Hospital-based study of the spectrum of skeletal dysplasias in children in Northern India

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Osteochondrodysplasia

- Complex group of bone & cartilage disorders affecting the fetal skeleton
- Disproportionate short stature & skeletal deformities
- More than 350 disorders
- Diagnosed based on clinical, radiographic & molecular criteria

*Superti-Furga A, Unger S. Nosology and classification of genetic skeletal disorders: 2006 revision. Am J Med Genet A. 2007 Jan;143(1):1-18

Constitutional disorders of bone

Type/particulars	Osteochondrodysplasias		Dysostosis
	Dysplasia	Dystrophy	
Abnormality of	Growth	Structure	Structure
Site	Multiple bone/cartilage of axial/appendicular skeleton, membranous &/or enchondral bone		Individual bones singly or in combination
Failure of	Gene expression		Blastogenesis
Phenotype	May evolve throughout life		Static

*Hall CM. International nosology and classification of constitutional disorders of bone (2001). Am J Med Genet. 2002 Nov;113(1):65-77

Approach to skeletal dysplasias

Radiological

- A – Anatomical localisation
- B – Bones
- C – Complications
- D – Death or lethality

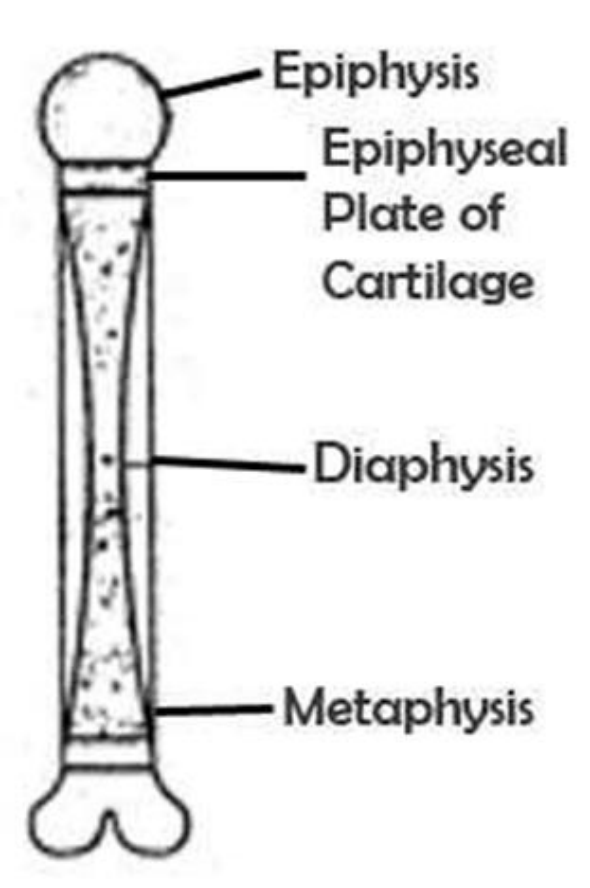
*Dutton RV. A practical radiologic approach to skeletal dysplasias in infancy. Radiol Clin North Am. 1987 Nov;25(6):1211-33

