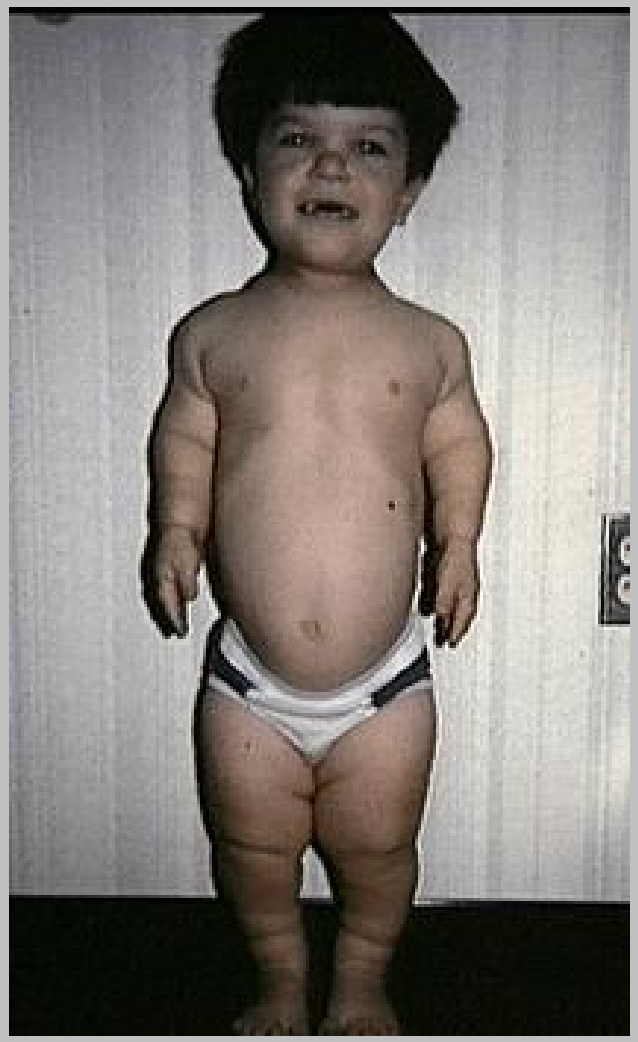
Clinical examples

Diego Velázquez

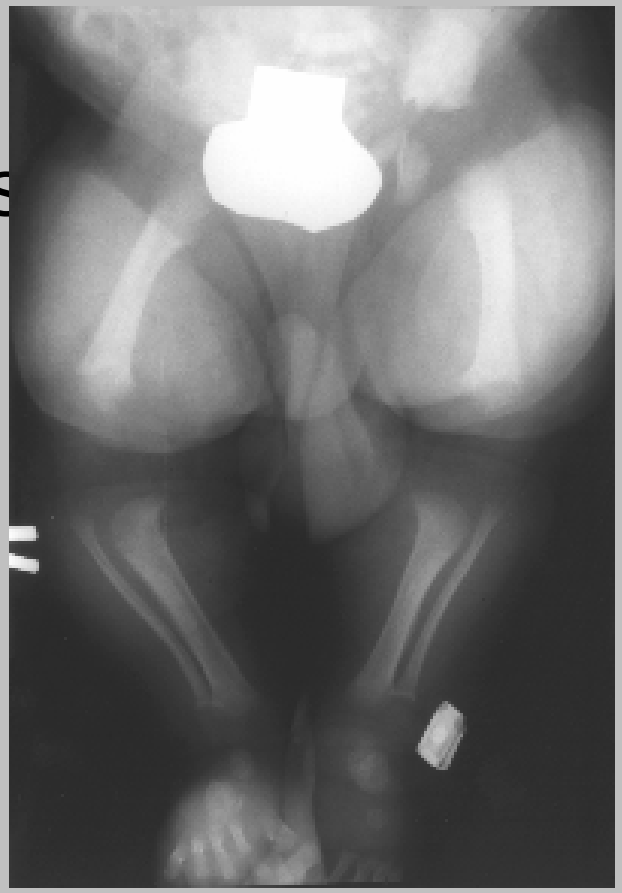
Achondroplasia

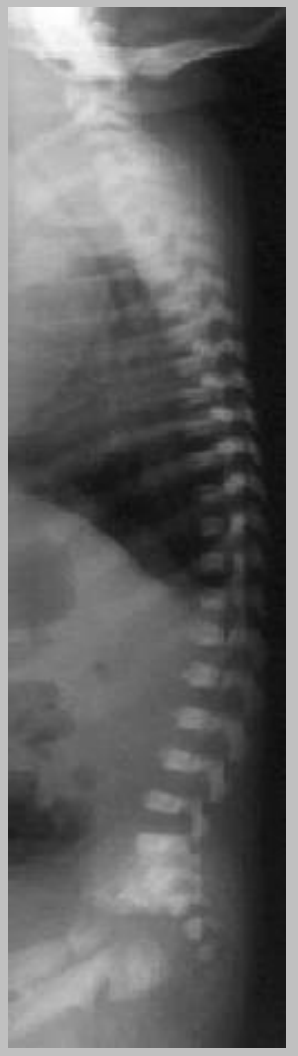
- Antenatal diagnosis
- 1 in 20 000 live births
- Medical challenges
- Psychosocial challenges
- Architectural challenges
- Mean height 130cm/125cm



Achondroplasia

Radiographic features





Achondroplasia: Medical complications

- Compression FM
- Sleep apnea
- Thoracolumbar kyphosis
- Spinal stenosis
- Hydrocephalus
- orthopaedic limb deformity
- ENT/Dental
- Obesity

Achondroplasia: Psychosocial challenges

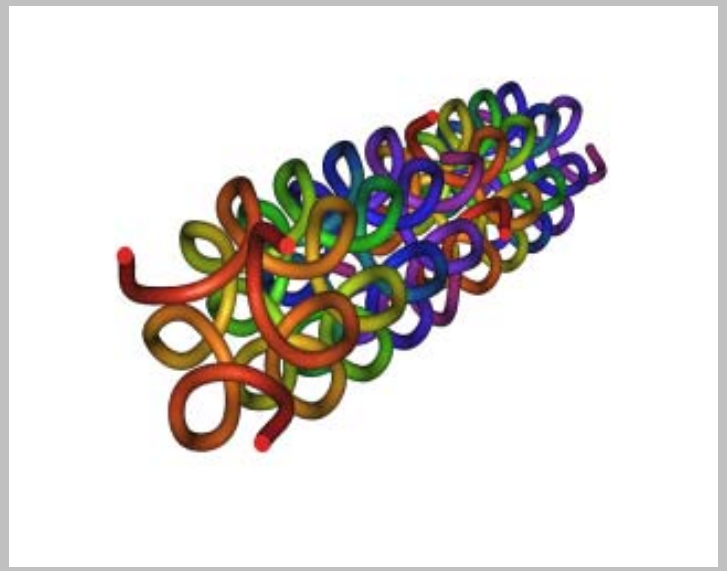
- Throughout life
- Multidisciplinary approach
- Support groups
- Peers
- Education of community/health workers
- Discussion of issues as arise and anticipatory guidance

Achondroplasia: Architectural challenges

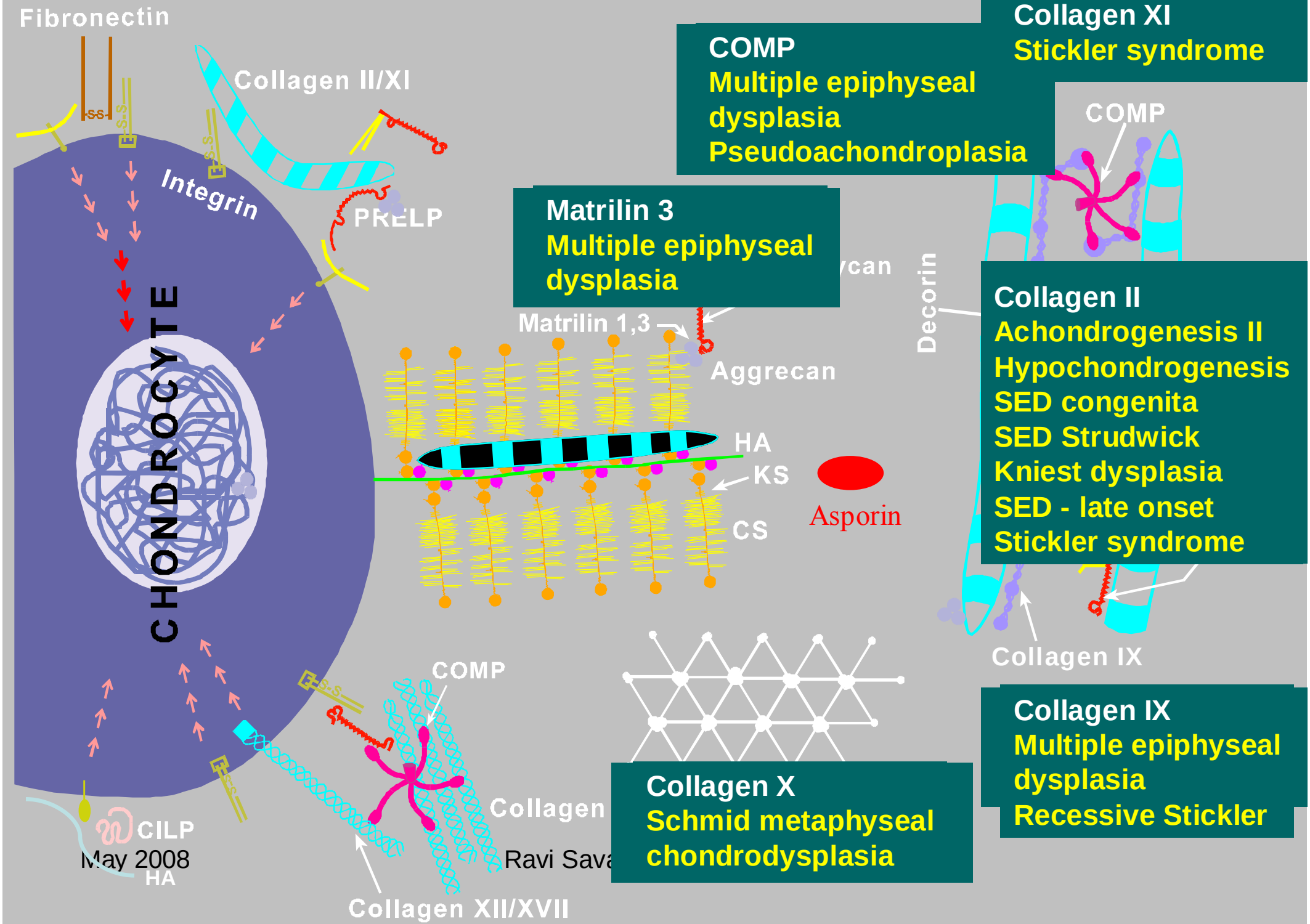
- Modifying environment to suit size
- school desks/chairs
- Occupational therapists
- Devices to aid autonomy
- Modified cars later in life

Translational Research

- Type II collagenopathies
- Screening of first 6 patients
- 3 mutations
- 3 different phenotypes
- Lab-Clinical Liaison
- Benefit to families



Mutations in extracellular matrix molecules



COMP
Multiple epiphyseal dysplasia
Pseudoachondroplasia

Collagen XI
Stickler syndrome

Matrilin 3
Multiple epiphyseal dysplasia

Collagen II
Achondrogenesis II
Hypochondrogenesis
SED congenita
SED Strudwick
Kniest dysplasia
SED - late onset
Stickler syndrome

Collagen IX
Multiple epiphyseal dysplasia
Recessive Stickler

Collagen X
Schmid metaphyseal chondrodysplasia

Molecular classification of skeletal dysplasias

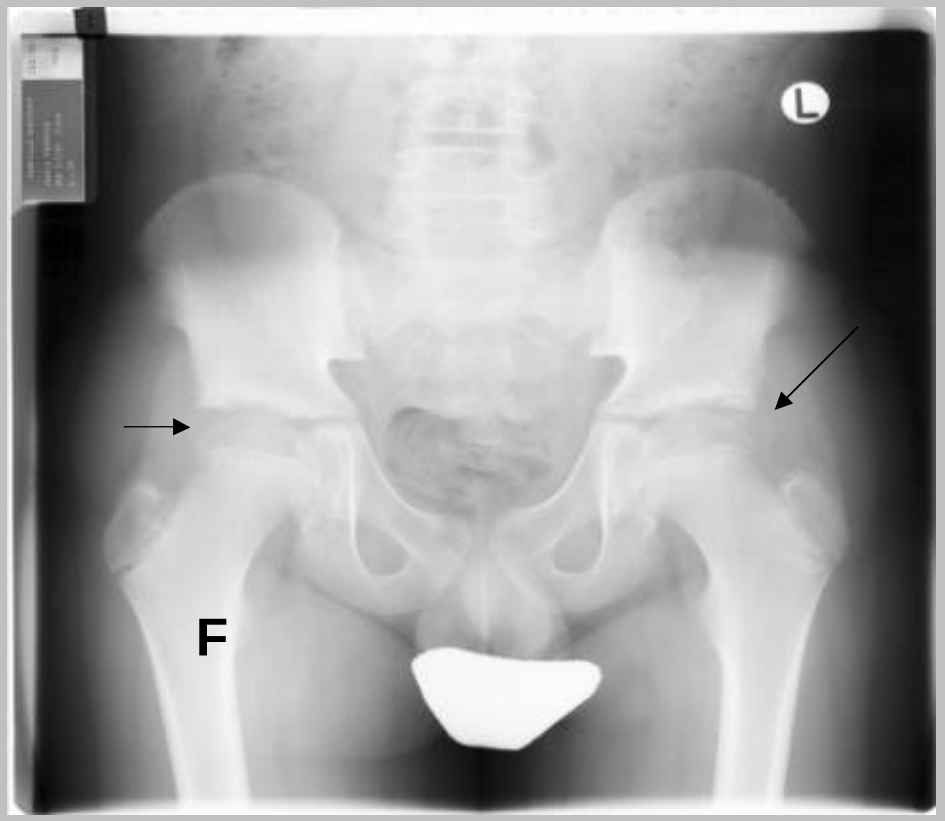
Structural cartilage proteins	Collagen type II	Kniest, Stickler, achondrogenesis 2
Cartilage metabolic pathways	Diastrophic dysplasia transporter	DTD, ATO 2, ACH1B, rMED
Local cartilage growth regulators	FGFR3	Achondroplasia, hypochondroplasia, TD
Transcription factors	CDMP-1	BDC, Grebe dysplasia
Cell membrane proteins	WISP3	PPD
Tumour suppressor genes	EXT 1, 2	Multiple exostoses
Signal transduction mechanisms	TGFβ-1, ROR2	Diaphyseal dysplasia, BDB

