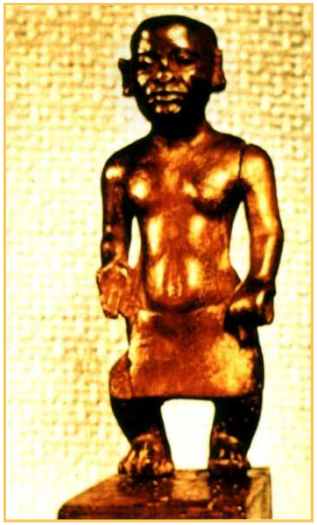

Skeletal syndromes

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Diagnosis of a primary skeletal dysplasia

Clinical approach : the presenting feature

- Short stature : rhizomelia/ mesomelia/ micromelia
- Congenital bowing
- Short ribs-Polydactyly
- Fractures

Diagnosis of a primary skeletal dysplasia

Clinical approach : the presenting feature

- Short stature : rhizomelia/ mesomelia/ micromelia

diagnosed antenatally

at birth

during infancy

Lethal Chondrodysplasia

- Marked Micromelia (US survey+ X-rays)
- Detected at 3-4 months of gestation
- Disproportion between body and head
- Immobility/ edema/ fetal hydrops/ polyhydramnios
- Radiological features specific on the different type

Importance of X-rays after pregnancy termination

Thanatophoric dysplasia

- First description in 1967 by P. Maroteaux
- Most common form of lethal CD 1/40 000

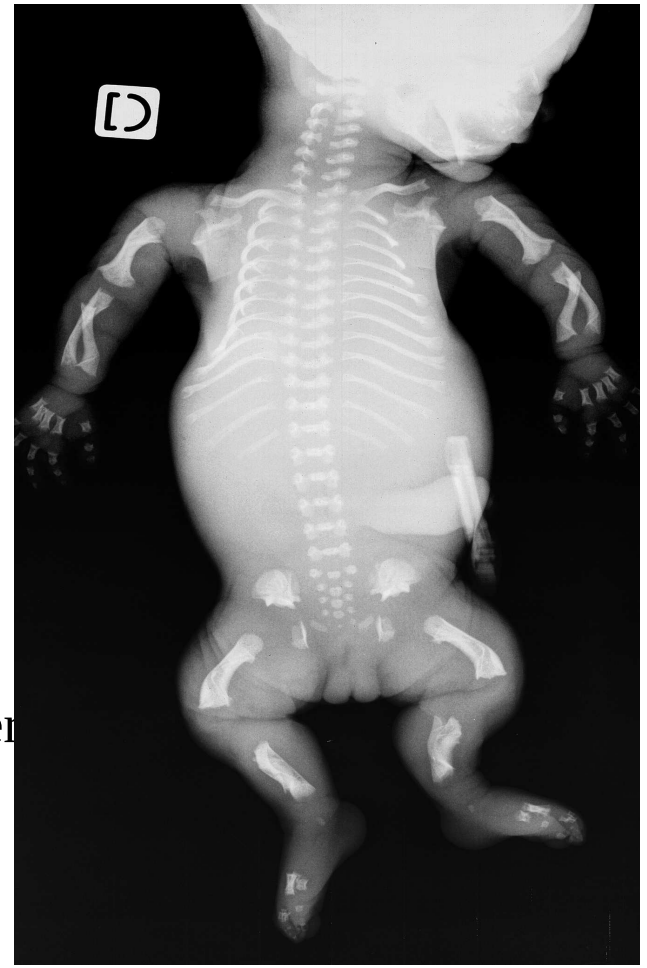
-Marked short limb dwarfism

- Relative large head

- Severe platyspondyly

-Horizontal acetabular roofs,

- Bowing of long bones
- Irregularity and flaring metaphyses
- TD 1: without cloverleaf skull, French telephone receiver
- TD2 : with cloverleaf skull, Straight micromelic femur



- **New autosomal dominant mutation**

in FGFR3

Achondrogenesis

- Marked micromelic dwarfism, distended abdomen, barrel shaped chest, short neck and trunk
- polyhydramnios
- X-rays : - poorly mineralized skull and absent or minimal ossification of vetebral bodies

  - Concave ends of tubular bones

  -Short iliac wings

Achondrogenesis

Two types :

Type I : major shortness and broadness of tubular bones with multiple spurs

-IA : Short and thin ribs with multiple fractures

Autosomal recessive inheritance

-IB: trapezoid femur

Autosomal recessive inheritance

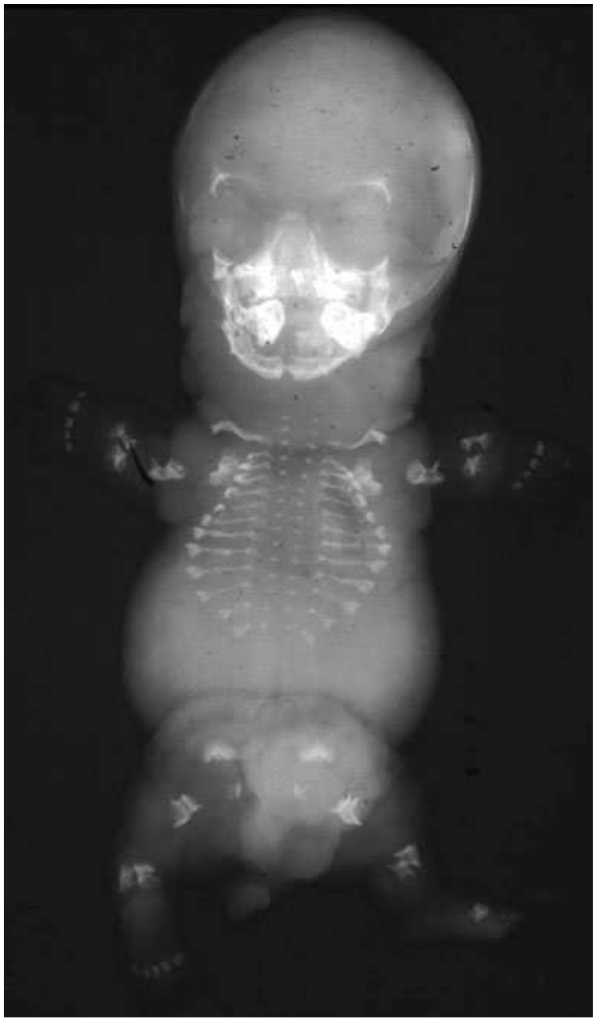
Mutations in DTDST (5q)

Type II : short femur with concave metaphyses

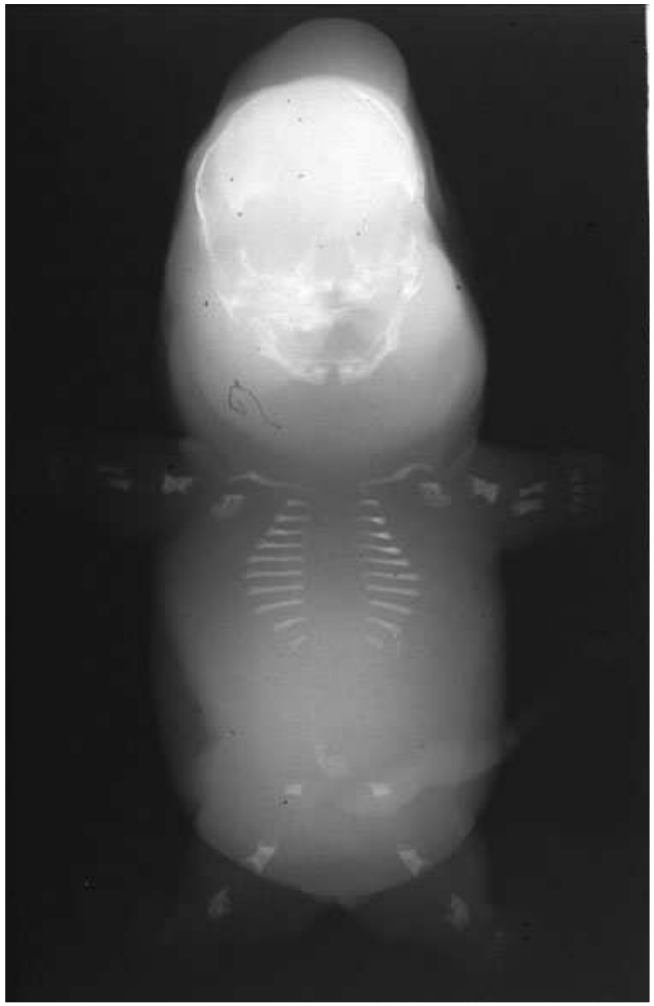
New mutation in Col2A1(12q13)

Value of the chondo-osseous morphology

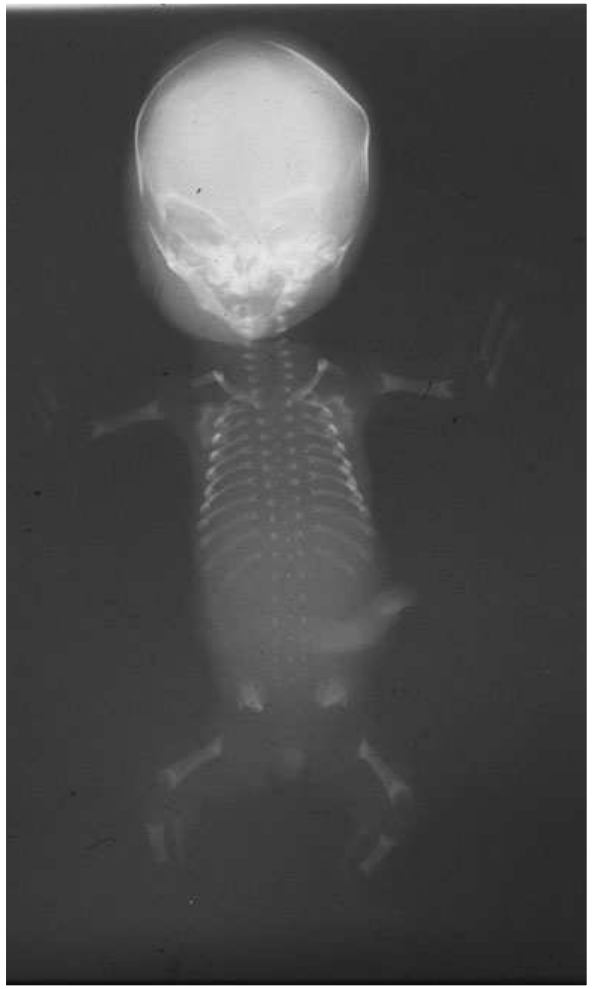
Achondrogenesis



Type Ia(AR,)



Type Ib (AR, DTDST)



Type II / hypochondrogenesis (new mutation COL2A1)

Clinical approach
disproportionate short stature **at birth**

- Achondroplasia : rhizomelia
- SEDC/ Kniest : micromelia, short trunk and flat face
- Diastrophic dysplasia : hitchiker thumb, club feet

Achondroplasia

- Incidence : 1/15000
- Rhizomeli c dwarfism
- Large head with prominent forehad, sadle nose
- Autosomal dominant transmission
- New Mutations in FGFR3 : 90 %

Achondroplasia

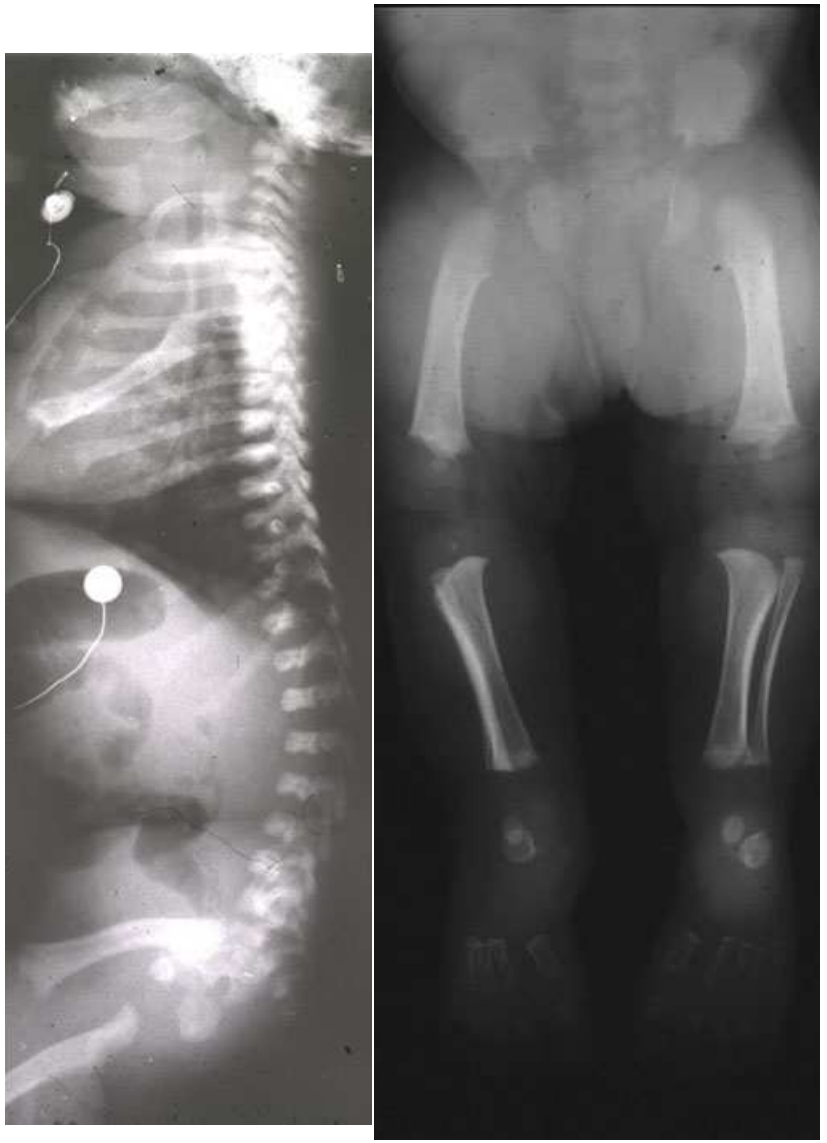
-Short pedicles with narrow vertebral canal