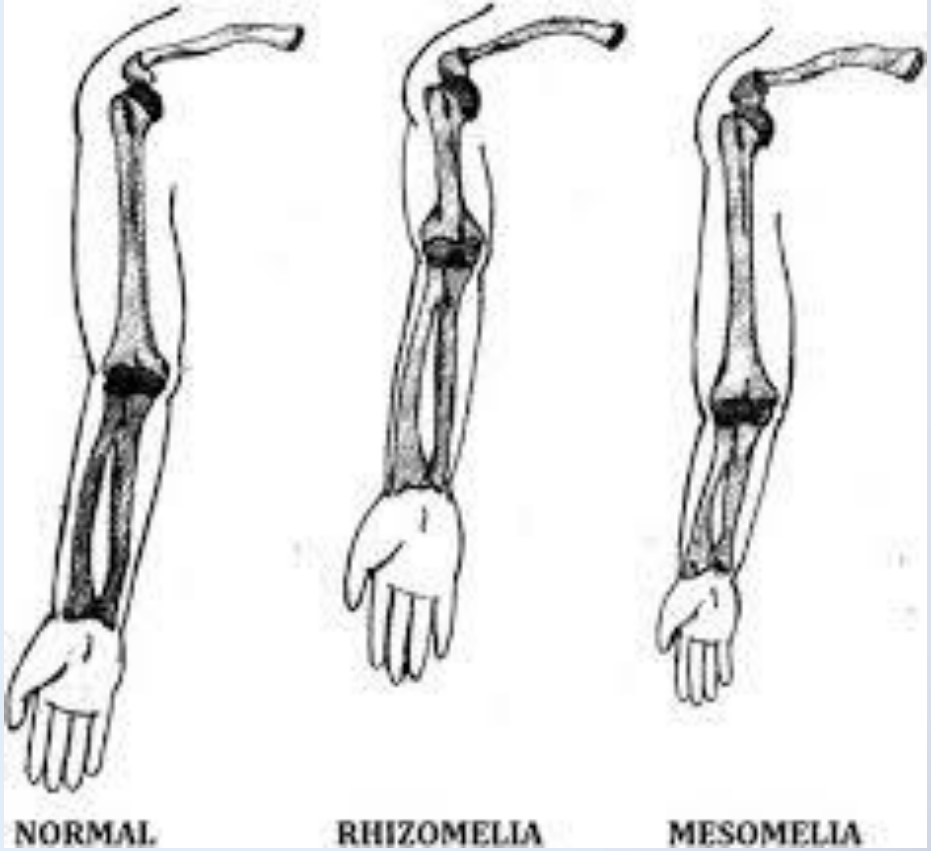
Based on Anatomical location

Axial skeleton		Appendicular skeleton	
Skull	Cranio/cranial	**Location**	Epiphyseal
Face	Facio/facial		Metaphyseal
Mandible	Mandibulo		Diaphyseal
Clavicle	Cleido		
Ribs	Costo	**Shortening**	Rhizomelic (proximal e.g. femur)
Spine	Spondylo/vertebral		Mesomelic (middle e.g. radius/ulna)
Pelvis	Ischio/ilio/pubic		Acromelic (distal- hands/feet)

*Dutton RV. A practical radiologic approach to skeletal dysplasias in infancy. Radiol Clin North Am. 1987 Nov;25(6):1211-33

