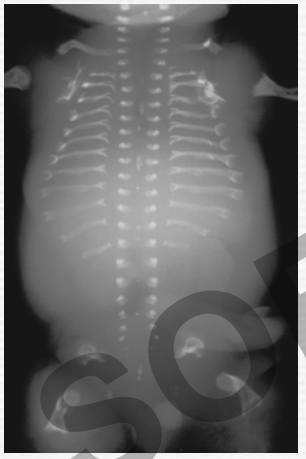
  Métabolique : Lysosomes/ Golgi/RE/ Mito …

  Voies de signalisation: INPPL1 /.
- **Difficultés nosologiques: manque de** spécificité des manifestations squelettiques, importance des manifestations extrao-sseuses, histoire naturelle ??

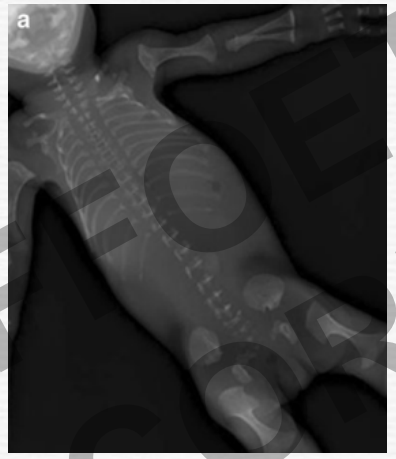
Nanismes létaux platyspondyliques: MOCOME

Rendement du Mocome : 50 %

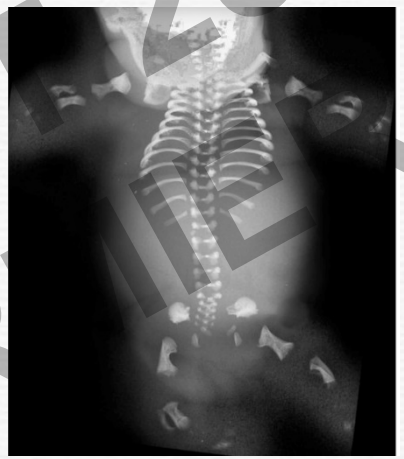
Place de l'exome?



TRIP11



TRPV4



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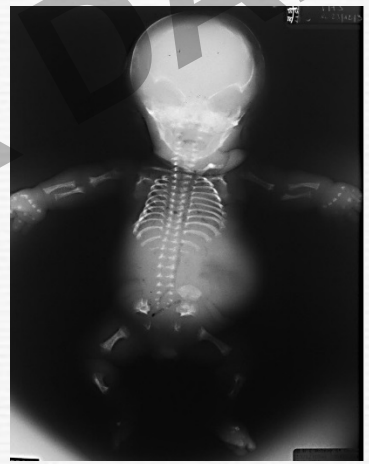
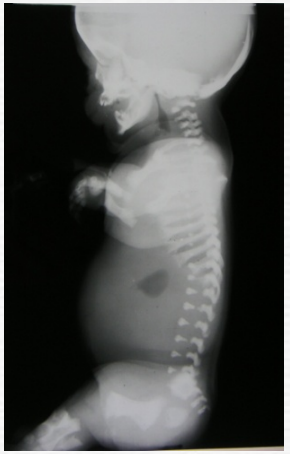


INPPL1



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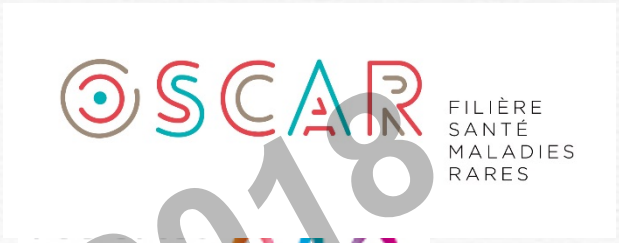

G. Baujat
C. Michot

C. Haudry
S.Monnot
S.Rondeau
J-P. Bonnefont
A. Munnich

B. Bessiére
T.Attié-Bitach
C.Quelin
M. Gonzales
……
SOFFOET

C Huber
C Mehawej
P Marzin

Dept of pediatrics
Torino, Italy:
E Biamino