Type II collagenopathies

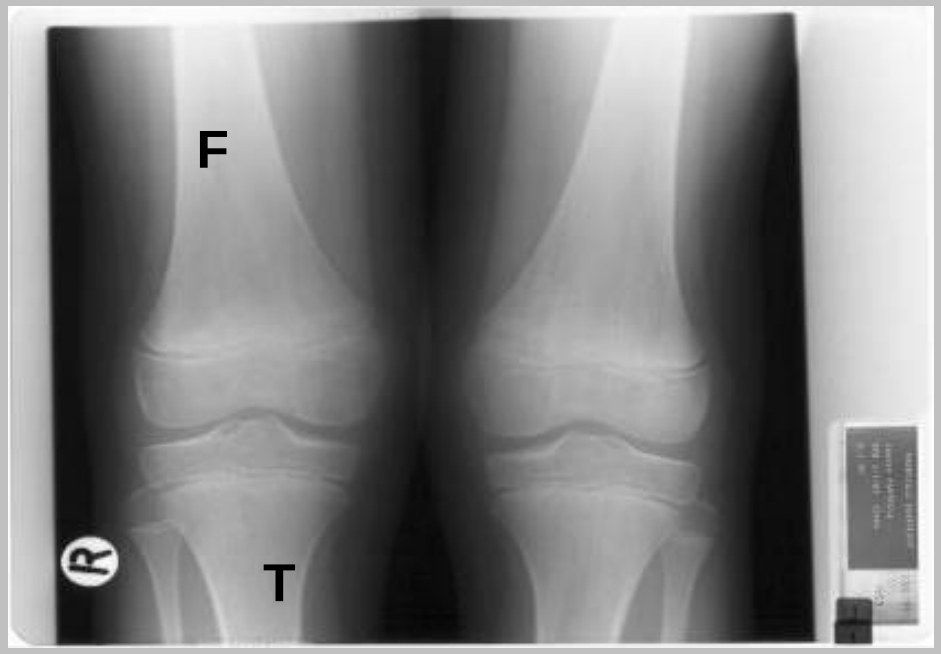
- Achondrogenesis II
- Torrance type PLSD
- Hypochondrogenesis
- SED congenita
- SEMD Strudwick
- Kniest
- Stickler syndrome
- SED with premature arthritis
- Intermediate phenotypes

JF

- Seen at age 19 years.
- Stiff and painful joints – ankles, left shoulder, neck and back over the few years.
- Normal palate and midface. Normal feet.
- Loss of extension both elbows – 10 degree bilaterally. Prominent interphalangeal joints.
- Ankle pain – operated in 1999 aged 16 years to remove loose cartilage
- MRI L shoulder – moderate OA in the superior compartment with multiple intra articular loose bodies.
- Mutation found: (Gly/Ala) next steps……



AP pelvis

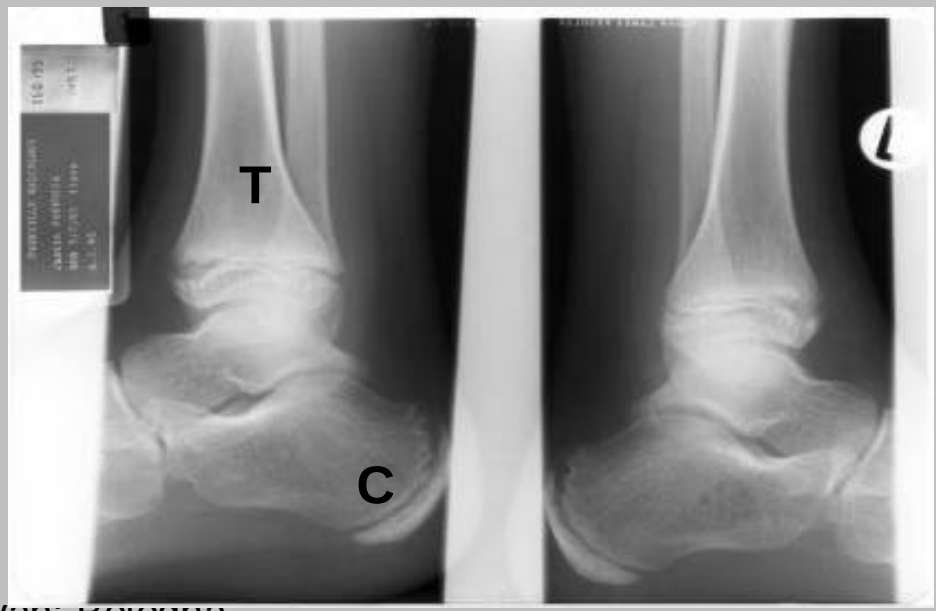


AP knees

F= femur

T= tibia

C= calcaneus



Lat ankle

Natural history studies

- CDP-TM (Savarirayan et al., 2003)
- Metatropic dysplasia (Kannu et al., 2007)

- Why we can do these studies.
- Why we must do these studies.

- Ongoing projects (achondroplasia)

Delineating the natural history

Metatropic dysplasia: History

- First described by Kaufmann (1893)
- Separated and named as distinct phenotype by Maroteaux, Spranger and Wiedemann (1966)
- *metatropos (Gr.)* dwarfism “with change”
- Over 75 cases reported from all ethnic groups
- Pathogenetic basis of the condition unknown

Metatropic dysplasia: Phenotype

- Initially short limbs with relatively long trunk
- Birth length normal
- Prominent joints with limited motion
- Scoliosis may be present at birth
- Caudal appendage/cutaneous skin fold
- Characteristic radiographic findings (SEMD)

Metatropic dysplasia: classification

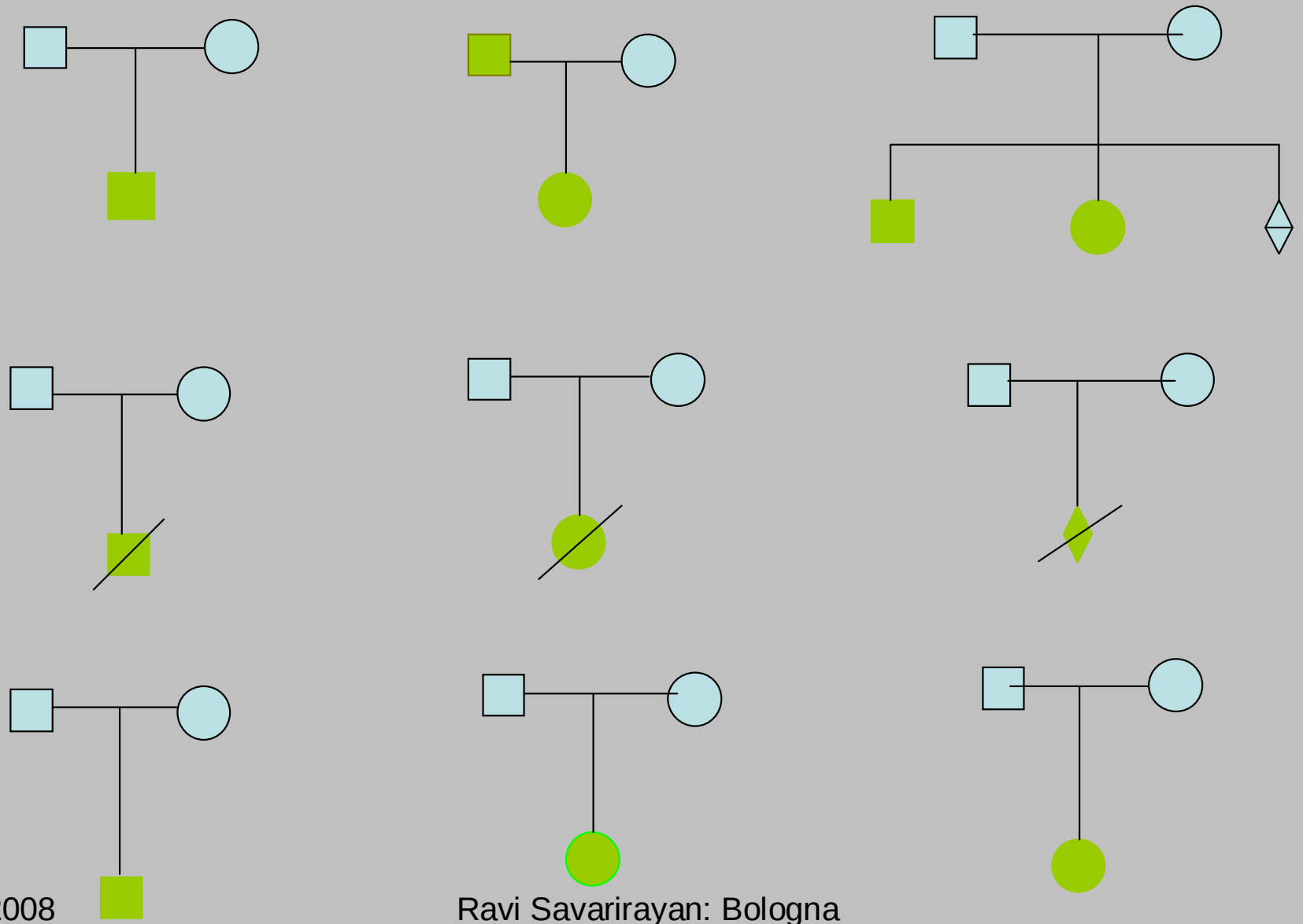
- Three subtypes proposed (Beck et al., 1983)
- Non-lethal recessive form
- Non-lethal dominant form
- Lethal recessive form

- Added to this are metatropic “variants”
- Unclear and confused situation

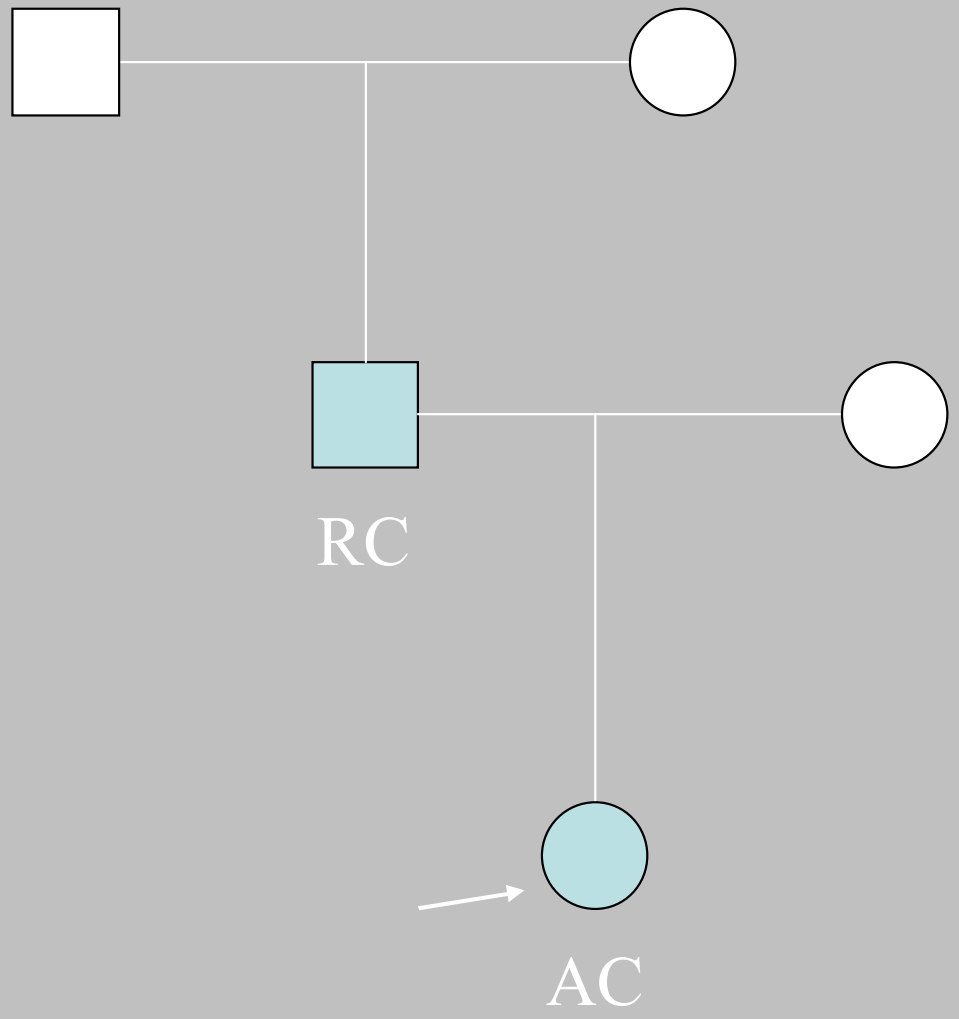
Metatropic dysplasia natural history study

- Eleven patients with metatropic dysplasia over past 35 years (9 Australia, 2 New Zealand)
- Age range 20 weeks of gestation to 70 years
- 6 females, 5 males
- One father and daughter pair
- One sib pair (parents unrelated)