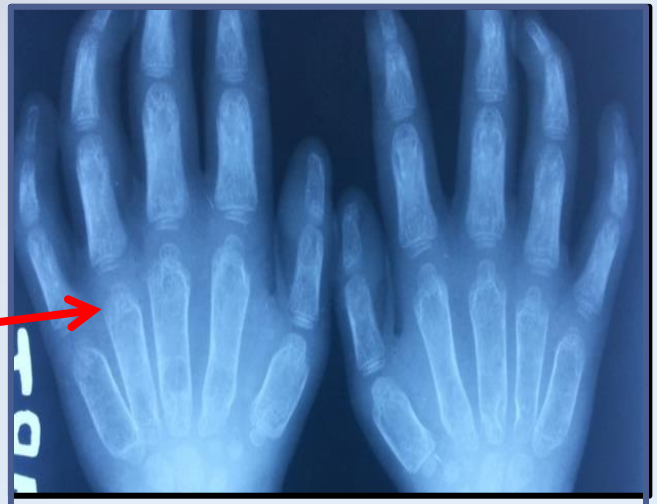
Appendicular skeleton



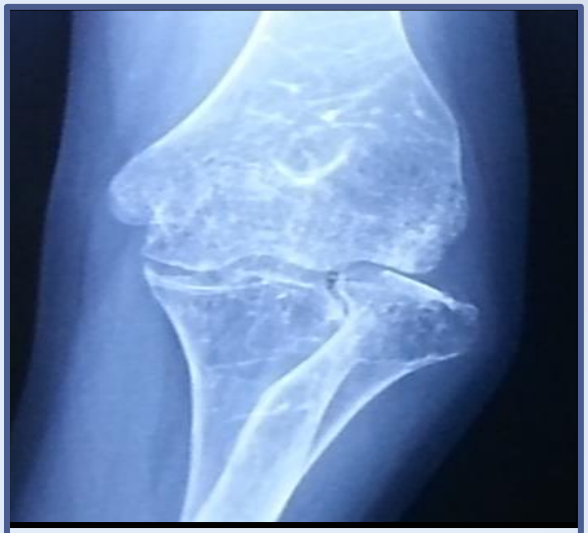


Bones

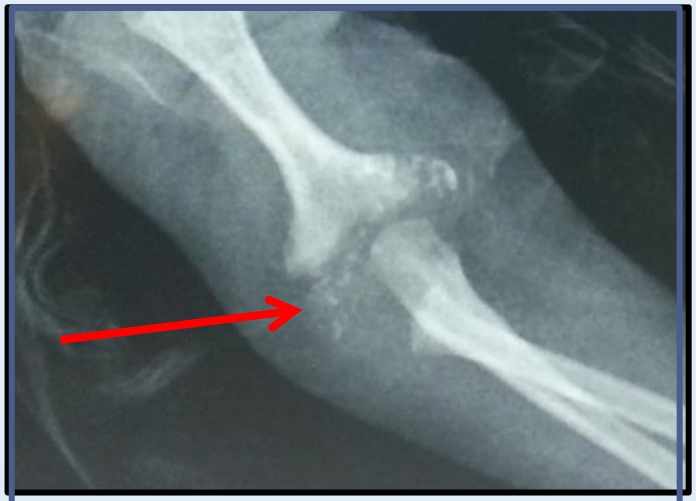
- **Structure** – abnormalities of bone density, presence of tumorous lesions
- **Shape** – whole or part of a bone
- **Size** - Absolute or relative to other bones (bone age to be considered)
- **Sum** - too many, too few or fused
- **Soft tissues** - wasting, excessive soft tissues, contractures & calcification



