Bone disorders : Presenting symptom II

- **Congenital bowing of the femora**

- **Short Ribs**

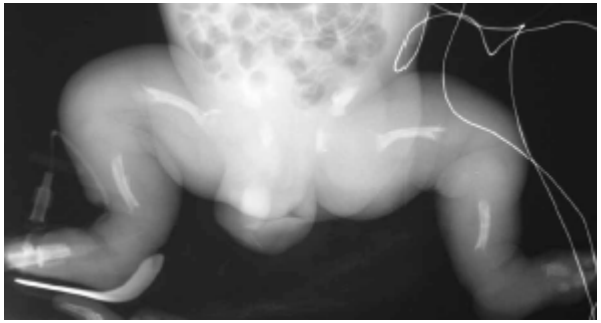
Congenital bowing of the femora

- Primary malformation or intrauterine mechanical forces bending a structurally normal weak bone
- Frequently diagnosed antenatally by ultrasound survey
- First diagnosis: Osteogenesis Imperfecta
- Occasional feature in various syndromes/ chondrodysplasia

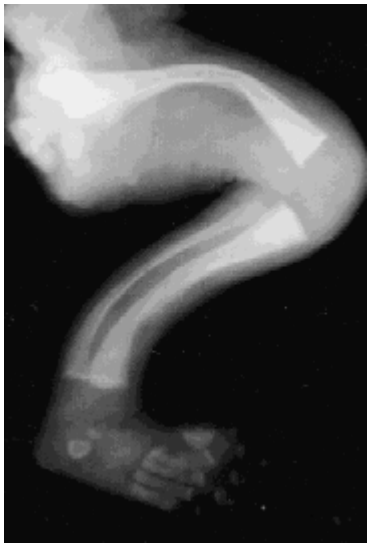
Bowing of the femora : a possible feature in

- Hypophophatasia
- Jeune thoracic dysplasia
- Thanatophoric dysplasia
- Antley-Bixler
- Oto-Palato-Digital syndrome

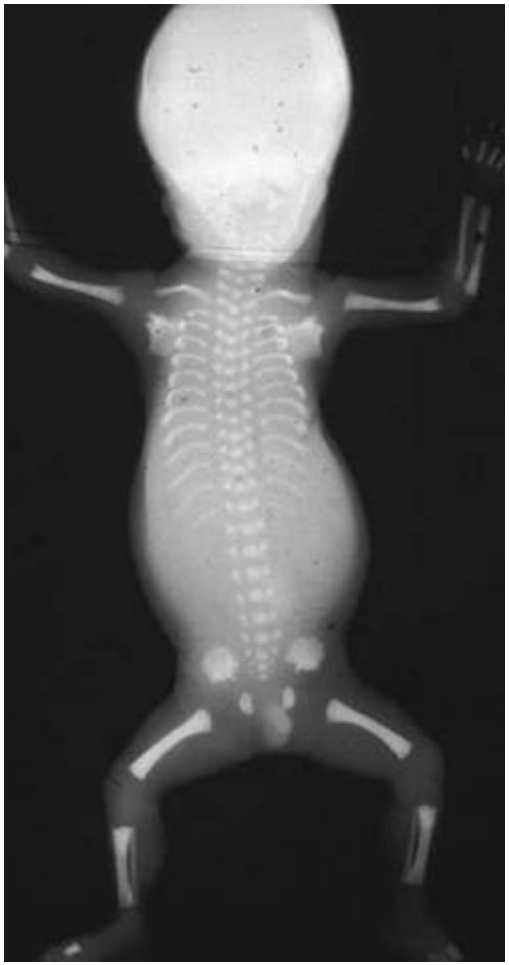
Congenital Bowing



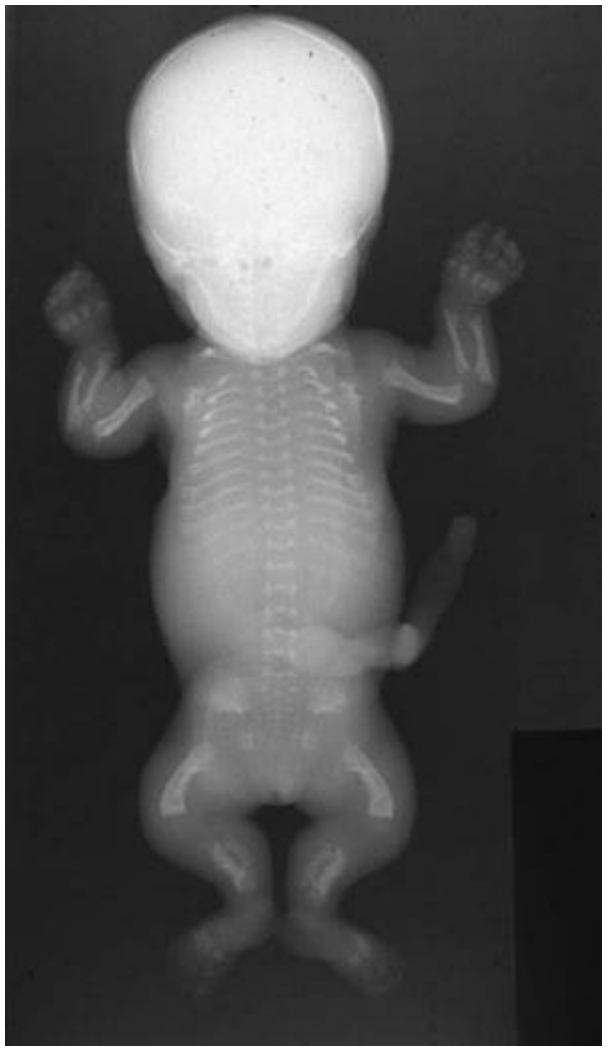
Hypophosphatasia



OPD



Majewski



Thanatophoric

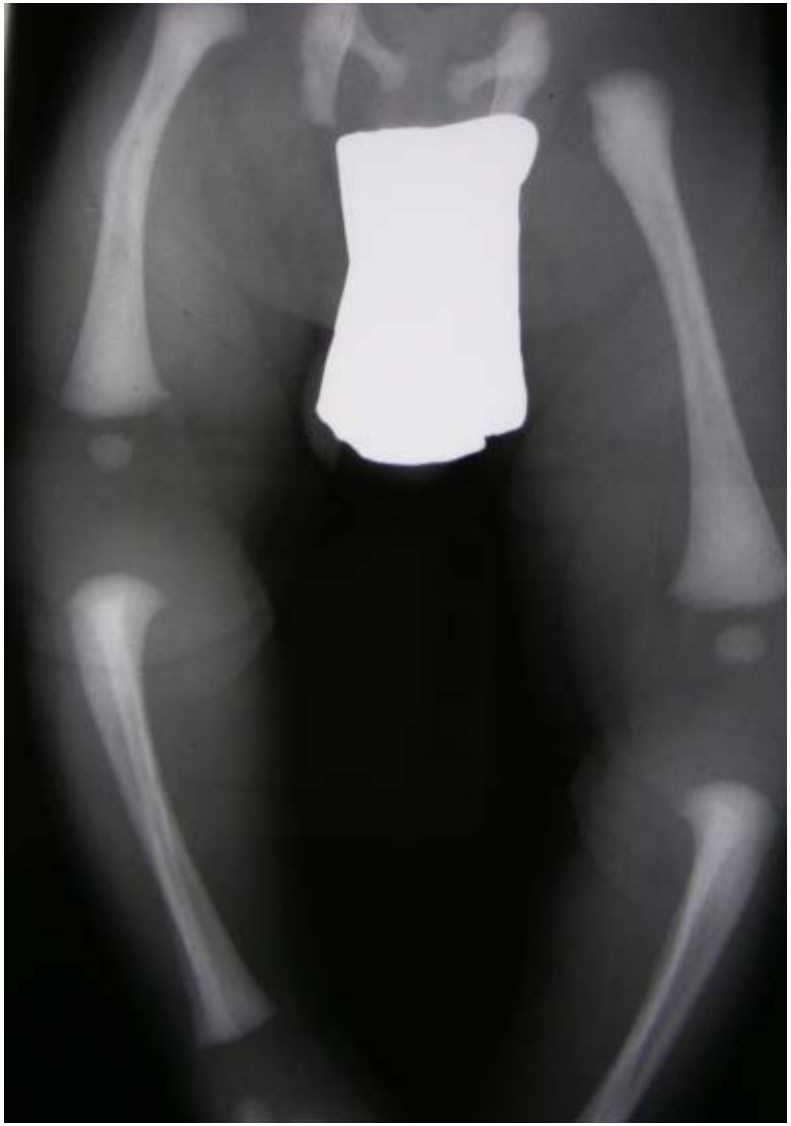
Group 17. Bent bone dysplasia

• Cumming syndrome	AR ?	
• Campomelic dysplasia	AD	SOX9
• Kyphomelic dysplasia	AR	
• Stüve-Wiedemann syndrome	AR	LIFR

Femoral hypoplasia	Sporadic
Osteogenesis Imperfecta	AD, Col1

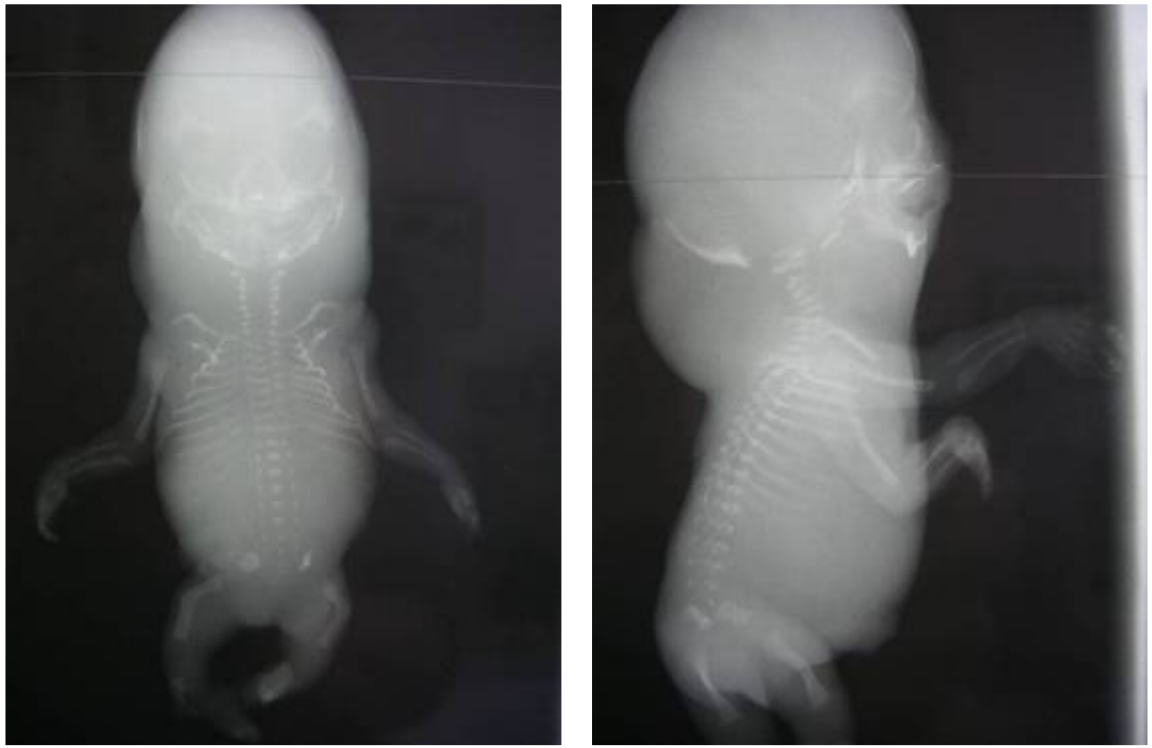
Femoral hypoplasia

- Bilateral asymmetric
- Variable severity
- Sporadic
- Maternal diabetes



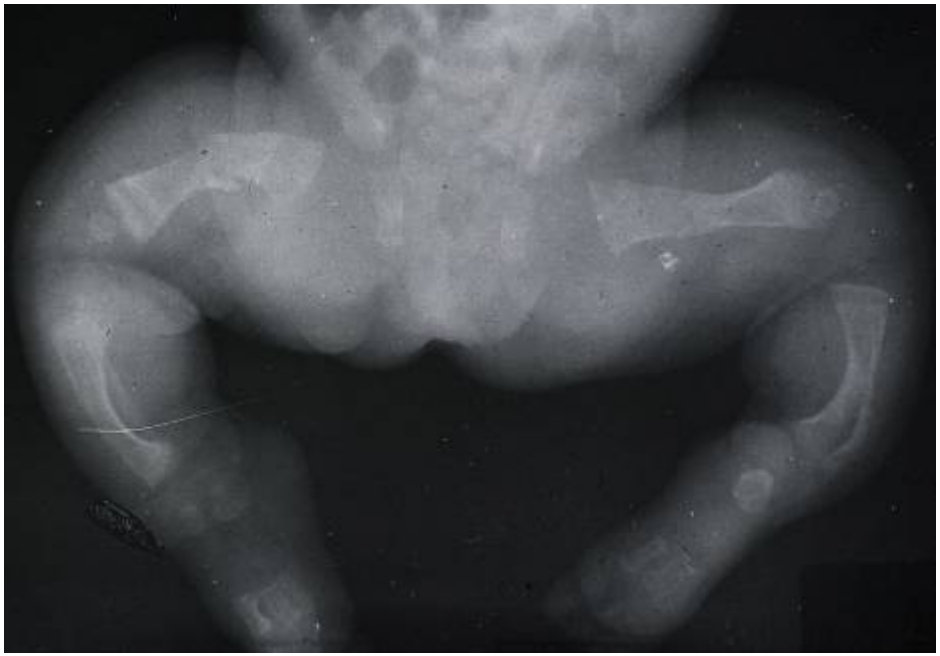
Cumming syndrome

- Cervical lymphocele
- Polycystic dyplasia of kidney/pancreas/liver
- Polysplenia
- Lung hypoplasia
- Laterality defect
- Stillborn
- AR inheritance



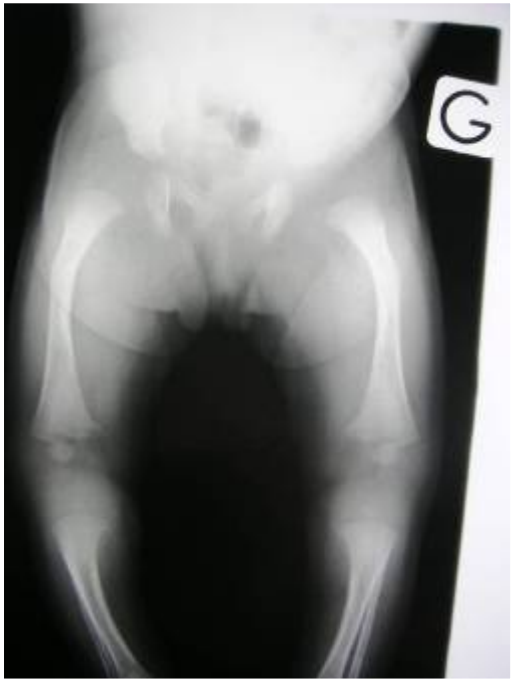
Osteogenesis Imperfecta

Lethal form



Profound limb shortening with broad crumbled long bones (20 W Preg)

Less severe form

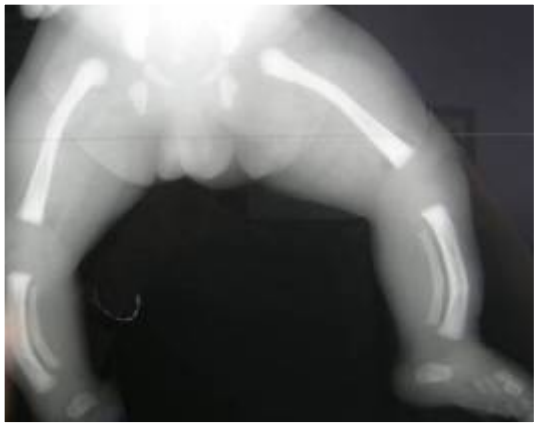


-Family history

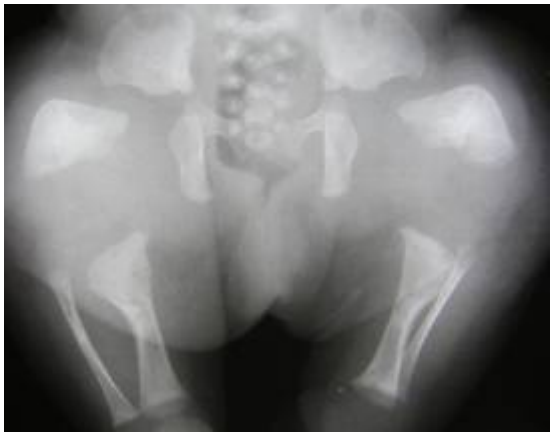
-Lack of osification of the skull vault bones

-Blue sclera at birth

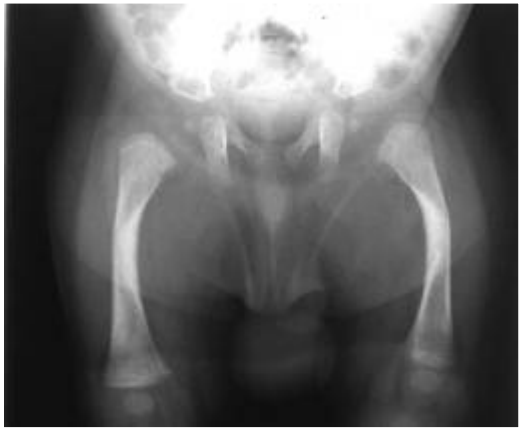
Bent bone dysplasia



Campomelic Dysplasia



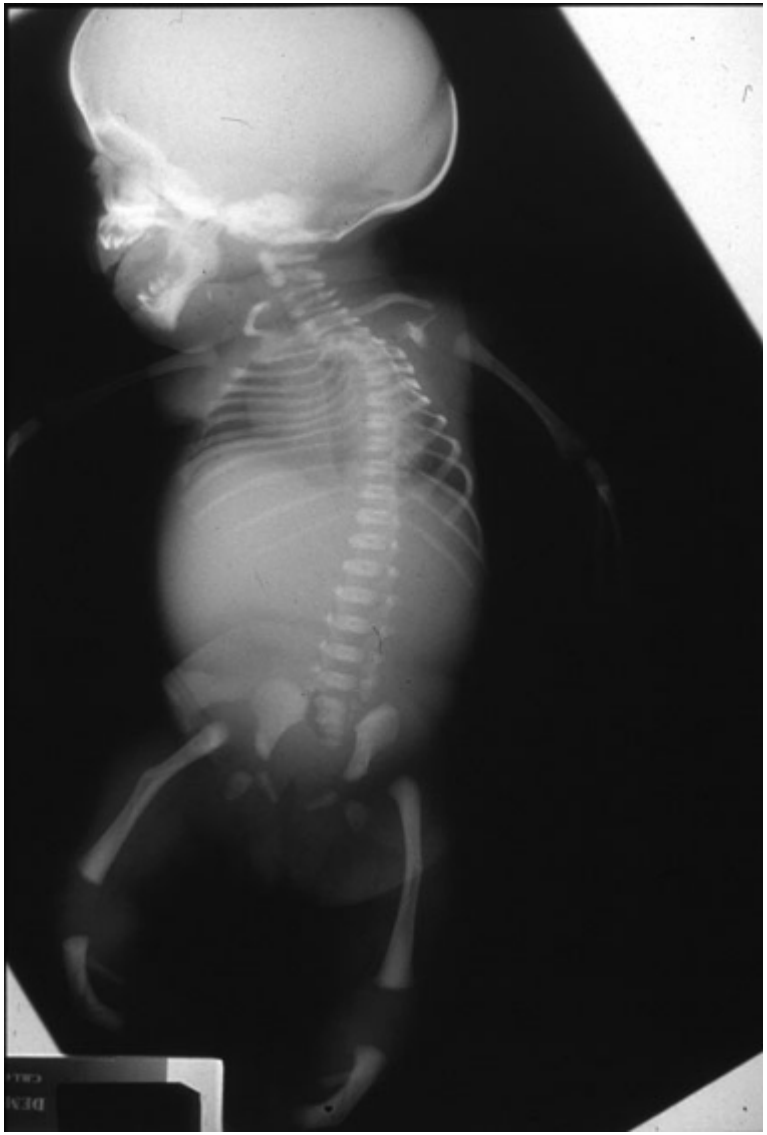
Kyphomelic dysplasia



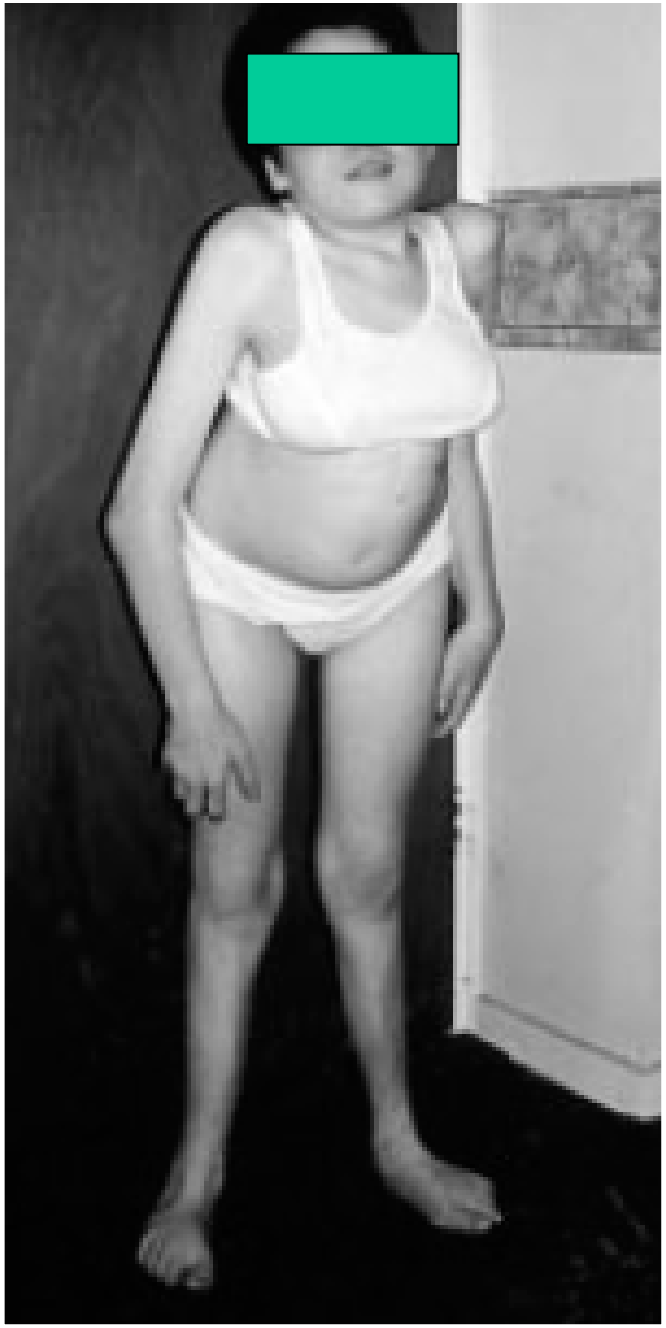
Stuve-Wiedemann Syndrome

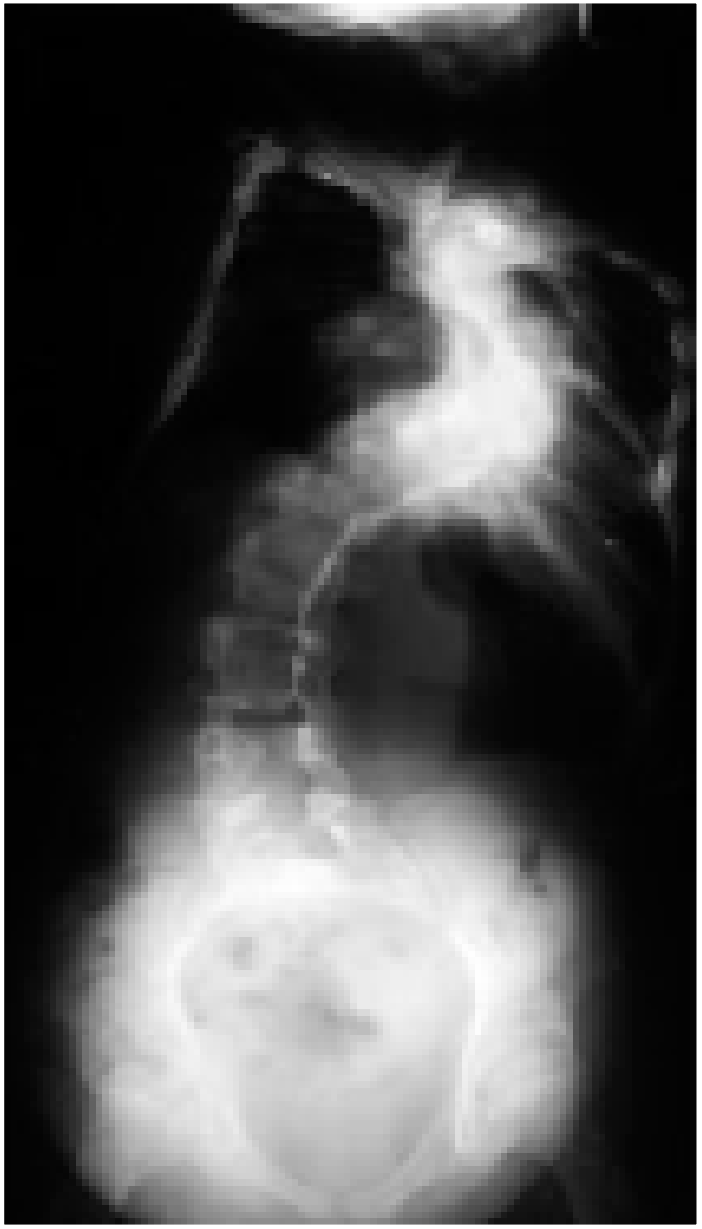
Campomelic dysplasia

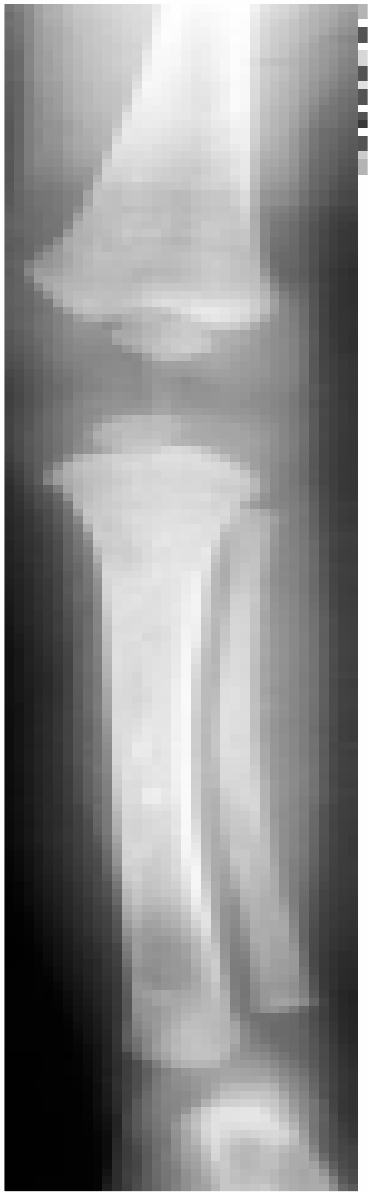
- Bent and slender long bones
- Very small scapula
- Hypoplatic pedicles of the thoracic vertebrae
- Narrow iliac wings with ichiopubic osification delay
- Cleft palate.Pierre Robin syndrome
- Tracheobronchial hypoplasia
- Hypoplastic lung
- Premature death ue to respiratory distress
- Sex reversal in males