-Short and thick tubular bones

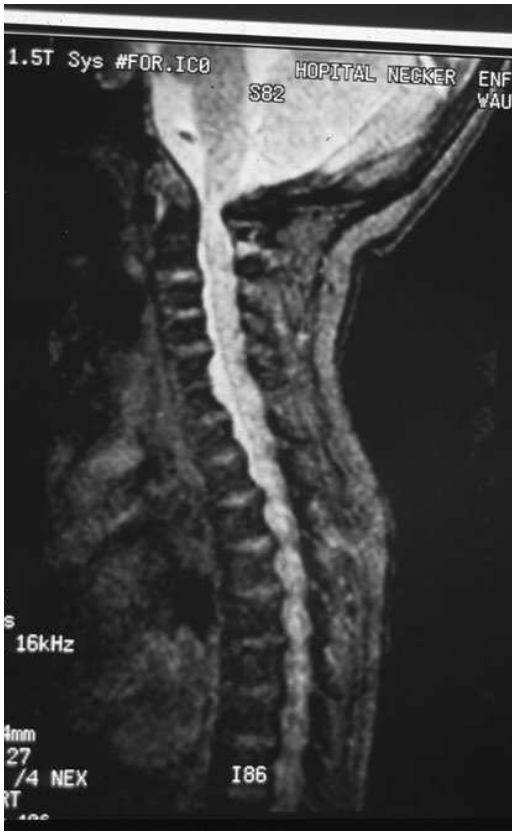
-Flared metaphyses, ball in-socket epiphyseal-metaphyseal junctions

-Squared iliac wings, flat acetabular roofs

-Fibula overgrowth



Achondroplasia : management

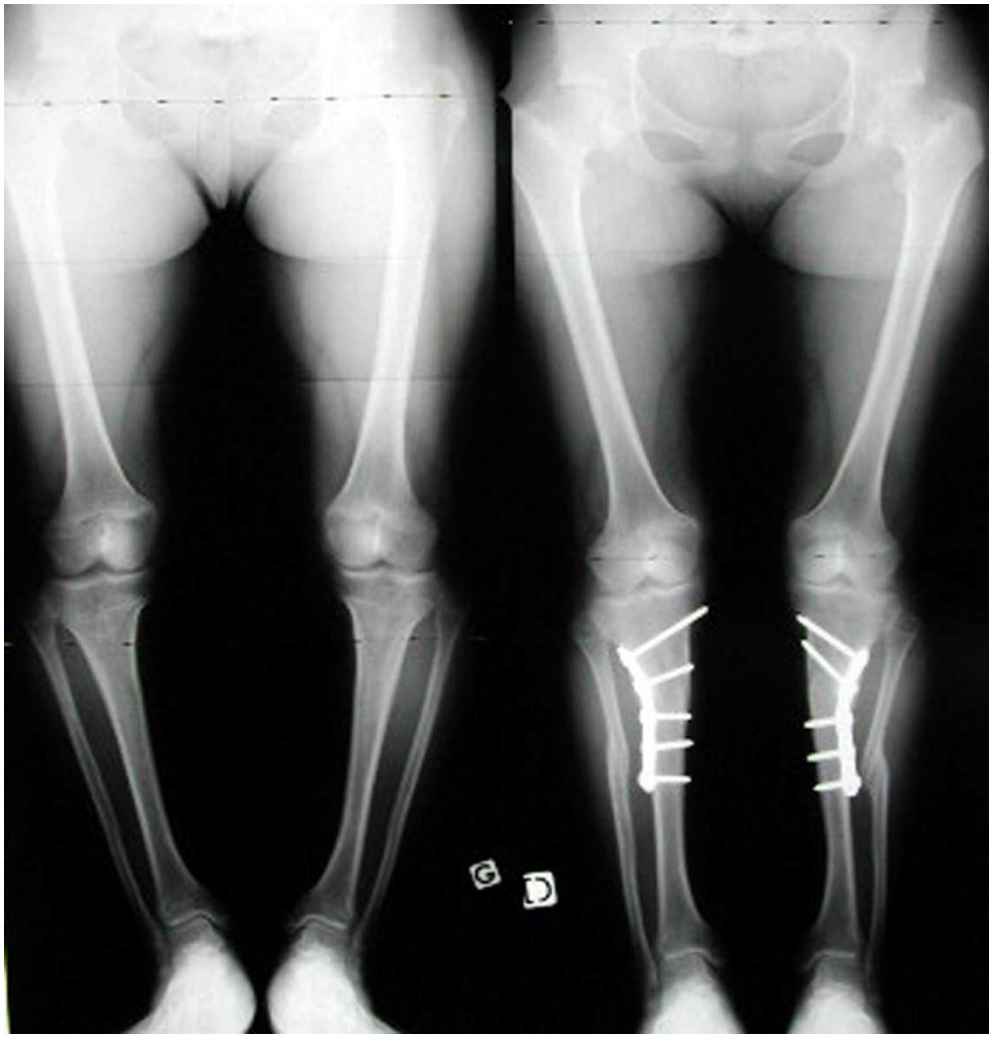


- Short stature (130 cm)

- Childhood :
  Narrow foramen magnum
  Respiratory difficulties/apnea
  Middle ear disease
  Gibbus in thoracolumbar region
  and then hyperlordosis

- Adulthood :
  Lumbar stenosis
  Obesity
  Deafness

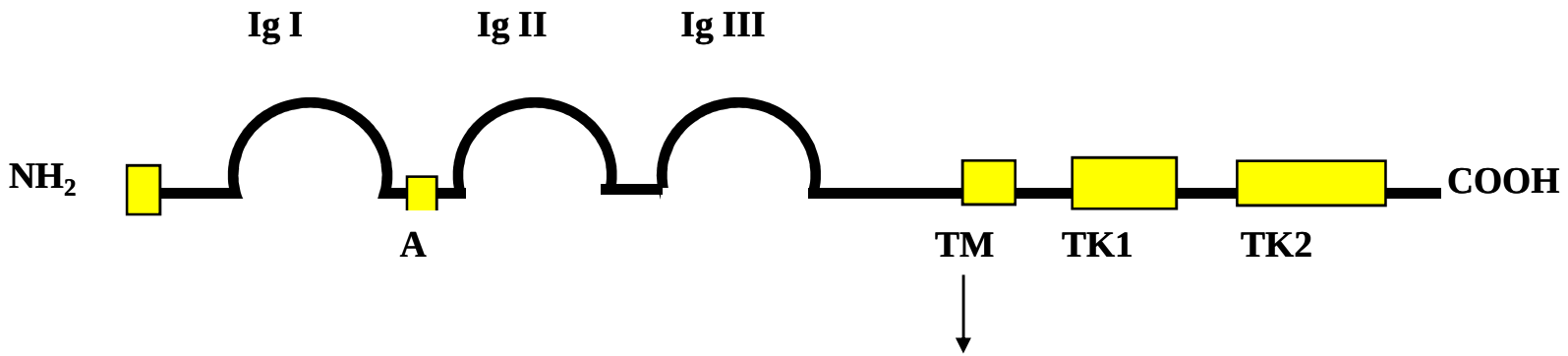
Achondroplasia and lower limb deformations



Molecular basis of achondroplasia

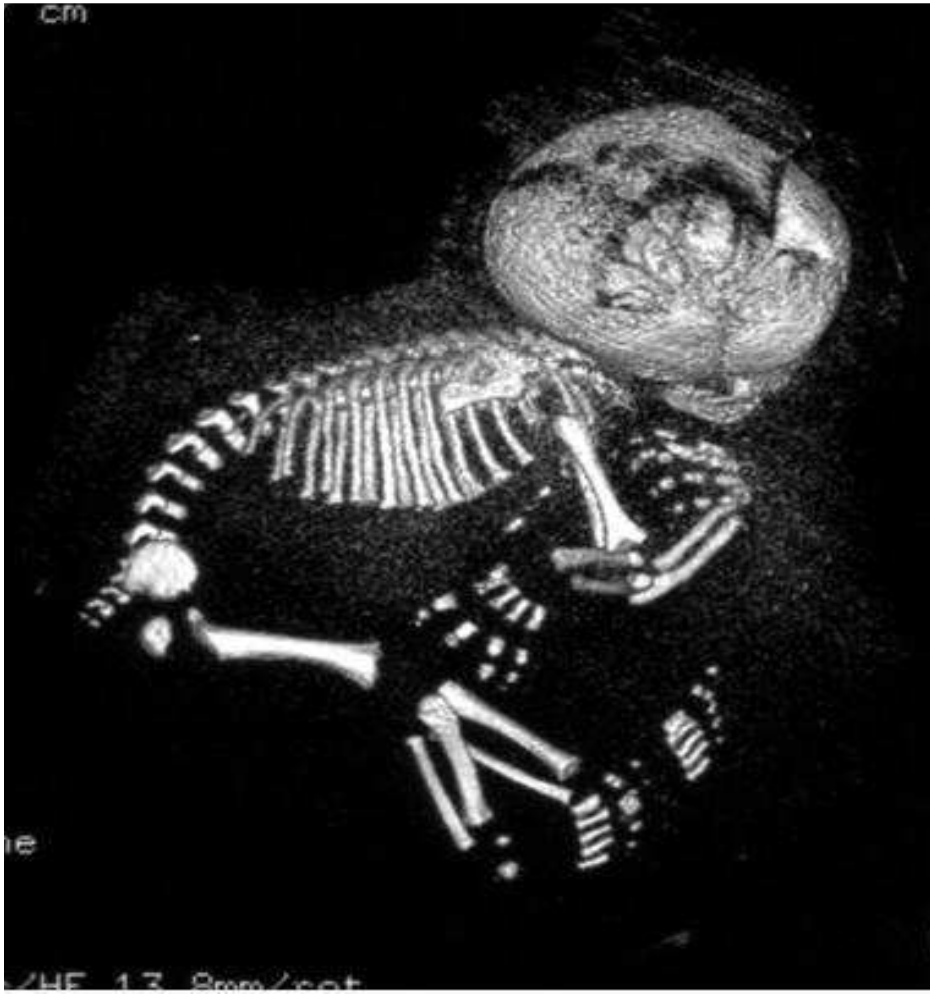
FGFR3 : Fibroblast Growth Factor Receptor 3