Bullet shaped metacarpals



Osteopenia

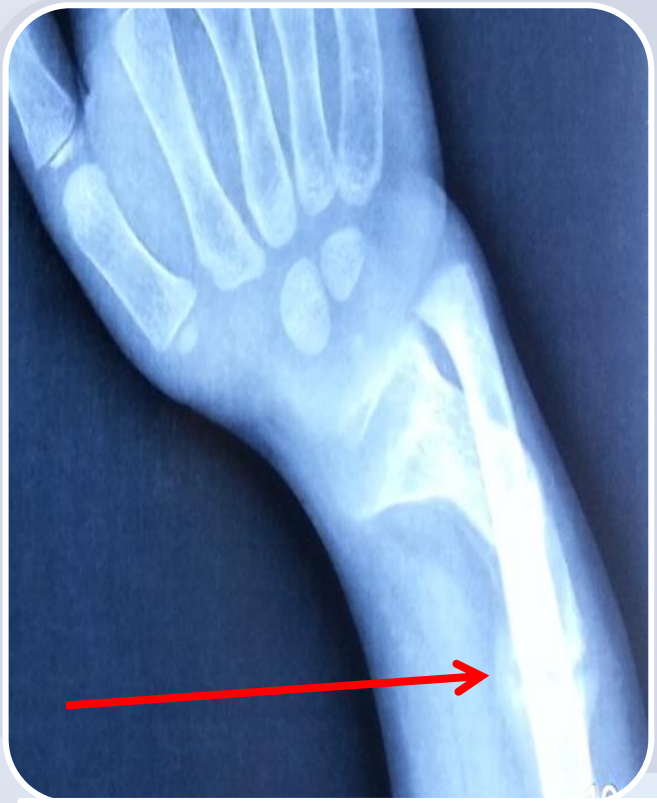


Punctate calcifications

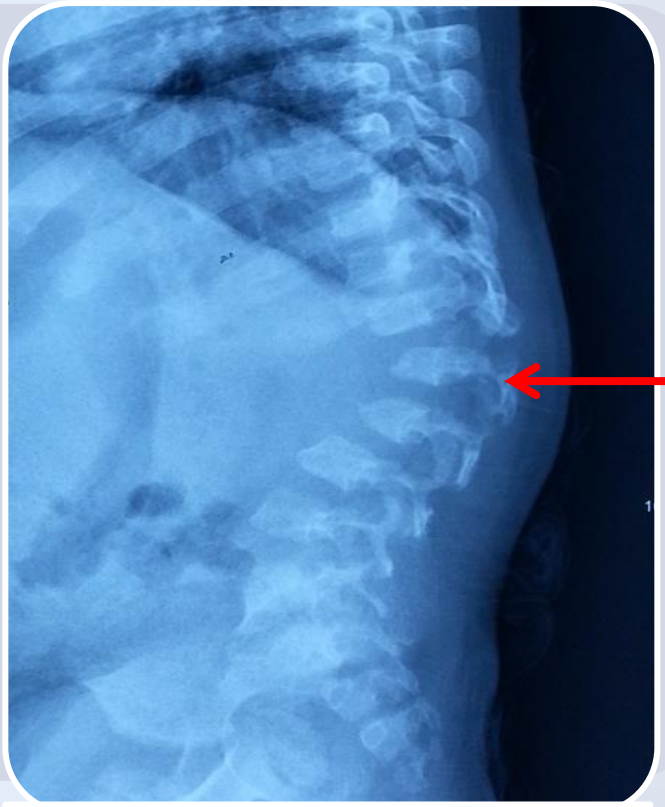
Complications

- Fractures – osteoporotic (e.g. osteogenesis imperfecta) & osteosclerotic (e.g. osteopetrosis) conditions
- Atlantoaxial subluxation – Mucopolysaccharidosis (MPS)
- Progressive scoliosis – Campomelic dysplasia
- Limb length discrepancies – Epiphyseal stippling, Dysplasia epiphysealis hemimelica, Ollier's disease, multiple cartilaginous exostoses
- Malignancy – Maffucci's syndrome

Complications



Fracture

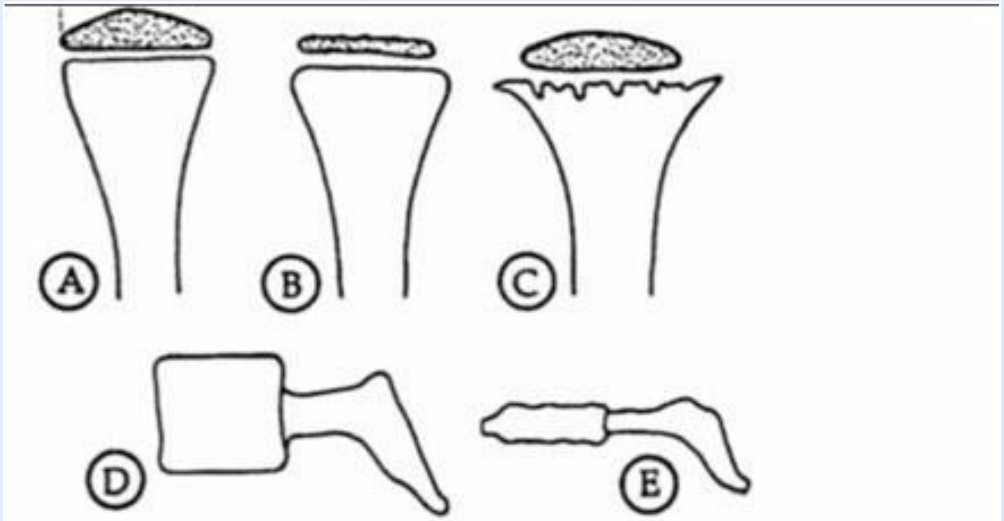


Kyphosis

Death or lethality

- If a dysplasia is lethal it helps to exclude or confirm a given diagnosis
- Helps identify subtype affected & different modes of inheritance

Radiological Classification



Involvement	Disease Category
A+D	Normal
B+D	Epiphyseal dysplasia
C+D	Metaphyseal dysplasia
B+E	Spondyloepiphyseal dysplasia
C+E	Spondylometaphyseal dysplasia
B+C+E	Spondyloepimetaphyseal dysplasia

*Alanay Y, Lachman RS. A review of the principles of radiological assessment of skeletal dysplasias. J Clin Res Pediatr Endocrinol. 2011;3(4):163-78

Genetic basis & molecular mechanisms

- Abnormalities in the patterning, development, maintenance & size of skeleton (axial/appendicular)
- Mutations in various families of genes
- The most common is Achondroplasia

caused by mutations in the FGFR3 gene

*Kornak U, Mundlos S. Genetic disorders of the skeleton: a developmental approach. Am J Hum Genet. 2003 Sep;73(3):447-74