Metatropic dysplasia: Pedigrees

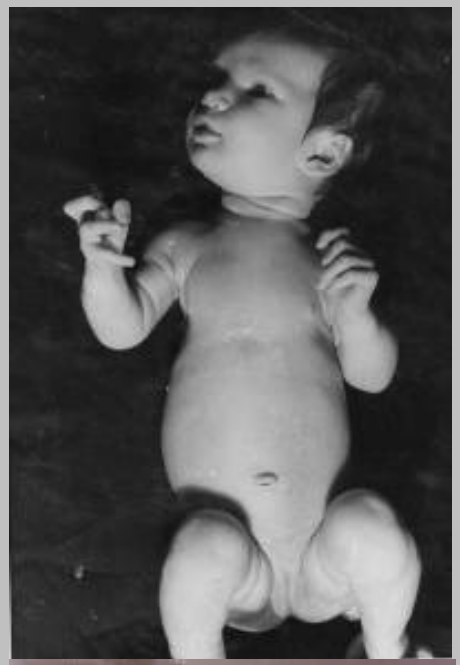


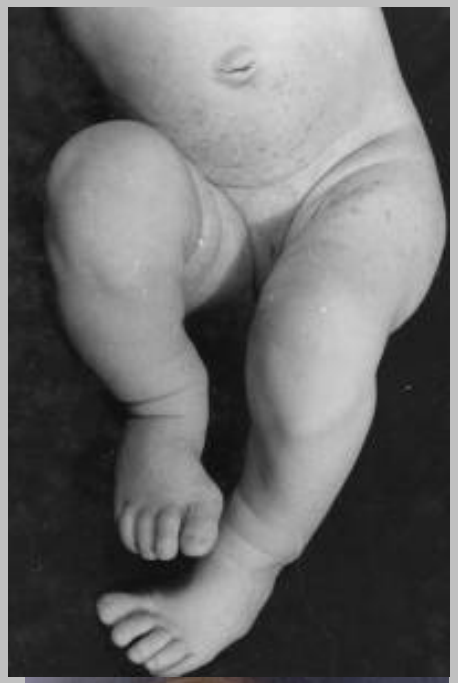
Metatropic dysplasia: Father and daughter

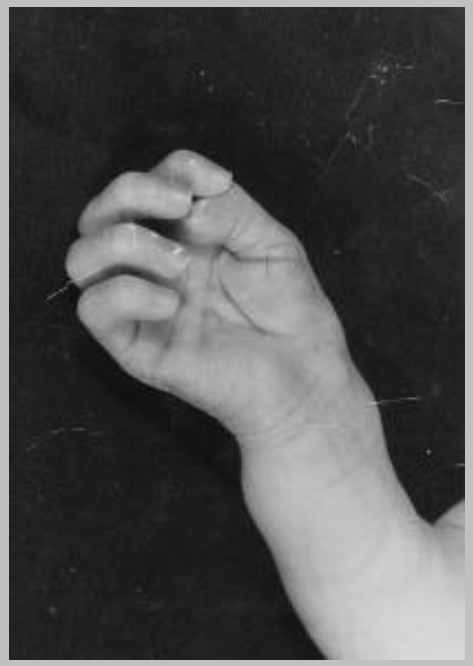


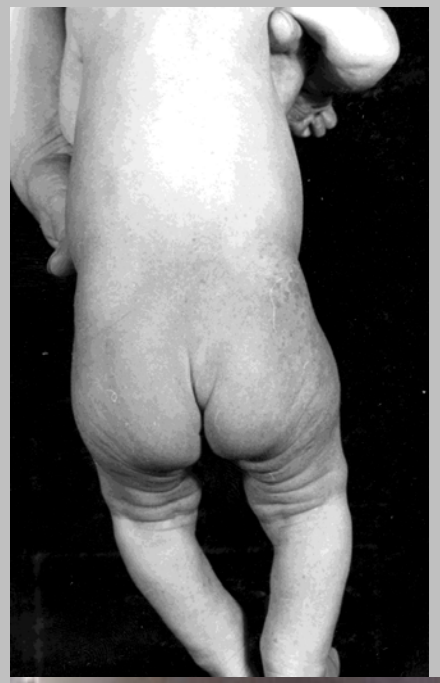
Patient AC

26 days

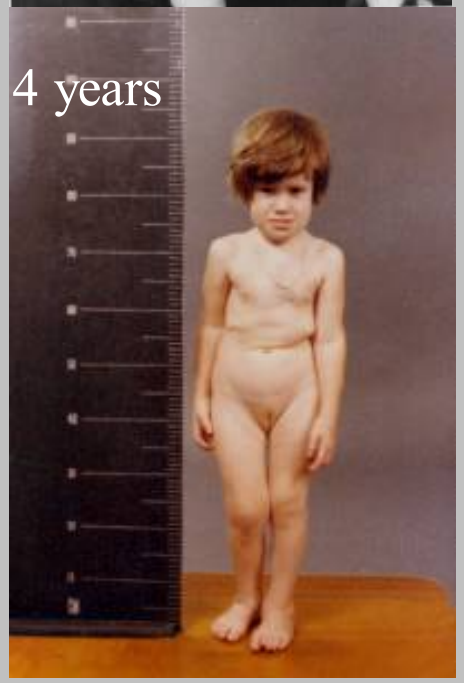


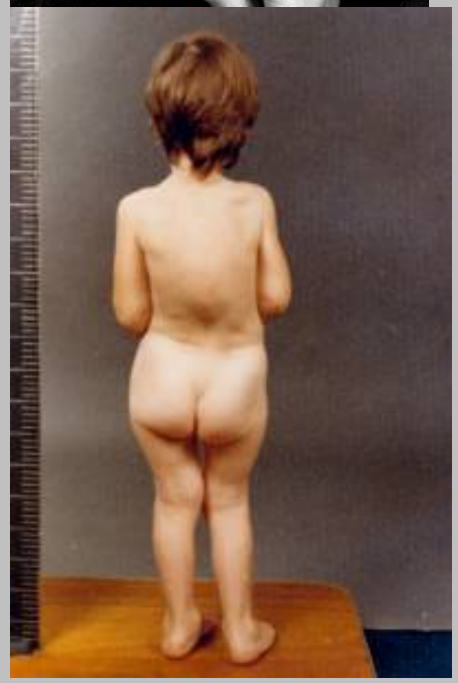






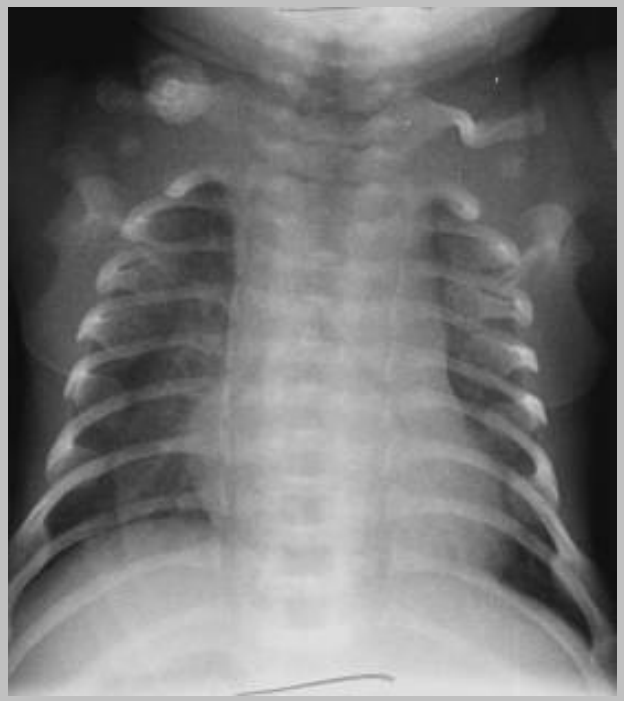
4 years

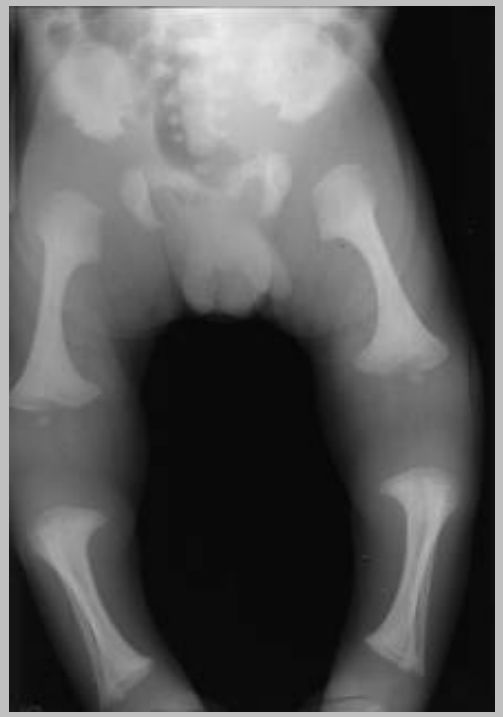


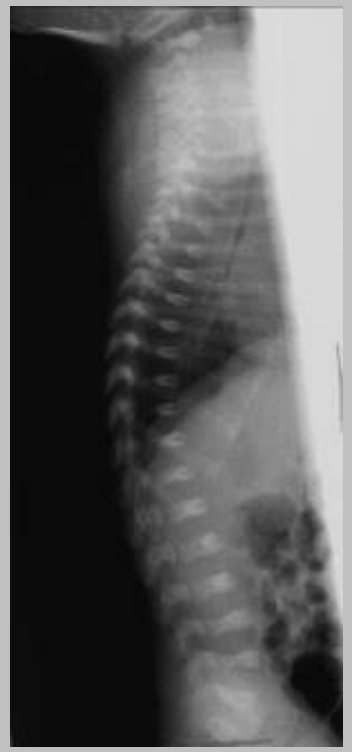


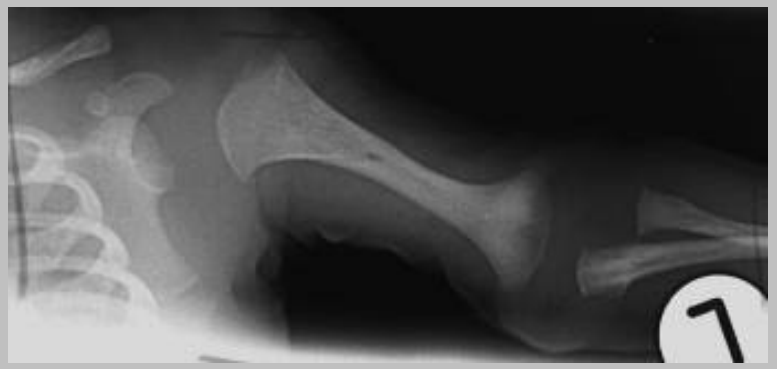
Metatropic dysplasia: radiology (AC)