Campomelic dysplasia : survivor





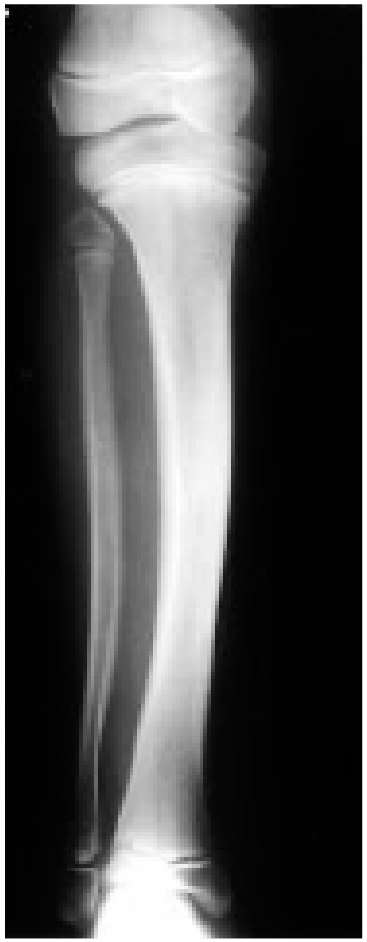


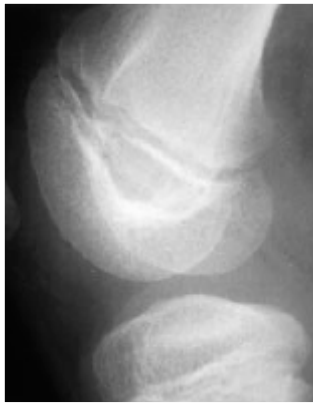
ischio-pubic-patella and ischio-vertebral syndromes

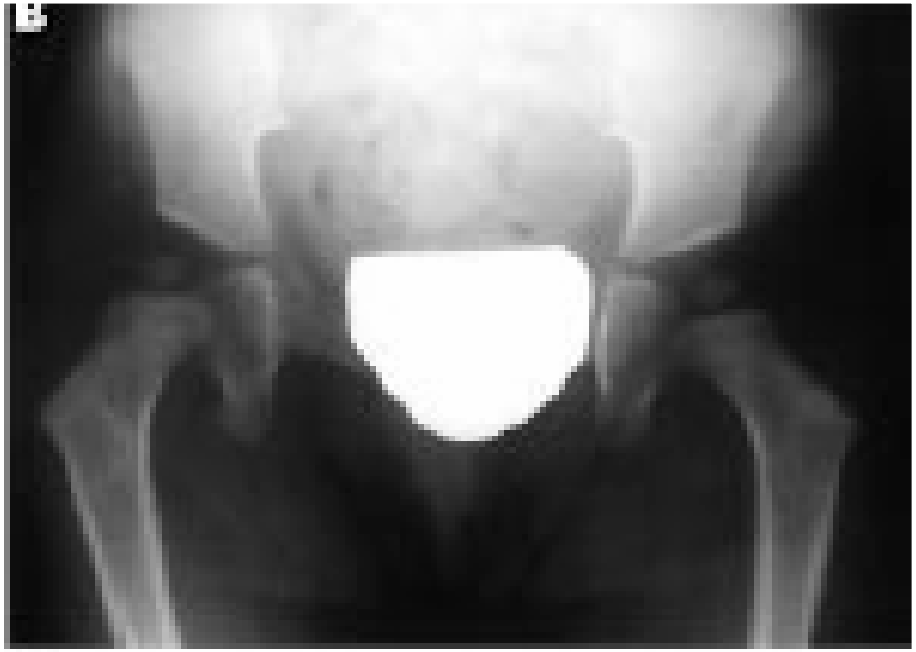
- Hypoplasia of the ischial rami
- Hypoplatic patella

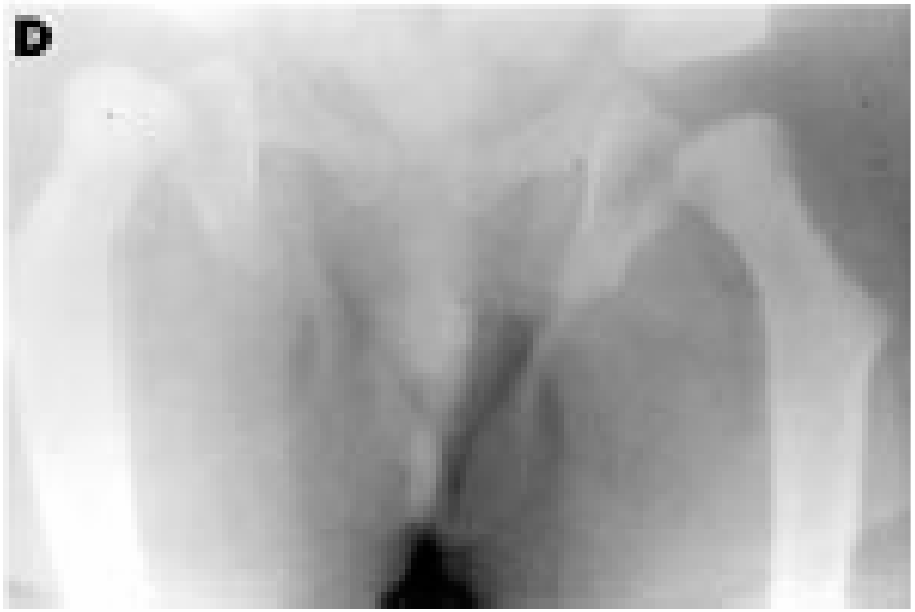
= overlap with the phenotype of CD survivor

Ischio-pubic-patella







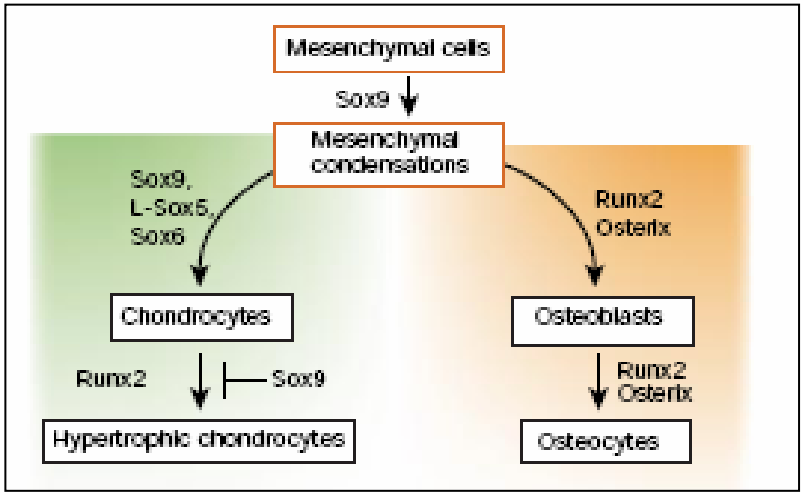


Campomelic dysplasia

- Autosomal dominant inheritance
- Involvement of *SOX 9* (17q24.3)

SRY-related HMG-Box gene 9

loss of function mutations or 17q deletions with positional effect (need for caryotype)



Kyphomelic dysplasia : a heterogeneous disorder

- First description in 1983 par Mac Lean et al
- Long term follow up of this patient :

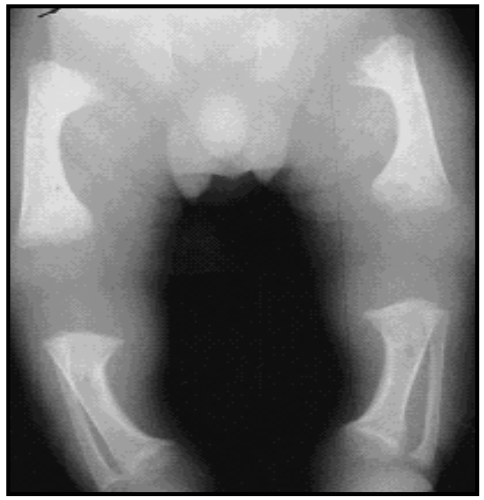
apparition of myotonia=Schwartz-Jampel type I syndrome

- Among the 20 observations reported to-day under the term of « kyphomelic dysplasia

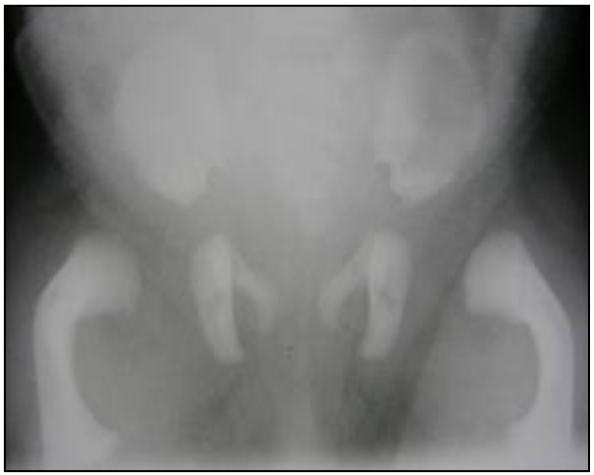
At least 3 distinct entities

Kyphomelic dysplasia «long term follow up »

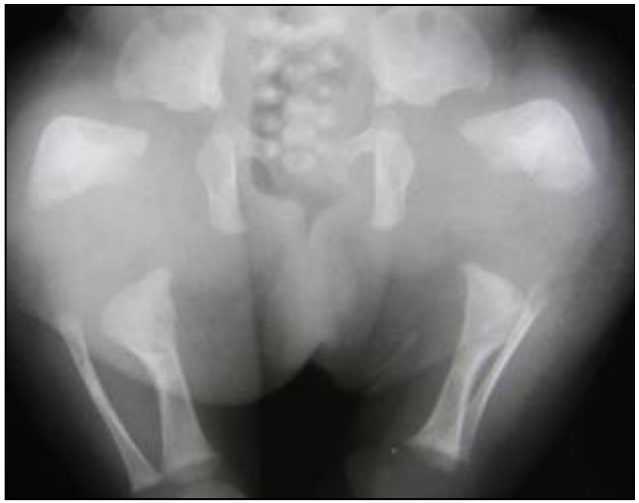
Myotonia
Schwartz-Jampel 1



Immune deficiency
Cartilage Hair Hypoplasia



Kyphomelic
Dysplasia



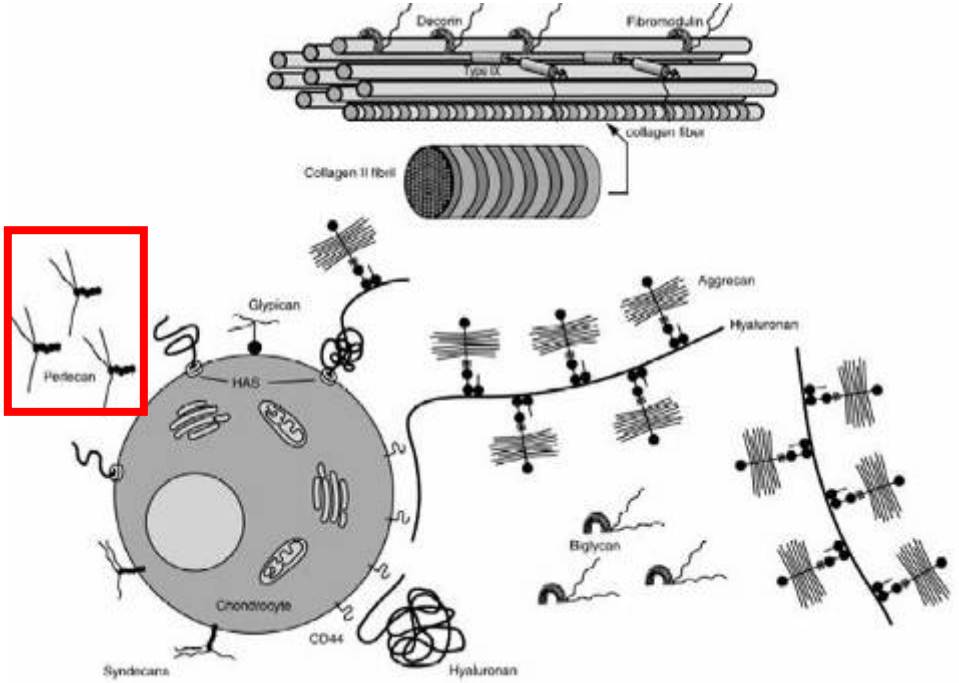
Kyphomelic dysplasia → Schwartz-Jampel type 1

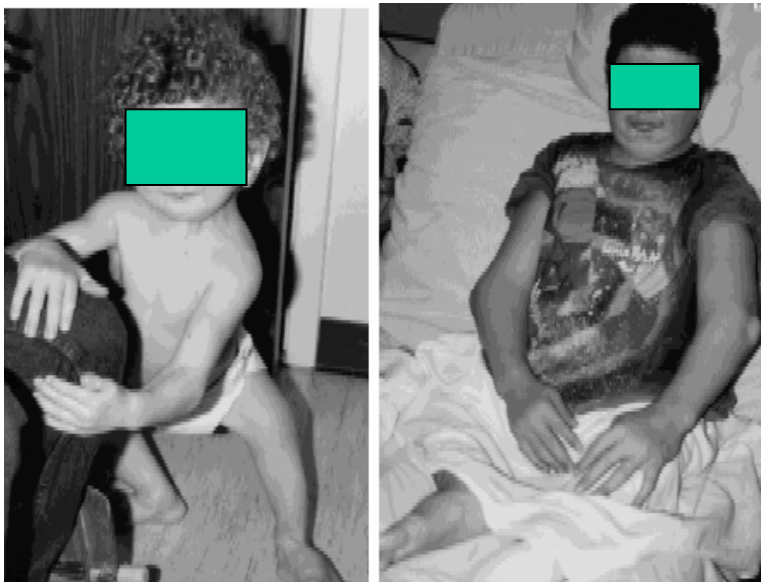
Myotonias

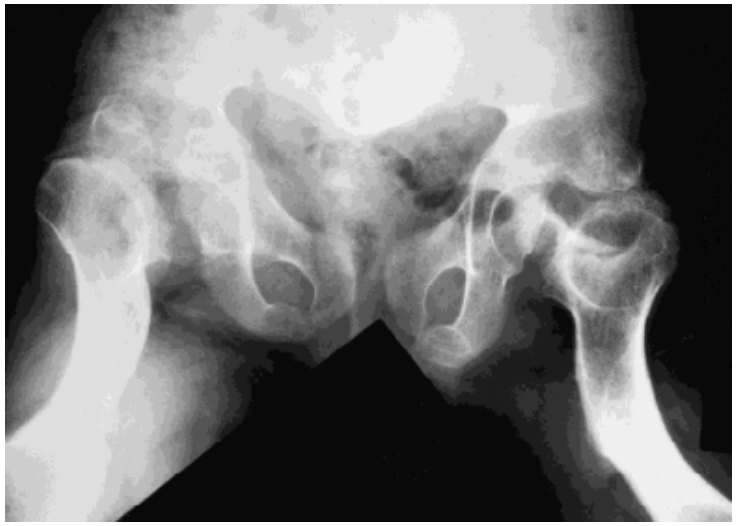
Blepharophimosis

Progressive joint contractures

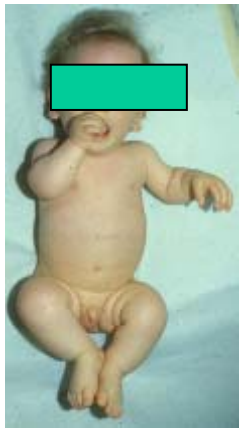
Perlecan mutations

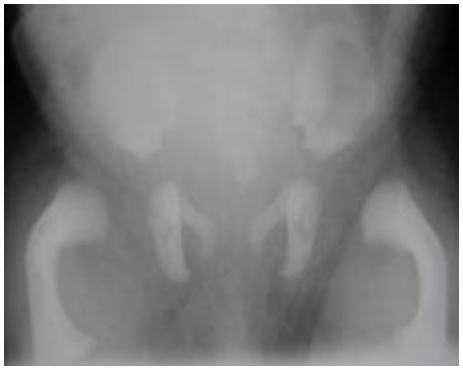


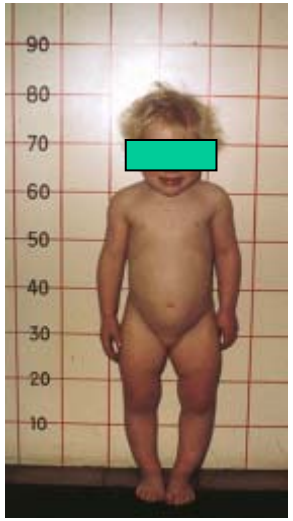


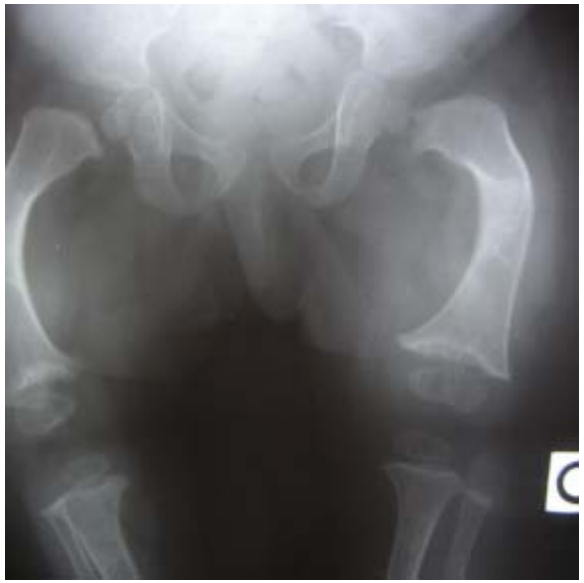


Kyphomlic Dysplasia → Cartilage Hair Hypoplasia







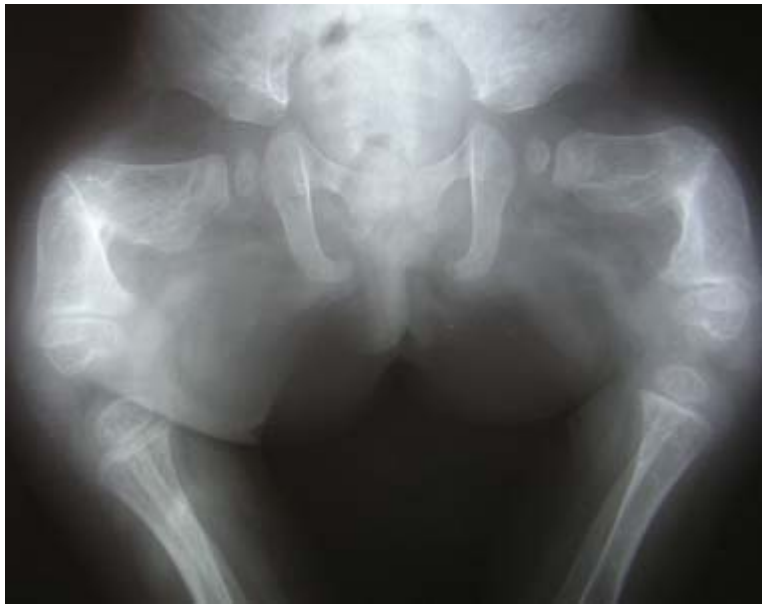


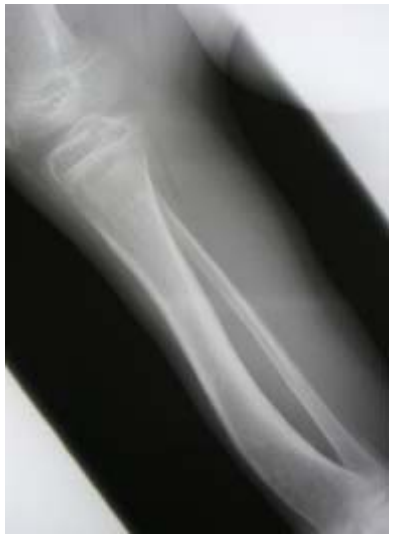
- Metaphyseal changes (knees, hands)
- Round epiphyses
- Immune deficiency

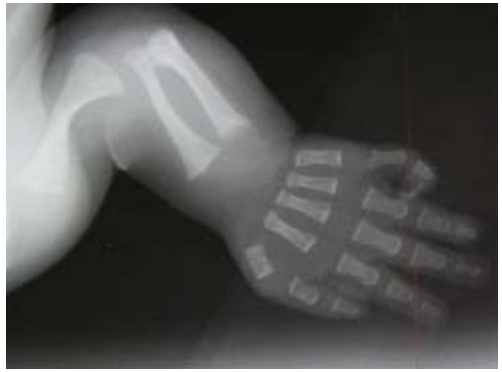
RMRP Mutations

(ribonuclease mitochondrial RNA processing)