localisation : 4p16, 19 exons

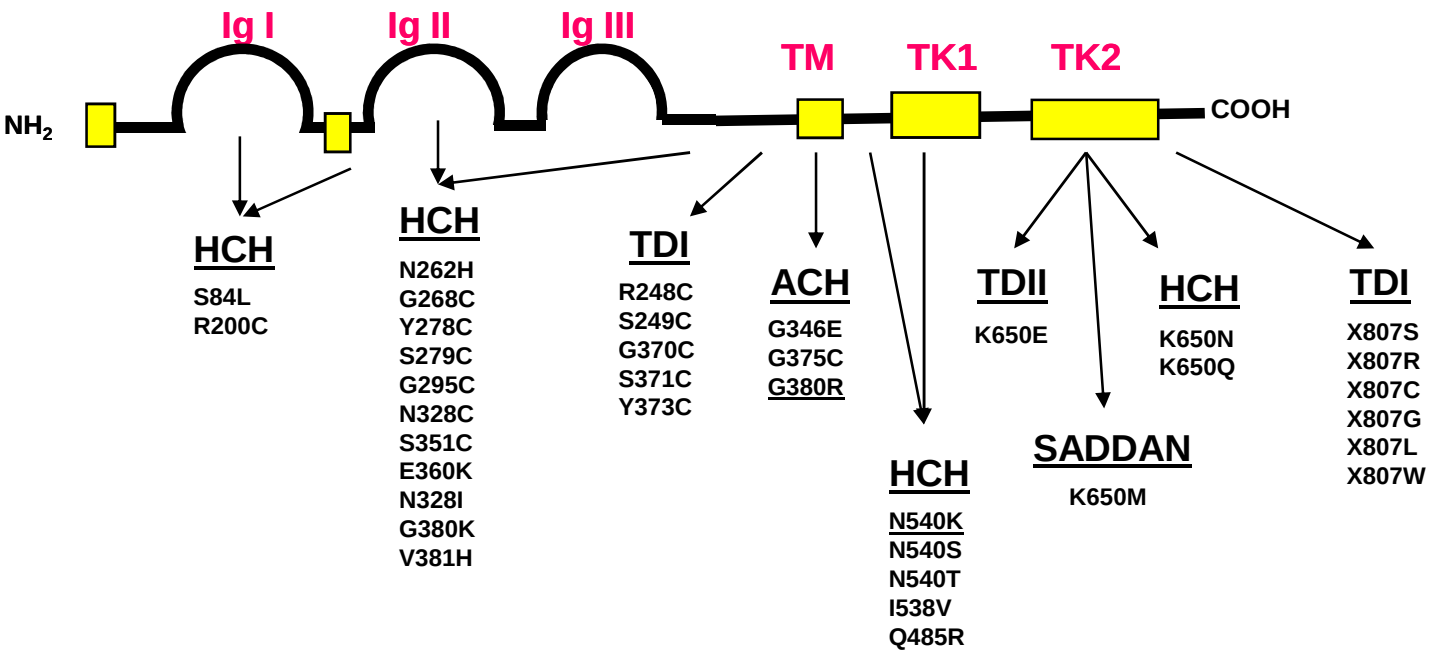


Common mutation : G380R

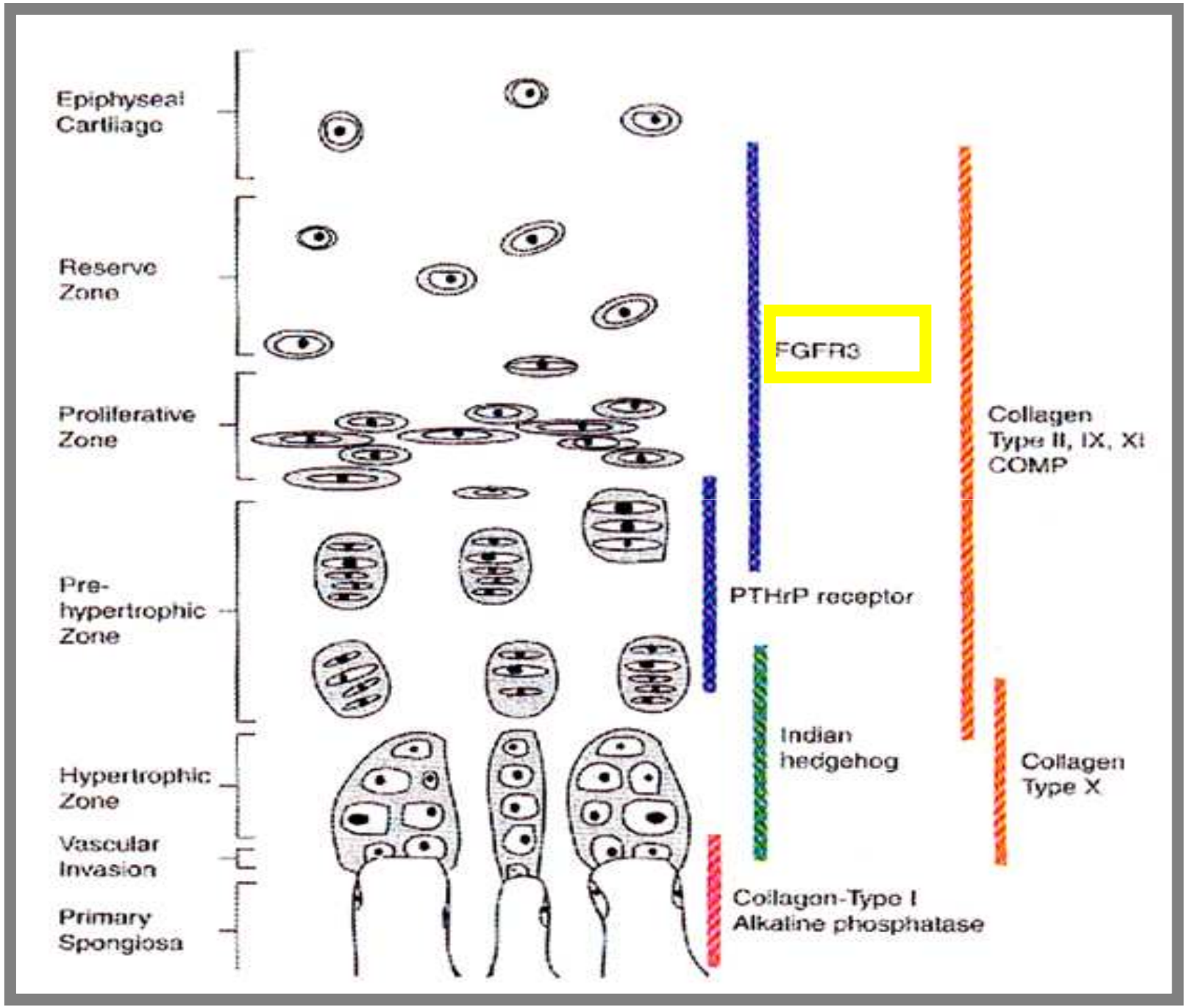
Antenatal diagnosis of achondroplasia



FGFR3 mutations in chondrodysplasia



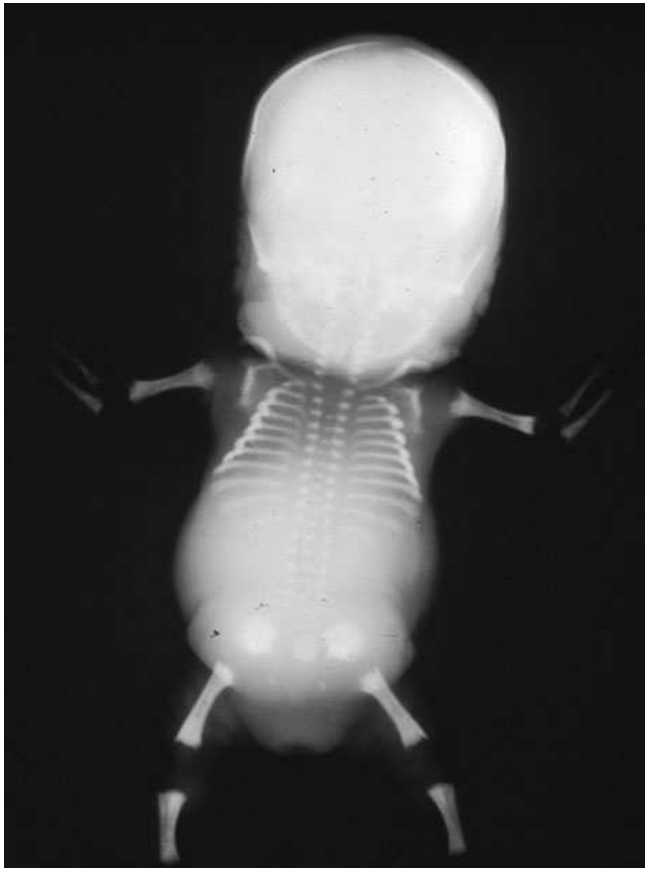
Legend
HCH : Hypochondroplasia
ACH : Achondroplasia
TD I : Thanatophoric Dysplasia Type I
TD II : Thanatophoric Dysplasia Type II
SADDAN : Severe Achondroplasia with Developmental Delay and Acanthosis Nigricans

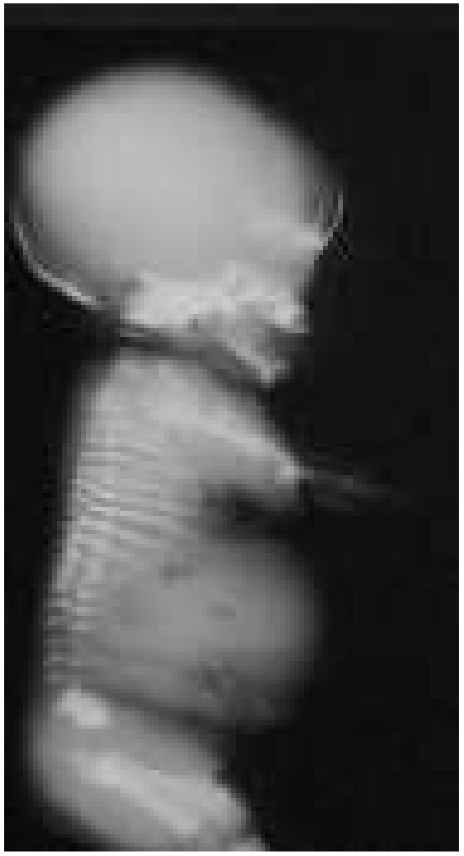

Epiphyseal Cartilage
Reserve Zone
Proliferative Zone
Pre-hypertrophic Zone
Hypertrophic Zone
Vascular Invasion
Primary Spongiosa
FGFR3
PTHrP receptor
Indian hedgehog
Collagen-Type I
Alkaline phosphatase
Collagen Type II, IX, XI
COMP
Collagen Type X

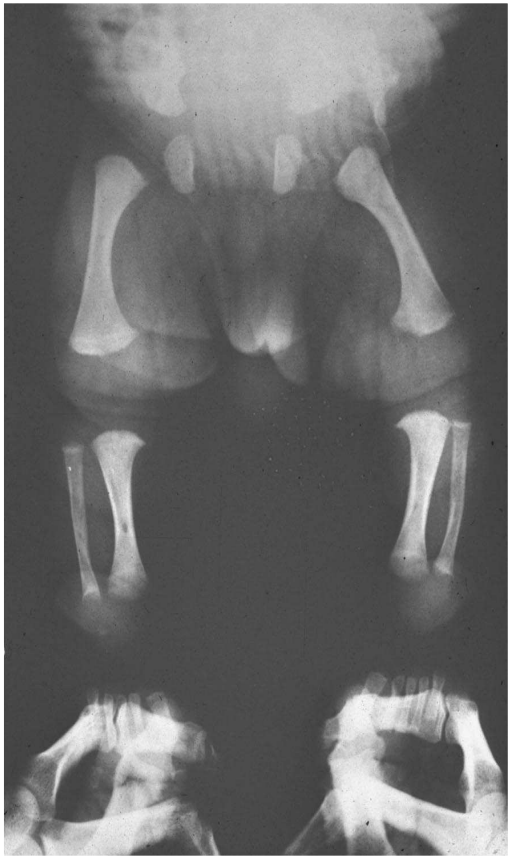
Clinical approach : disproportionate short stature

- Achondroplasia : rhizomelia
- SEDC/ Kniest : micromelia, short trunk and flat face
- Diastrophic dysplasia : hitchiker thumb, club feet

Spondylo-Epiphyseal Dysplasia Congenita/ Kniest





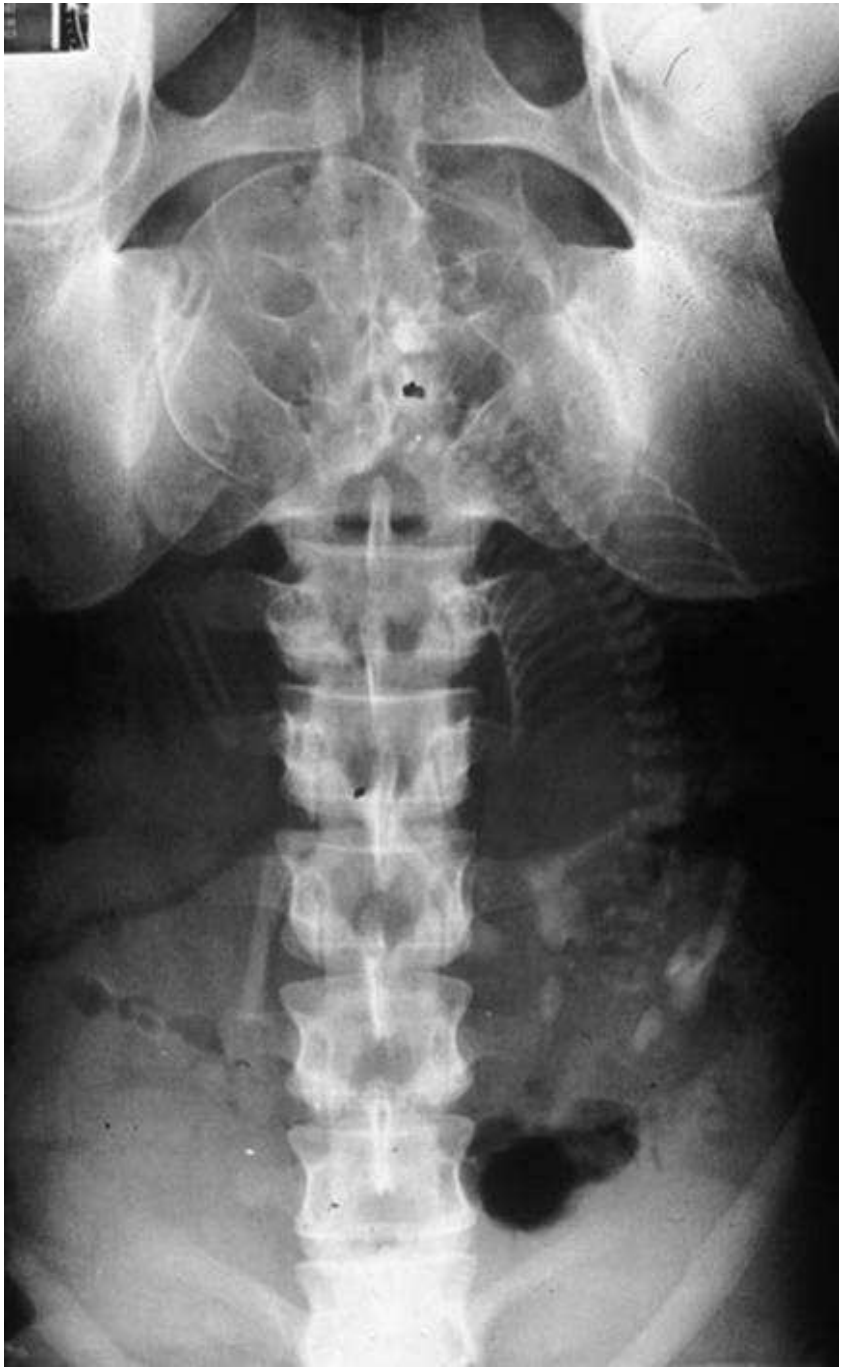


- Absent pubic ossification,
- No ossification of epiphyses at knee
- Ovoid or pear shaped vertebrae