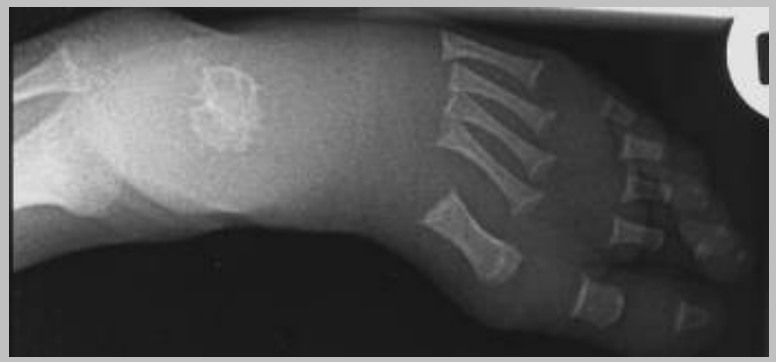
Age 1 month





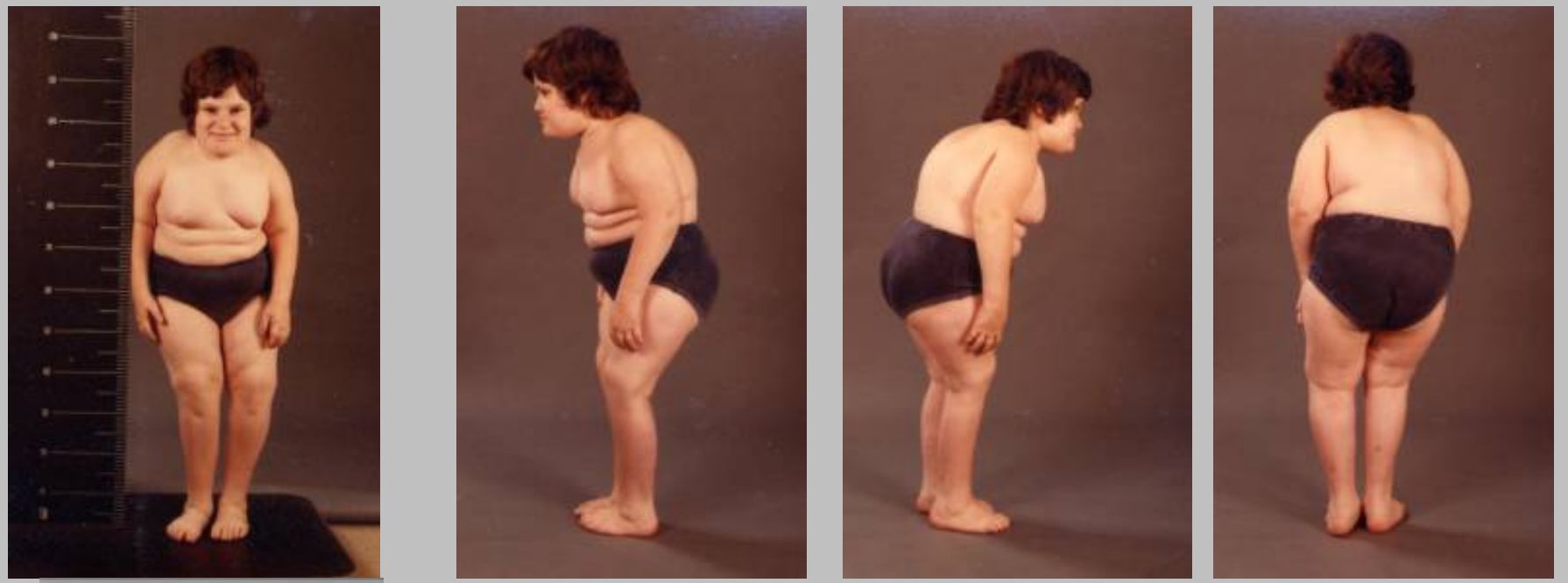




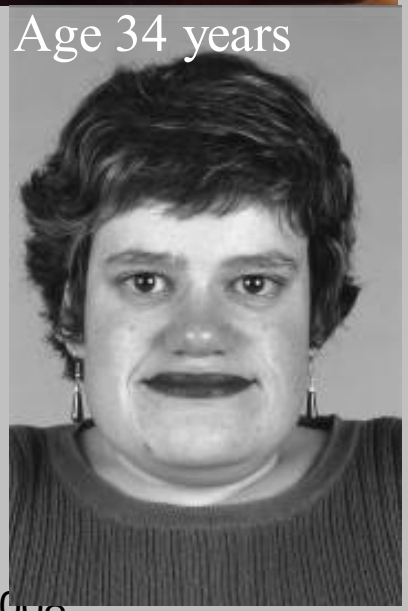


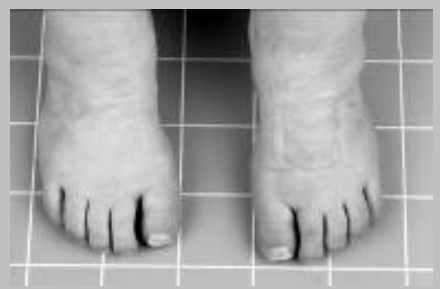
Age 12 years

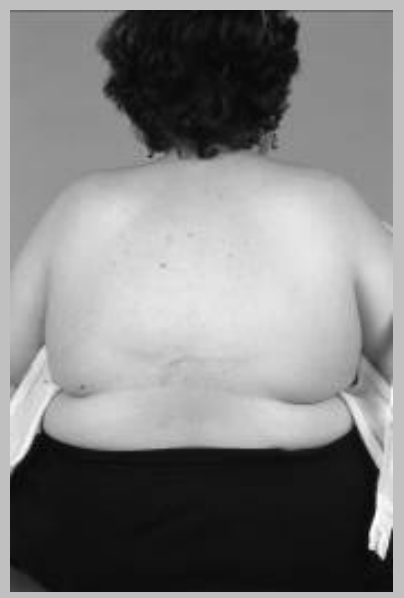
Patient AC



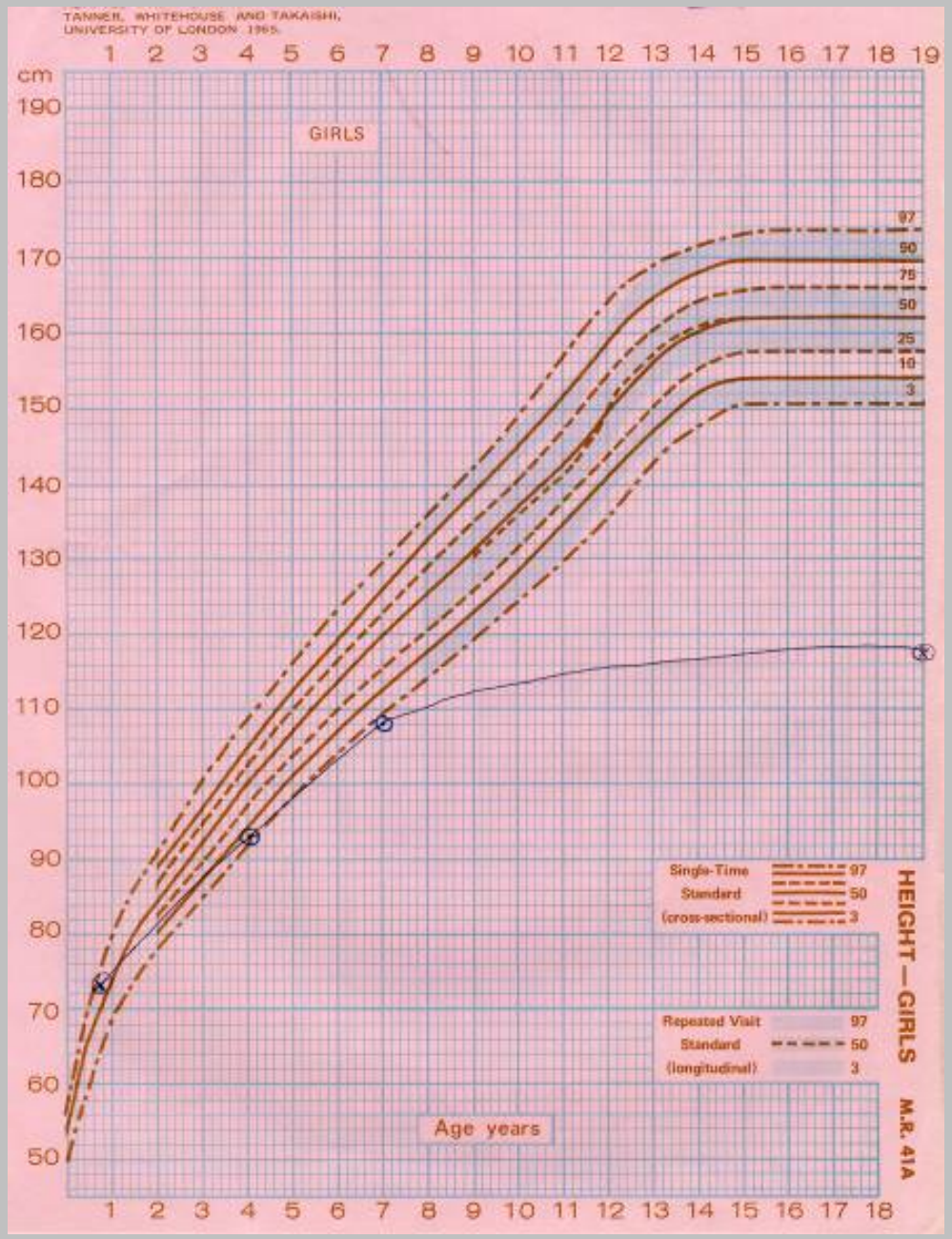
Age 34 years







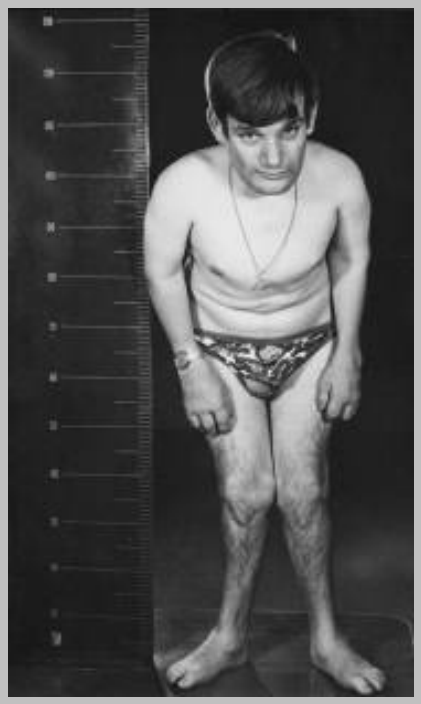
Patient AC: Linear growth

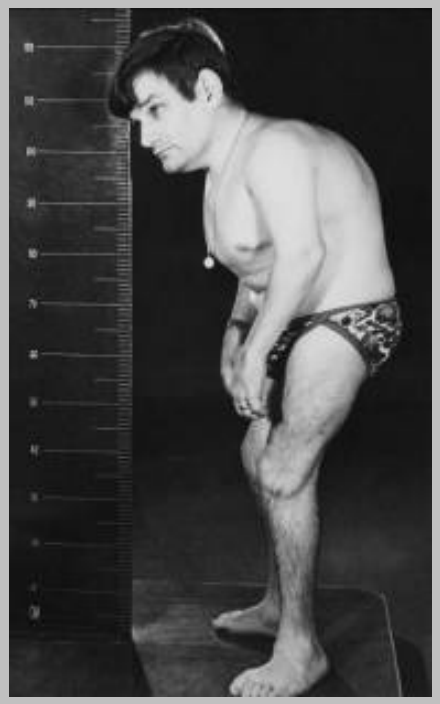


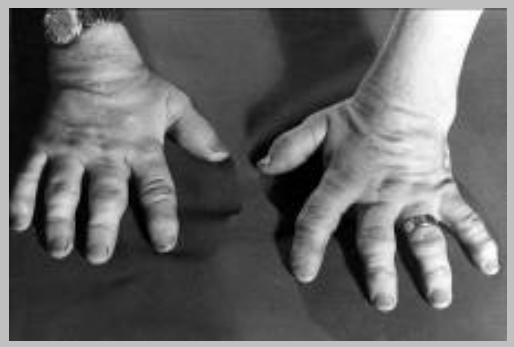
May 2008

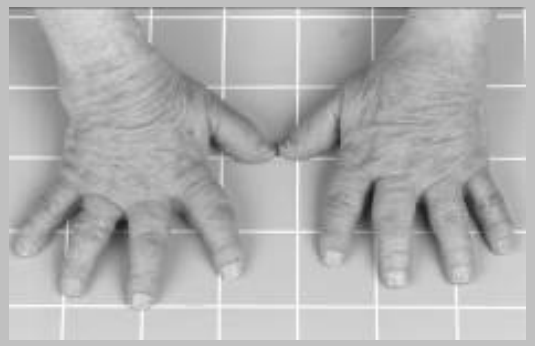
Patient RC

Age 36 years

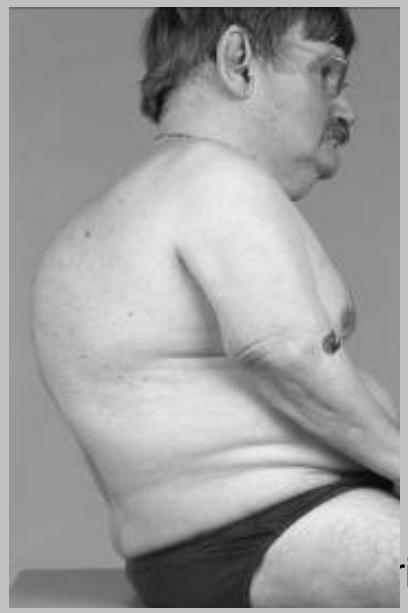


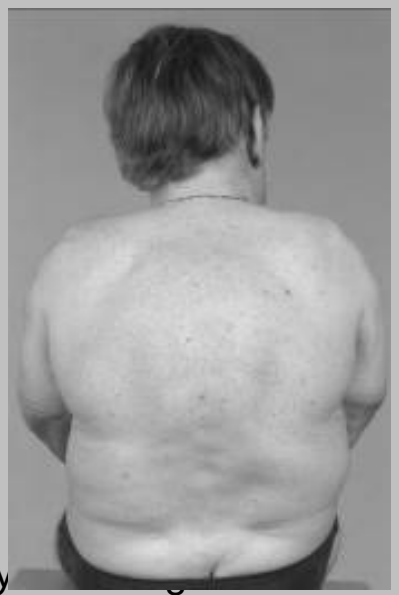


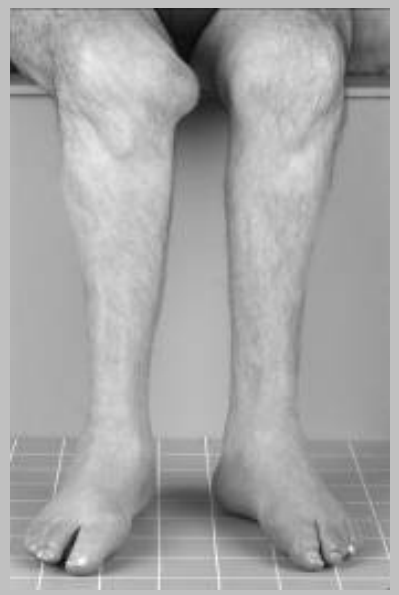




Age 70 years







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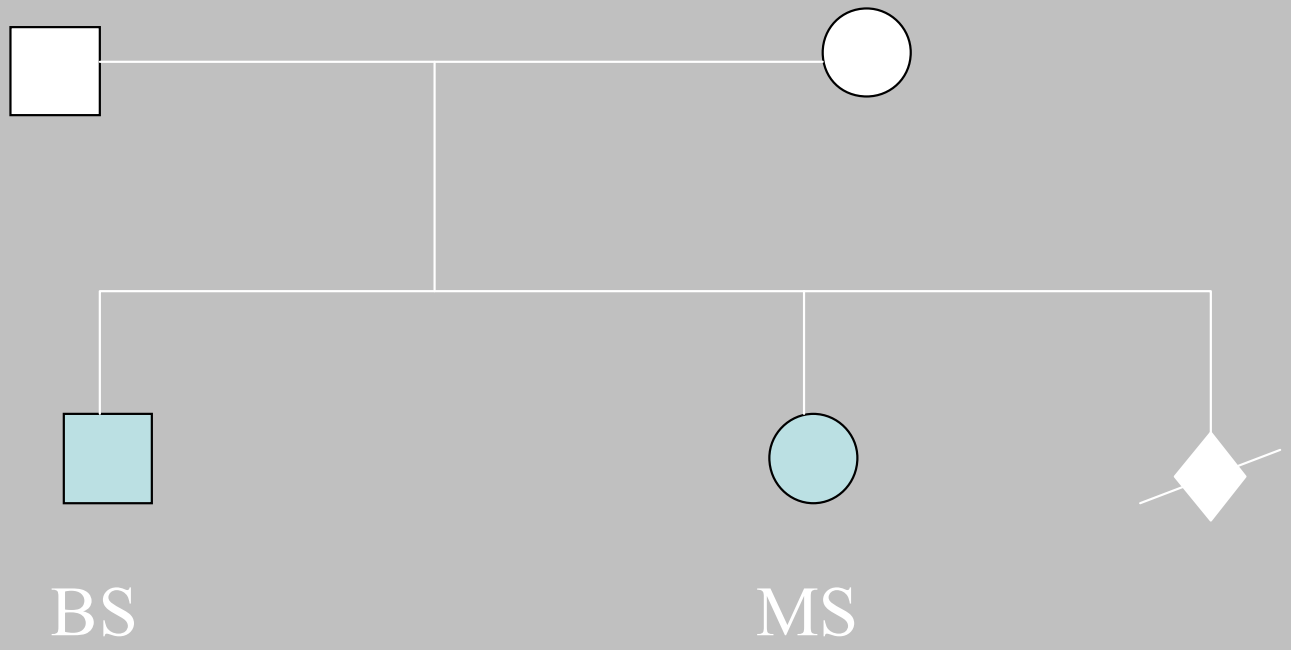
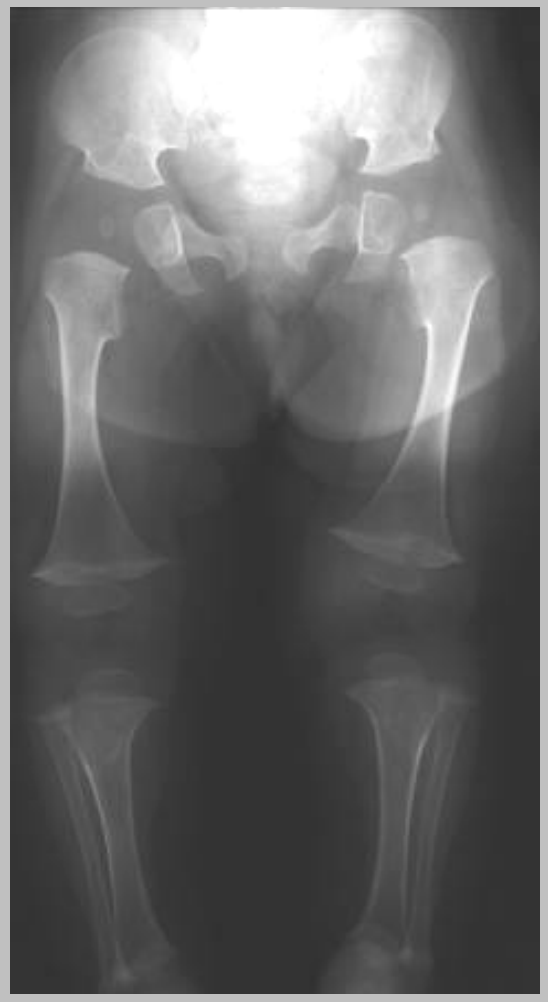