Kyphomelic dysplasia





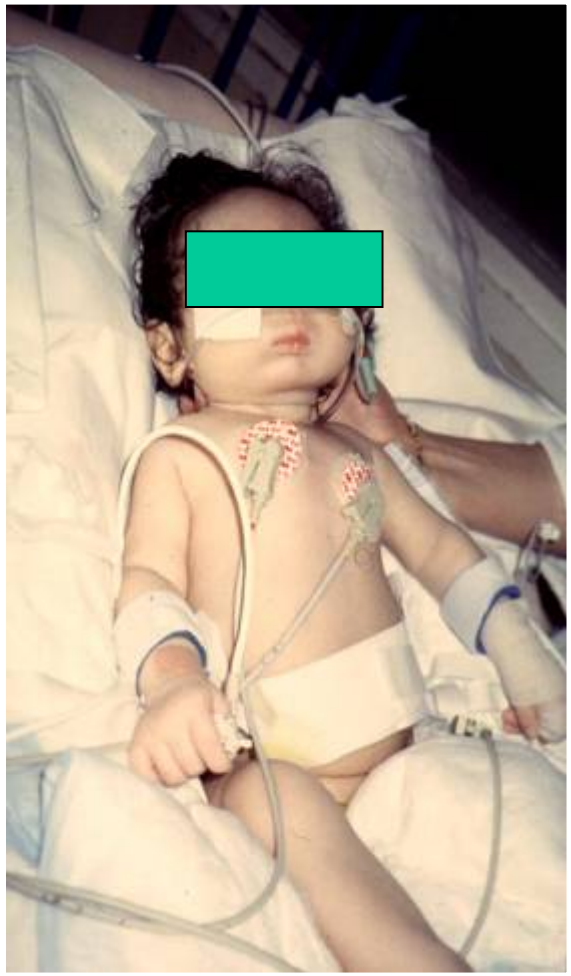


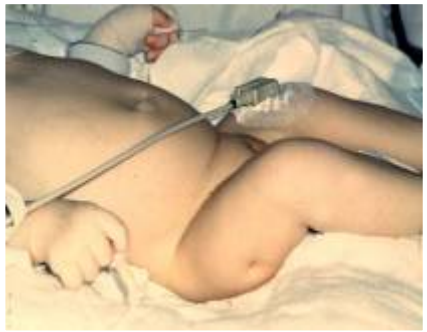
- Autsomal recessive inheritance
- Short and stubby long bones with major incurvation of the femora
- Short and wide iliac wings
- Short humeri with a dumbbell shape

Stüve-Wiedemann syndrome

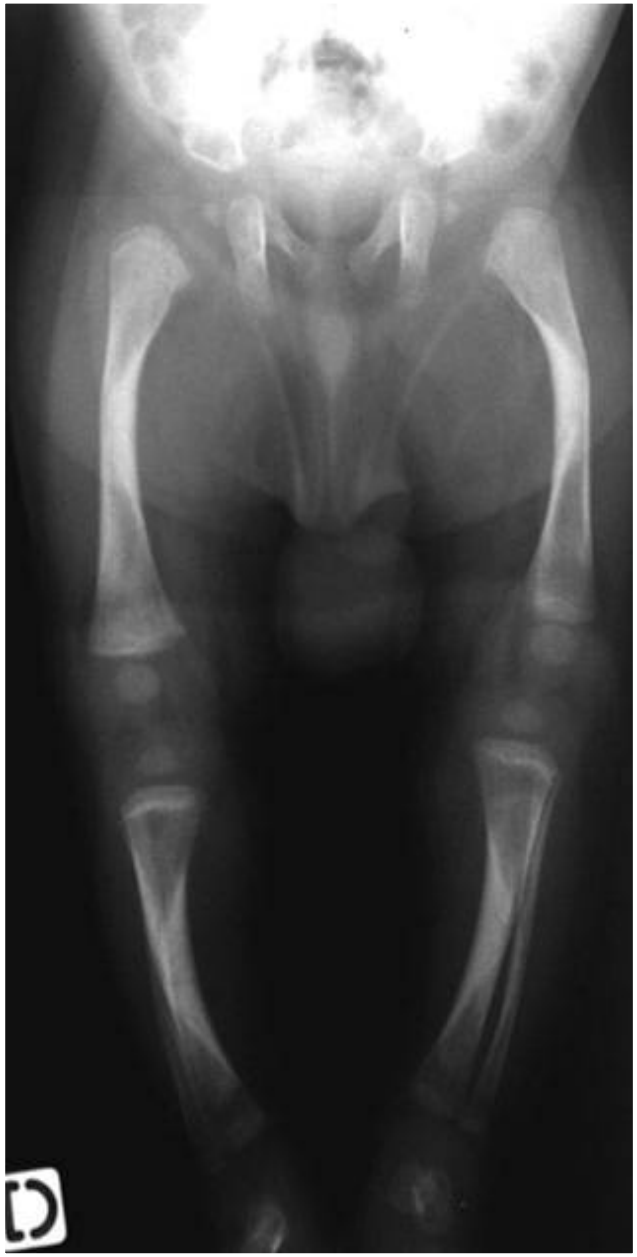
- Original description in 1971
- Autosomal recessive inheritance
- Bowing of the lower limbs with internal cortical thickening and metaphyseal enlargement
- Camptodactyly
- Feeding and respiratory difficulties
- Early death of hyperthermia
- Rare survivors : spontaneous fractures, dysautonomia symptoms, normal intelligence

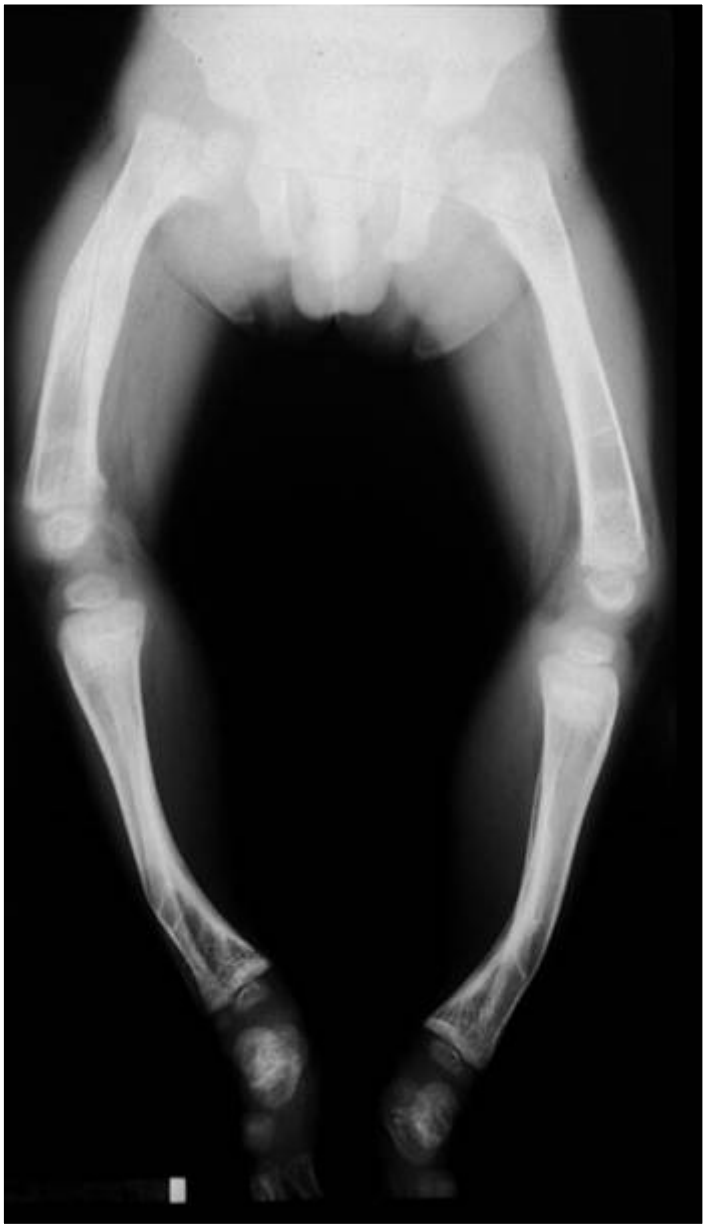
Stüve-Wiedemann syndrome

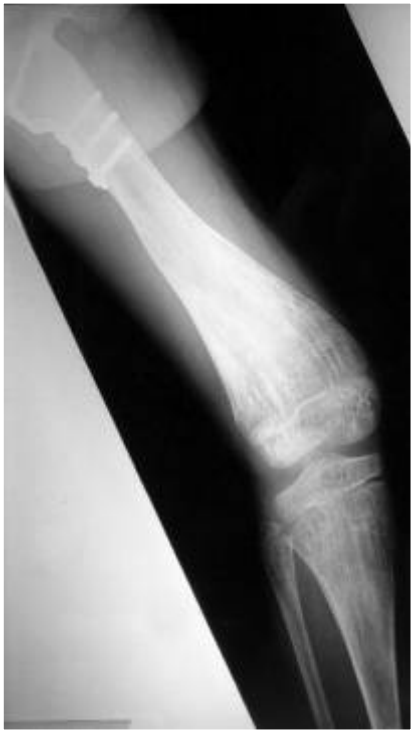


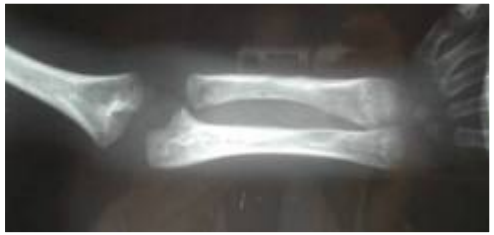


Stüve-Wiedemann syndrome

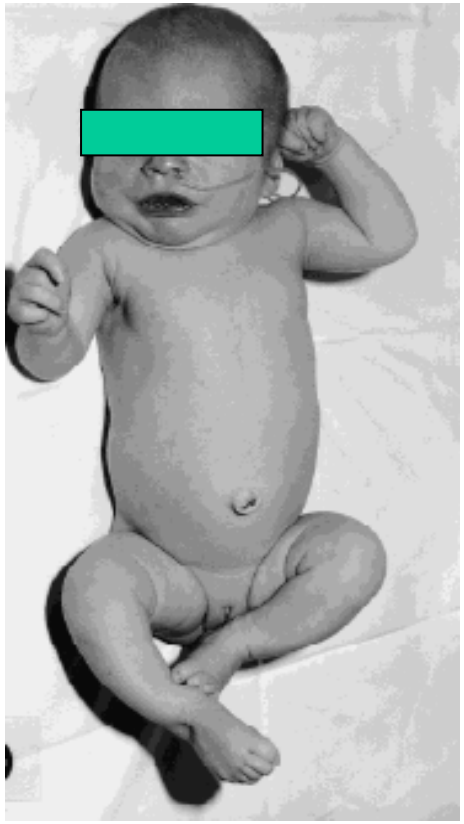




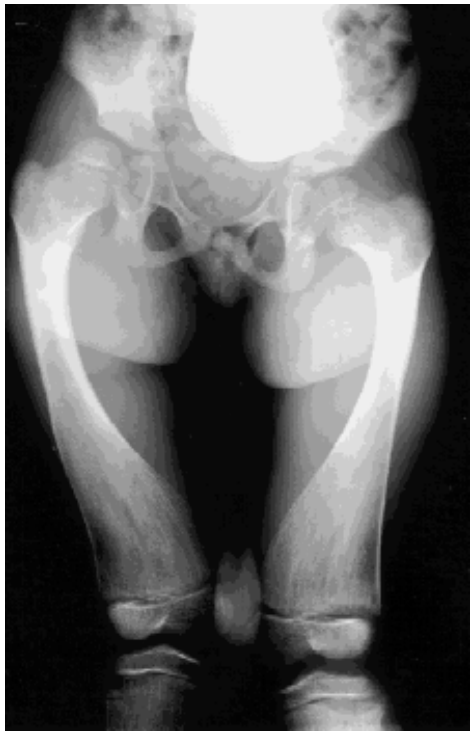




Schwartz-Jampel Syndrome type 2



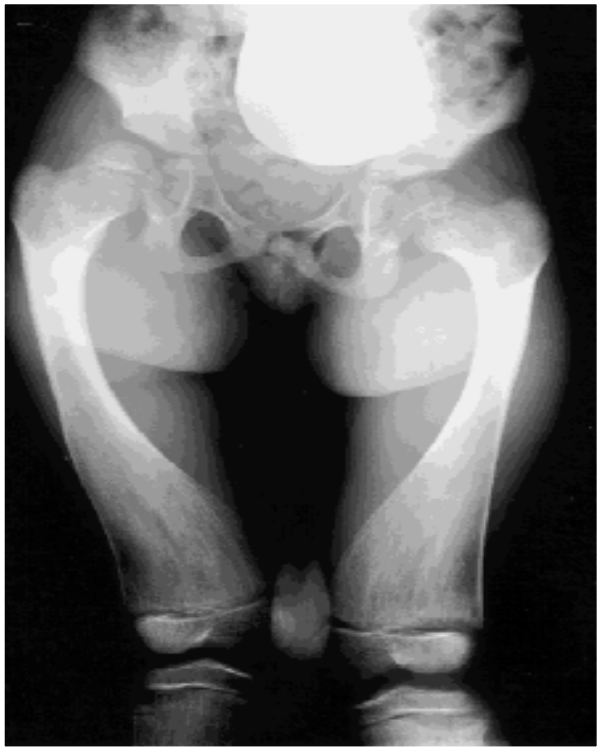
- Camptodactyly, contractures
- Myotonia
- Feeding and respiratory difficulties
- Hyperthermia
- Bowing of the lower limbs
- Early death



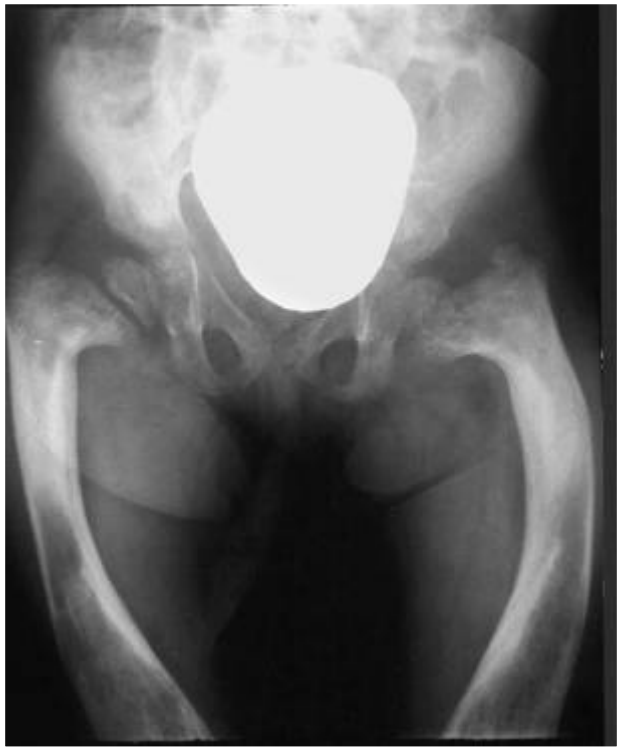
Exclusion of perlecan

Brown et al, 1997

Schwartz-Jampel Type 2/ Stüve-Wiedemann syndrome



Schwartz-Jampel syndrome 2



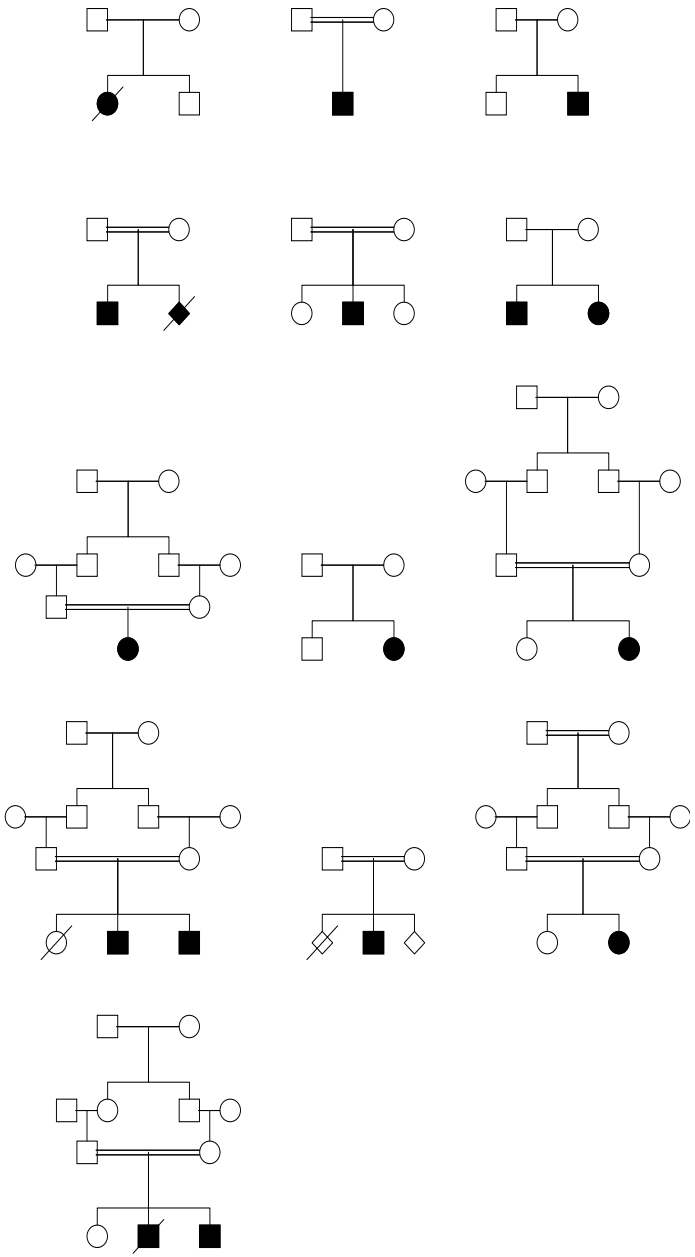
Stüve-Wiedemann syndrome

Clinical, radiological and histological overlap

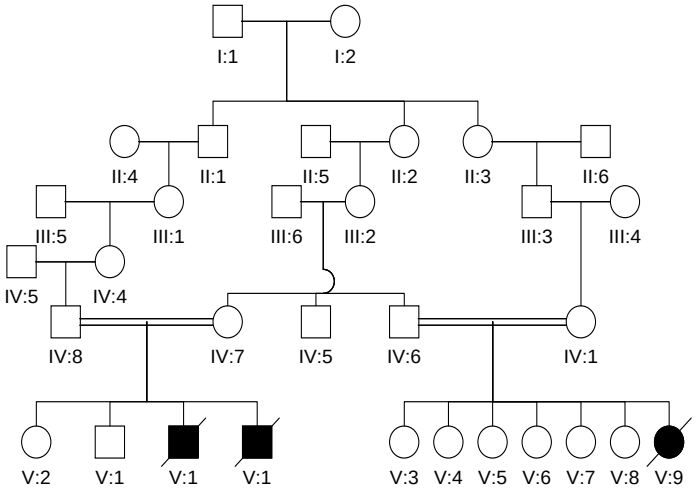
= a same entity

Stüve-Wiedemann syndrome

Families

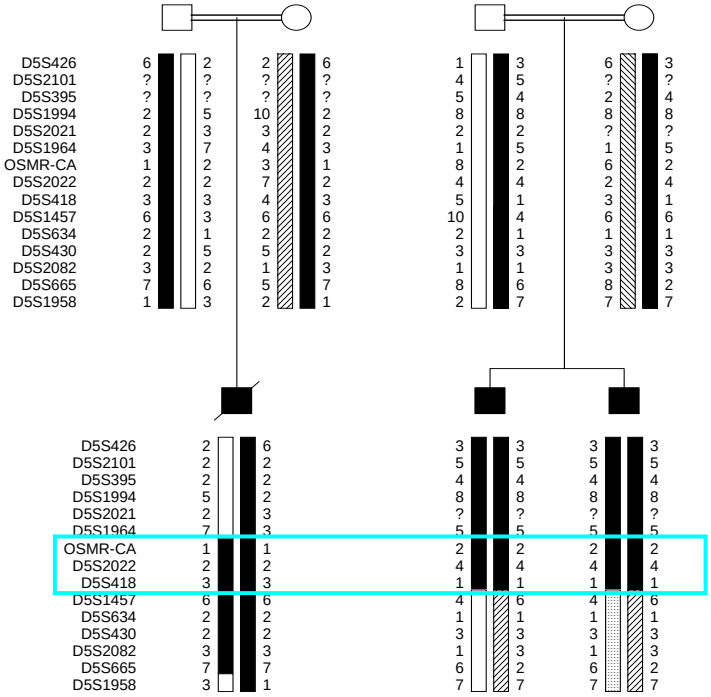


- 19 families including 14 inbred families
- Origins : UAE (5), France (3), Gypsy (2), Italy (2), Israel (2), Canada (1), Portugal (1), Senegal (1), Turkey (1), Yugoslavia (1)
- 22 affected children :
  Early death 15 / Still alive 7



Stüve-Wiedemann syndrome

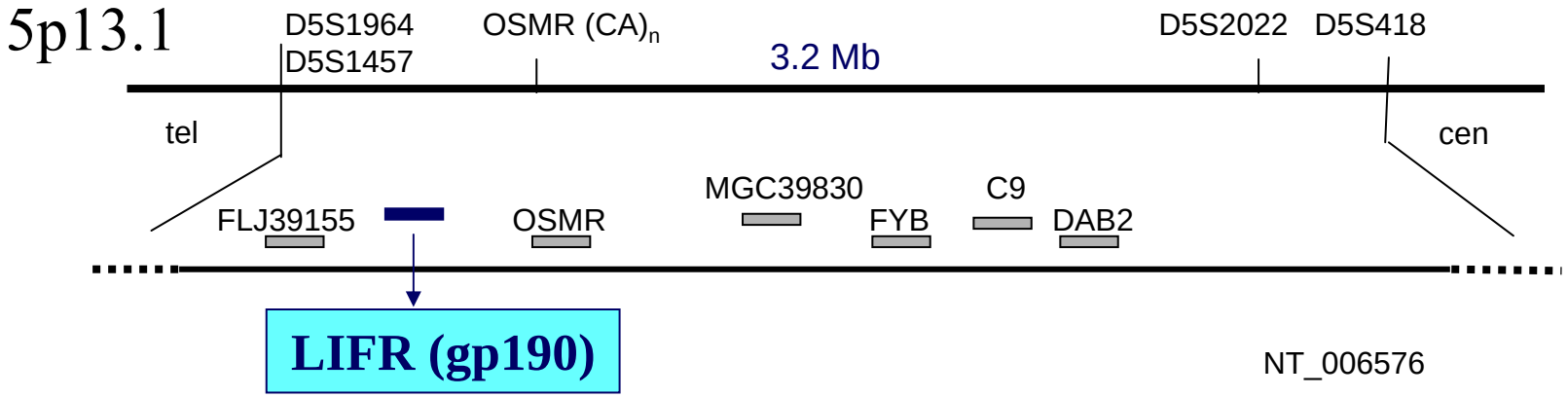
Linkage analysis



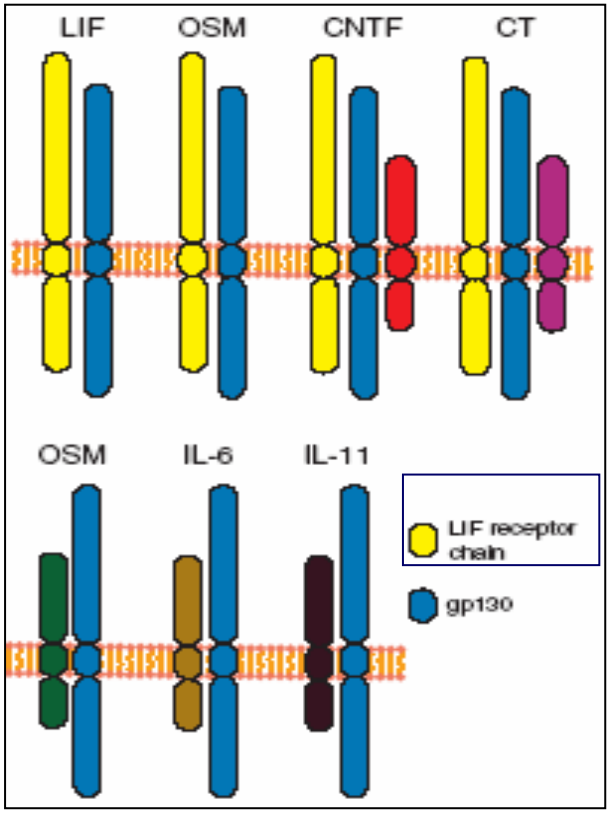
Region of homozygosity : 5p13

loci	cM	0.00	0.05	0.10	0.20	0.30
D5S1964		- ∞	5.4	4.87	3.35	1.89
	0.986					
OSMR-CA		8.99	7.59	6.24	3.77	1.86
	1.04					
D5S2022		9.86	8.44	7.07	4.56	2.56
	0.097					
D5S418		**10.66**	9.21	7.78	5.06	2.76
	1.07					
D5S1457		1.05	3.09	2.81	1.85	0.19