Inheritance Pattern

- Genetically heterogeneous
- Inherited as AD, AR, XLR & XLD
- Rarely chromosomal deletions/duplications, germline mosaicism & uniparental disomy
- Intrafamilial & interfamilial variability

Molecular Pathogenetic Classification

Superti-furga et al grouped molecular defects of skeleton as

- Group 1: Extracellular structural proteins
- Group 2: Metabolic pathways (including enzymes, ion channels, transporters)
- Group 3: Folding, processing & degradation of macromolecules
- Group 4: Hormones & signal transduction mechanisms
- Group 5: Nuclear proteins & transcription factors
- Group 6: Oncogenes & tumour suppressor genes
- Group 7: RNA/DNA processing & metabolism

*Superti-Furga A, Bonafé L, Rimoin DL. Molecular-pathogenetic classification of genetic disorders of the skeleton. Am J Med Genet. 2001;106(4):282-93

Prenatal diagnosis

- Meticulous sonographic examination - thanatophoric dysplasia & osteogenesis imperfecta
- Previously affected child with a molecularly confirmed diagnosis - molecular analysis of DNA (CVS/Amniocentesis)→ direct mutational analysis/ linkage analysis

Prevalence

- Orioli et al (1978 -83) crude prevalence rate -2.3/10000
- Gustavson & Jorulf- 4.7/10 000
- Camera & Mastroiacovo - 2.4/10 000
- Barbosa-Buck, Orioli et al (2012) - 3.2 per 10,000
- **Kulkarni et al - 19.6/10,000 live born & lethal dysplasias- 5.2/10,000 deliveries**

*Orioli IM, Castilla EE, Barbosa-Neto JG. The birth prevalence rates for the skeletal dysplasias. J Med Genet. 1986 Aug;23(4):328-32

*Gustavson K-H, Jorulf H. Different types of osteochondrodysplasia in a consecutive series of newborns. Helv Paediatr Acta.1975;30:307-14

*Barbosa-Buck CO, Orioli IM, da Graça Dutra M, Lopez-Camelo J, Castilla EE, Cavalcanti DP. Clinical epidemiology of skeletal dysplasias in South America. Am J Med Genet A. 2012 May;158A(5):1038-45

*Kulkarni ML, Samuel K, Bhagyavathi M, Sureshkumar C. Skeletal dysplasias in a hospital in Southern India. Indian Pediatr. 1995 Jun;32(6):657-65

Aims & Objectives

- To study the clinico-radiological spectrum of skeletal dysplasias in children

- To establish a molecular diagnosis wherever possible

Materials and methods

- 51 children with disproportionate short stature or skeletal deformities included (0-18 years of age)
- Cross-sectional study
- Lok Nayak Hospital, New Delhi, India (March 2013-14)
- Pediatric/orthopedic OPD, genetic clinic & admissions in pediatric/orthopaedic wards

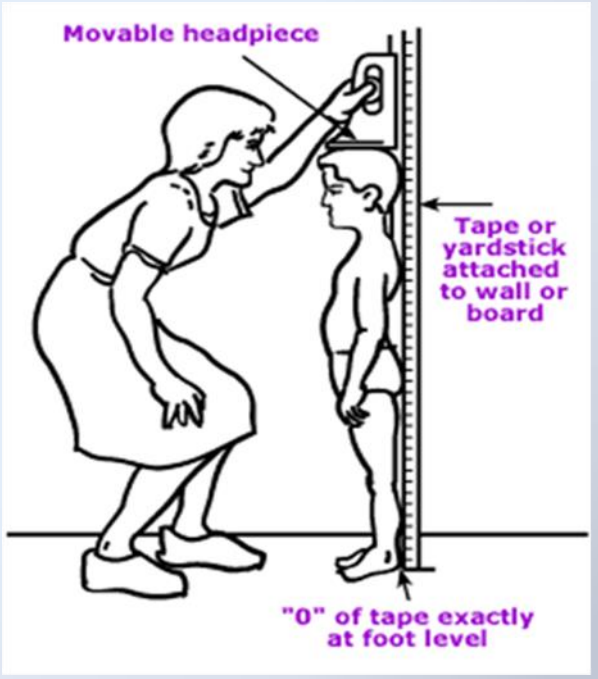
Methodology

- ✓ Detailed **history taking** with special emphasis on
  - Age of noticing the problem
  - Family history – 3 generation pedigree chart & h/o consanguinity
  - Maternal antenatal history & review of ultrasounds (current & previous pregnancies)
  - Developmental history
- ✓ Detailed head to toe examination including dysmorphology assessment