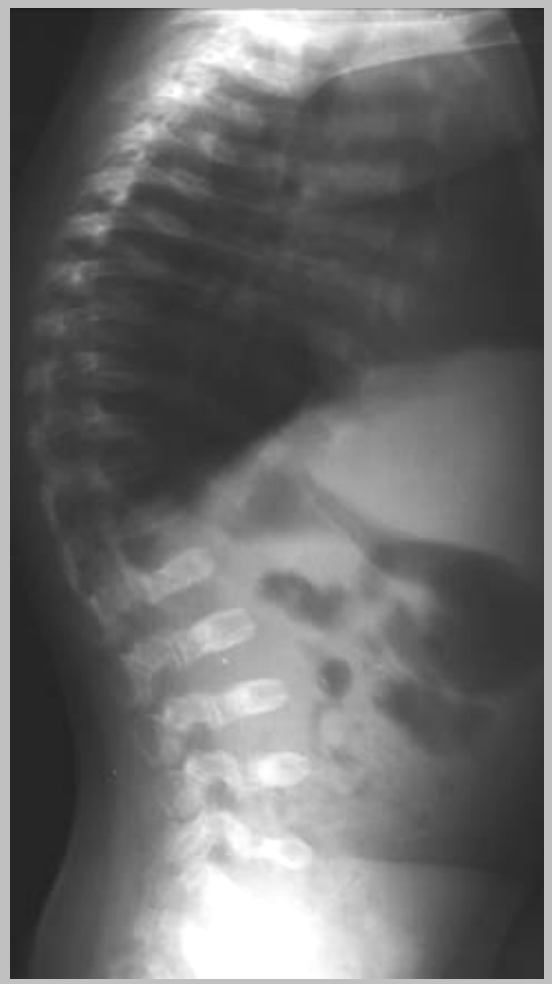
Metatropic dysplasia
Brother and sister

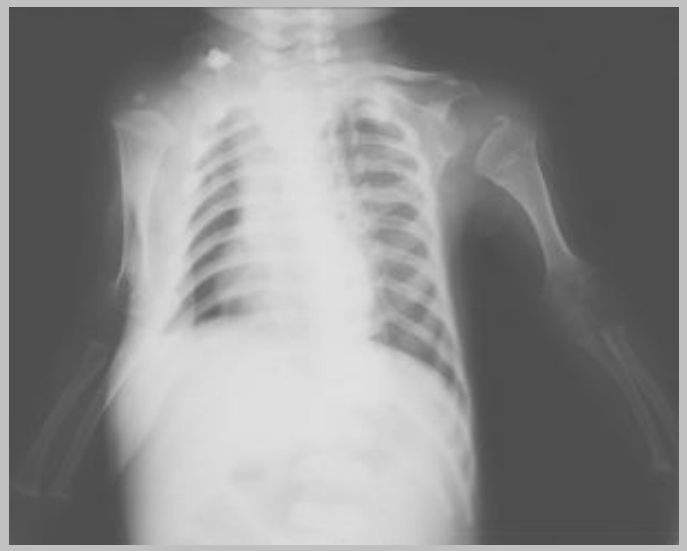


Metatropic dysplasia: Patient MS

Age 7 months





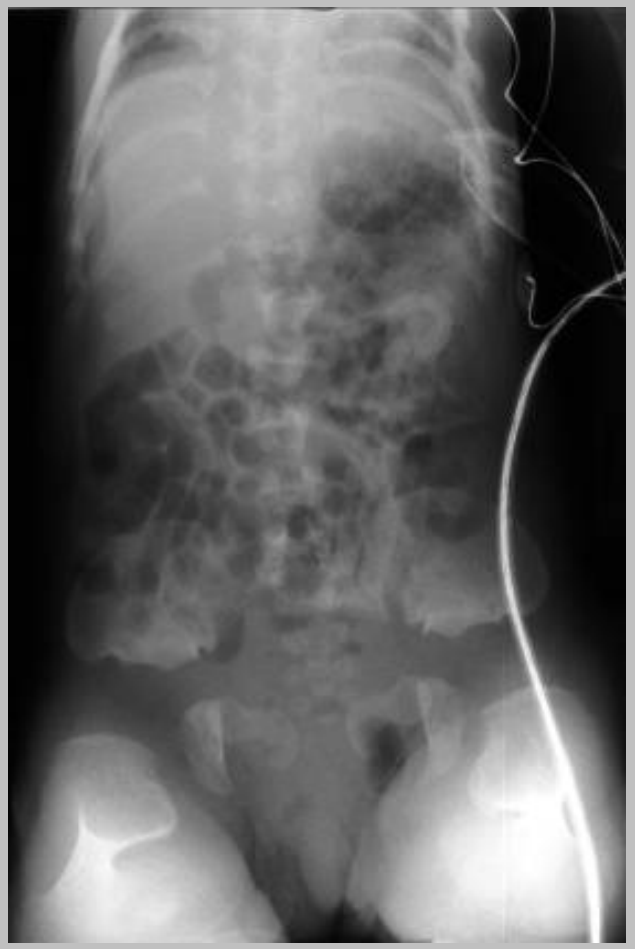


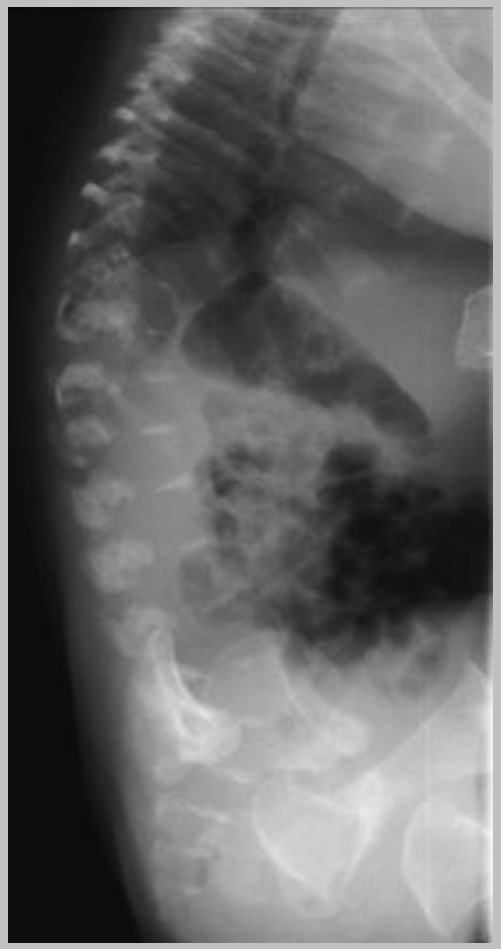
“Lethal” metatropic dysplasia: Patient GW

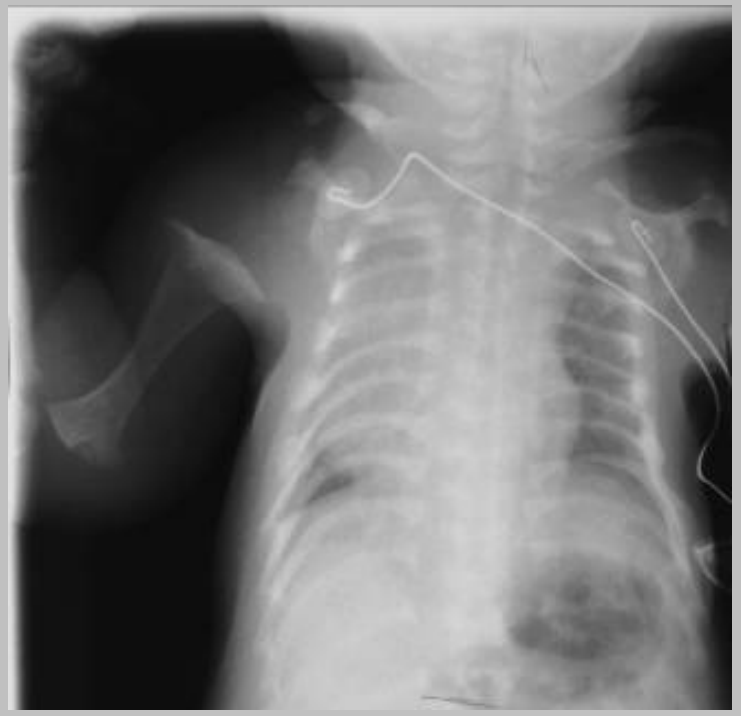
- Second child, unrelated parents (F25, M23)
- Short long bones noted @ 20 weeks gestation
- Born with short limbs, long trunk
- Recurrent episodes respiratory distress as neonate
- Stridor, partial vocal cord paralysis
- Died age 3 months due to respiratory arrest in setting viral bronchiolitis

Patient GW: Radiology

Age 2 months



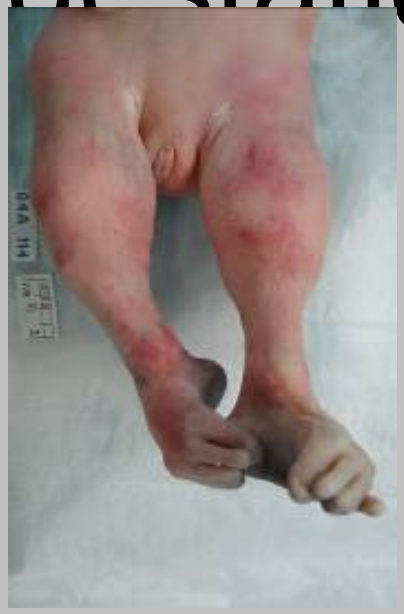


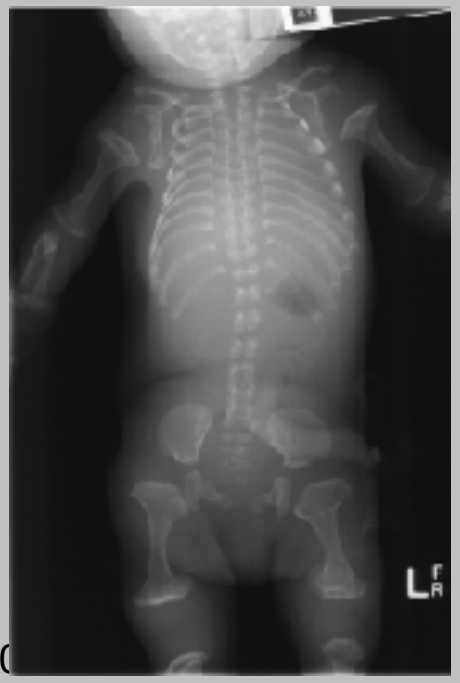


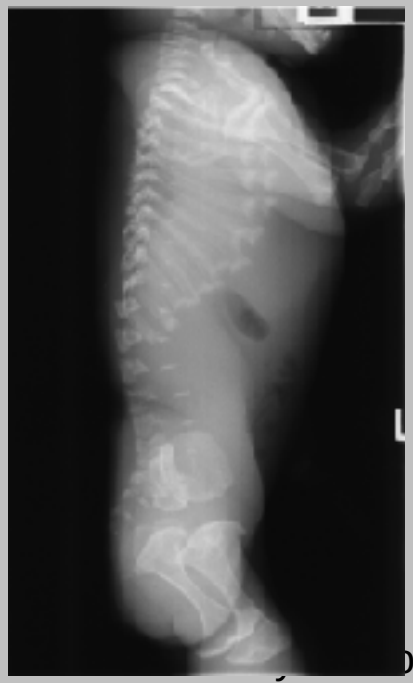
Metatropic dysplasia: Antenatal diagnosis Patient TW