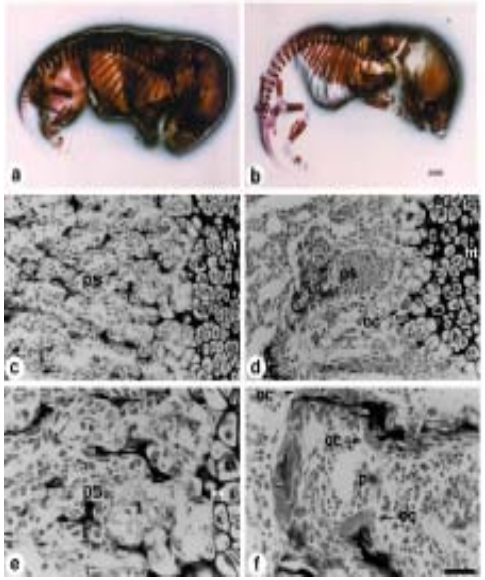
Map of the region encompassing the SWS gene



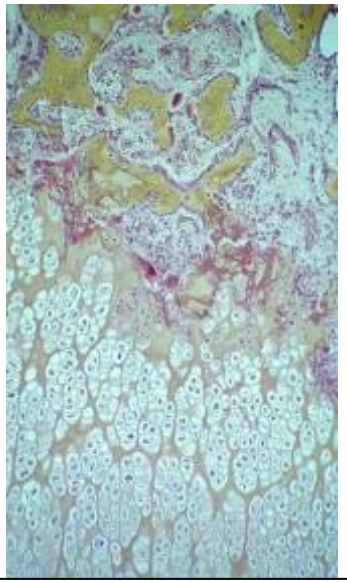
LIFR (gp190)



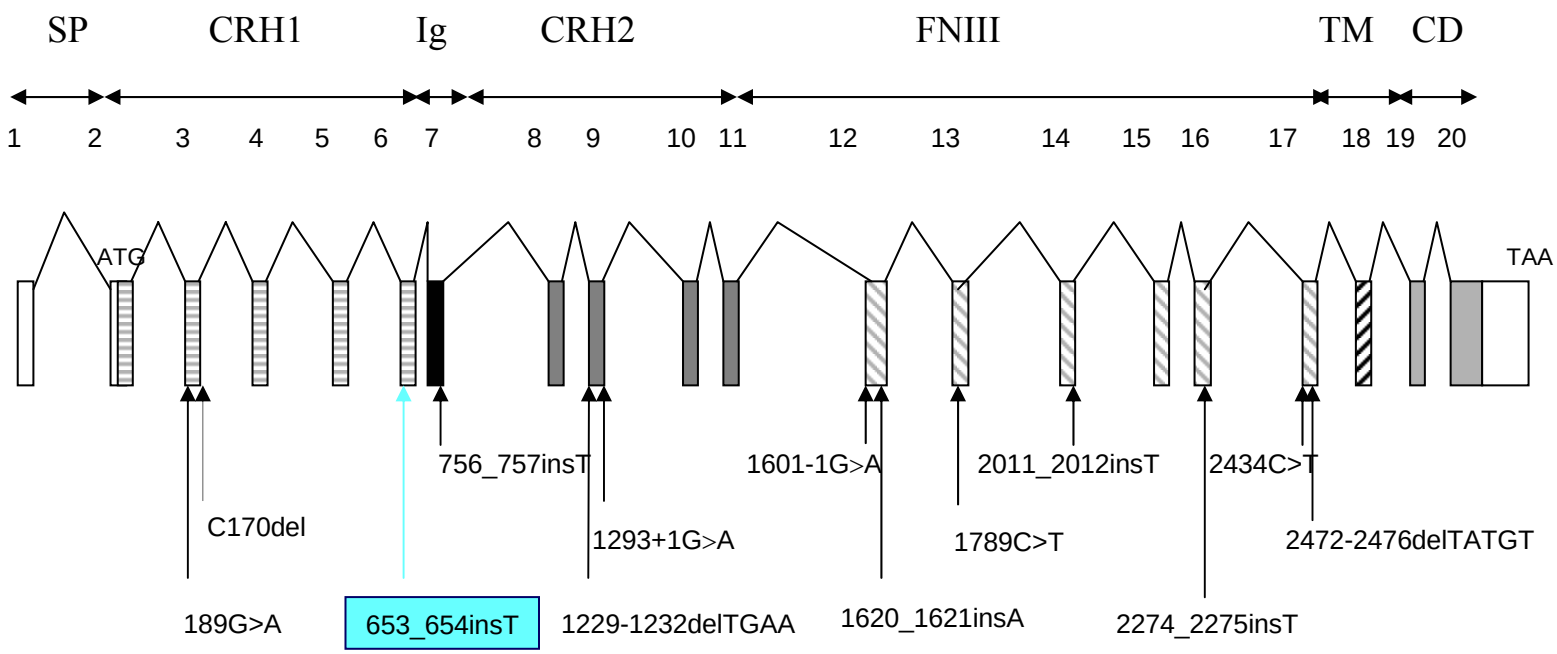
LIFR-/- mice



SWS patient



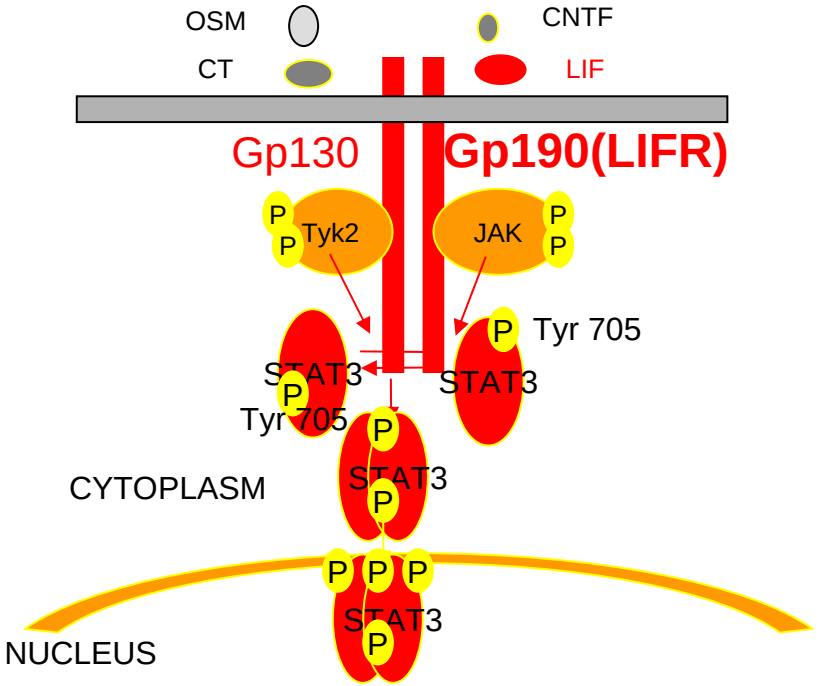
Stüve-Wiedemann syndrome LIFR screening

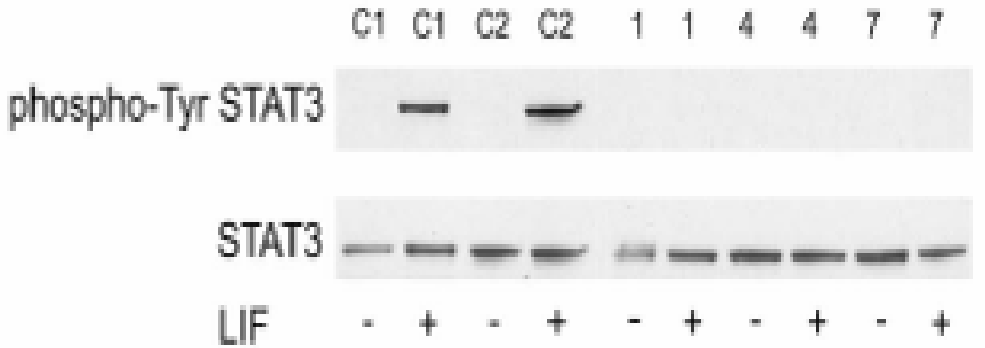


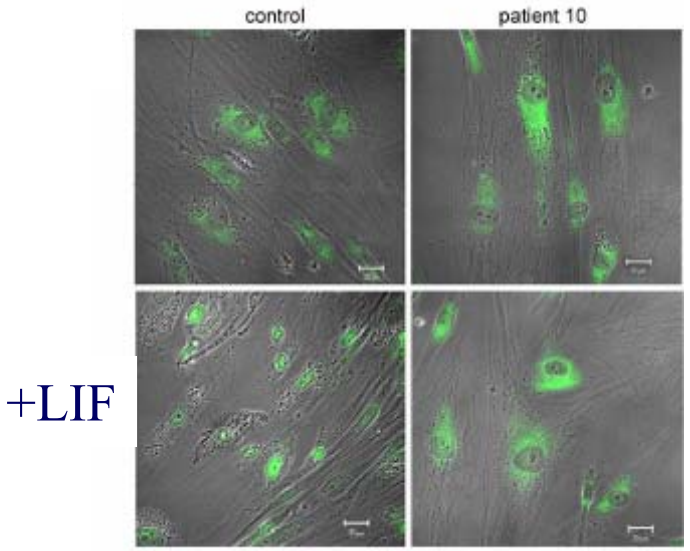
LIFR (gp190)

Stüve-Wiedemann syndrome

STAT pathway







Inactivation of the STAT pathway in Stüve-Wiedemann syndrome

Stüve-Wiedemann syndrome — Genetic heterogeneity

Total of 36 SWS families (19 + 17)

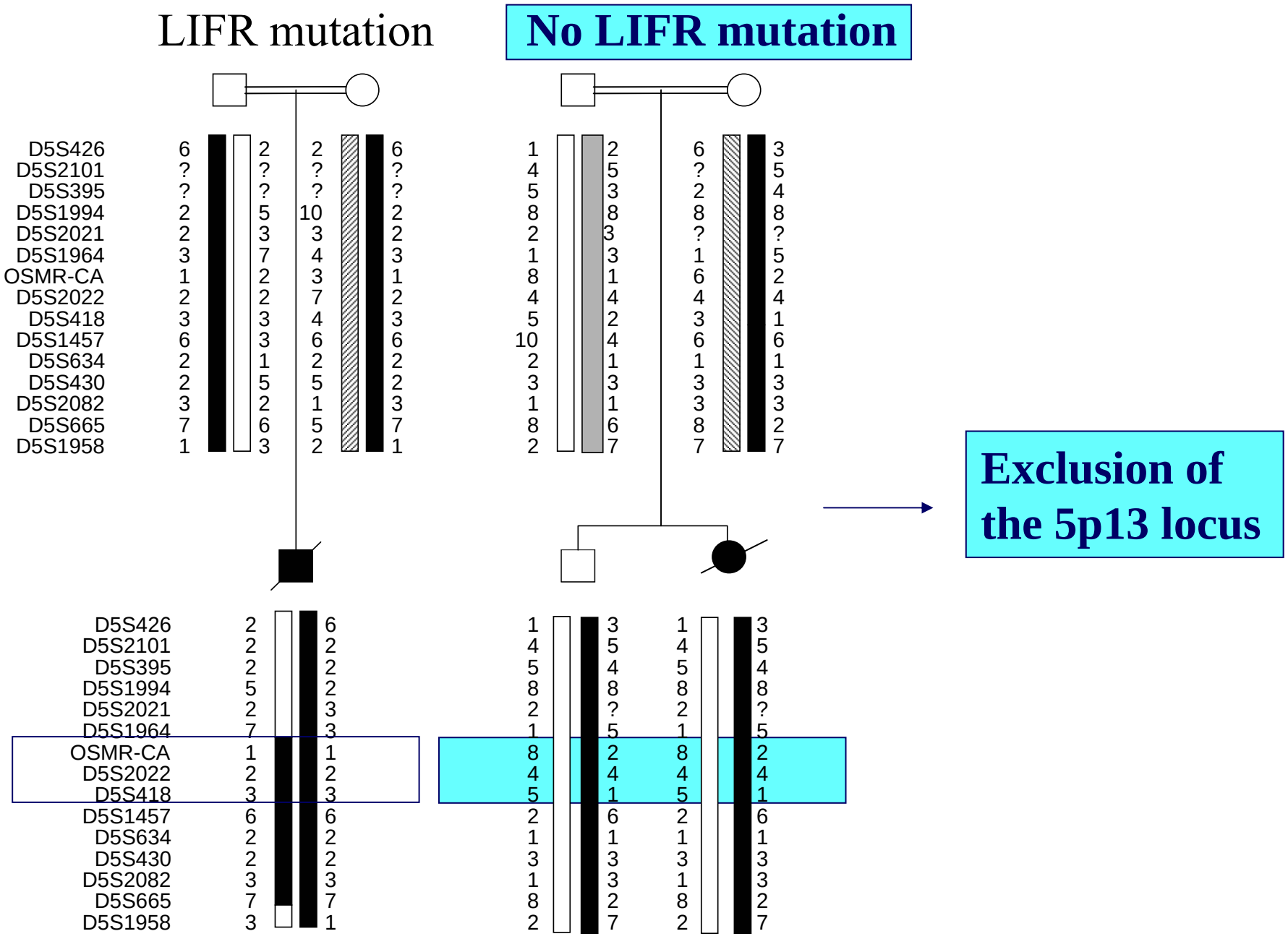
- LIFR mutations in 29 families (19 + 10)
- No LIFR mutation in 7 families (5 inbred families)

→ Linkage analysis

→ Functional studies

Stüve-Wiedemann syndrome

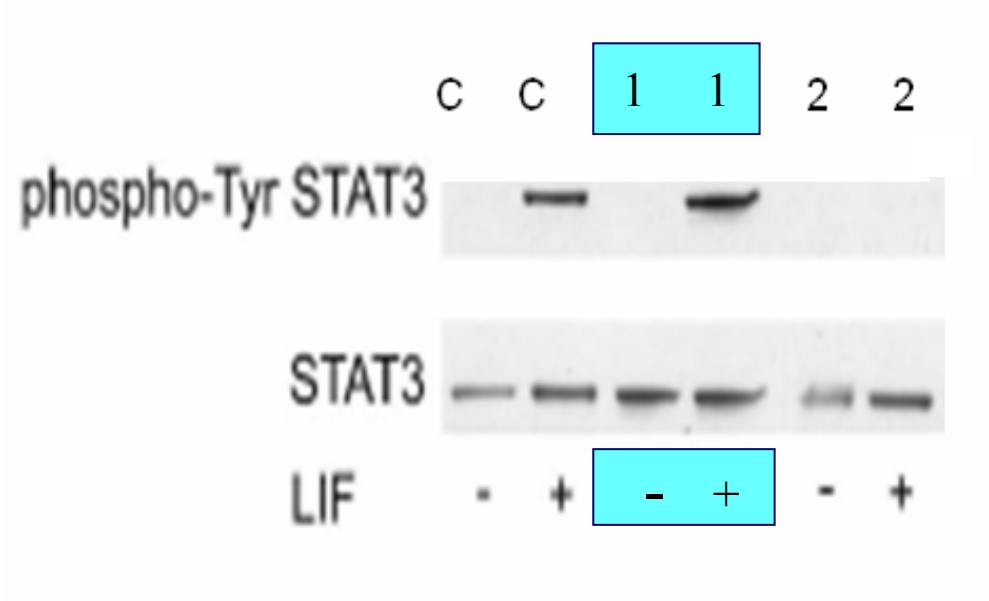
5p13 locus



Stüve-Wiedemann syndrome

STAT pathway

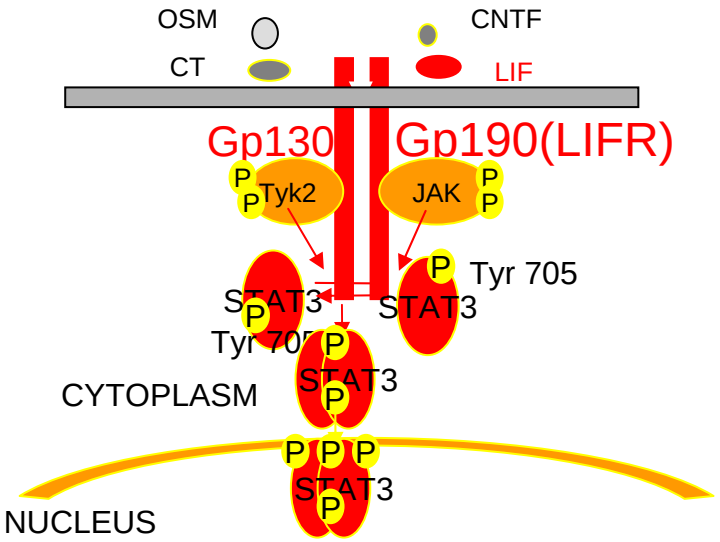
Skin fibroblasts from 4 patients without any LIFR mutation



1= no LIFR mutation
2 = LIFR mutation

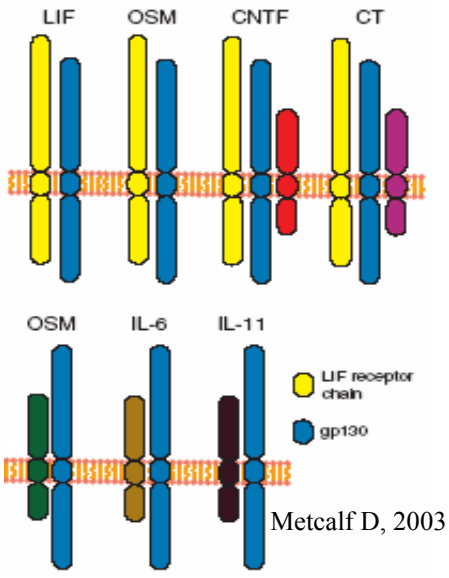
1 = normal activation of STAT pathway

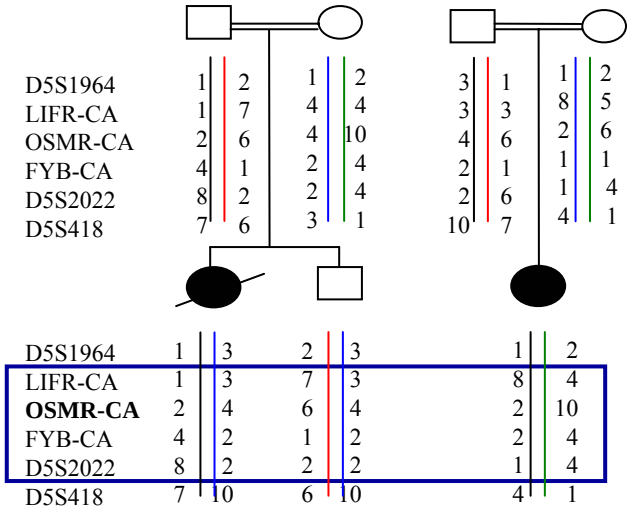
Candidate genes ?

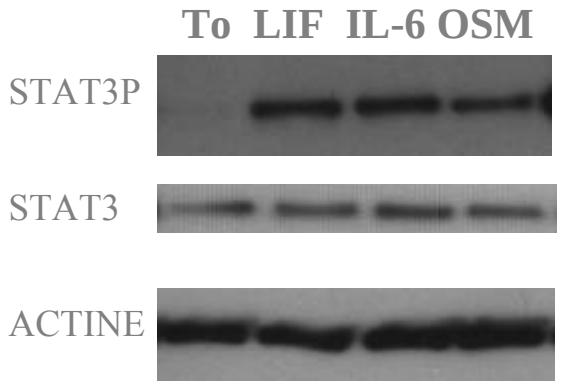


Stüve-Wiedemann Syndrome

Candidate genes







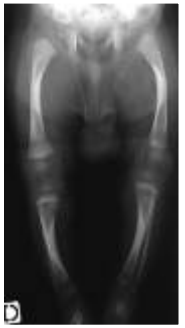
normal STAT3 phosphorylation
in response to LIF/ IL-6/ OSM

Exclusion

1. **OSMR**
2. **LIF**
3. **gp130**

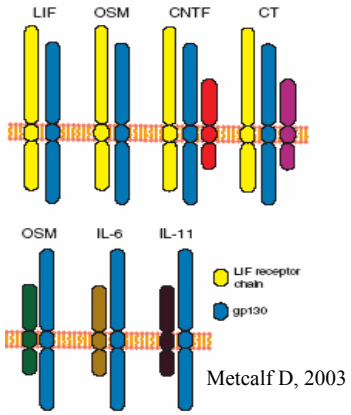
36 families with Stüve-Wiedemann syndrome

1. Clinical homogeneity



2. Genetic heterogeneity

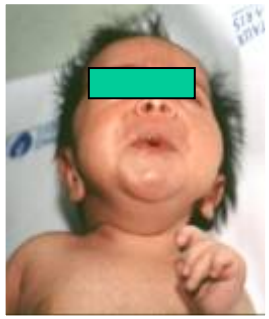
- ➢ LIFR major gene (80 %)
- ➢ Other gene ?



Metcalf D, 2003

Overlap Stüve-Wiedemann/Crisponi syndromes

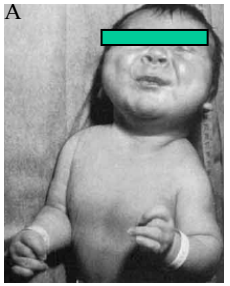
Stüve-Wiedemann



Bowing of the lower limbs
Normal intelligence

- Trismus, camptodactyly
- Hyperthermia
- Early death
- Survivors : kyphoscoliosis
  temperature instability

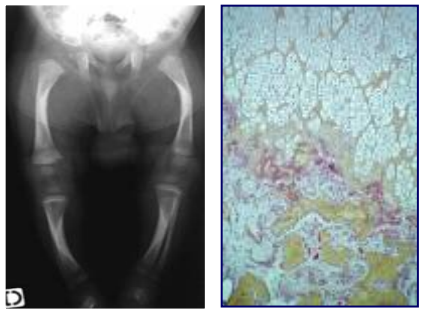
Crisponi



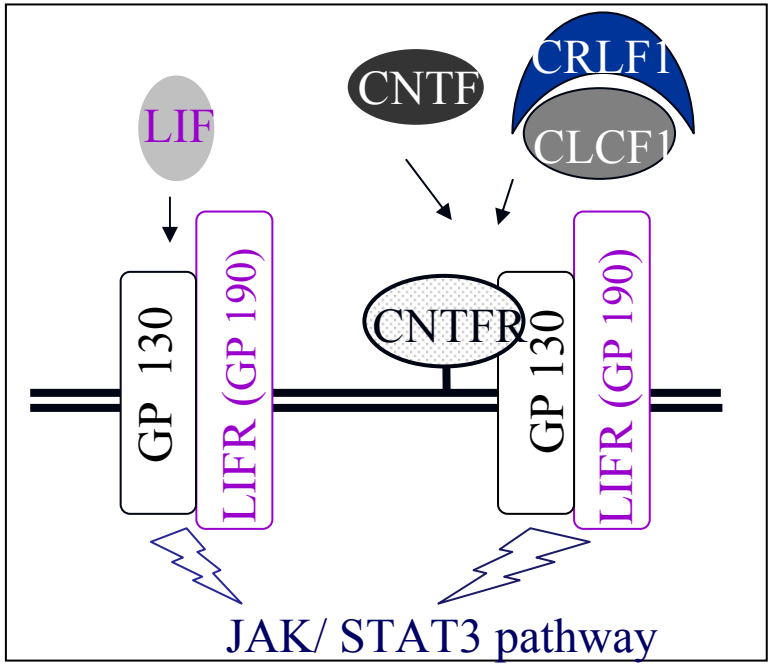
Seizures
Psychomotor delay

⇩

LIFR mutations



Dagoneau et al,
Am J Hum Genet 2004



⇩

Dysautonomia

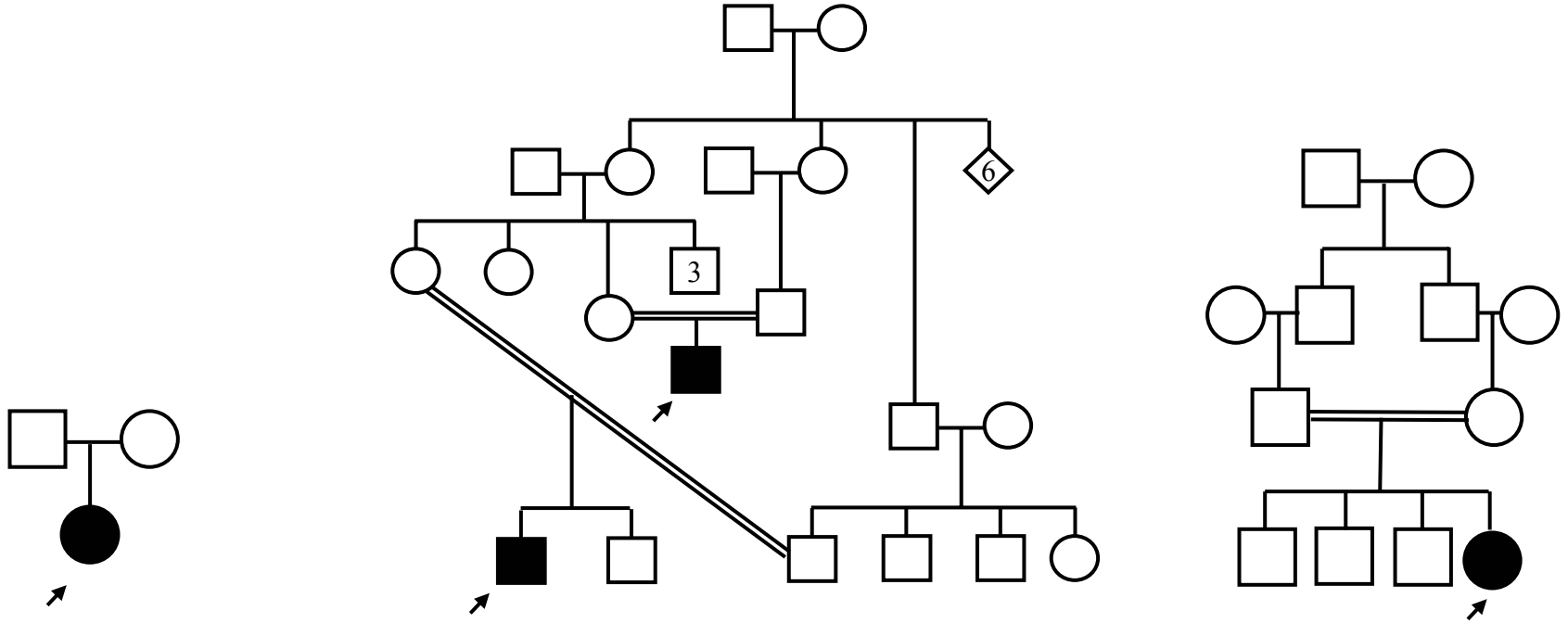
Crisponi syndrome

- First description in 1996 by Crisponi
- 19 cases: Sardinia (12), Northern Italy (1), Portugal (1)
- Muscular contraction of facial muscles in response to stimuli or during crying with trismus
- Dysmorphic features
- Bilateral camptodactyly