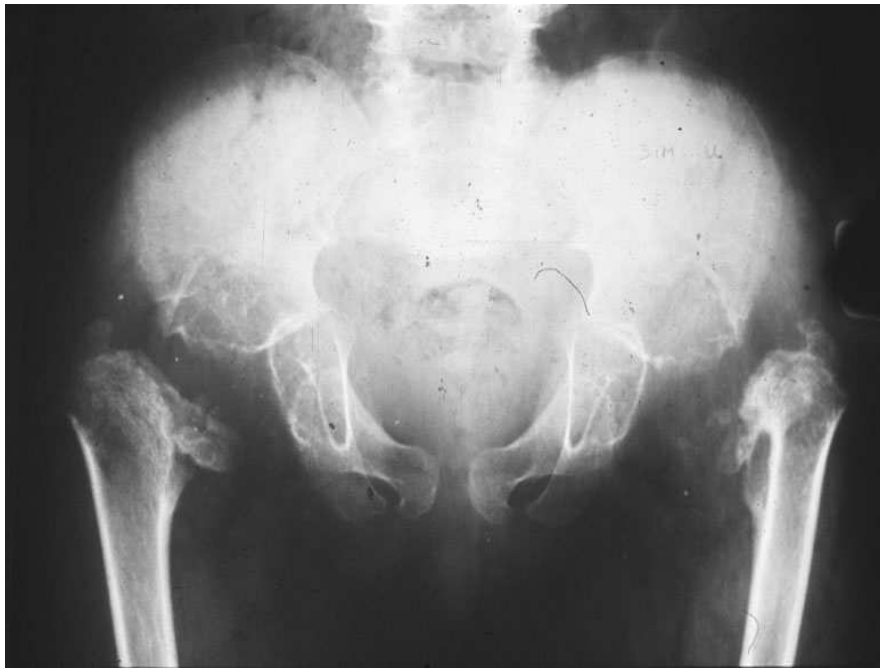
Spondylo-epiphyseal dysplasia congenita

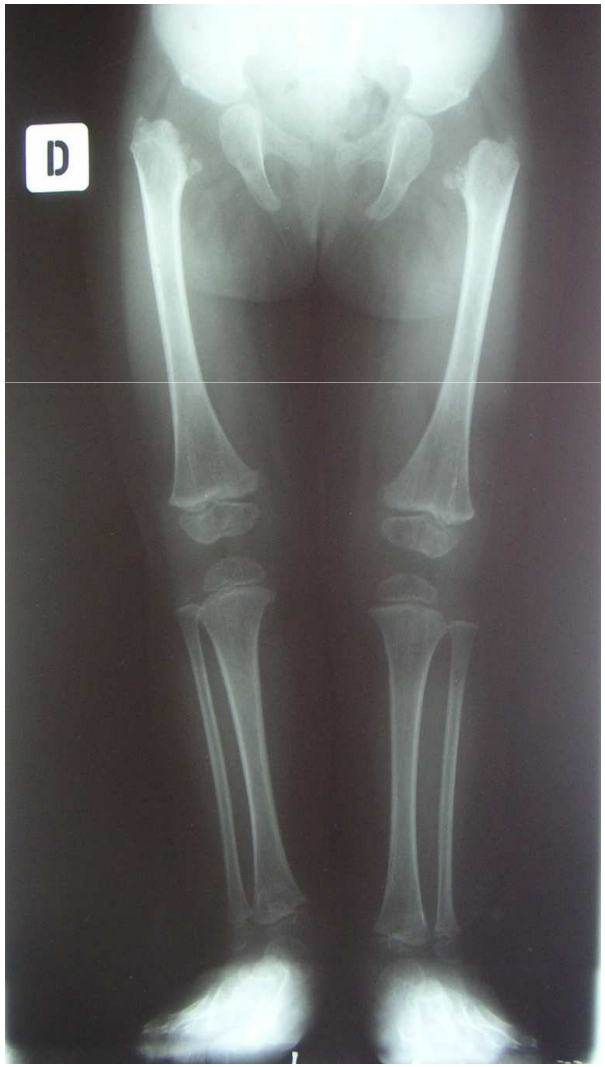
- Short stature at birth
- Platyspondyly
- Epiphyseal dysplasia
- +/-Myopia
- Deafness
- Cleft palate, Pierre Robin

Antenatal diagnosis of SEDC



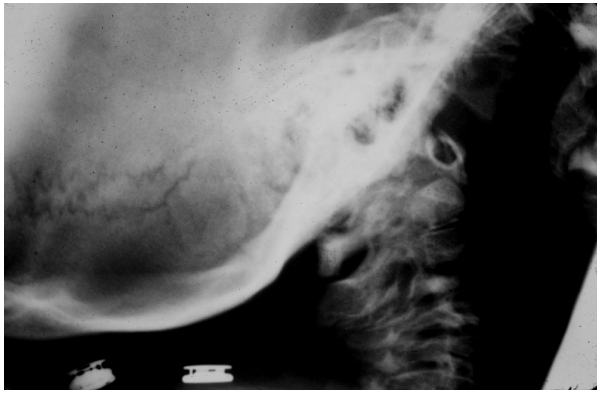
SEDC evolution- 10years

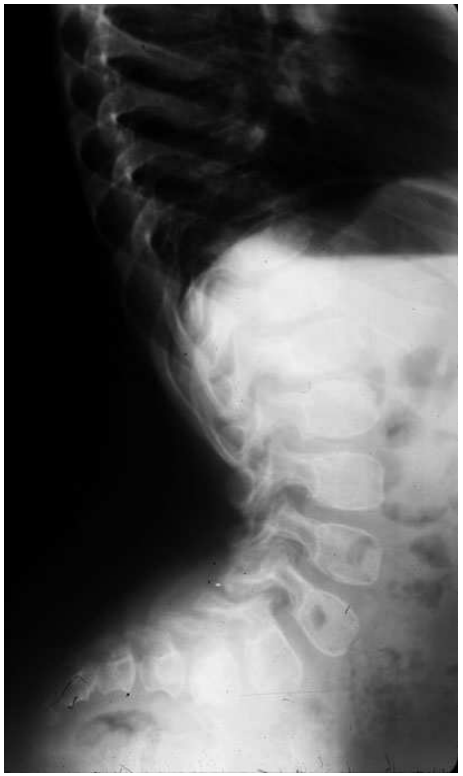




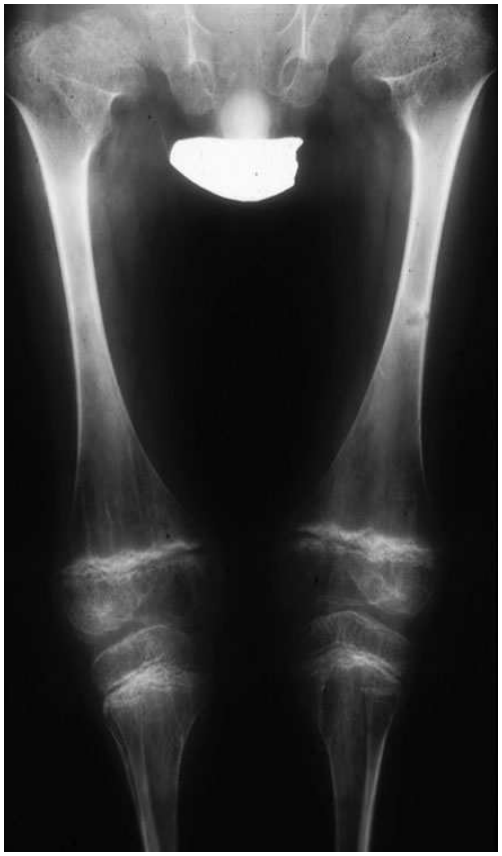
Spondylo-epiphyseal dysplasia congenita

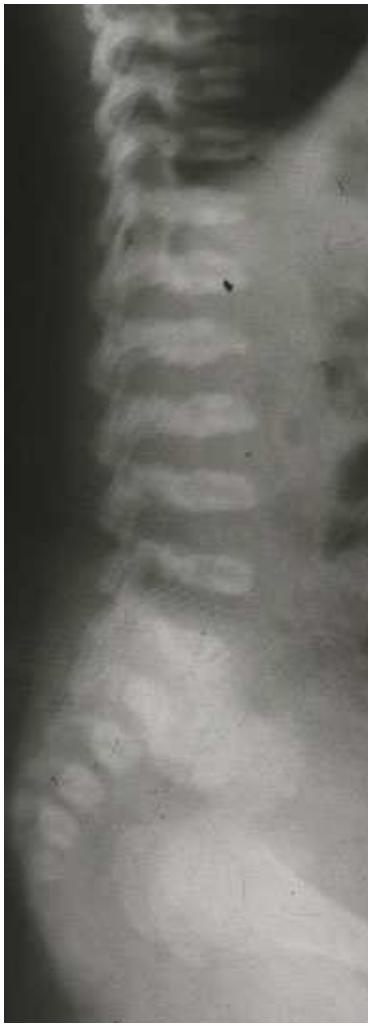
- Platyspondyly
- Increased thoracic kyphosis
- C1-C2 dislocations, odontoid hypoplasia