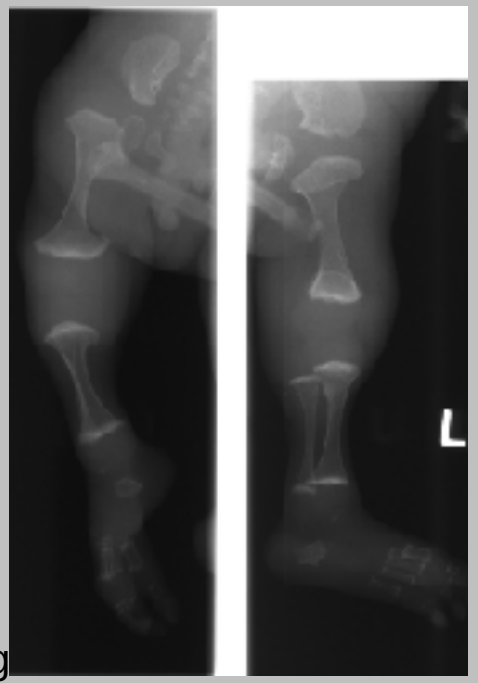
- First pregnancy to healthy, unrelated parents
- Ultrasound @ 18 week gestation showed short limbs, platyspondyly, small chest, short ribs, and fixed extension of knees
- Normal karyotype, 46XX
- Elective termination @ 20 weeks gestation
- Definitive diagnosis at post mortem

Fetus TW (20 weeks gestation)









Metatropic dysplasia:
1. ENT/Respiratory Complications

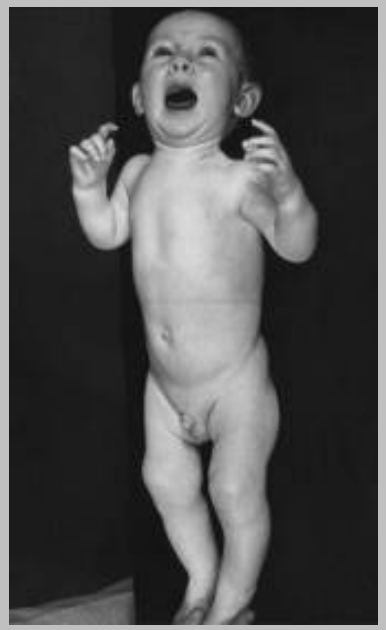
- In our cohort 2 patients (GW/SD) died from upper respiratory tract dysfunction with abnormal vocal cords/arytenoid fusion/laryngotracheomalacia
- Third case had respiratory arrest and found to have severe laryngotracheomalacia (direct vision)
- Numerous examples of “respiratory” demise/stridor/respiratory arrest in literature
- Need to be aware of/manage this complication in infancy especially if stridor
- Natural history is to improve with time
- Later hearing loss (high freq S/N) in 3/5 followed to adulthood (supports *Genevieve et al, 2005 AJMG*)

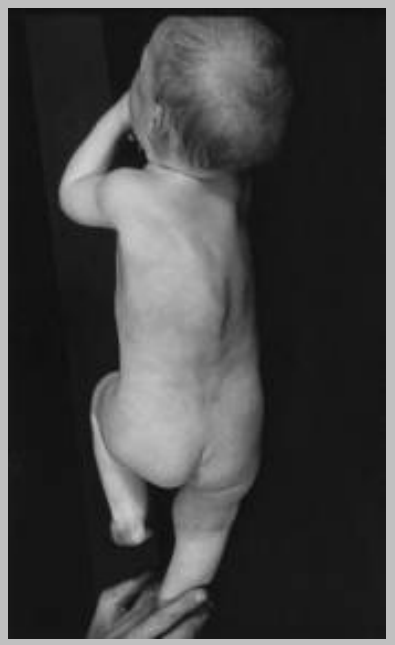
Metatropic dysplasia: 2. Natural history of spinal changes

- In all three cases followed over 30 years progressive kyphoscoliosis occurred
- One case (RM) had ant./post. spinal fusion at age 2 years, repeat anterior fusion at age 4 years, and posterior spinal osteotomy/Harrington rod insertion at age 7 years
- Another case (BS) had anterior fusion at age 9 years. At age 39 years (Ht=107cm), severe kyphoscoliosis, symptoms of spinal canal stenosis.
- C1-C2 instability in only 1 case (none of 5 followed to adulthood)

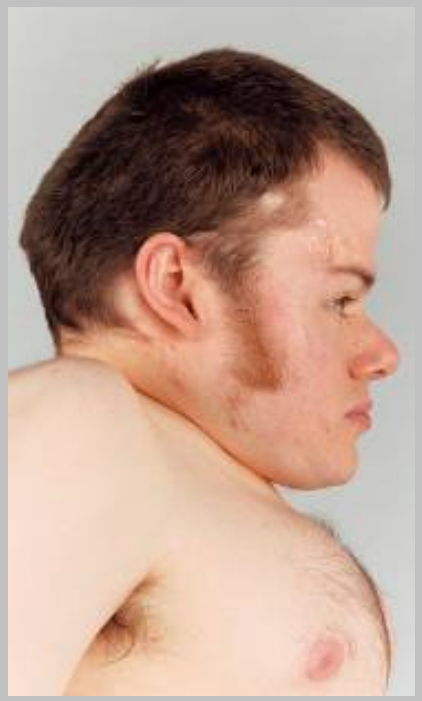
Patient RM: Spinal changes)

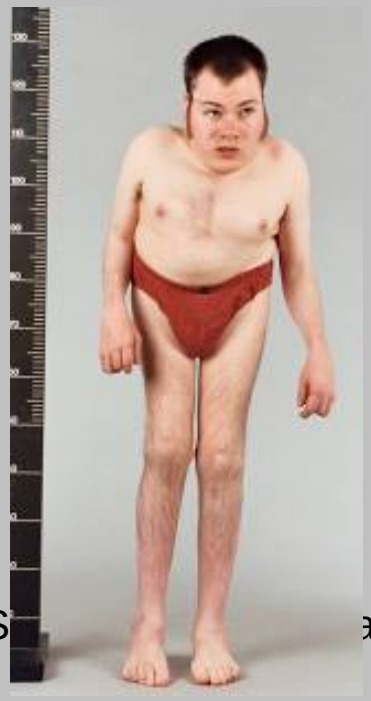
Age 7 months

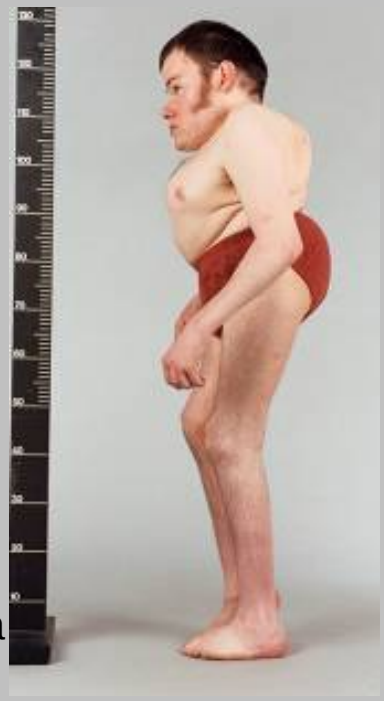


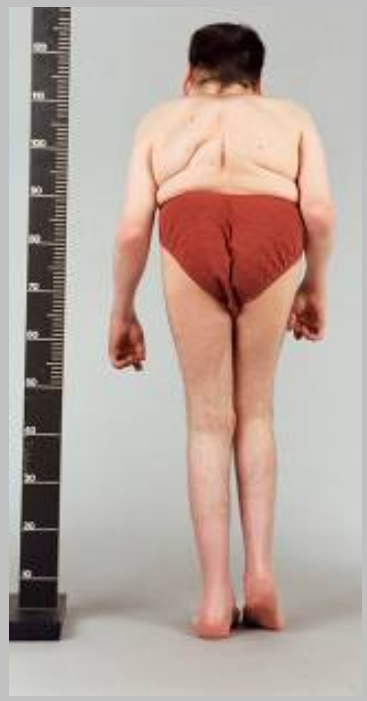


Age 35 years



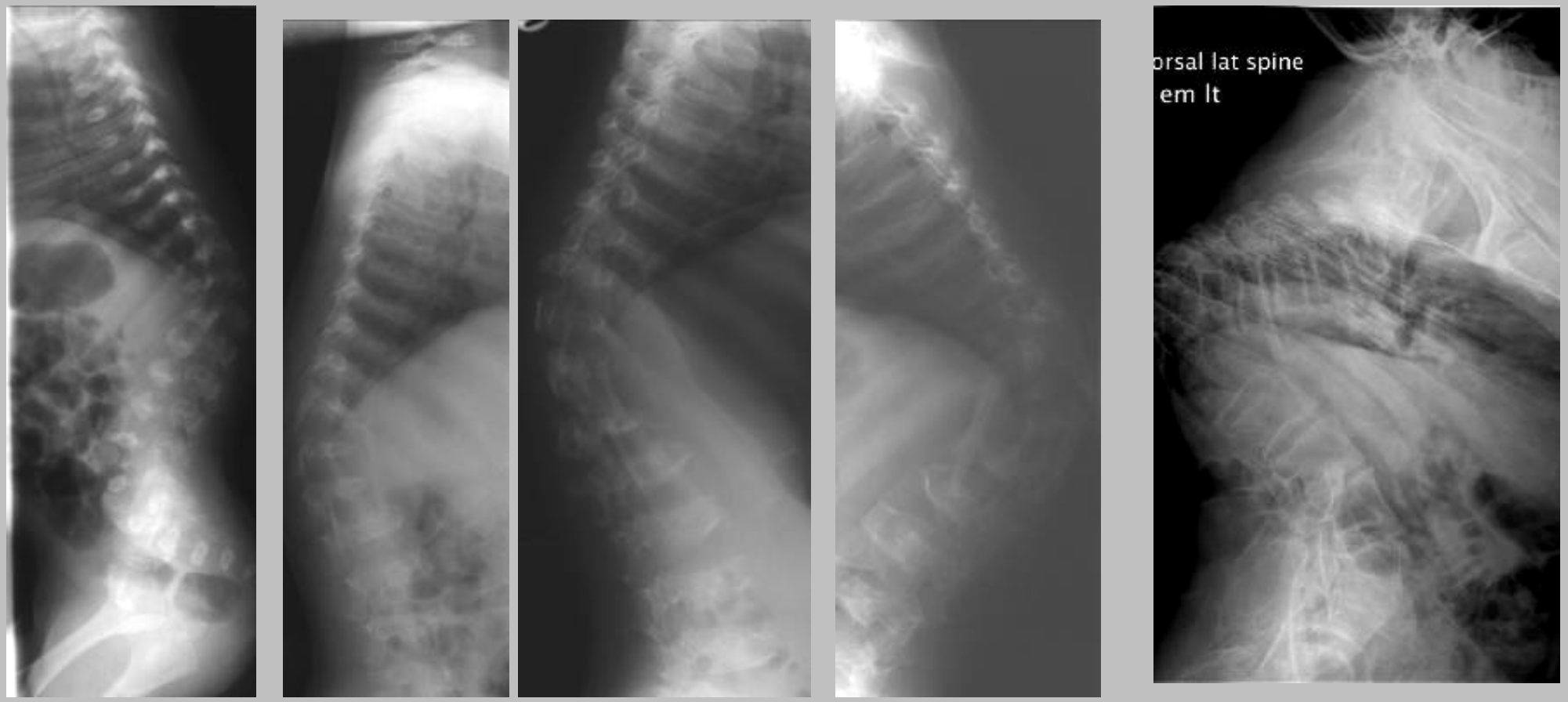






Patient RM: Spinal changes

3 wks 1 year 3 years 5 years 35 years



Metatropic dysplasia
3. Longterm functional outcome

- In all five adult patients (age 33-70 years) function well with respect to ADL
- Intellect normal in all cases
- Patient RM (aged 33) rides a bike and can climb stairs
- All able to drive modified motor vehicles
- One uses wheelchair for longer distances (AC)
- SOB due to restrictive lung disease in 3/5 adults
- Very little in way of arthritic symptoms reported in these adults
- Final adult height 107-135 cm.
- Hearing loss in 3/5 adults

Metatropic dysplasia: Conclusions

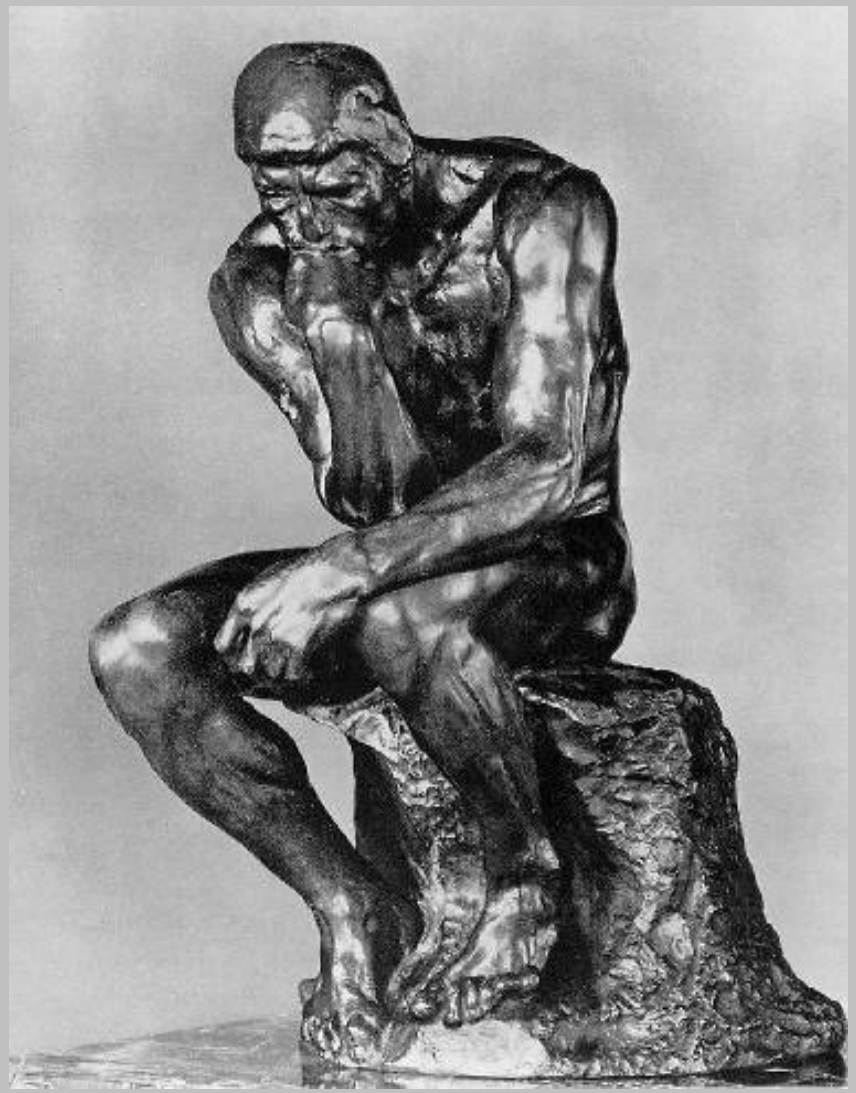
- Based on these data, little evidence to support three distinct entities
- Overlap between “mild”, “classic”, “lethal” forms
- Many cases in literature who died classified as “lethal recessive”
- Our father/daughter cases, sib cases, and “lethal” cases clinically and radiographically alike
- In reported families ratio affected:unaffected not 1:4 (more like 1:20)