Crisponi et al, 1996

- Clinical course : feeding difficulties and hyperthermia responsible for an early death
- Survivors: disappearance of the contractions but seizures, temperature instability, scoliosis

Three families with Crisponi syndrome



Sardinia **Gypsy** **Yemen**

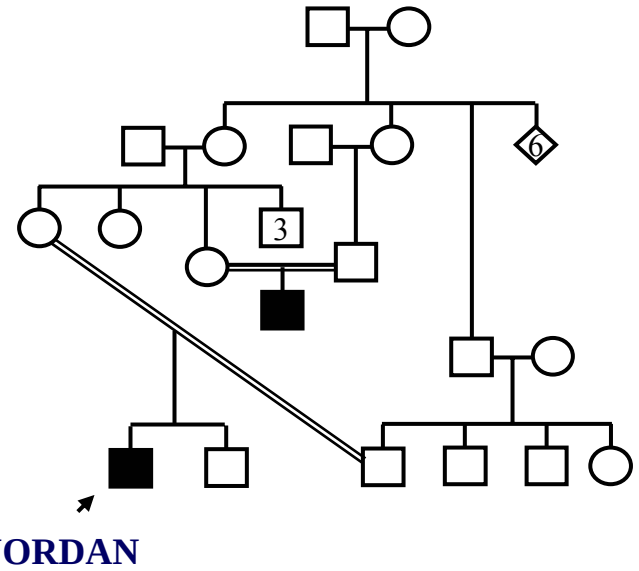
JORDAN :

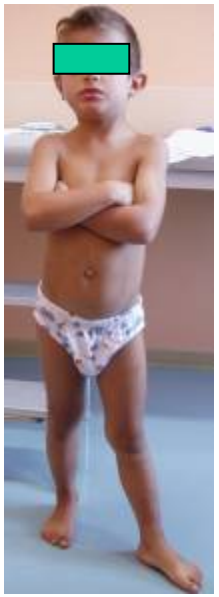
At birth : W = 2830g, L= 48cm, OFC = 33cm

- Camptodactyly
- Muscular contractions of facial muscles, trismus
- Major feeding difficulties

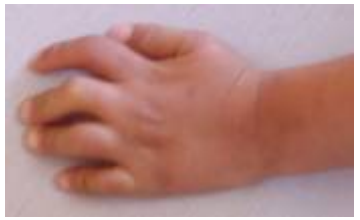
Clinical Course :

- Disappearance of the contractions and feeding difficulties
- Access of hyperthermia and then profuse sweating in the back
- Kyphoscoliosis and short stature

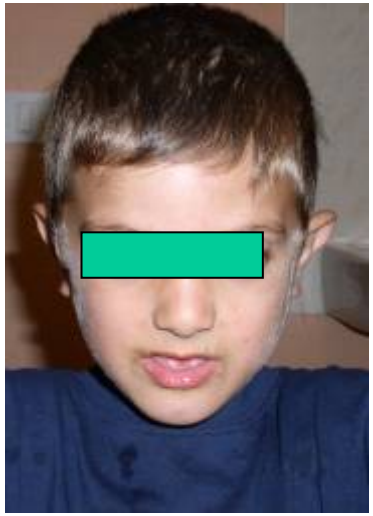


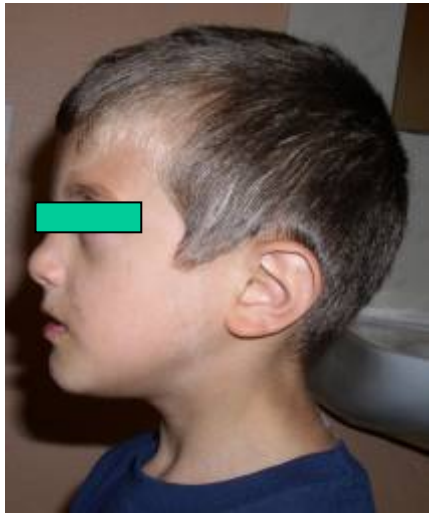


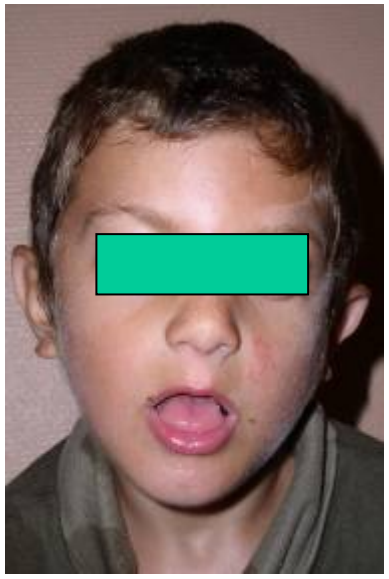
4 years

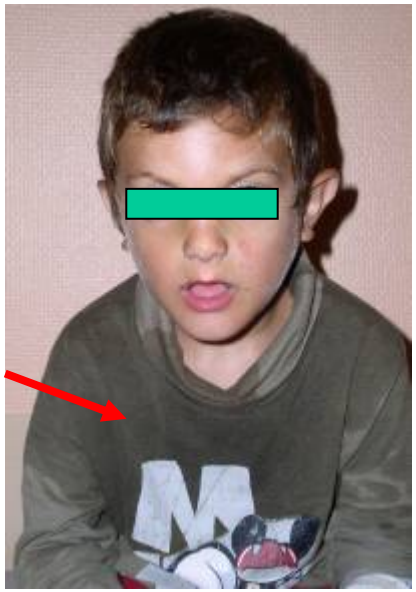


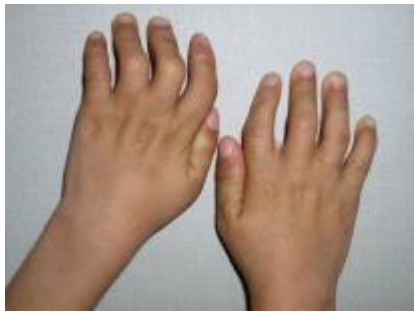
JORDAN at 6 years

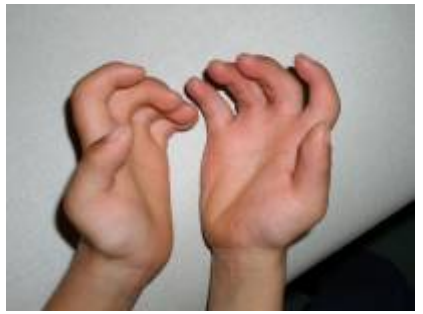


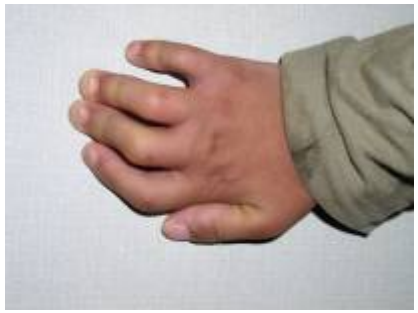


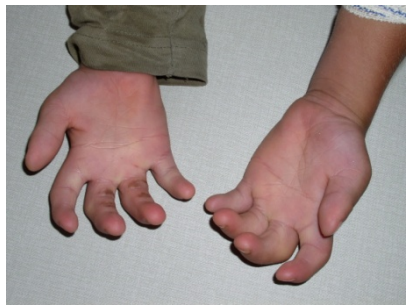






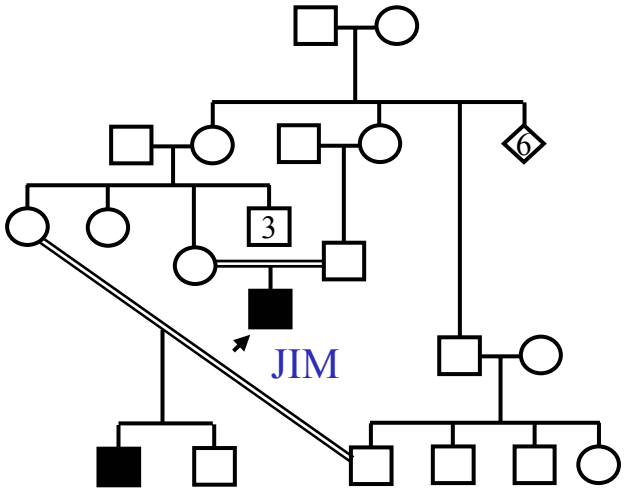




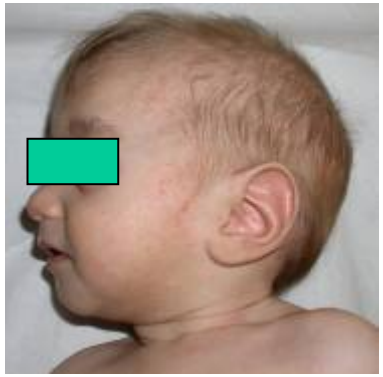


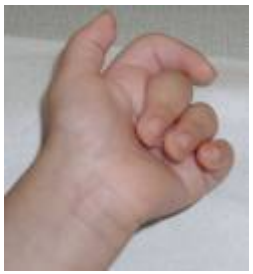
JIM : First cousin of Jordan

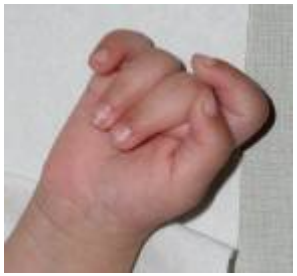
- W= 3290 g, L = 51 cm, OFC = 35 cm
- Camptodactyly
- Elbow contractures
- Facial contractions during crying
- Feeding difficulties



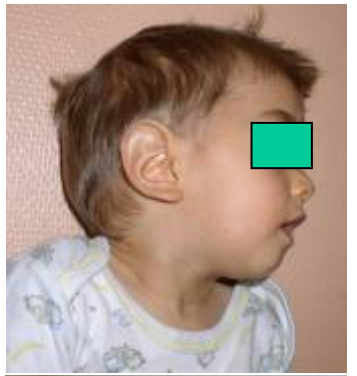
JIM at 6 months

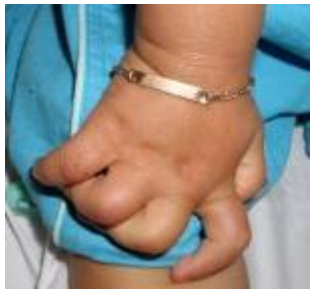


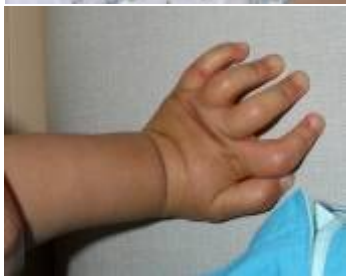




JIM at 18 months

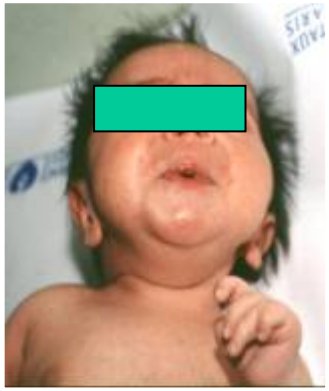






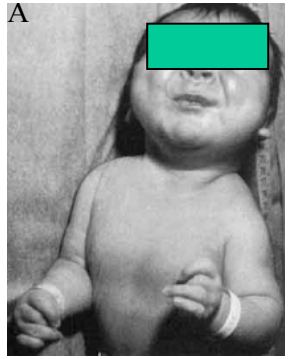
Overlap Stüve-Wiedemann / Crisponi syndromes

SWS



Trismus
Camptodactyly
Feeding difficulties
Hyperthermia
Early death
Survivor : kyphoscoliosis
temperature instability

CRISPONI

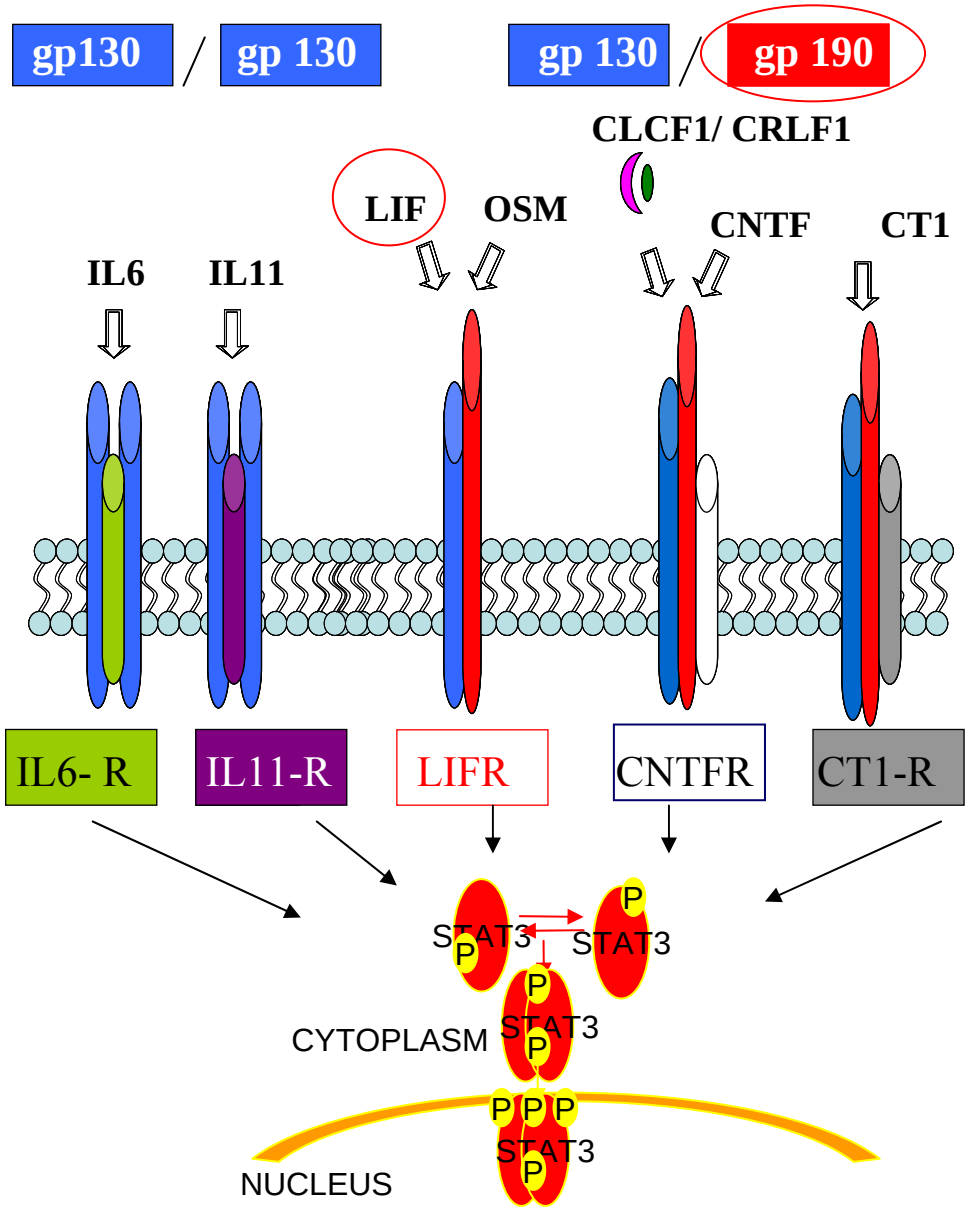


Bowing of the lower limbs
Normal intelligence

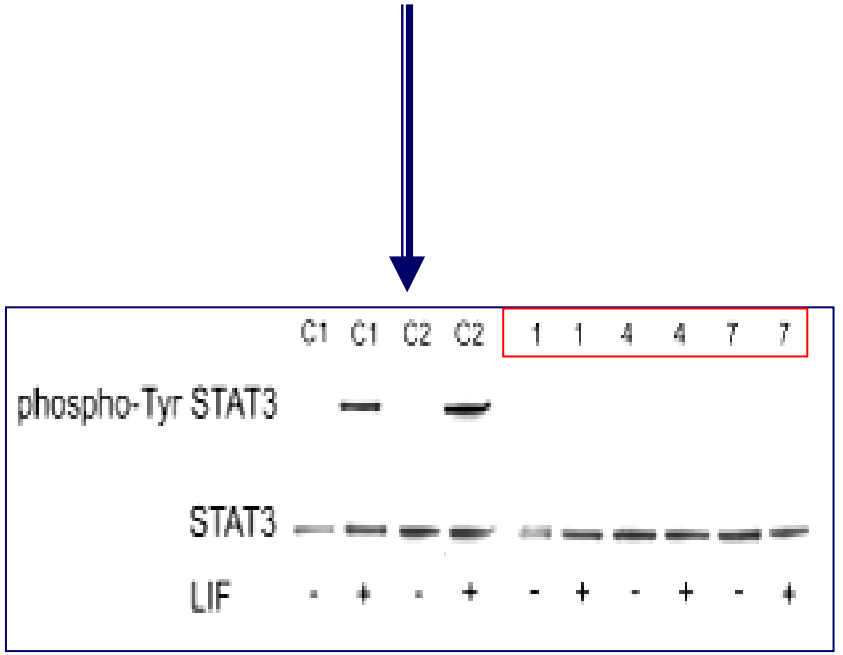
Seizures
Mild psychomotor delay

⇒ LIFR candidate gene in Crisponi syndrome

IL-6 type cytokines and their receptors



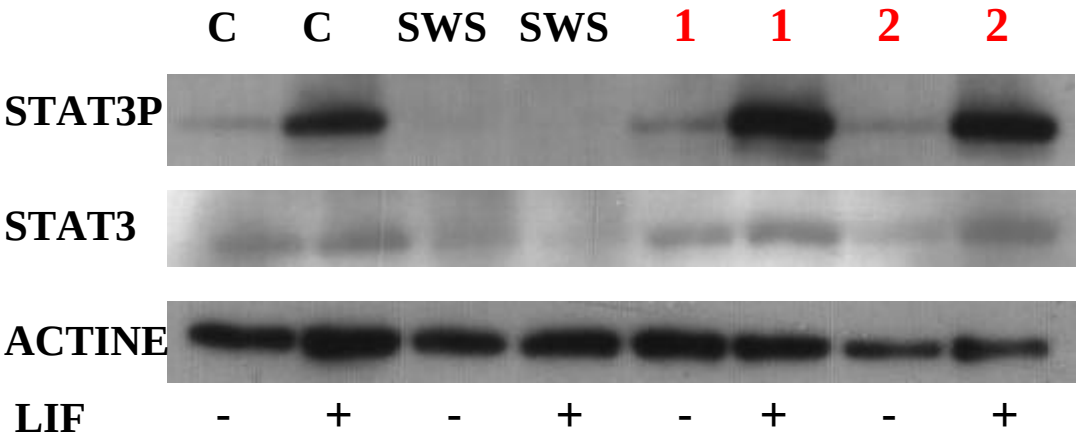
LIFR (gp190) mutations in SWS



Inactivation of JAK/ STAT3 pathway in SWS

LIFR: candidate gene in Crisponi syndrome

- STAT3 phosphorylation in response to LIF in Crisponi syndrome

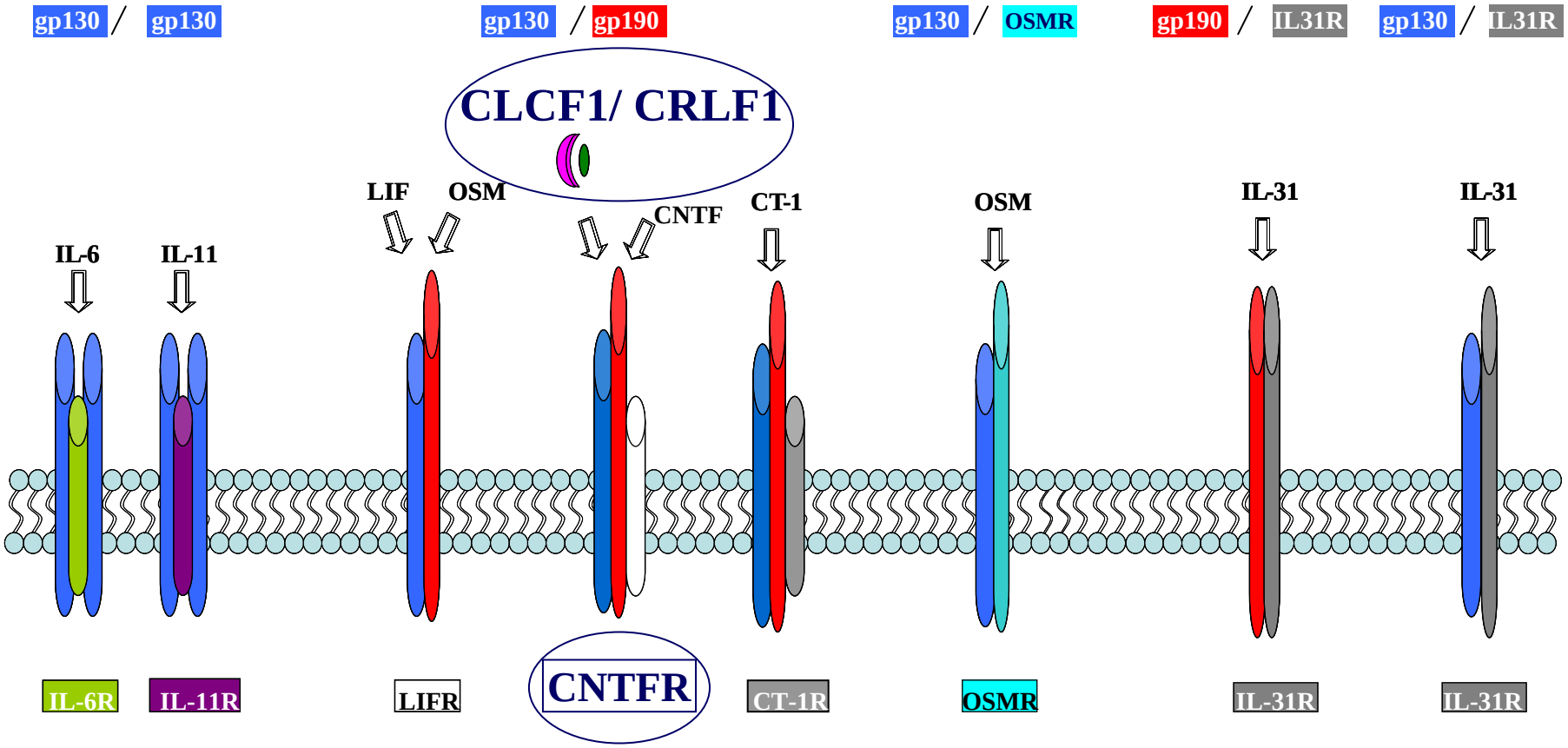


1, 2 : fibroblasts from Crisponi patients

- Third family : exclusion of LIFR by direct sequencing

⇒ Exclusion of LIFR in all three Crisponi families

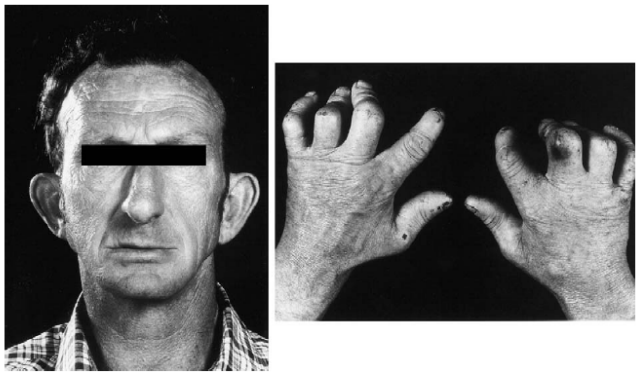
Other candidate genes in Crisponi syndrome ?