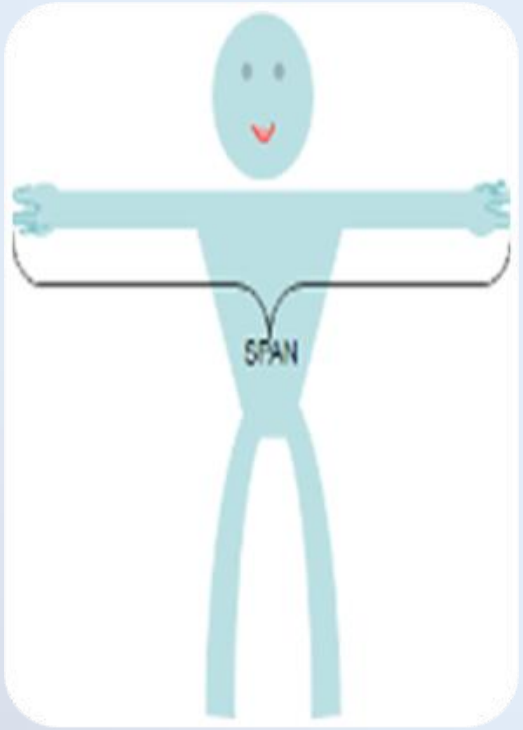
Anthropometry

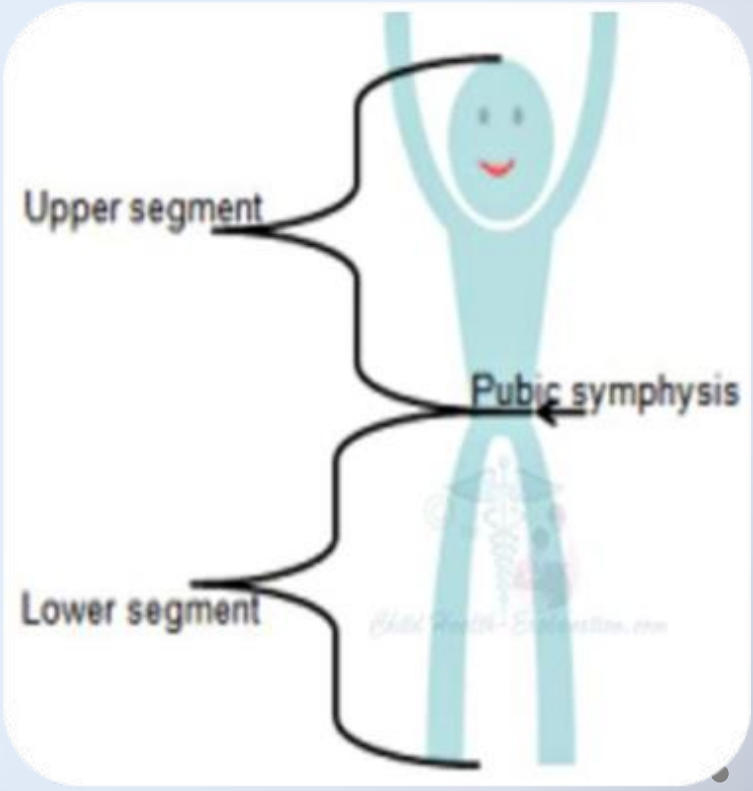
The Anthropometric data were collected as follows-

- **Height** – using stadiometer with head in Frankfurt plane (3 readings)
- **Length** – < 2 years & those who could not stand, recumbent stature using an infantometer or using a non-stretchable flexible tape



- **Armspan –** distance btw the tips of middle fingers with both arms outstretched
- **Upper Segment: Lower Segment Ratio(US:LS)** – LS measured from the symphysis pubis to the heel & US derived by deducting the LS from height