Metatropic dysplasia: Conclusions

- Condition might be caused by single dominant gene (important in endochondral ossification and in ?expressed in respiratory cartilage)
- Various “subtypes” accounted for by variable expression and sib recurrence by gonadal mosaicism
- Early complications include laryngotracheomalacia (monitor)
- Late complications include spinal deformity (how best to manage?) and sequelae and hearing loss
- Good longterm intellectual outcome and function
- Elucidation of genetic basis important to settle these issues

Kannu..Savarirayan, *AJMG, 2007*

Listening to our families



Listening to our families

- Qualitative study looking at experiences of parents at time of diagnosis of achondroplasia and pseudoachondroplasia
- Structured questionnaire given to each parent in the home
- Families from cities and rural areas
- Impact of diagnosis
- Good and bad experiences documented
- Main themes extracted for discussion/action

Hill et al, AJMG, 2003

Listening to our families

- Many parents felt let down by their physicians
- Setting and manner of diagnosis delivery crucial
- Vivid recall of time around diagnosis
- Time to “expert” consultation important
- Data used to develop information packs for health care workers/families/patients
- Patient input now part of our program to offer feedback and improve our services

Listening to our families

- Throughout life
- Multidisciplinary approach (genetic counsellors)
- Support groups
- Peers
- Education of community/health workers
- Discussion of issues as arise and anticipatory guidance

Relevance to common disease processes

Is any of this relevant to more common diseases?

- Widely relevant to common conditions and disease processes such as short stature, osteoarthritis and osteoporosis

1. Osteoarthritis “genes”

- Polymorphism in small ECM molecule (asporin) predisposes Japanese populations to knee and hip osteoarthritis
- Implications for population genetic screening, therapeutic management and prevention targeting of high risk groups

Nat Genet 37, 2005 (Kizawa et al.)

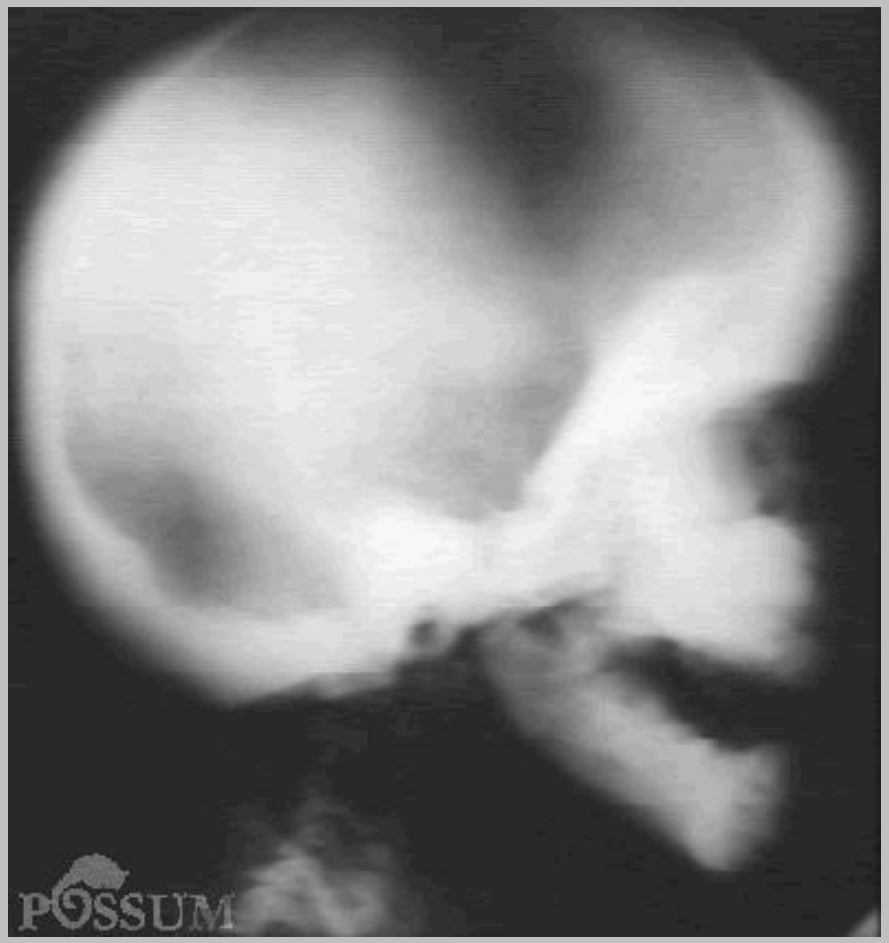
2. “Genes” for lumbar disc disease (LDD)

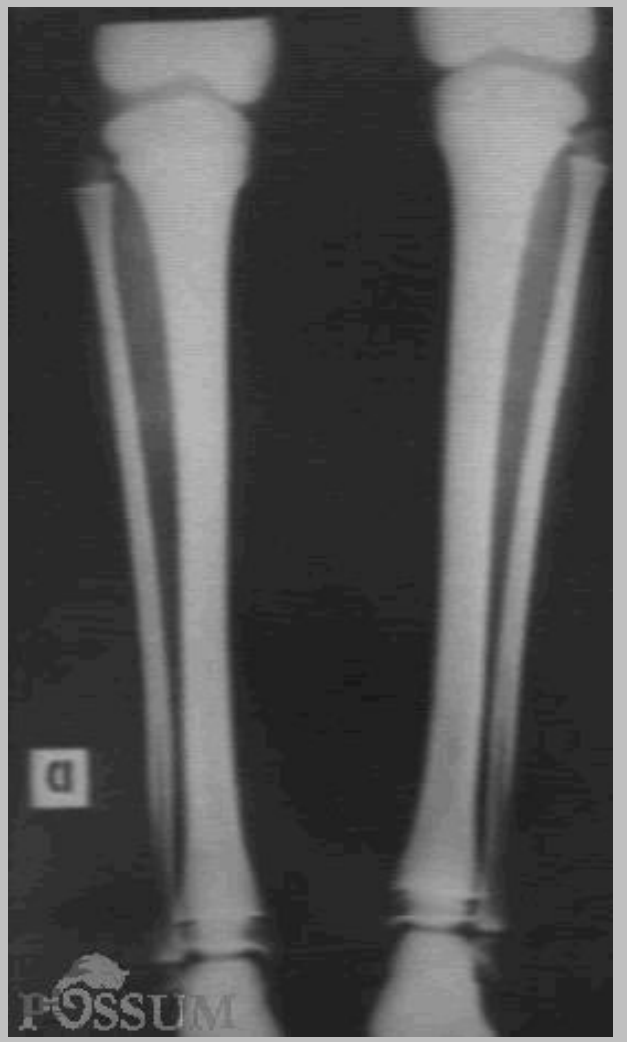
- LDD caused by degeneration of intervertebral disks
- Common cause back pain/sciatica/spinal surgery
- Functional SNP (1184T-C) in *CILP* associated with LDD susceptibility
- Effects mediated by inhibition of *TGFB1* induction of cartilage matrix genes in disks

Seki et al., Nat Genet, June 2005

3. Osteoporisis ‘genes’

van Buchem disease



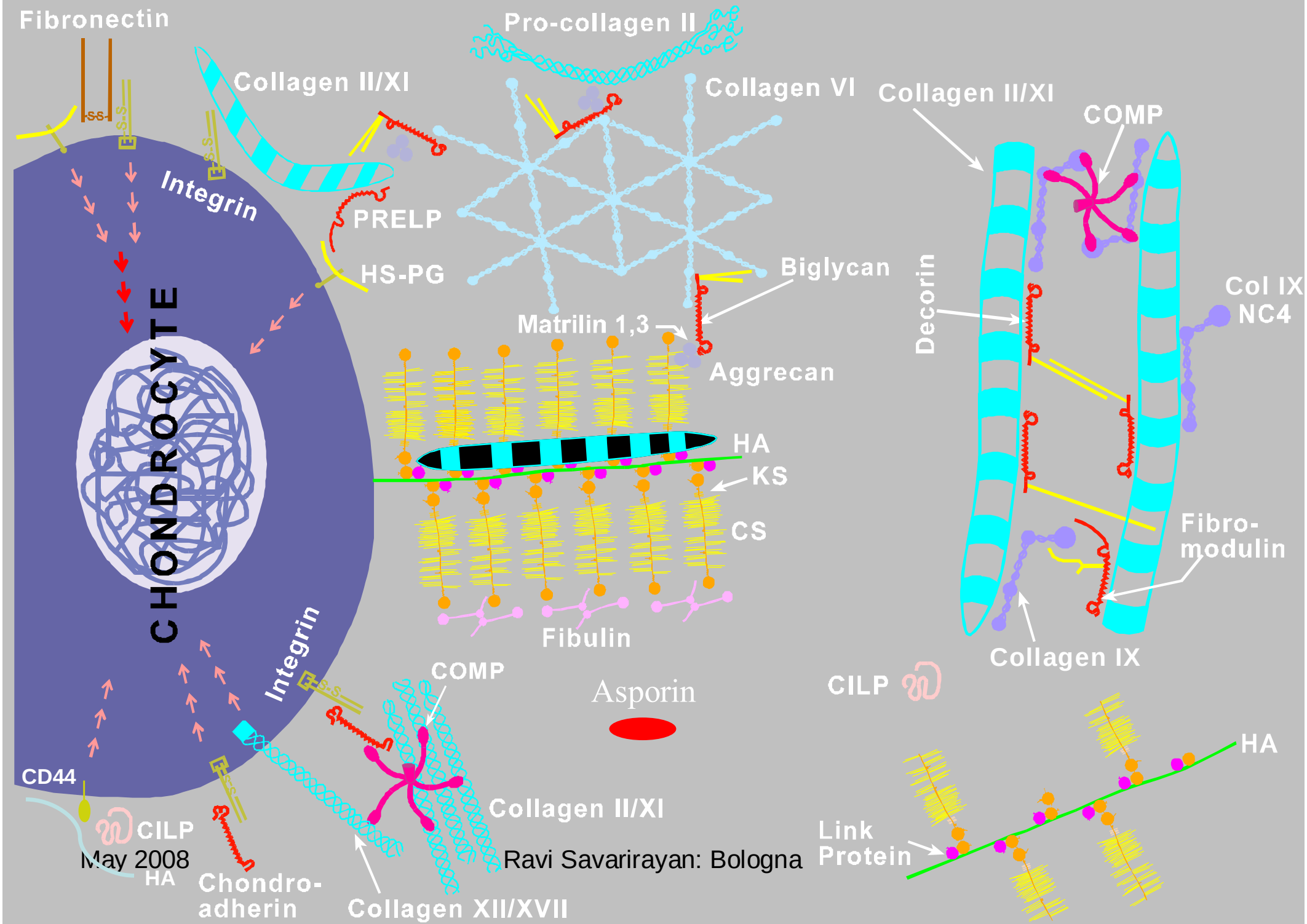


Osteoporosis “genes”

- Sclerosteosis/Van Buchem disease gene (SOST)
- Different polymorphisms in this gene associated with increased and decreased BMD in elderly Dutch white men and women (n=2000) at femoral neck and lumbar spine
- Public health implications