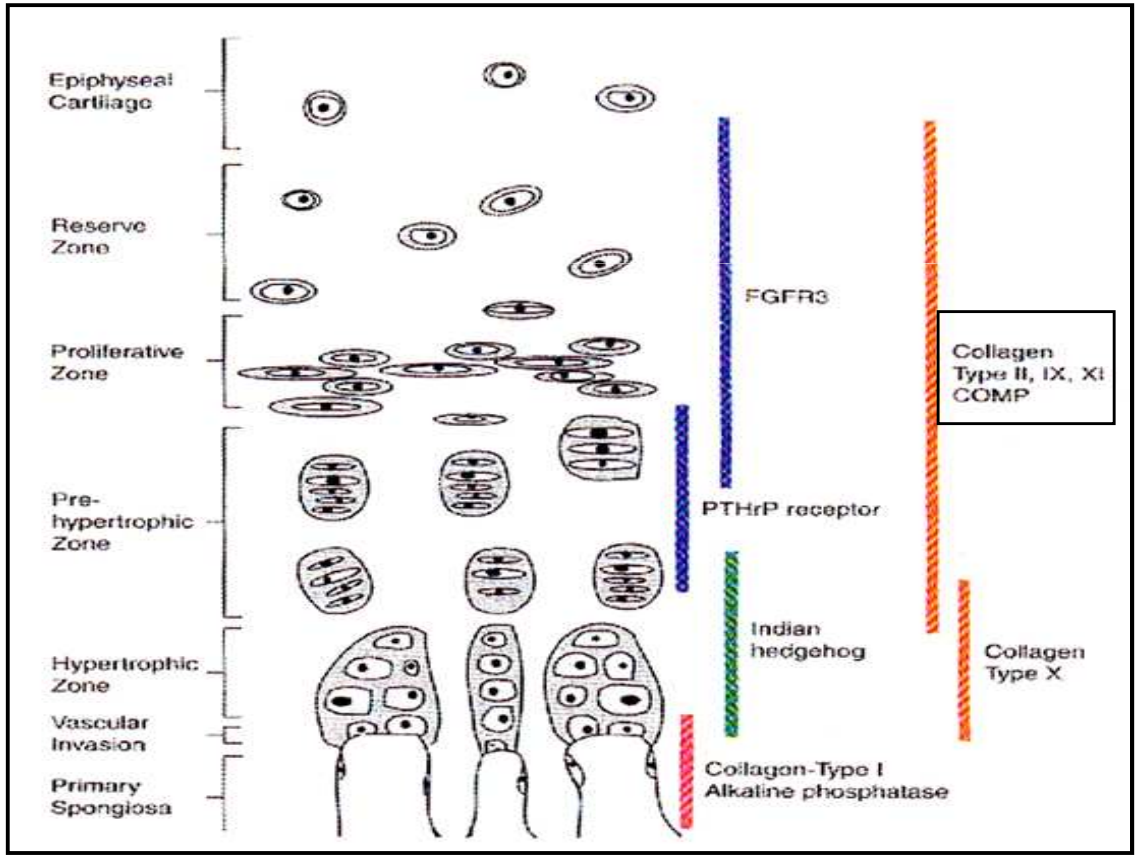
Kniest – Evolution arthroses



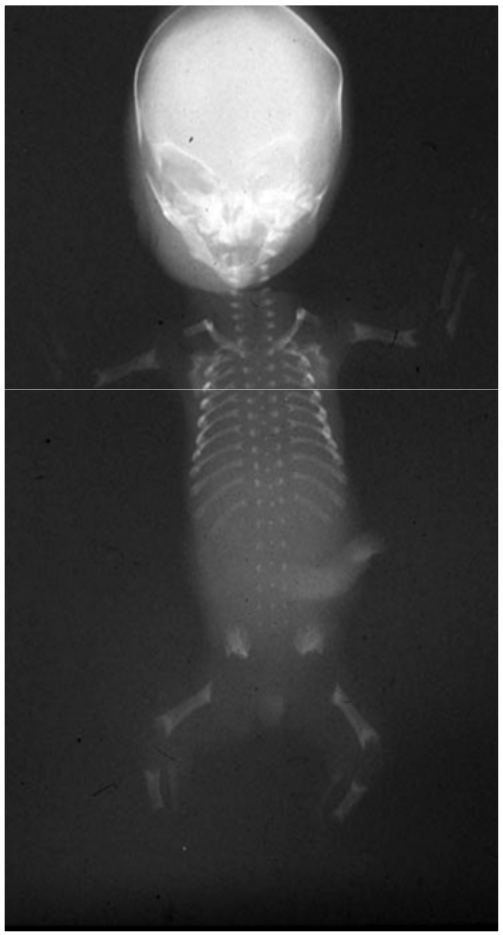


Molecular basis of SEDC/ Kniest

Heterozygous mutations in COL2A1 (65 exons, 12q13.1)



Col2A1 and phenotypic variability



Achondrogenesis type II

Stickler

Myopia

Retinal detachment

« Collagen group »

19 types of collagens

- Type II, IX and X expressed in cartilage
- Col2A1: Kniest, Stickler, SEDC, Achondrogenesis type II, hypochondrogenenesis
- Col9A1 : Stickler
- Col9A2, Col 9A3: MED
- Col10A1 : Schmid metaphyseal dysplasia
- Col11A1 : Stickler
- Col11A2 : OSMED

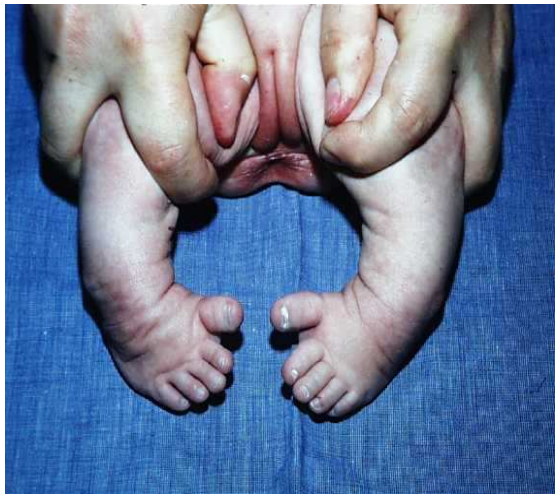
Clinical diagnosis : disproportionate short stature

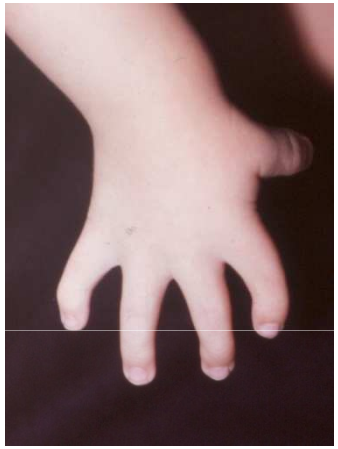
- Achondroplasia : rhizomelia
- SEDC/ Kniest : micromelia and flat face
- Diastrophic dysplasia : hitchiker thumb, club feet

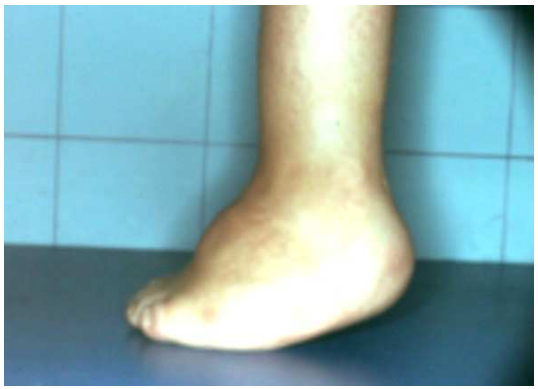
Diastrophic dysplasia

- Autosomal recessive (5q31.2, DTDST)
- Micromelic dwarfism at birth
- Foot deformities
- Hitch hiker thumb (hypoplasia of the 1st MC)
- Cleft palate
- Deformed earlobes , cystic masses in anthelix

Diastrophic dysplasia







Diatrophic dysplasia

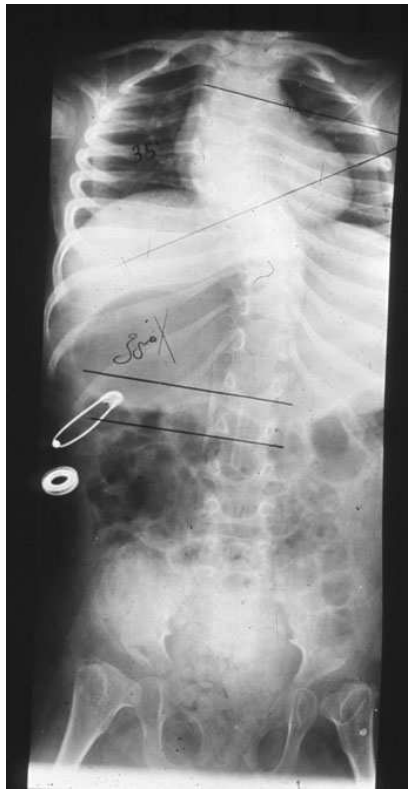
Diastrophic dysplasia

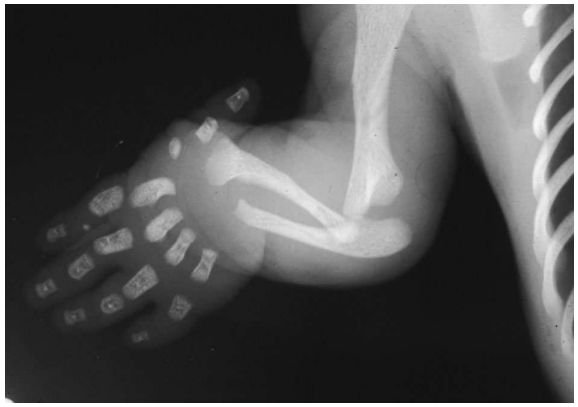
•Short rounded first MC and accelerated carpal ossification