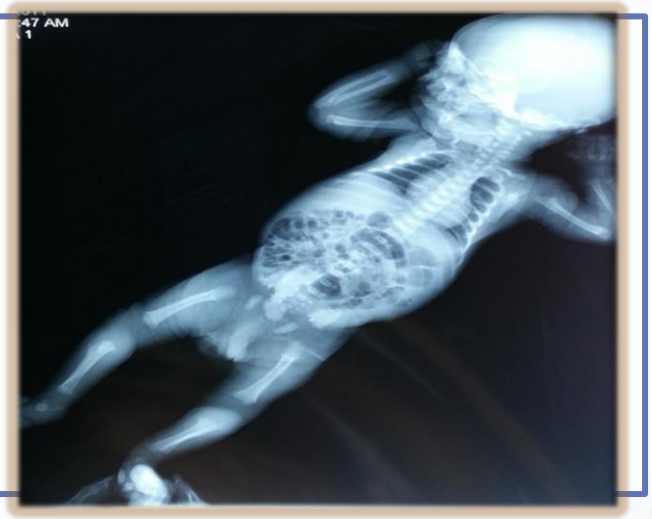


Radiological Survey

Standard skeletal survey

- Skull – AP & Lateral
- Chest PA/AP view
- Dorso lumbar spine – AP & Lateral
- Pelvis AP including both femora
- Long bones including wrist & feet

Infantogram



Radiological Classification

The radiological abnormalities involving -

- The epiphysis, metaphyses or diaphysis
- The spine
- Multiple areas – spondylometaphyseal/ epimetaphyseal

Radiographs

Epiphyseal dysplasia

Metaphyseal dysplasia

Spondylo-dysplasia

Radiological Diagnosis

Discussed with senior radiologist having special interest in skeletal dysplasias & also utilizing databases

- POSSUM web base
- London Dysmorphology database
- Spranger's text book of skeletal dysplasia
- European skeletal dysplasia registry

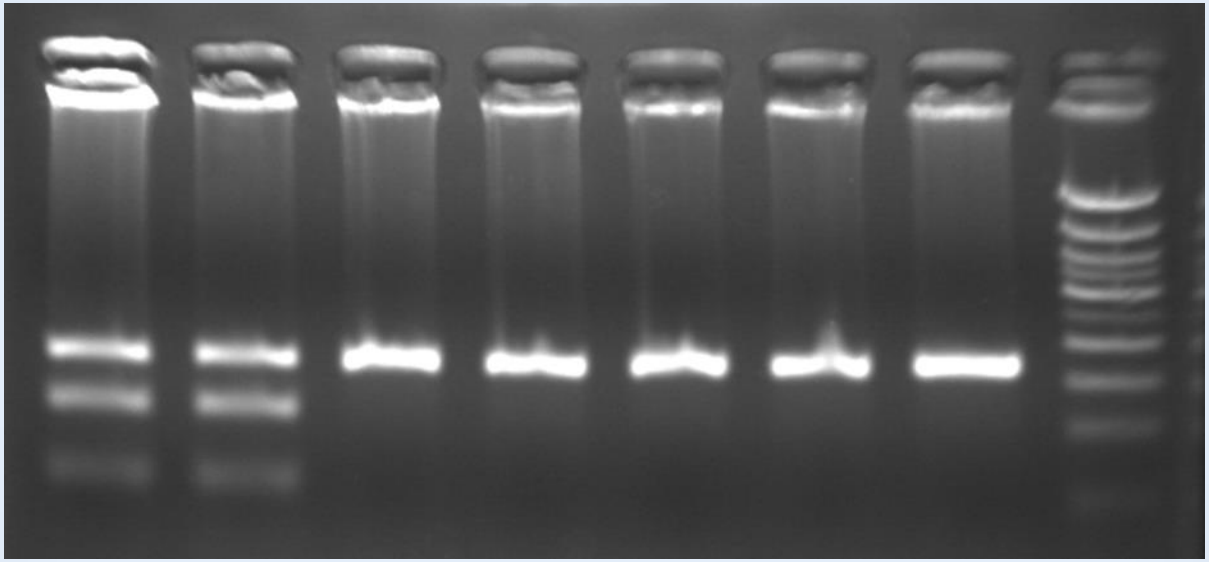
Ancillary Investigations

- Mucopolysaccharidosis → urinary testing for glycosaminoglycans & enzyme analysis for typification
- Serum Calcium, Phosphorus, Alkaline Phosphatase, Vitamin D3 levels
- Thyroid profile