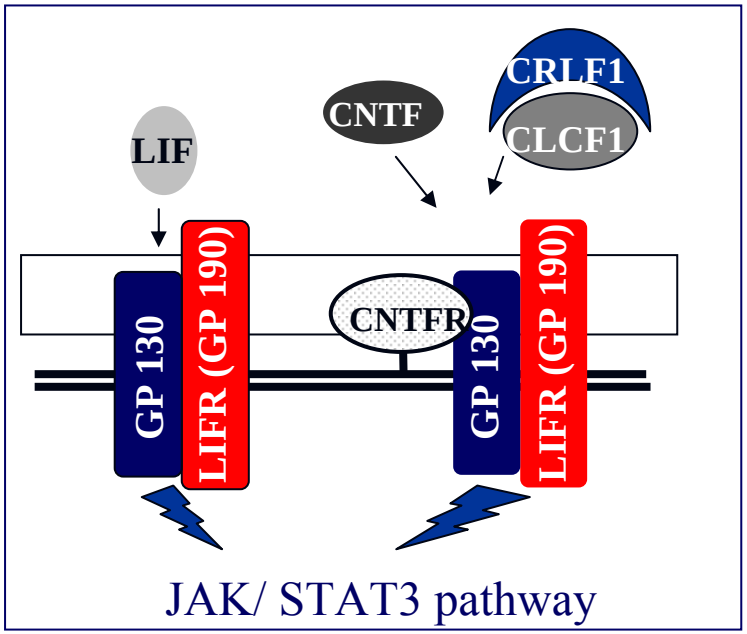
CRLF1/ CLCF1 mutations: Cold Induced Sweating Syndrome

Cold induced sweating syndrome (CISS)

- First description in 1978
- Paradoxical sweating in the back and chest
- Camptodactyly, kyphoscoliosis
- 6 cases from 4 families : CRLF1 mutations 3/4
  CLCF1 mutations 1/4

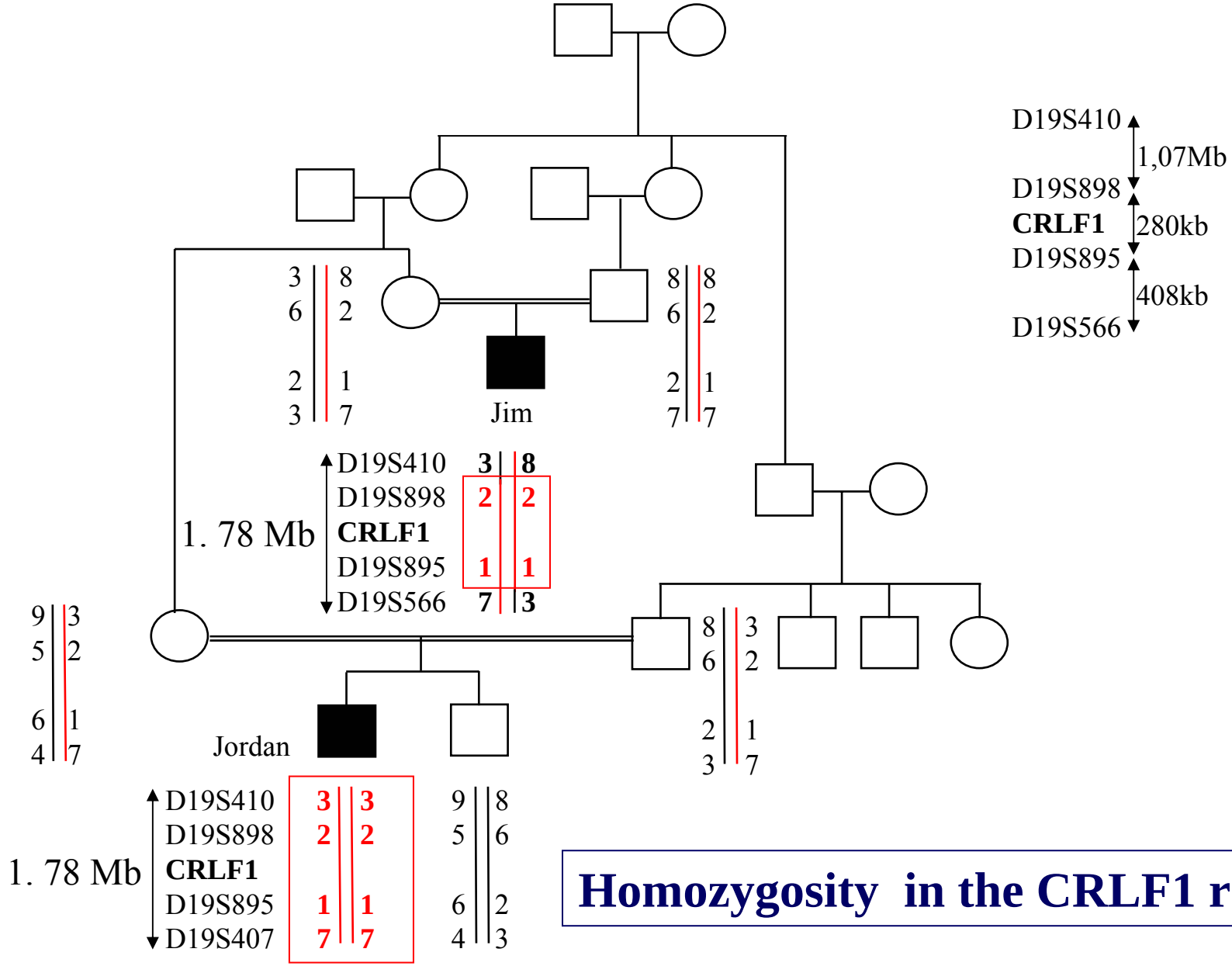


Hahn et al, 2006



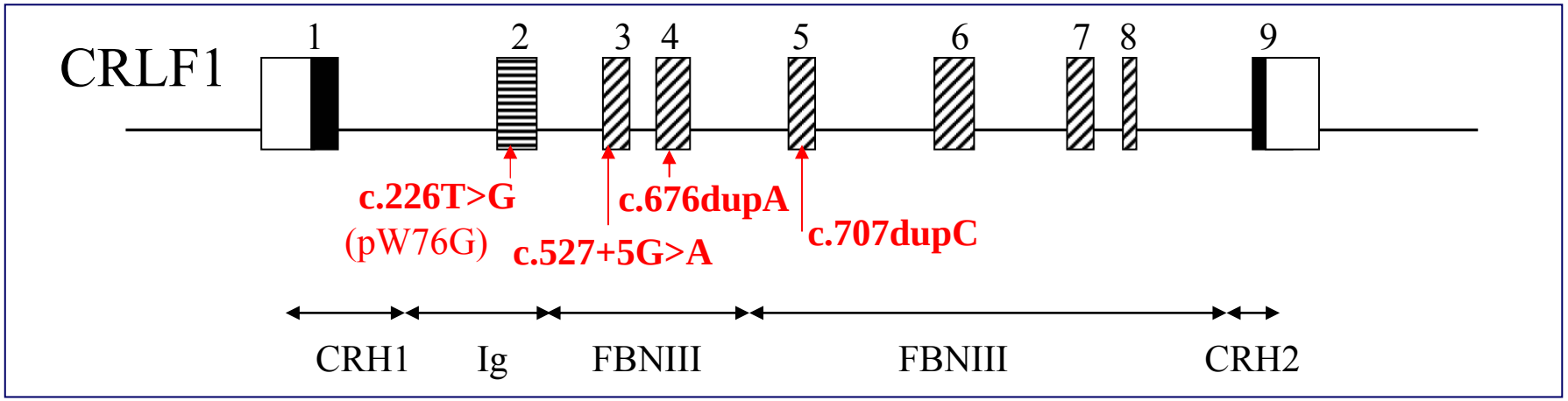
JAK/ STAT3 pathway

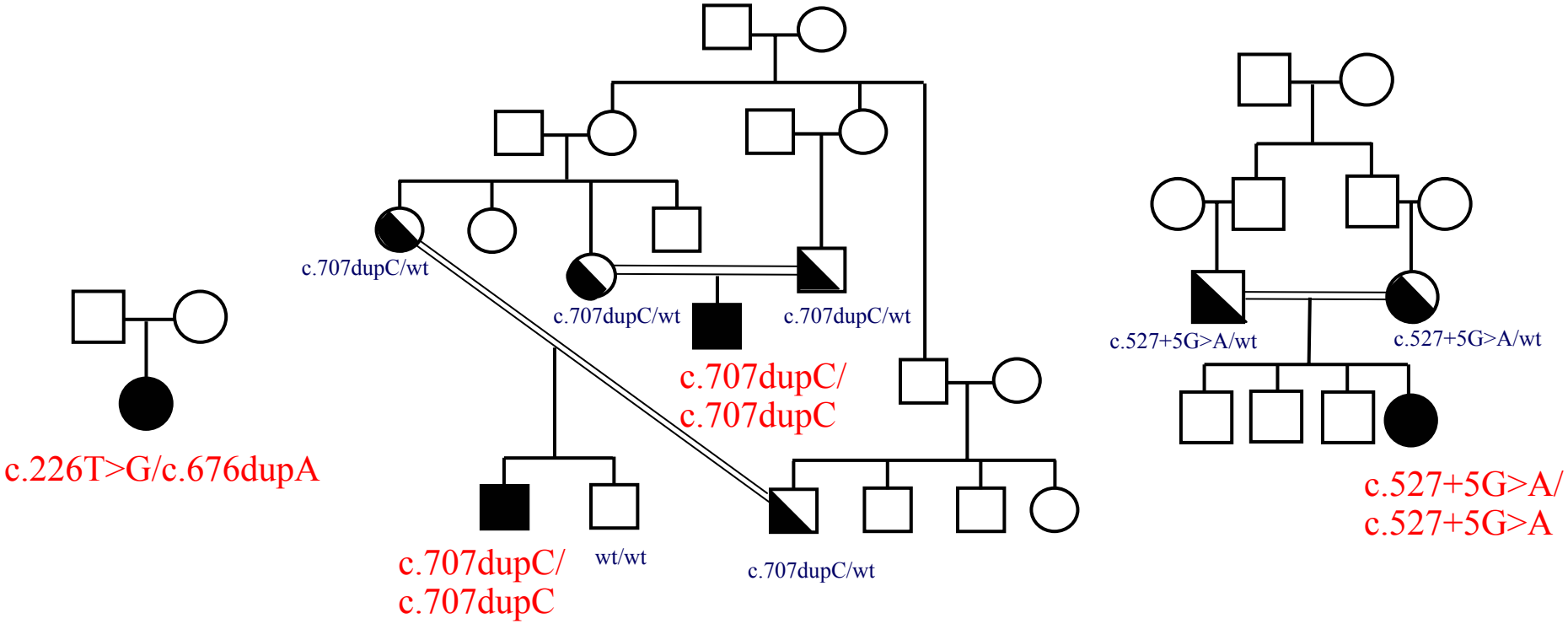
Linkage analysis in the CRLF1 region (19p12)



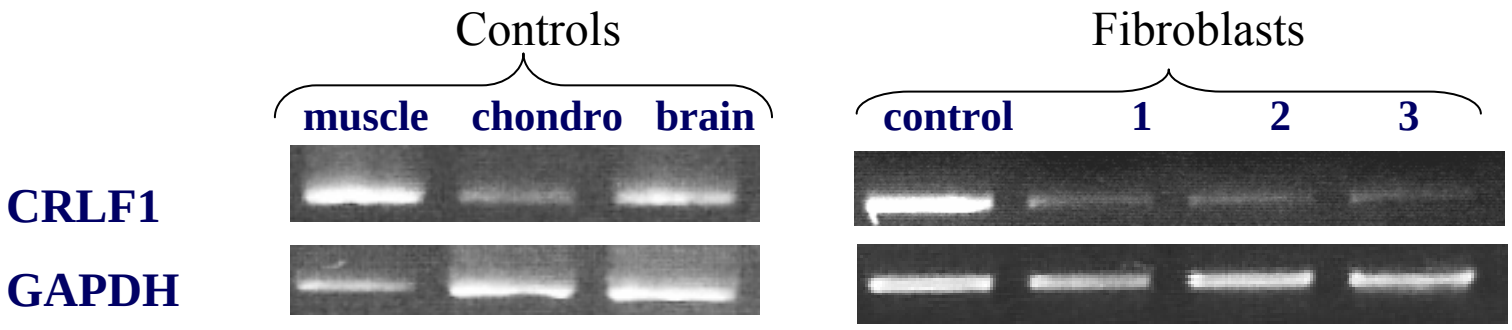
Homozygosity in the CRLF1 region

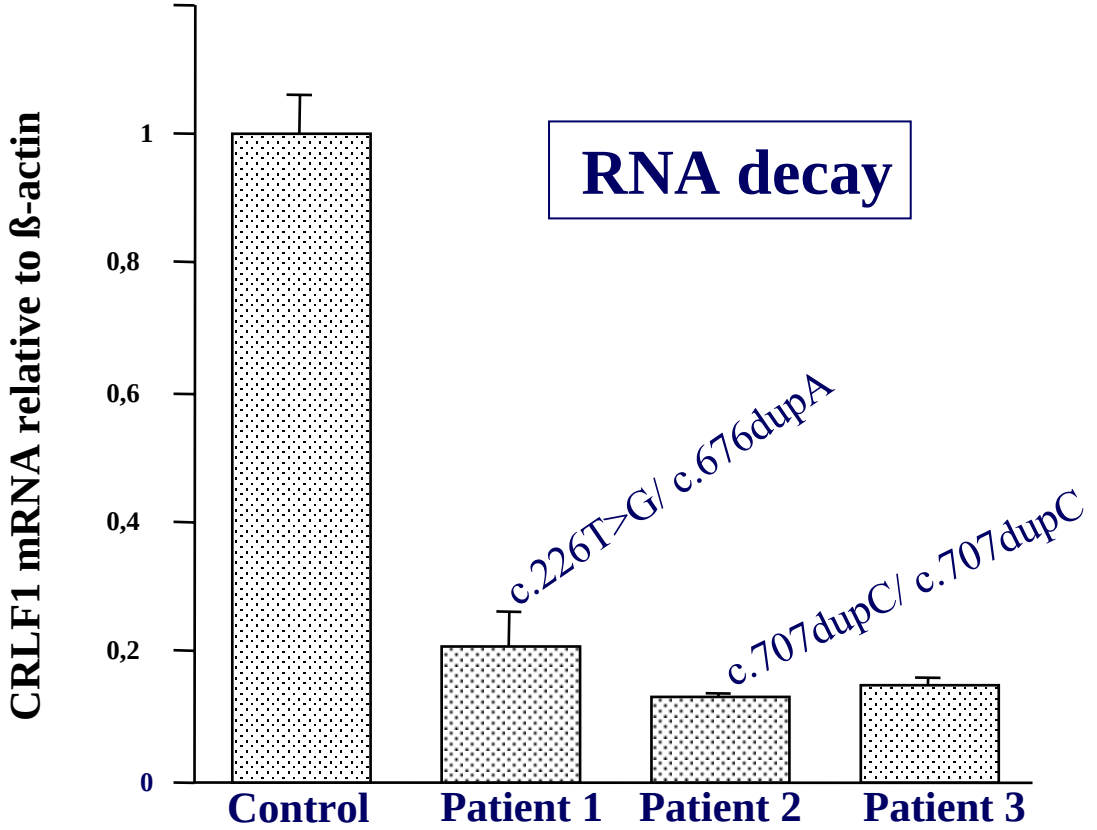
Direct sequencing of CRLF1



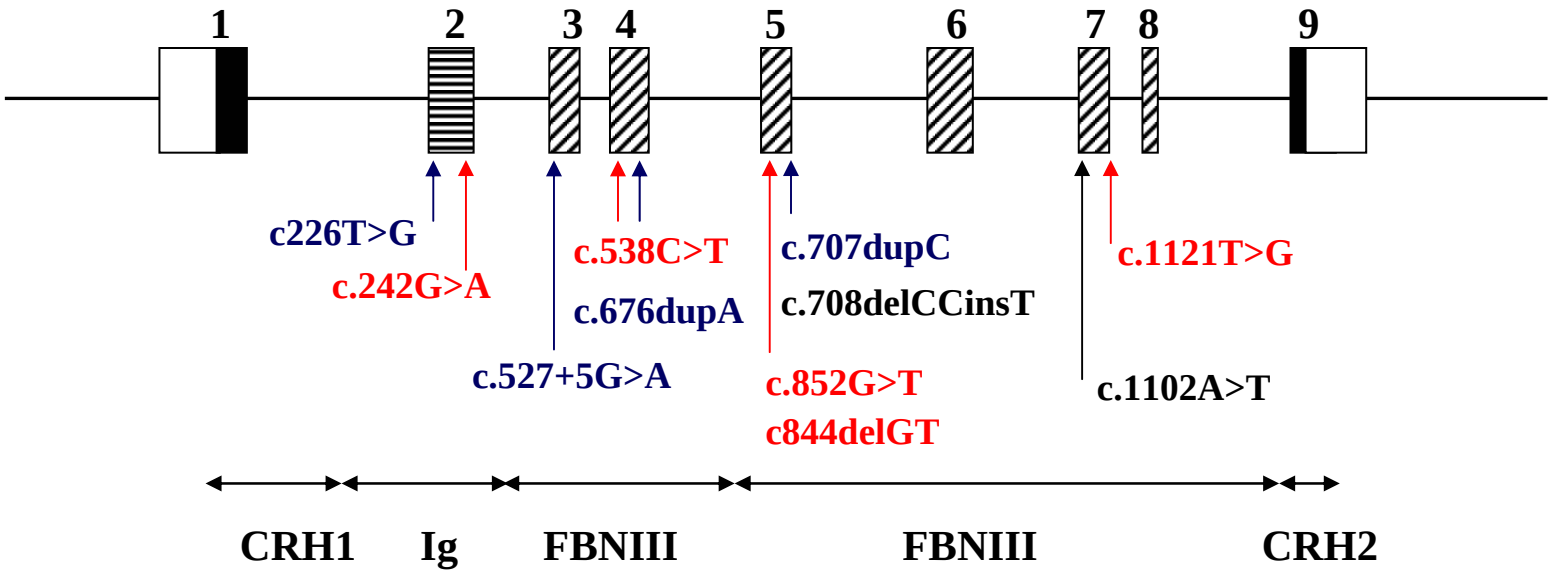


RT-PCR analysis of CRLF1





CRLF1 mutations in Crisponi syndrome/CISS



→ Mutations identified in our series of Crisponi patients

→ Mutations identified by Crisponi et al

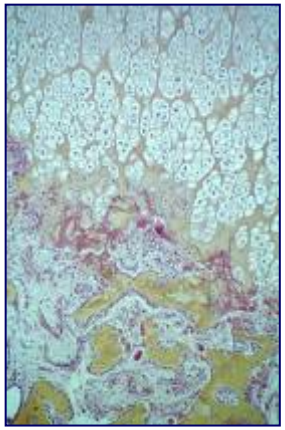
→ Mutations identified in CISS

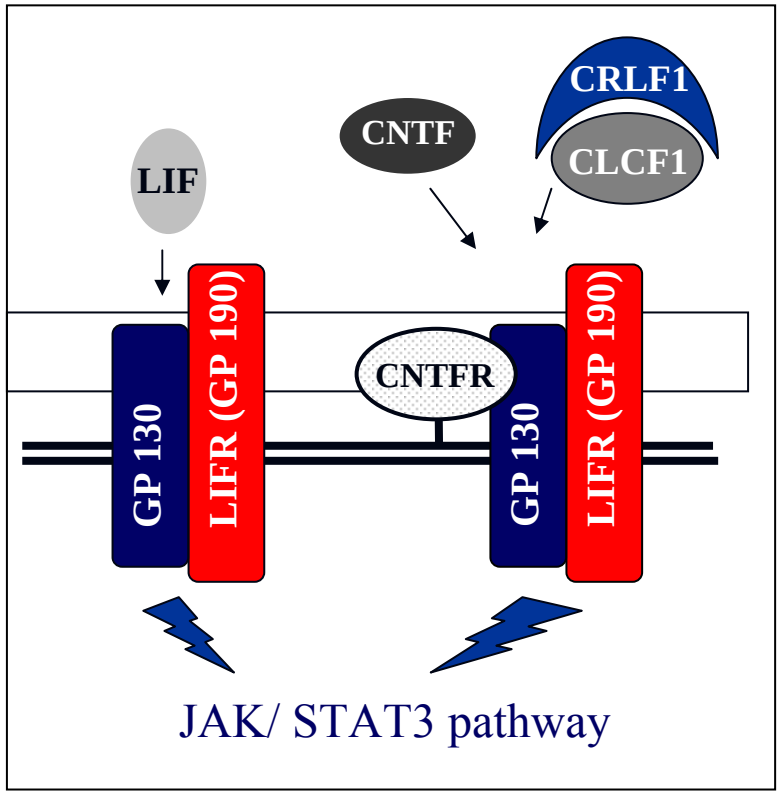
Conclusion

Bone manifestations

LIFR pathway

SWS





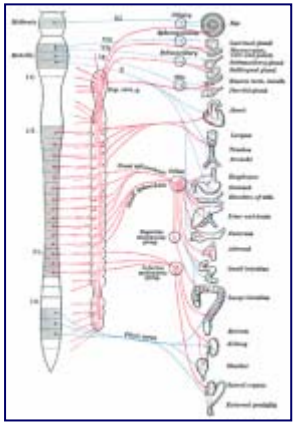
Dysautonomia

CNTFR pathway

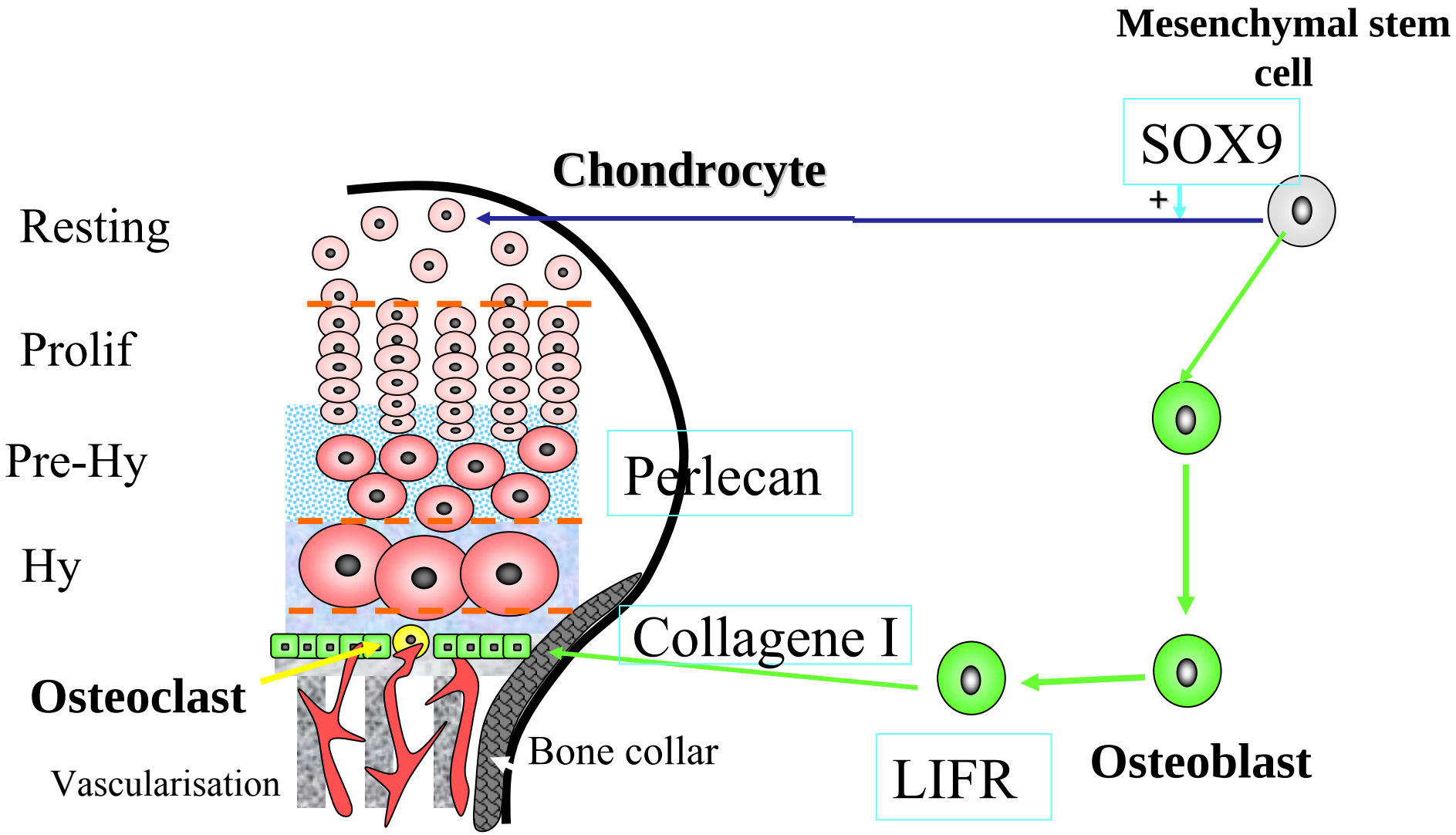
CISS

Crisponi syndrome

SWS



Molecular basis of bent bone dysplasia



Importance of the diagnosis :

- Genetic counselling

Cumming : AR (?)/ SWS : AR (LIFR)/ Campoméeic: AD (Sox9)/ Kyphomelic : AR (?)