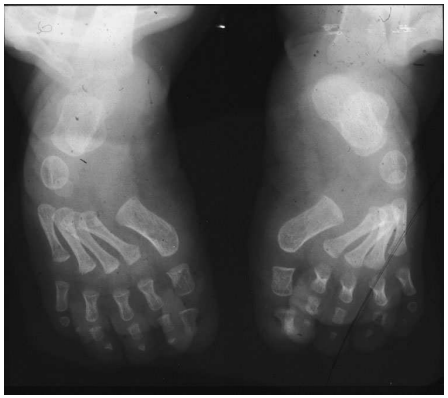
• Dislocations of large joints

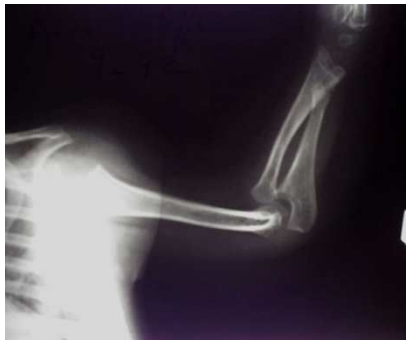
•Twisting long bones

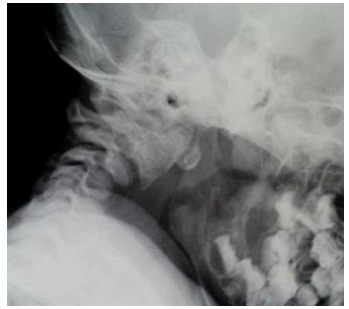
•Cervical kyphosis



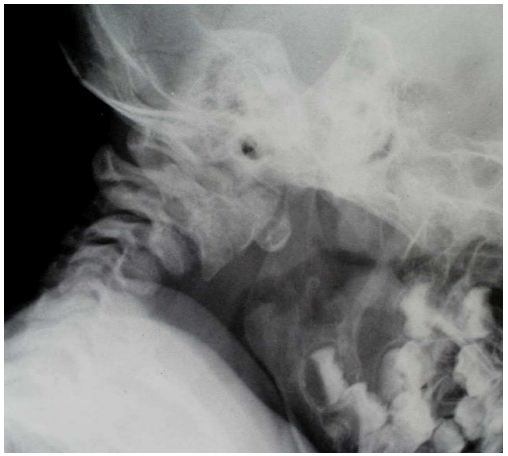


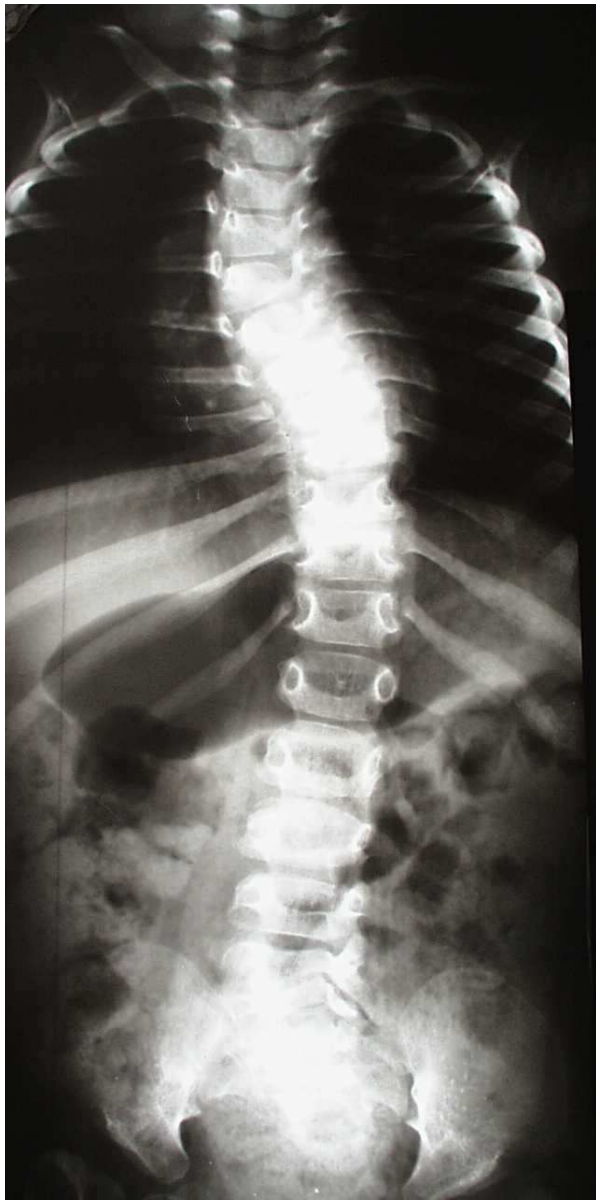


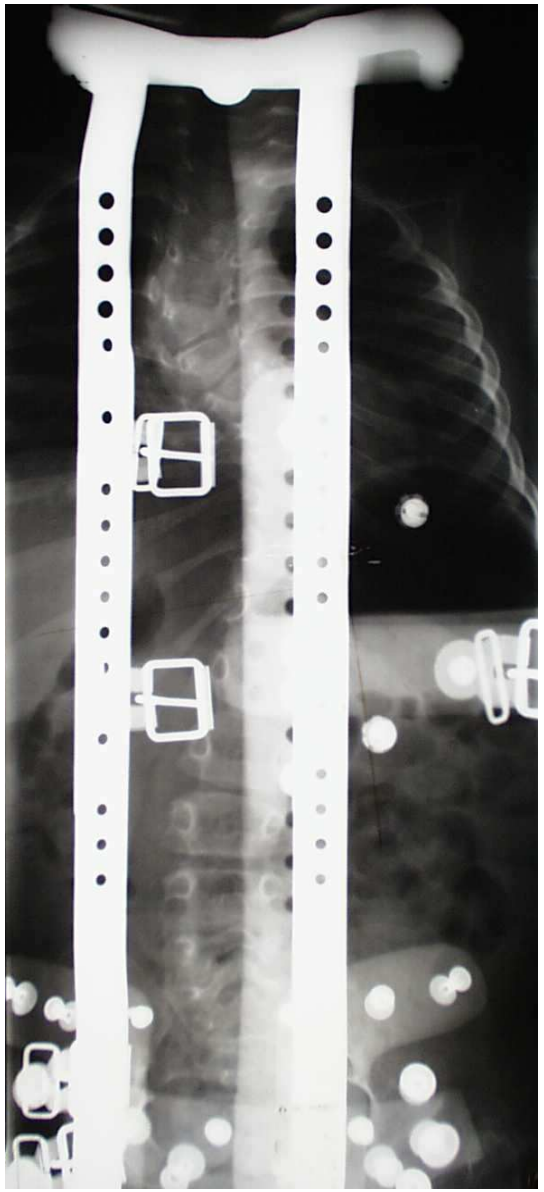




Diastrophic dysplasia- evolution

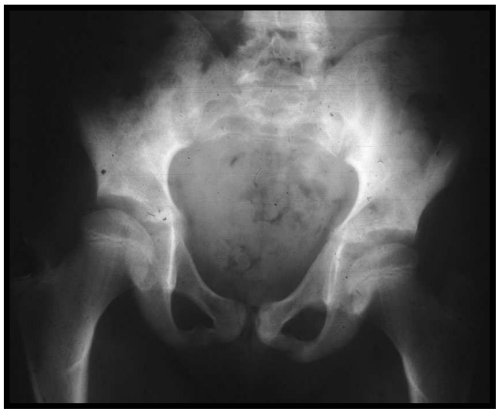


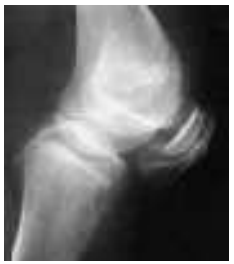




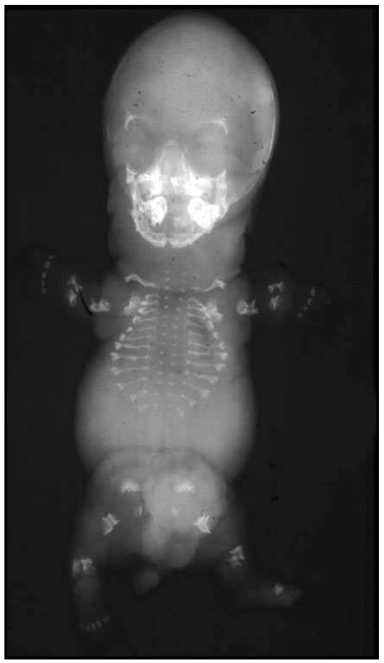
Molecular basis of diastrophic dysplasia

- Mutations in the gene coding for cell-surface transporter protein, SLC26 A2 (sulfate transporter)
- 25 % recurrence risk for families
- Phenotypic variability within DTD spectrum





MED



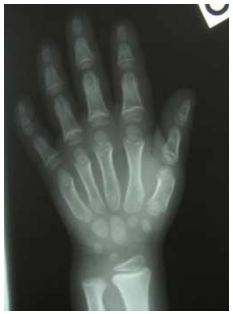
Achondrogenesis Ib

Clinical diagnosis : disproportionate short stature

During childhood/infancy

- Metaphyseal dysplasia
- MED/ Pseudoachondroplasia
- Dyschondrosteosis : mesomelia
- Hypochondroplasia
- SED tarda

Metaphyseal dysplasia

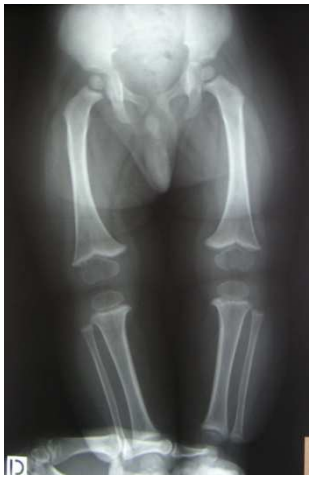


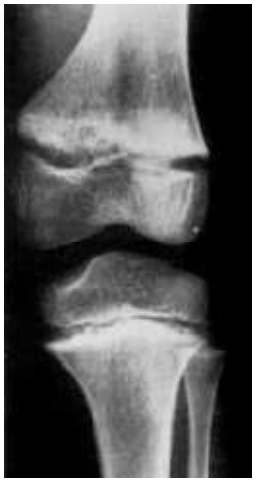
Mc Kusick type, AR, RMRP mutation

Short limb dwarfism in early childhood

Short MC, Phalanges

Immune deficiency,Hirschprung, sparse hair



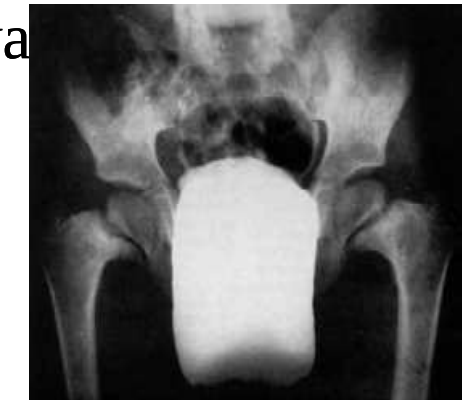


Metaphyseal Dysplasia, type Schmid

Varus incurvation of lower limbs, coxa va

Final stature : 140-150 cm

AD, **Col X**



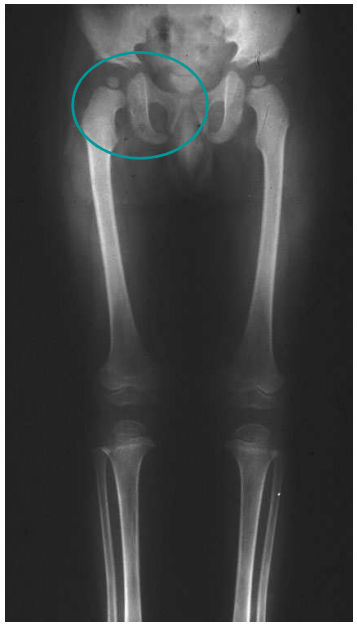
Multiple epiphyseal dyplasia

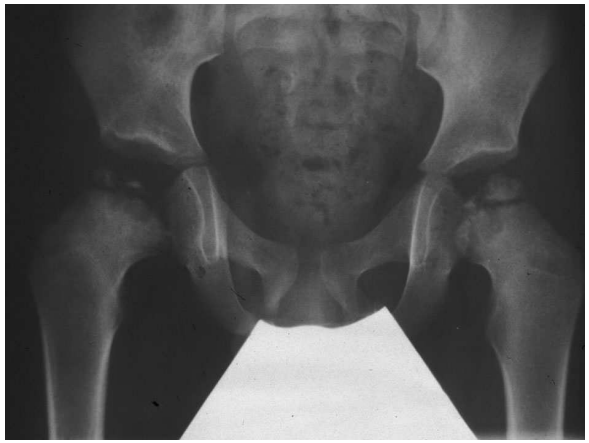
- Short stature
- Pain,
- Arthrosis

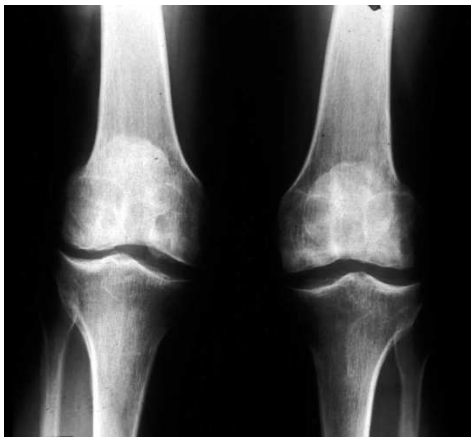
- Epiphyseal dysplasia
- Delayed bone age

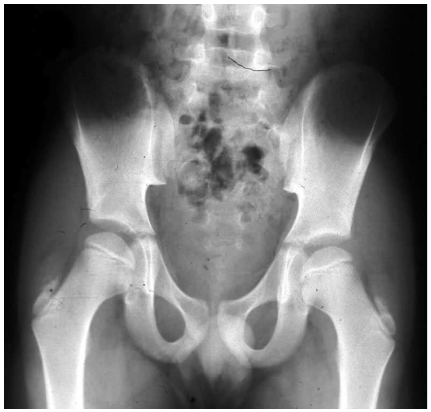
- Genetic heterogeneity
- AD, AR

COMP, COL9A1, A2, A3, Matrillin, DTDST, mucolipidosis type III ….





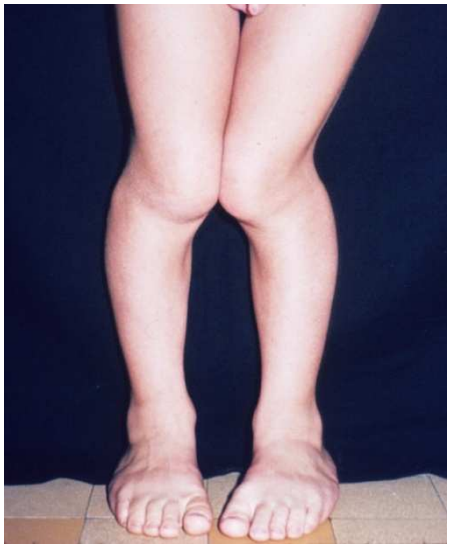




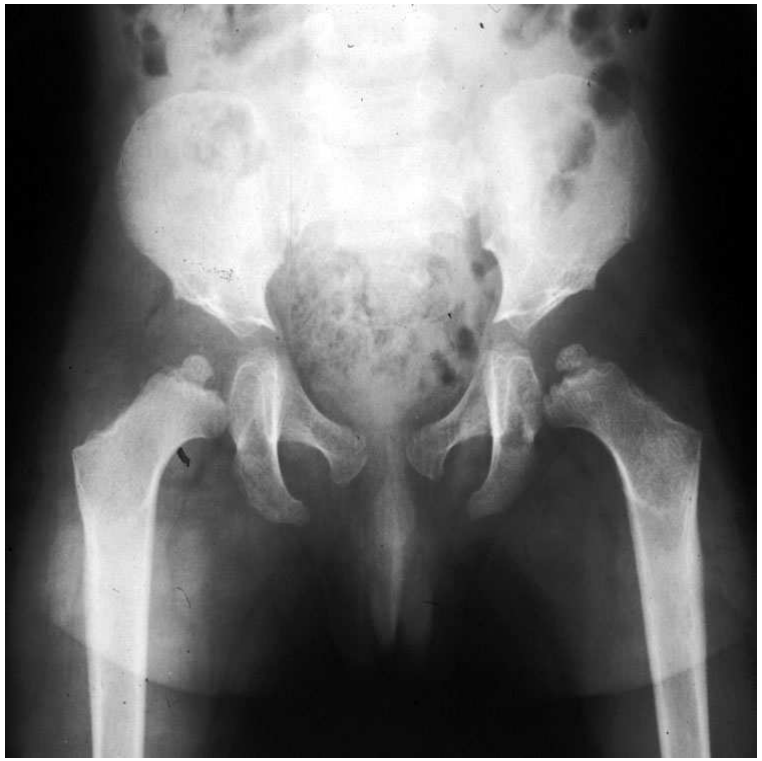
Pseudoachondroplasia

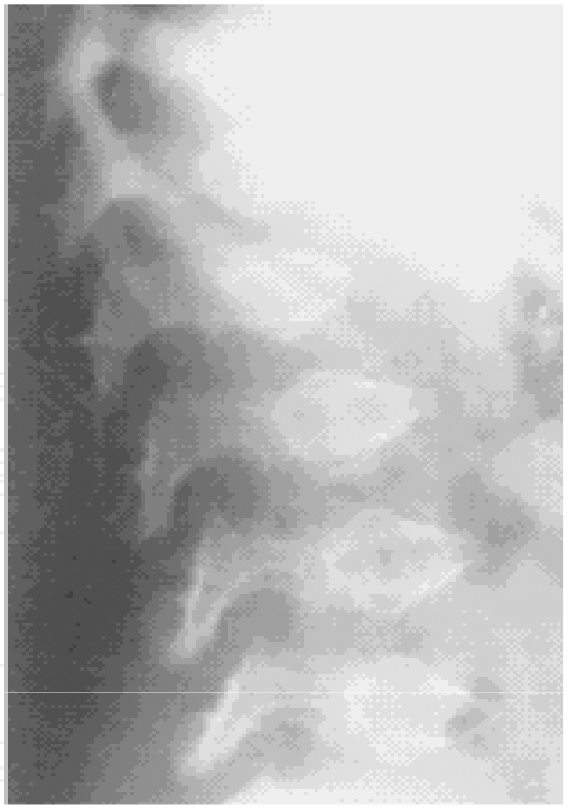
- **Normal stature at birth**
- Wadling gait at 2
- Brachydactyly
- Hyperlaxity, osteoarthropathy
- Scoliosis/ kyphosis
- Valgus deformity of lower legs
- Cervical instability