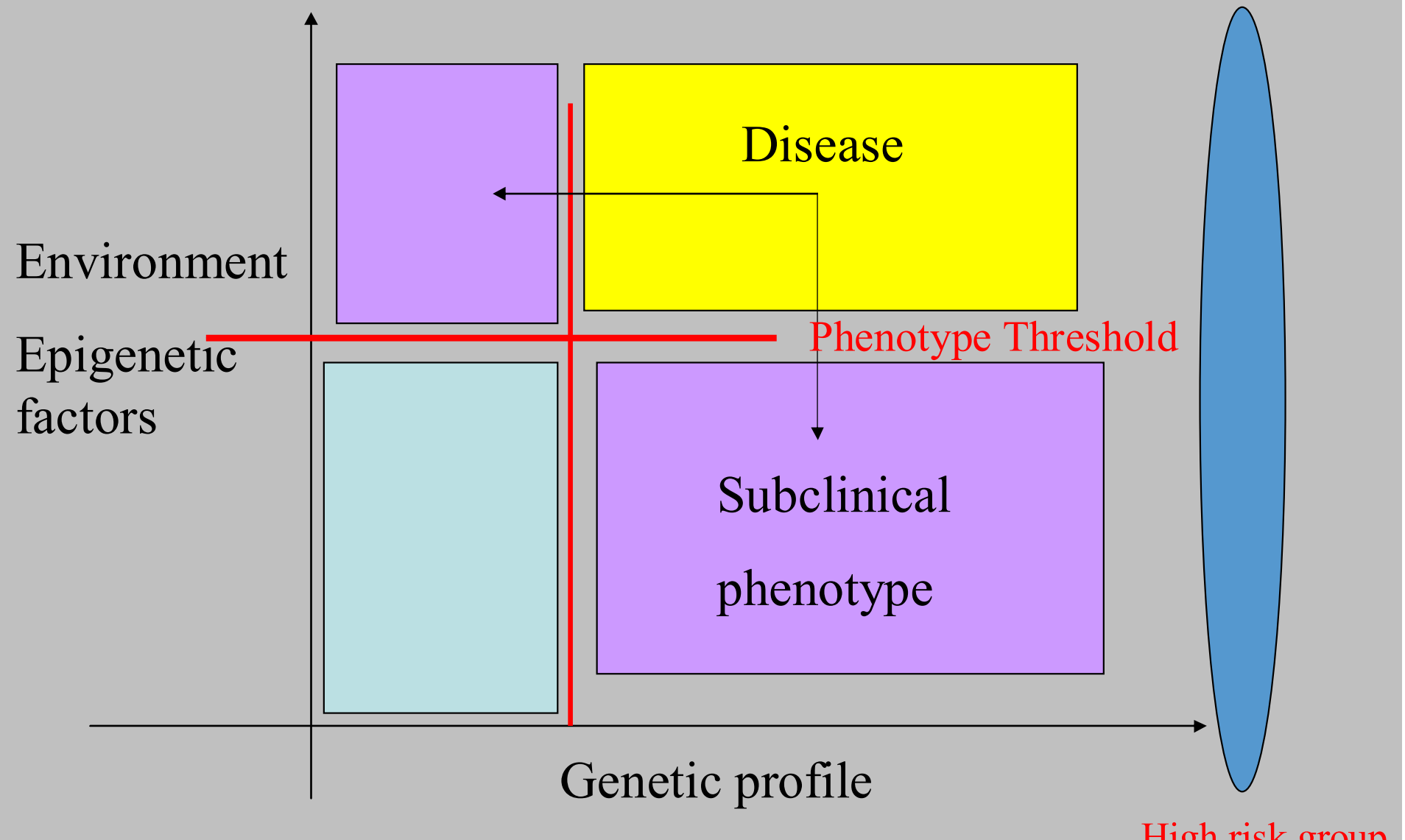
Uitterlinden et al., Am J Hum Genet Dec 2004

THE CHONDROCYTE AND ITS MATRIX CONSTITUENTS



May 2008 Ravi Savarirayan: Bologna

“Personalised Genomics”



May 2008

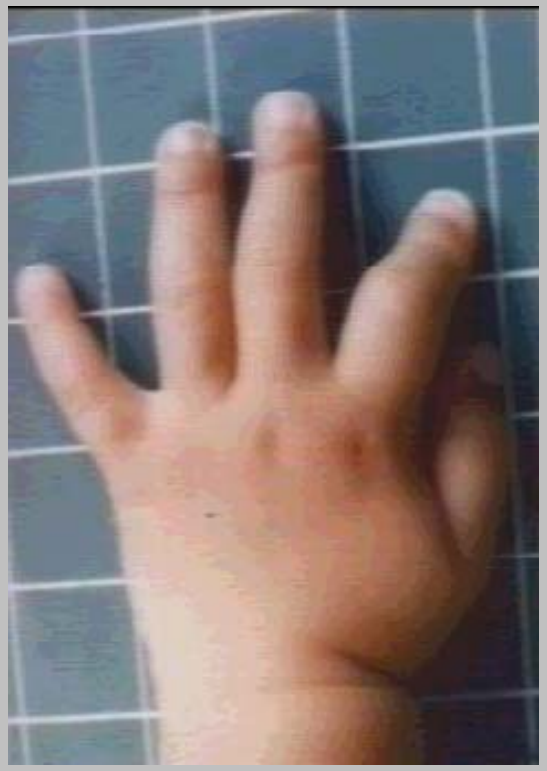
Ravi Savarirayan: Bologna

4. Short stature

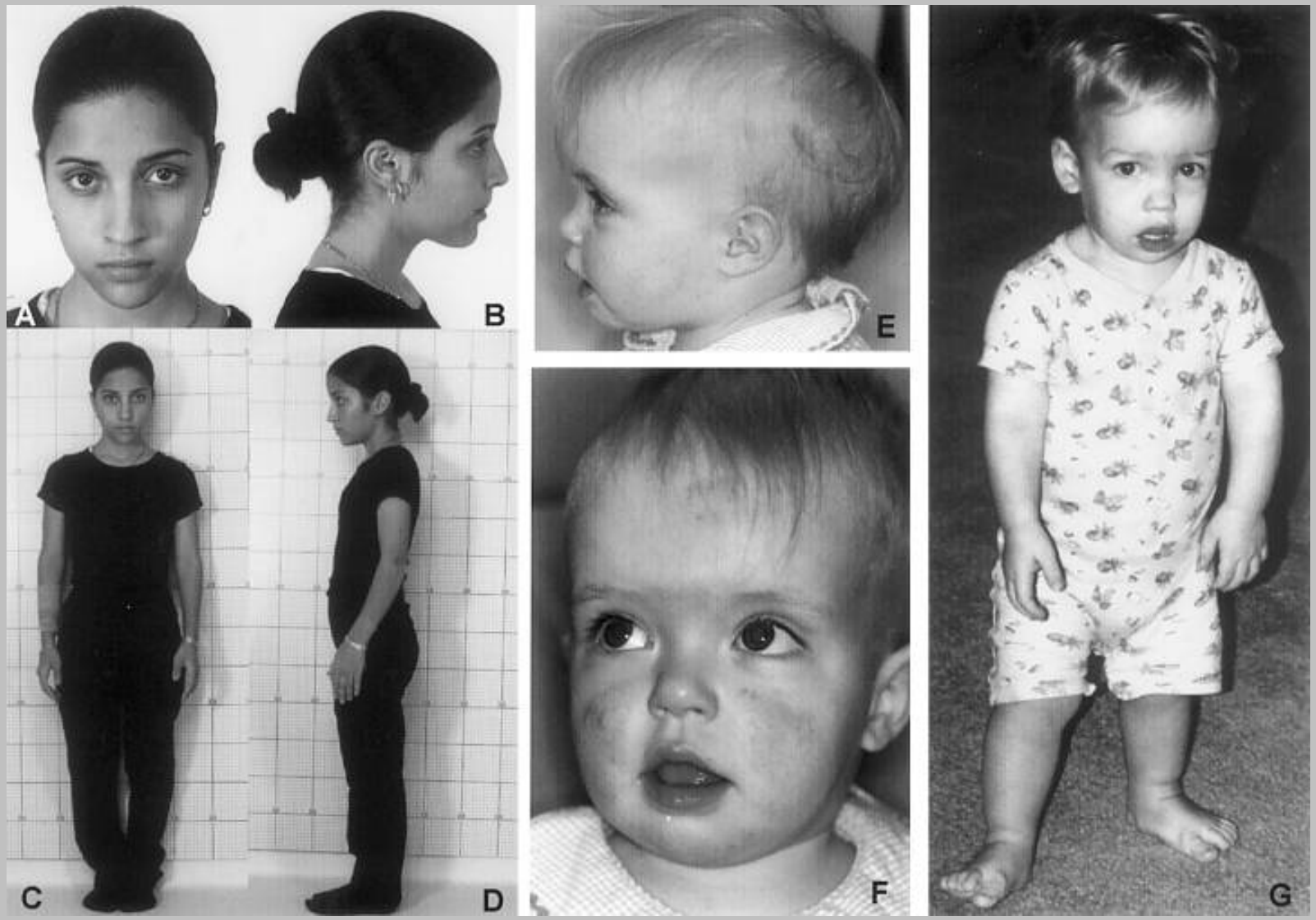
- Patients presenting with “idiopathic” or “constitutional” short stature might well have an underlying skeletal dysplasia/genetic cause

1. HYPOCHONDROPLASIA

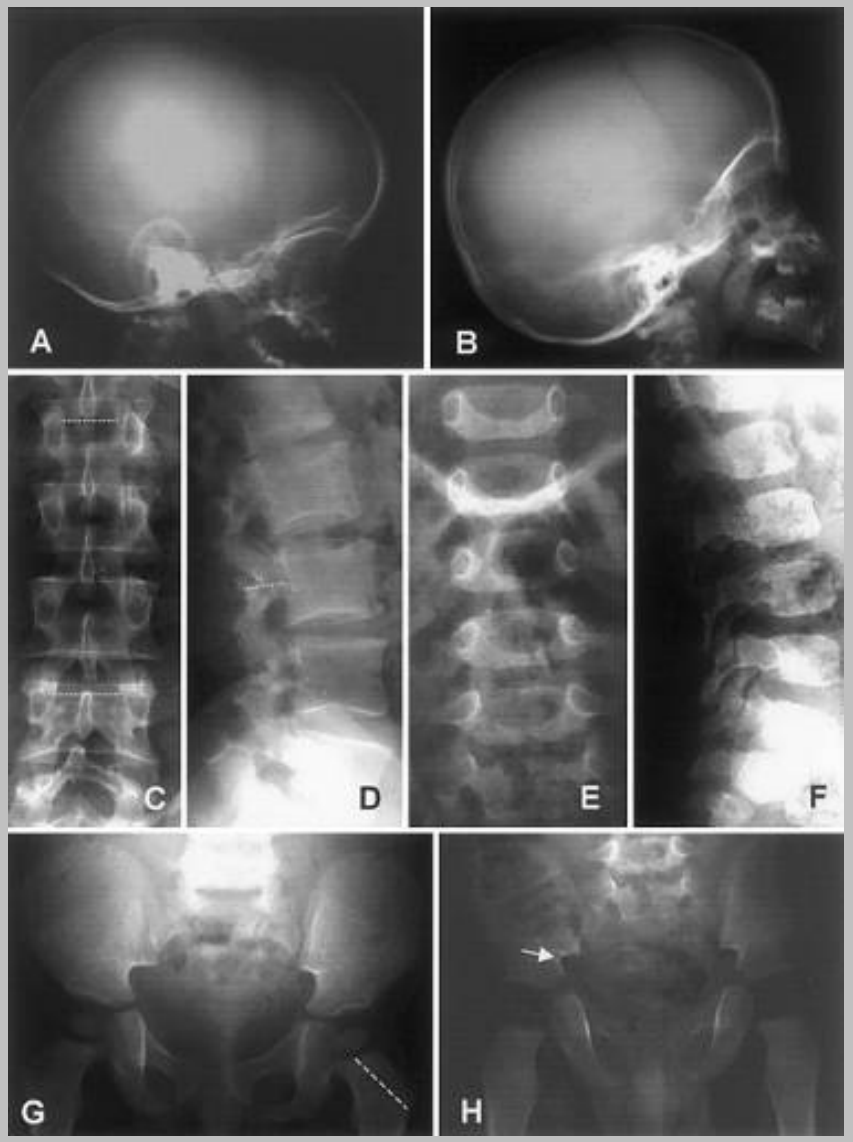
- Clinical
- Radiographic
- Common mutation in 45-50% *(FGFR3;N540K)*
- “Familial” short stature



HYPOCHONDROPLASIA



HYPOCHONDROPLASIA

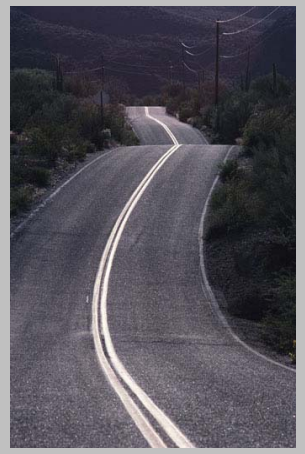


FGFR and height

- It is likely that many cases of “familial” short stature have this condition
- Other polymorphisms in these FGFR genes (and others such as *COL11A1*) probably predispose to final adult height in our populations

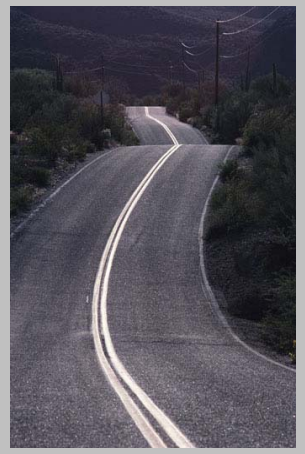
Where are we going?
Brave new world?

The road ahead……



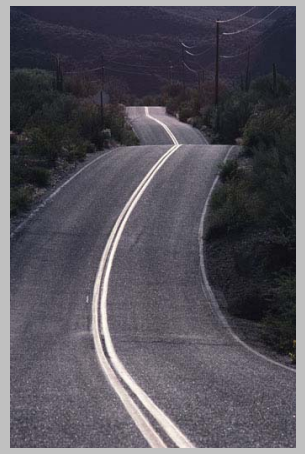
- More prenatal testing options/choices will be available to families
- Medical conditions such as congenital hip dysplasia, scoliosis, spinal degeneration, limb deficiency, osteo-arthritis, club feet, will have accurate genetic markers identified to allow selection of embryos through IVF/PGD.
- Ethical issues of who will pay for this technology and who will decide if it to be employed and for whom?

The road ahead……



- More specific/confirmatory genetic tests for these conditions or predispositions
- Targeted anticipatory counselling regarding lifestyles and risk factors to avoid for certain predispositions (i.e. arthritis)
- Population screening for predisposition “genes” and polymorphisms
- Issues of how this will affect our lives, employment, insurance, marriage prospects?

The road ahead……



- Better treatment/management strategies due to better understanding of the pathogenesis of these conditions
- Platform for biomaterial development and new therapeutic approaches
  - Recombinant growth factors and autologous bone marrow therapy as adjunct to current management
- Further dissection of molecular pathways of the musculoskeletal system and interacting factors (environment, sex, age)

MELBOURNE BONE DYSPLASIA PROGRAM

- Clinical diagnosis/management
- Basic research
- Applied testing of new research
- Long term natural history studies
- International links for gene tests and collaborative clinical/molecular projects (Manchester)
- MCRI Theme Grant over 3 years
  In addition to NHMRC Project and ARC Discovery grants

MELBOURNE BONE DYSPLASIA PROGRAM