- Prognosis

Short Rib-Polydactyly group

- Narrow thorax, short ribs
- Short long bones
- Polydactyly
- Trident acetabular roof
- Autosomal recessive inheritance

Short rib polydactyly group : 6 entities

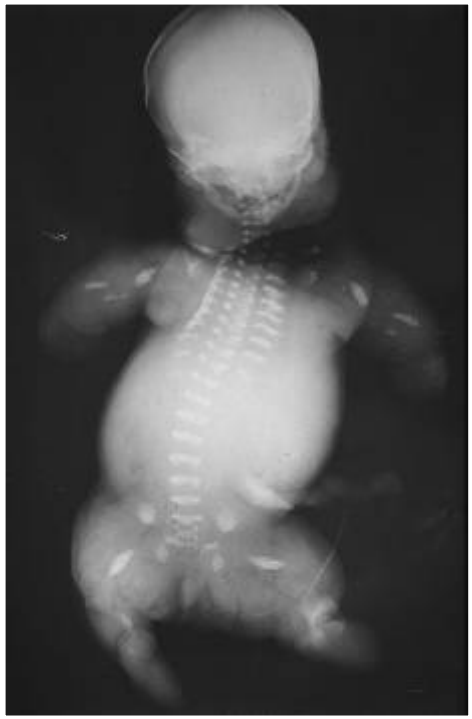
- 4 lethal chondrodysplasia: variable malformations

- Type I : Saldino-Noonan,
- Type II : Majewski : polydactyly, tibia agenesis
- Type III : Verma-Naumoff, metaphyseal spurs
- Type IV : Beemer : round metaphyses

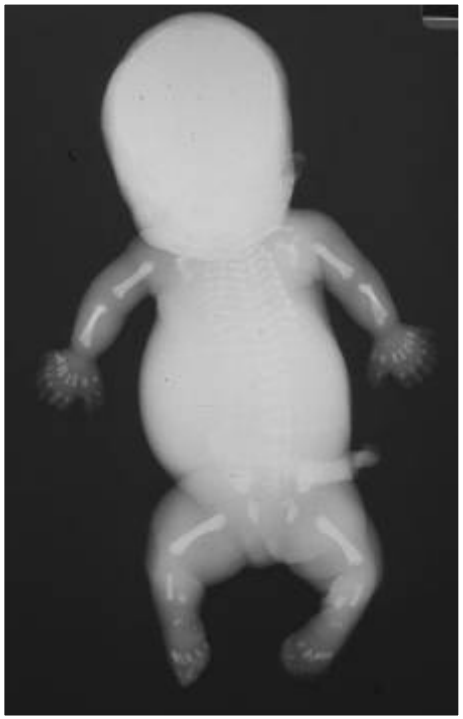
-Jeune thoracic dysplasia: kidney, liver and eye involvement

-Ellis van Creveld : frenulae, dysplastic nails, heart malformation

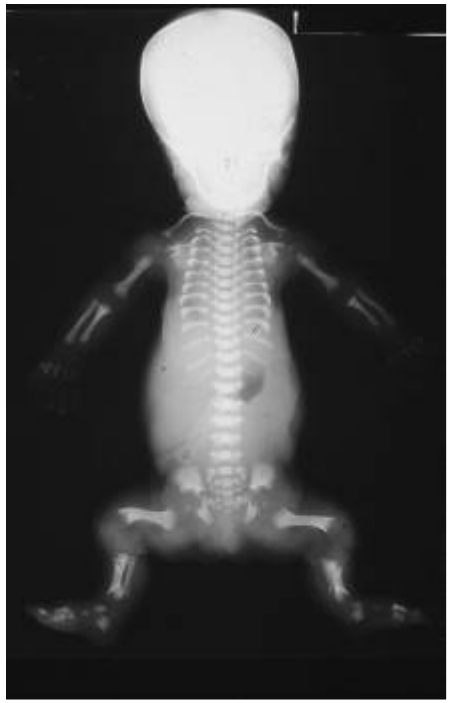
Short rib polydactyly group : lethal forms



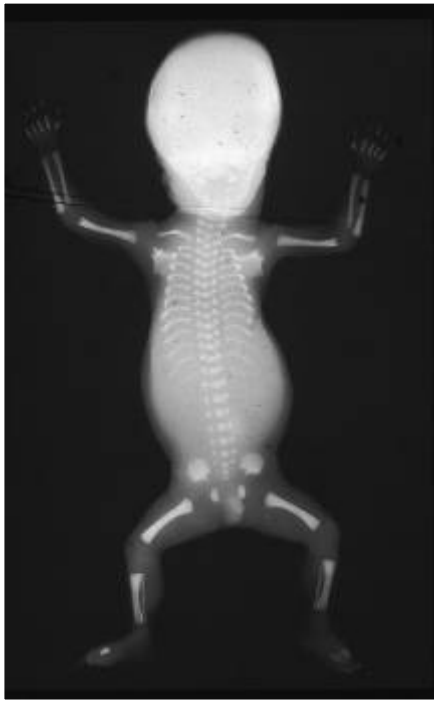
Type I



Type II



Type III



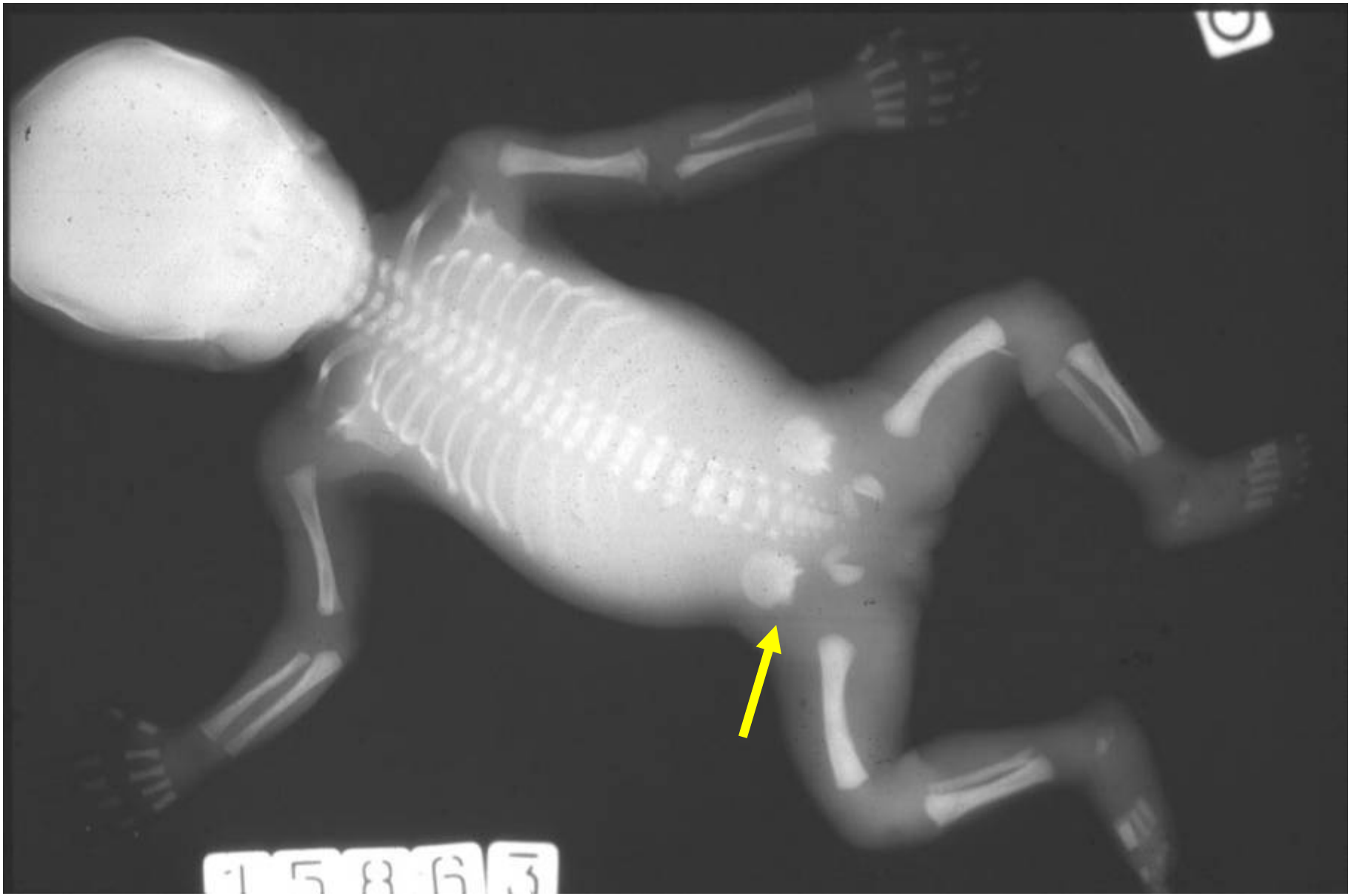
Type IV

Chondrodysplasias diagnosed at birth

- chondroectodermic dysplasia or Ellis van Creveld syndrome

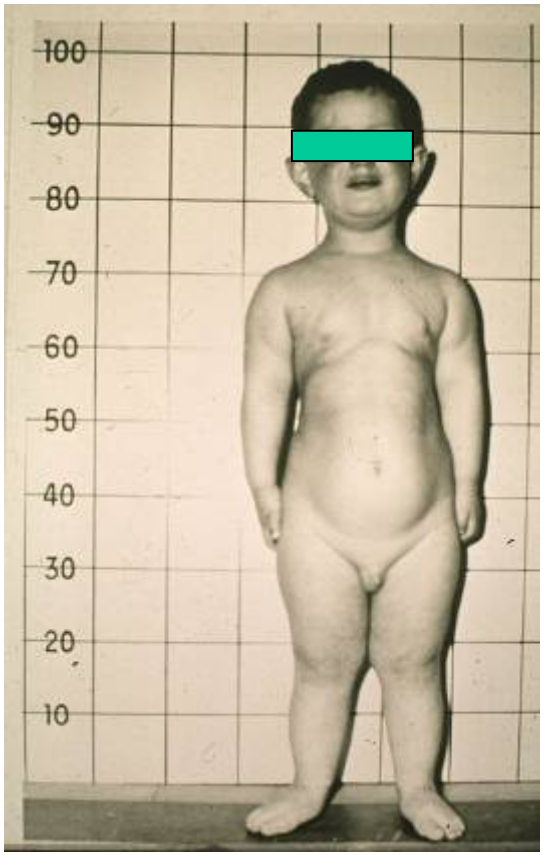
- Asphyxiating thoracic Dysplasia (Jeune)

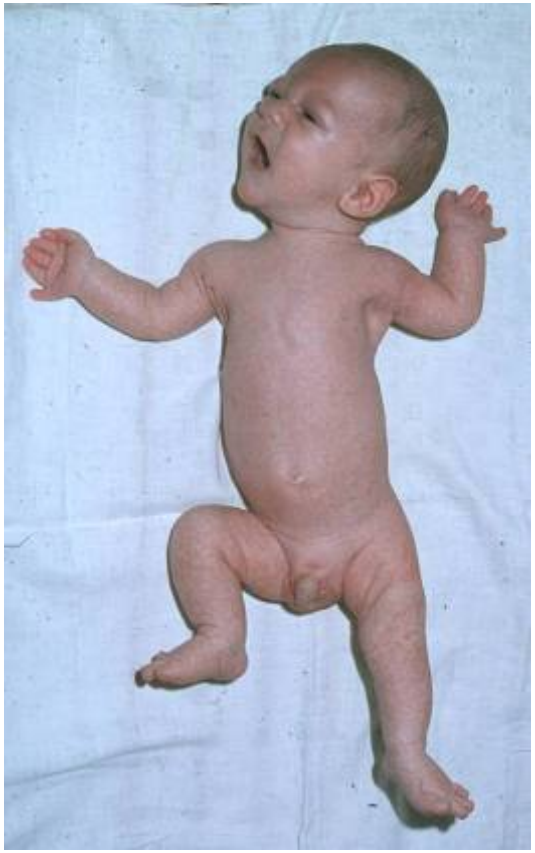
EVC/ Jeune

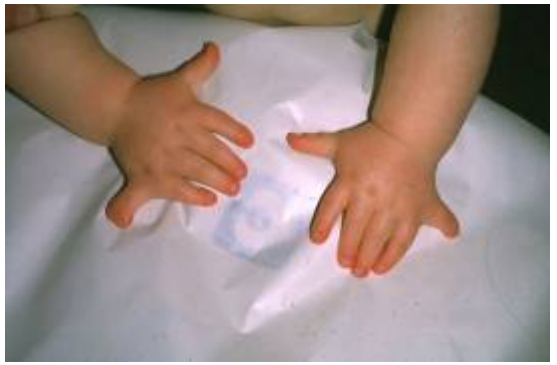


•(Ellis Van Creveld syndrome

- Teeth and ungueal dysplasia
- Frenulae
- heart malformtaion(septal defect)

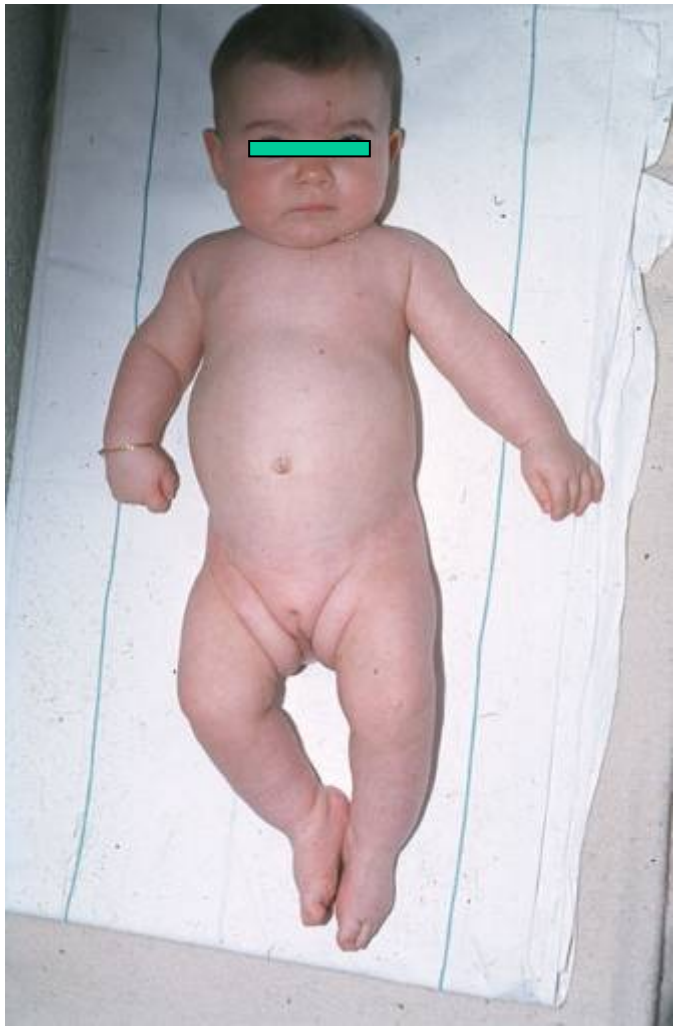






Asphyxiating thoracic dysplasia (Jeune)

- Cystic renal disase
- Liver involvement
- Retinal degeneration



Short rib polydactyly group : ciliopathy spectrum

1. *evc1/evc2* (4p16) (2000) : mediator of Ihh signaling, localisation at the base of chondrocyte cilia (2007)

2.ATD : identification of *IFT80* mutations in 3/ 39 families (2007)

IFT 80 : intraflagellar transport protein involved in the elongation and maintenance of cilia

Heterogeneous condition!

Short rib polydactyly group : cilia disorders ?

Molecular analysis of I*FT80* in a series of 26 fetuses and children from 14 families diagnosed either with ATD or SRP type III

No mutation

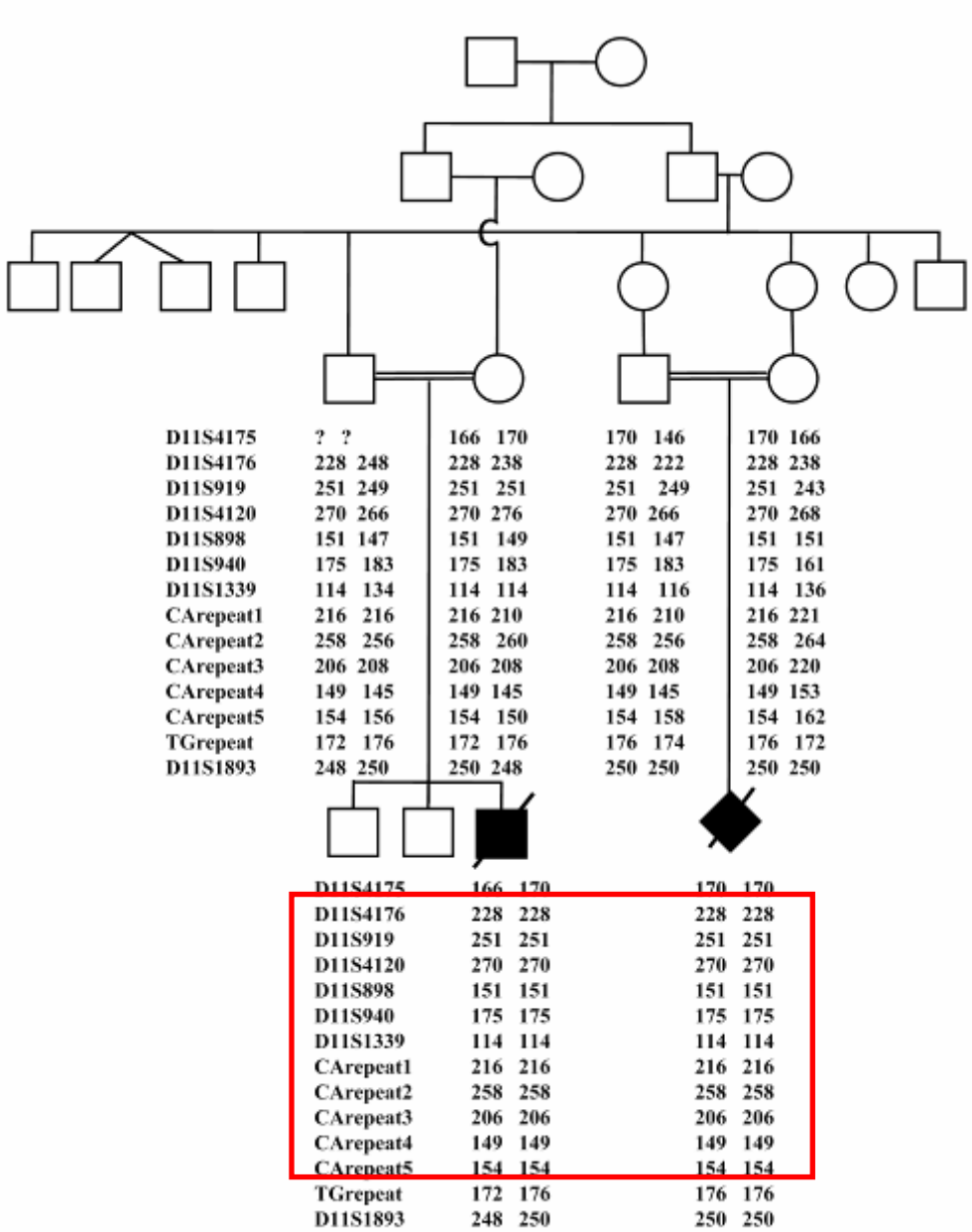
Genome wide search in a large consanguineous family of Morocco origin

Common region of homozygosity : 11q4.3 region

20.4 Mb, 85 genes

4 referenced in the cilia database
-KDEL
-Rab39
-GUCY1A2

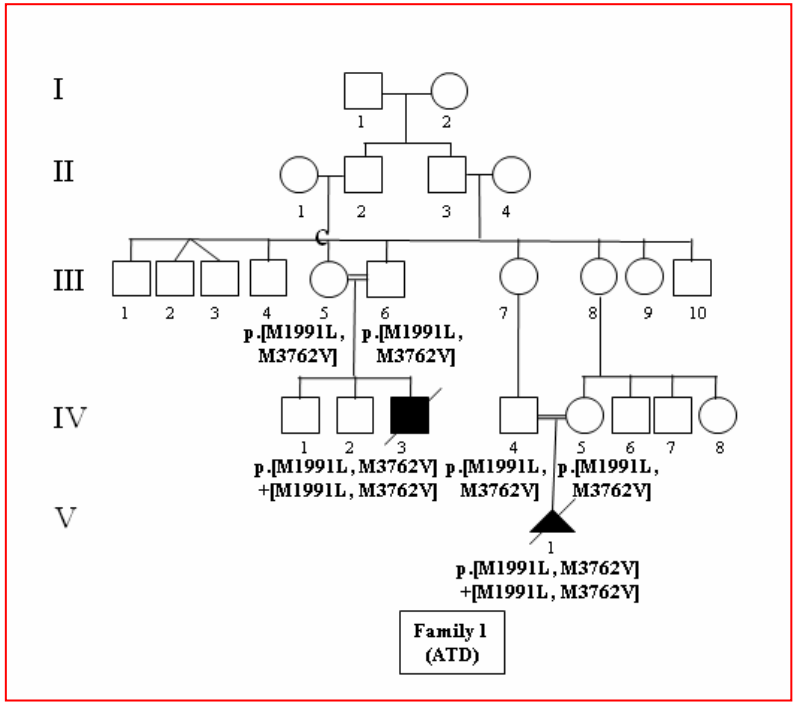
DYNC2H1



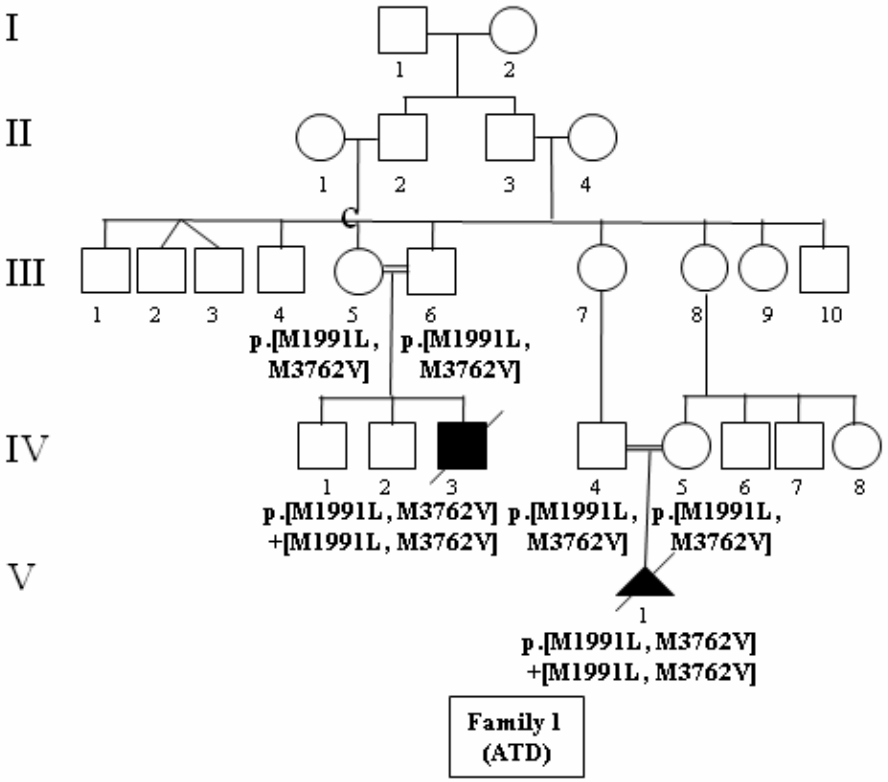
DYNC2H1 : 90 exons

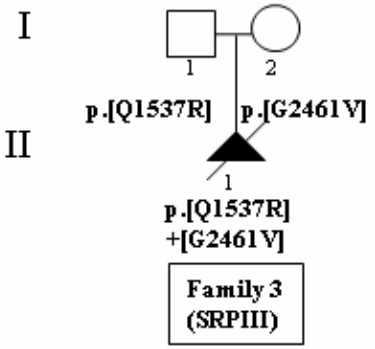
Encodes a subunit of a cytoplasmic dynein complex directly involved in the generation and maintenance of cilia