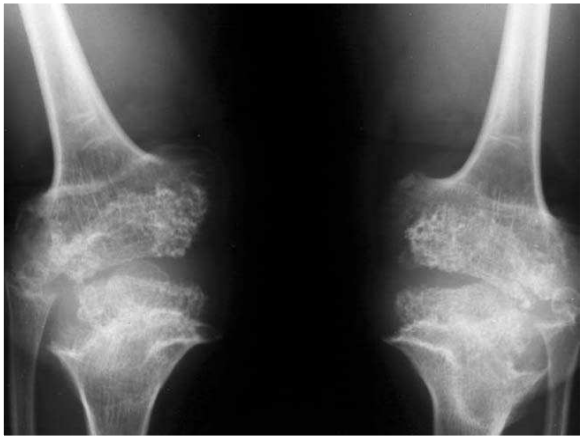
Dominant mutation in *COMP*

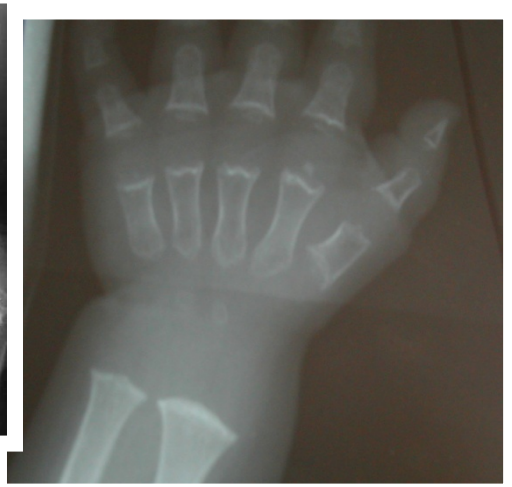


Pseudoachondroplasia

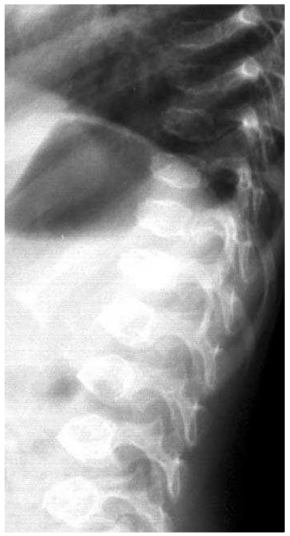


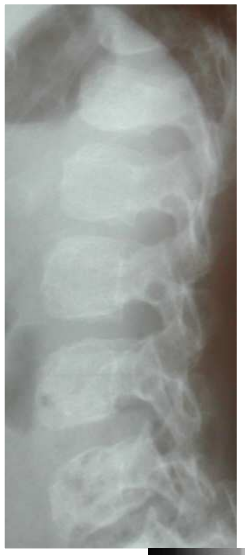


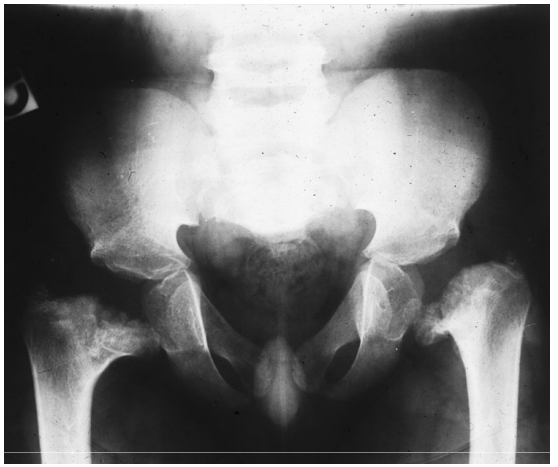


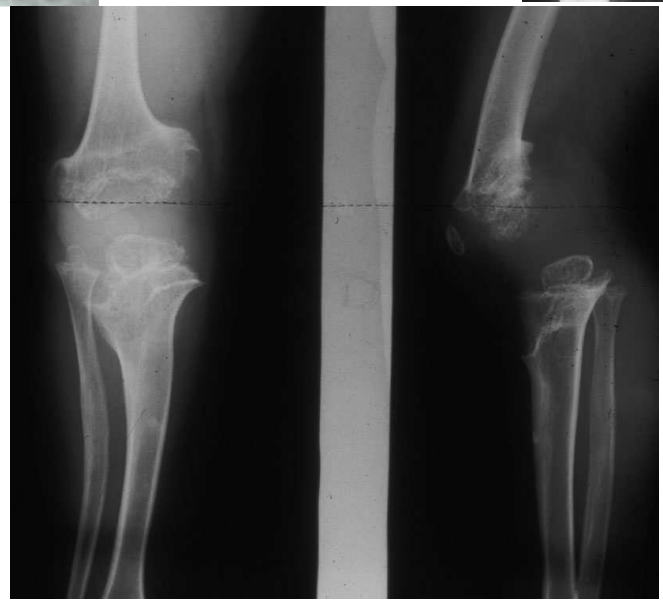


Pseudoachondroplasia



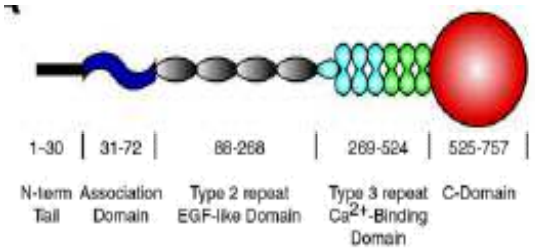






COMP mutations in pseudoachondroplasia

- Amino acid substitutions clustered within exon 8 to 14 (type III, calmodulin like repeats)



- Consequences for the structure of this region and its ability to bind calcium

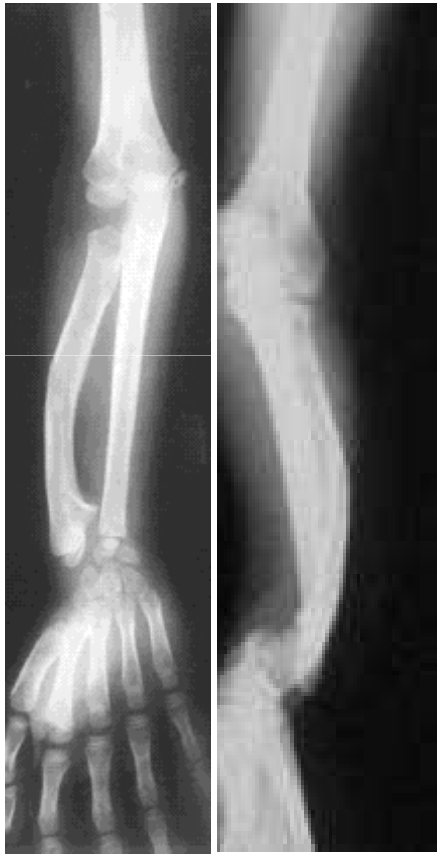
Dyschondrosteosis

- Original description : Léri and Weill, 1929
- Mesomelic dysplasia
  - Short stature (<-2.5 SD)
  - Shortness of forearms and lower legs
  - Madelung deformity
  - Limited motion of elbows and wrists

- AD inheritance
- Females more severely affected
- Necessity of forearm X-rays
- Intra/interfamilial variability

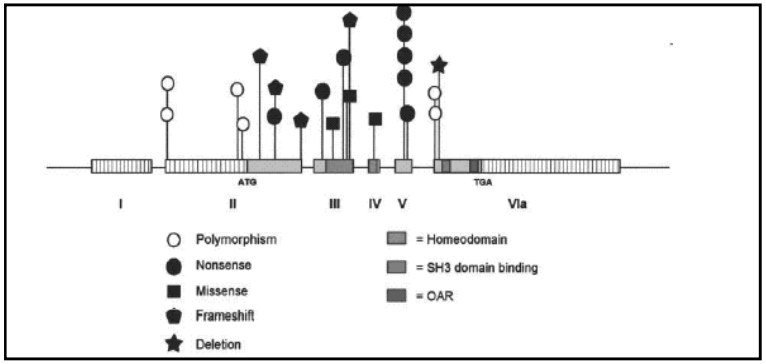
Radiologic manifestions of dyschondrosteosis

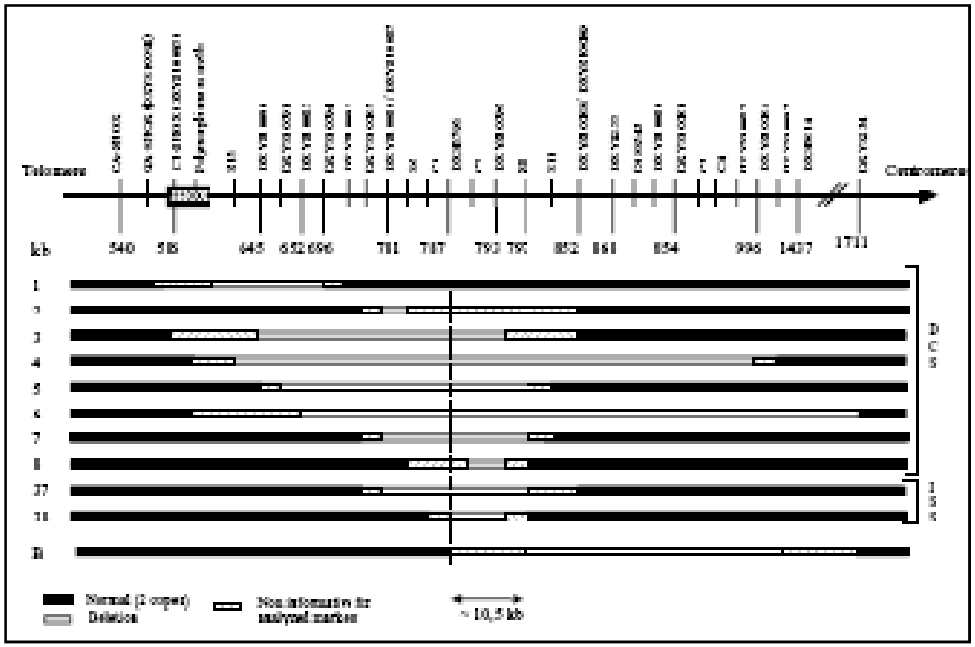
- Shortening and bowing of radius
- Triangulation of distal radial epiphyses
- Wedging of carpal bones between distal radius and ulna
- Subluxation of distal ulna
- Shortening of tibiae



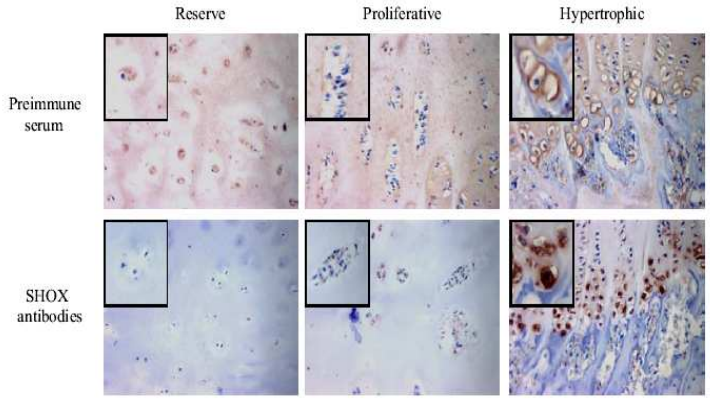
Molecular basis of dyschondrosteosis

- Deletions of PAR 1 region (Xp22.3) of variable sizes
- Point mutations or partial deletions of **SHOX gene** (6 exons)





- Transcription factor



SHOX and phenotypic variability

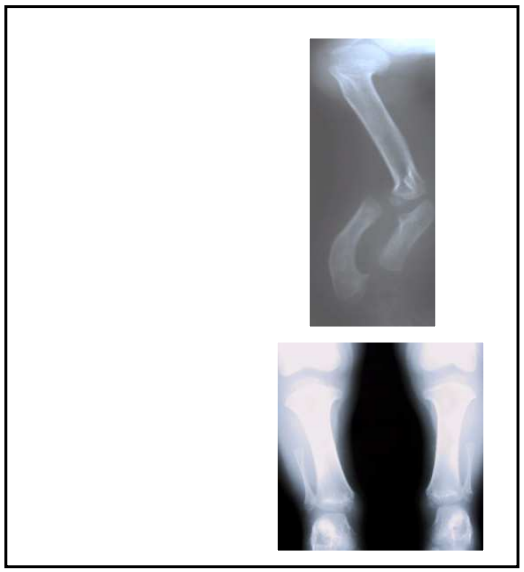
Haploinsufficency of SHOX responsible for :

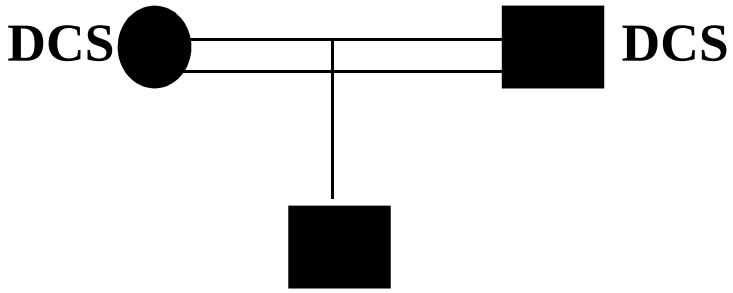
- Short stature in Turner syndrome

- Dyschondrosteosis

- Some idiopathic short stature cases

Loss of function responsible for Langer mesomelic dwarfism



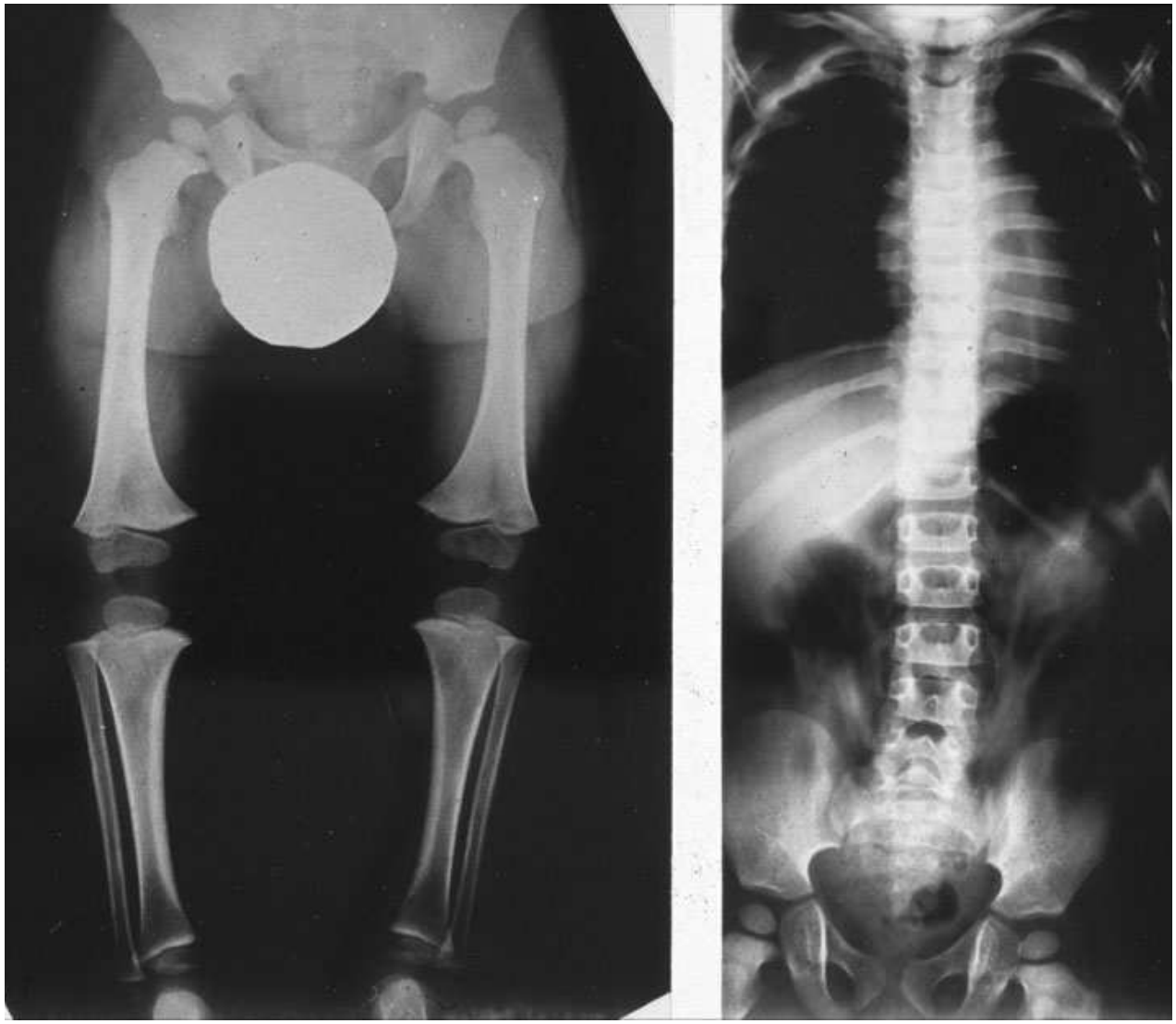


Langer

Hypochondroplasia

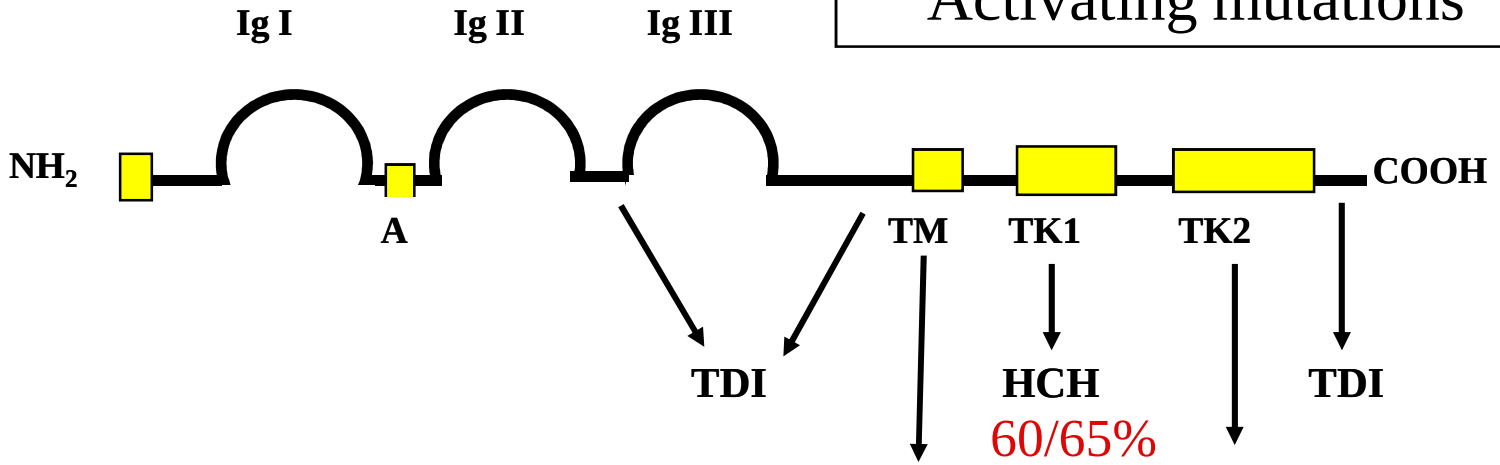
- First description in 1913 by Ravenna
- Decrease interpediculate distance from 1st to 5th lumbar vertebrae
- Macrocephaly, stubby hands and feet
- Mild short limb dwarfism
- Mild metaphyseal flaring
- Short and broad femoral neck
- Autosomal dominant
- Underdiagnosed

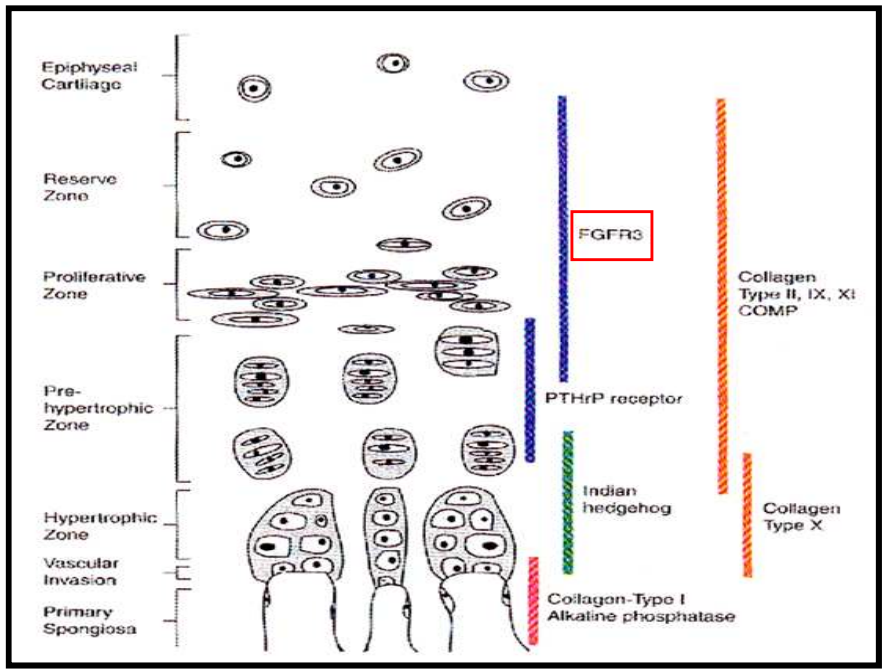
Hypochondroplasia

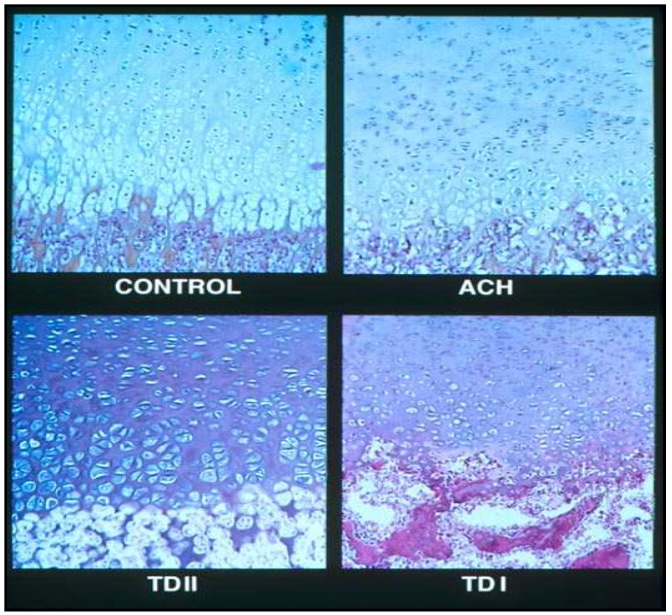


FGFR3 mutations

Activating mutations

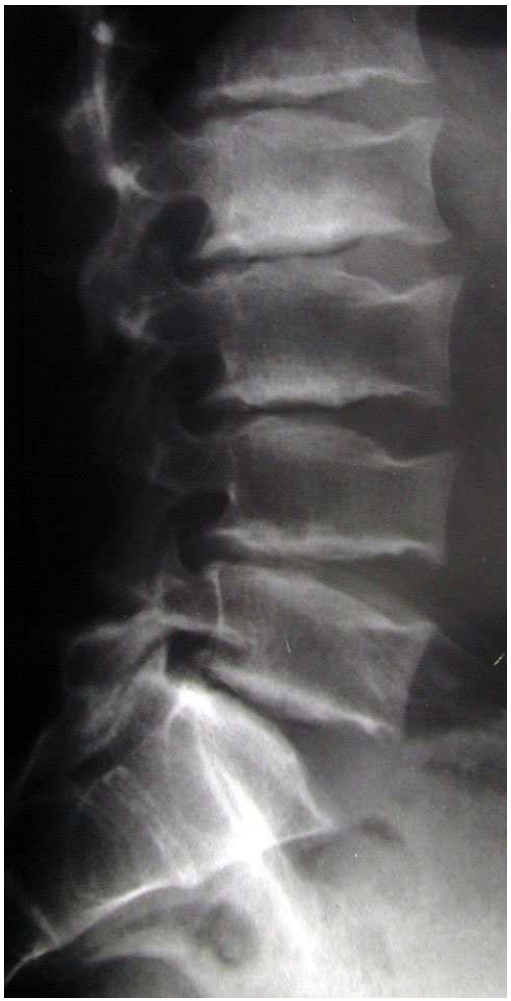






SED tarda

- Normal stature at birth
- Progressive growth curve decrease between 3 and 5
- Dorsal pain
- Short trunk
- Platyspondyly
- X-linked : only affected males
- *Sedlin* mutation



Conclusion

- Importance of the natural history for the diagnosis
- Value of the extraskeletal features
- Specificity of the skeletal features but need for long term follow up
- Diagnosis not only important for the genetic counseling but also for appropriate management