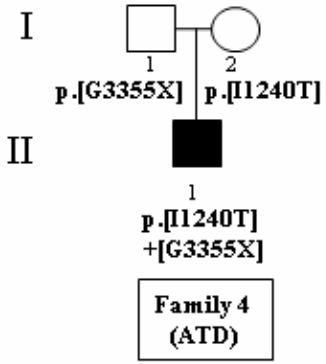
Identification of two missense mutations p.Met1991Leu, p.Met3762Val

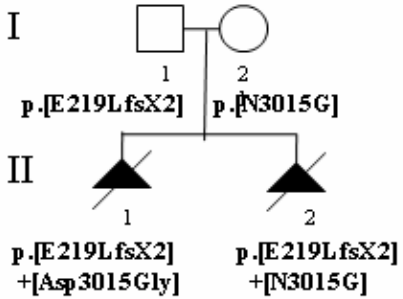


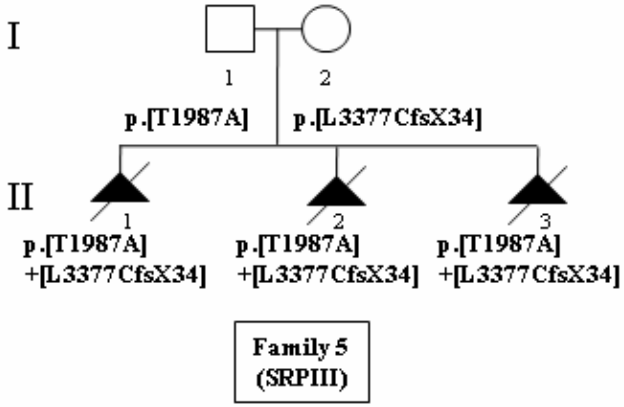
Exclusion of *DYNC2H1* in the 5 other CS families
Identification of mutations in 4/ 8 non CS families


I
II
III
IV
V
p.[M1991L, M3762V]
p.[M1991L, M3762V]
p.[M1991L, M3762V] +[M1991L, M3762V]
p.[M1991L, M3762V]
p.[M1991L, M3762V]
p.[M1991L, M3762V] +[M1991L, M3762V]
Family 1 (ATD)

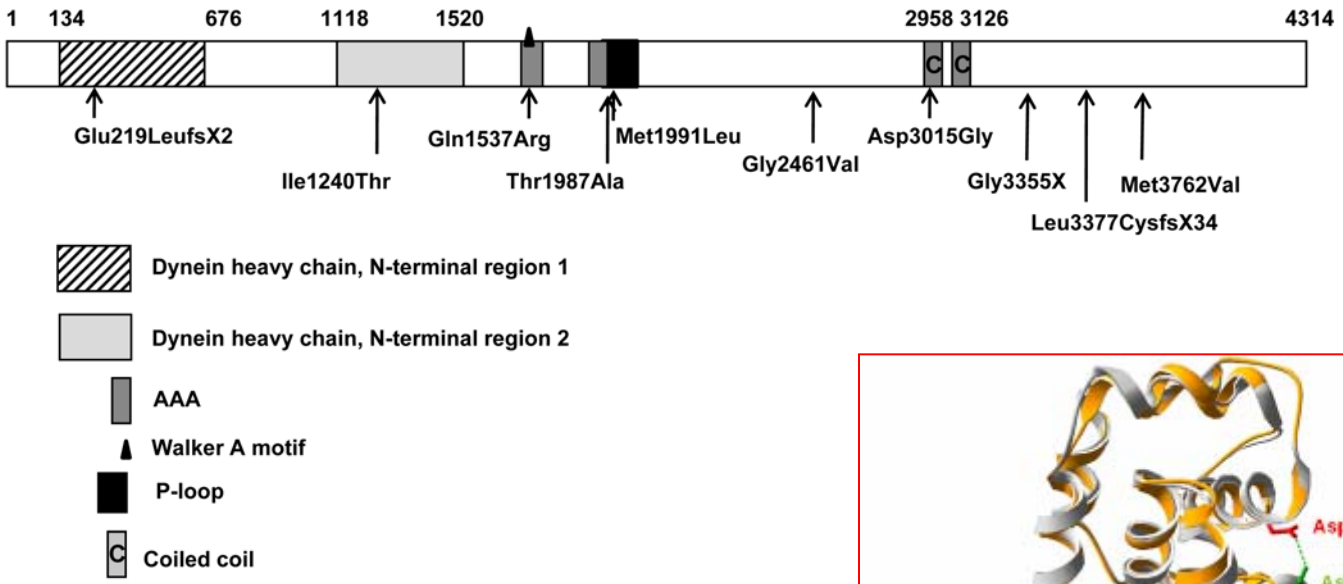

I
II
p.[Q1537R]
p.[G2461V]
p.[Q1537R] +[G2461V]
Family 3 (SRPIII)

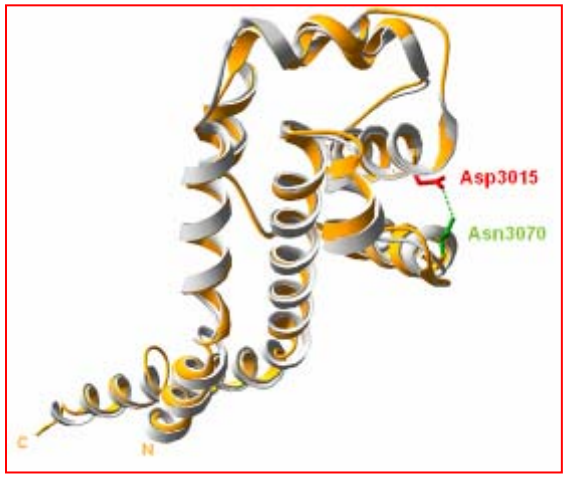

I
II
p.[G3355X]
p.[I1240T]
p.[I1240T] +[G3355X]
Family 4 (ATD)


I
II
p.[E219LfsX2]
p.[N3015G]
p.[E219LfsX2] +[Asp3015Gly]
p.[E219LfsX2] +[N3015G]
Family 2 (ATD)

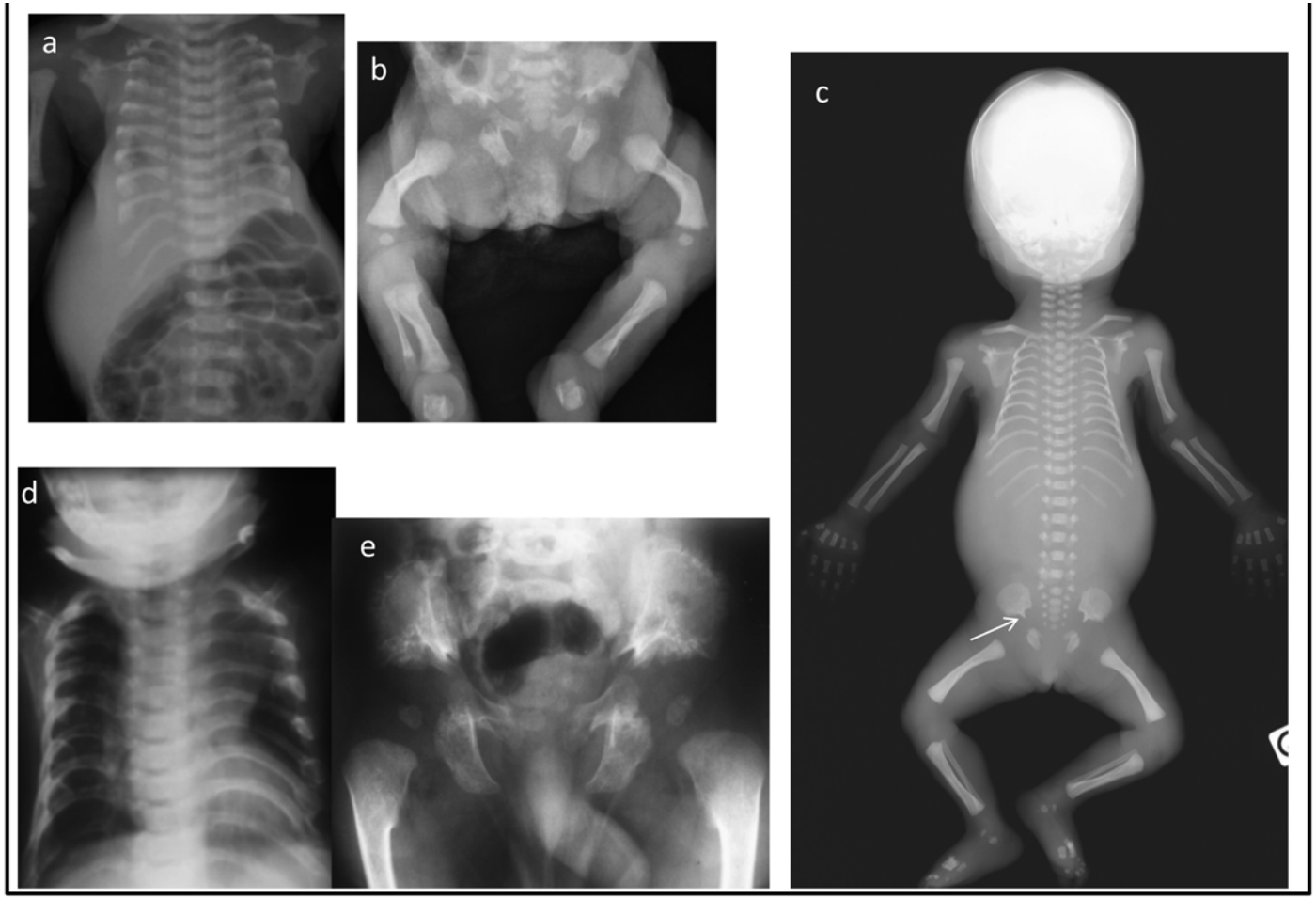

I
II
p.[T1987A]
p.[L3377CfsX34]
p.[T1987A] +[L3377CfsX34]
p.[T1987A] +[L3377CfsX34]
p.[T1987A] +[L3377CfsX34]
Family 5 (SRPIII)

Localisation of *DYNC2H1* mutations

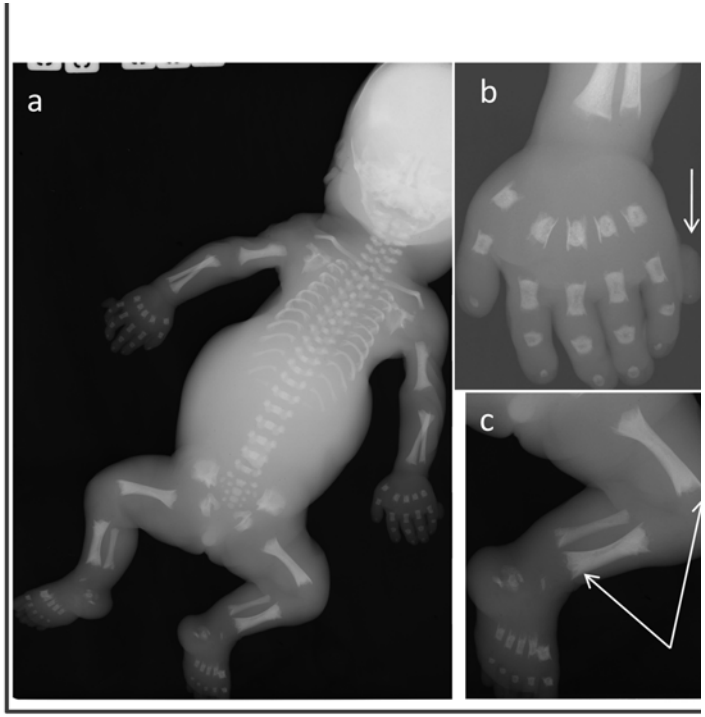


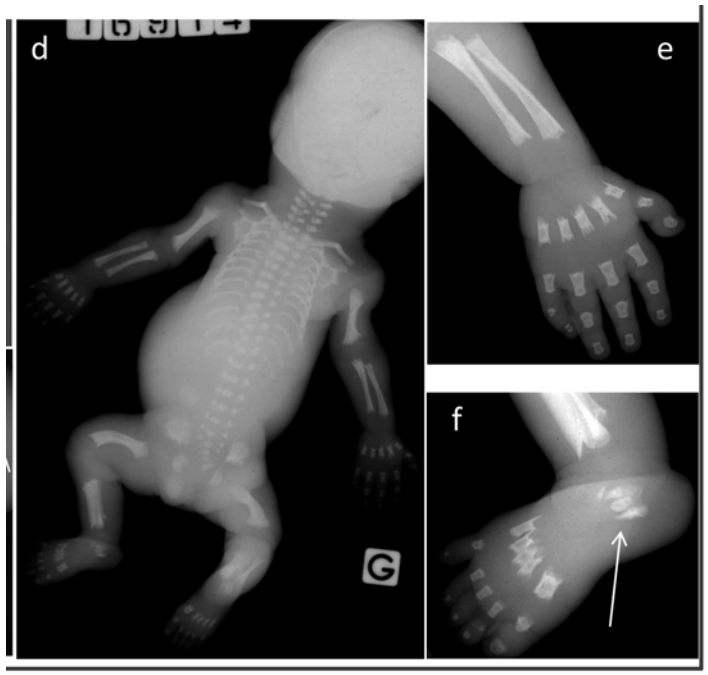


Diagnosis : ATD in 3 families

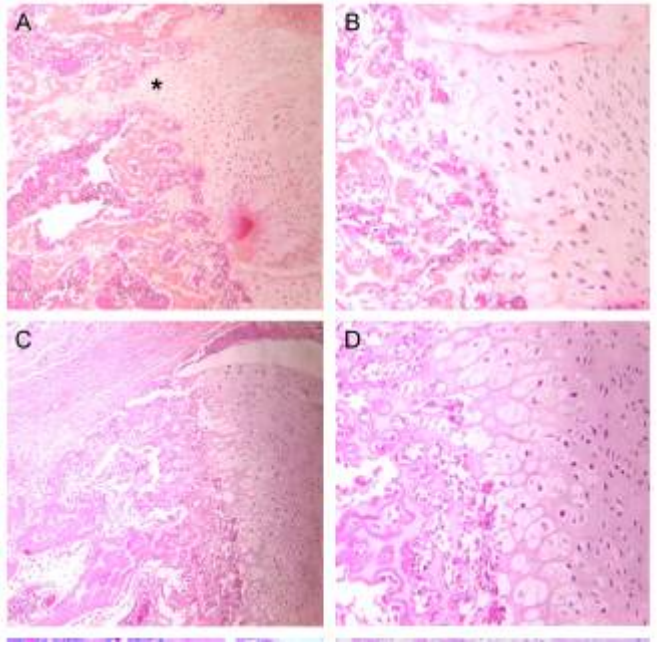


No renal, liver or eye involvement





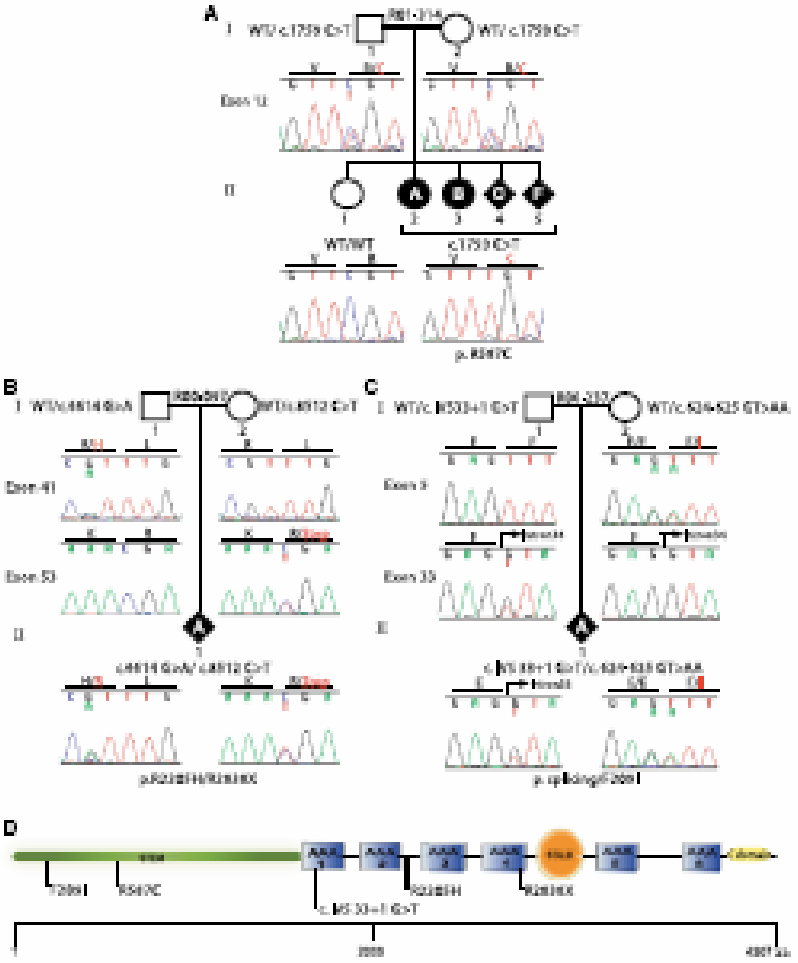
SRP type III in two families:
BL postaxial polydactyly
Periduodenal pancreas
Renal tubular microcysts

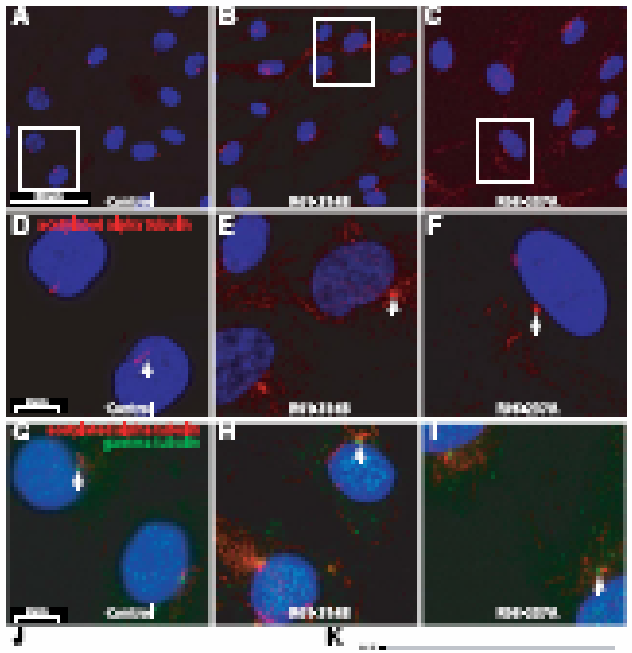


April 2009

Ciliary Abnormalities Due to Defects in the Retrograde Transport Protein DYNC2H1 in Short-Rib Polydactyly Syndrome

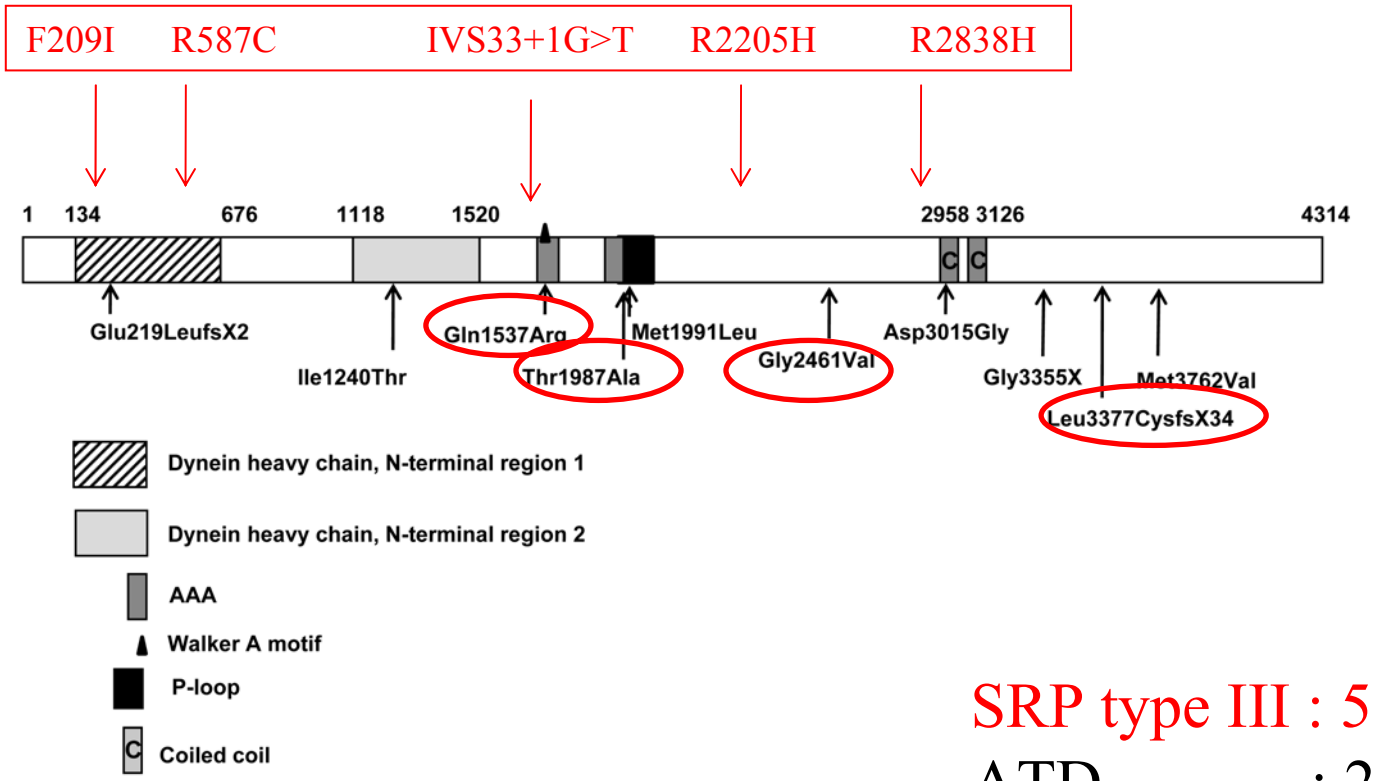
Amy E. Merrill,[1,2] Barry Merriman,[3] Claire Farrington-Rock,[1] Natalia Camacho,[2] Eiman T. Sebald,[1] Vincent A. Funari,[1,4] Matthew J. Schibler,[7,8] Marc H. Firestein,[2] Zachary A. Cohn,[1] Mary Ann Priore,[1] Alicia K. Thompson,[9] David L. Rimoin,[1,3,4,5] Stanley F. Nelson,[3] Daniel H. Cohn,[1,3,4] and Deborah Krakow[1,2,3,6,*]





SRP chondrocytes
Abnormal primary cilia

Localisation of *DYNC2H1* mutations ATD and SRP III



SRP type III : 5 cases

ATD : 2 cases

Short rib polydactyly group : Conclusion

CILIA disorders

4Genes identified

-*evc1* and *evc2* involved in 2/3 of EVC cases

-*IFT 80* involved in only 3 cases of ATD

-*DYNC2H1* involved in ATD and SRP type III,

ATD and SRP type III =variants of a single disorder