Molecular Diagnosis

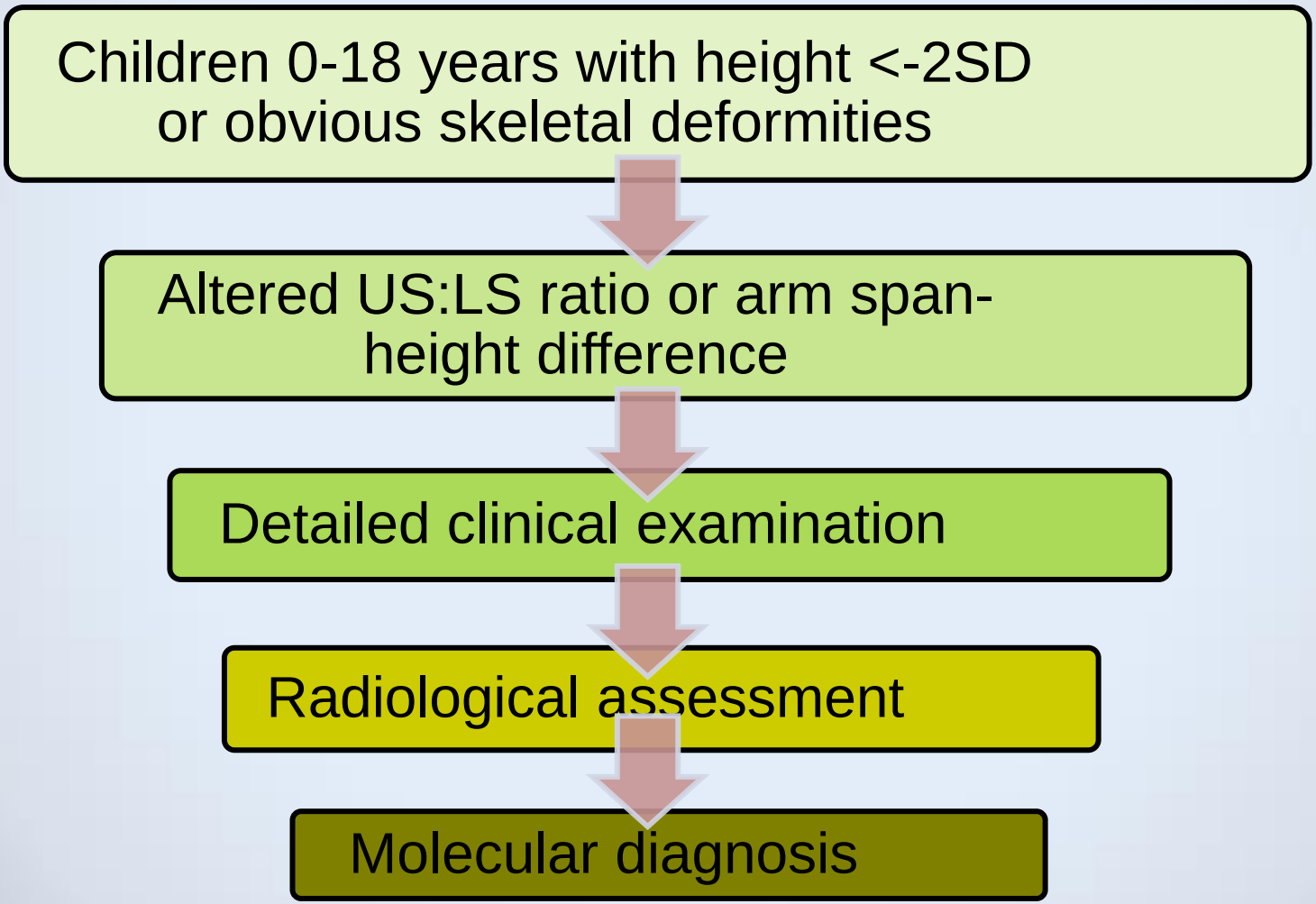
- Achondroplasia & Hypochondroplasia → PCR for mutations at FGFR codons 380 & 540 respectively
- Other genetic diagnosis→ samples sent to researchers & collaborators engaged in delineating the particular skeletal dysplasia

Molecular Diagnosis

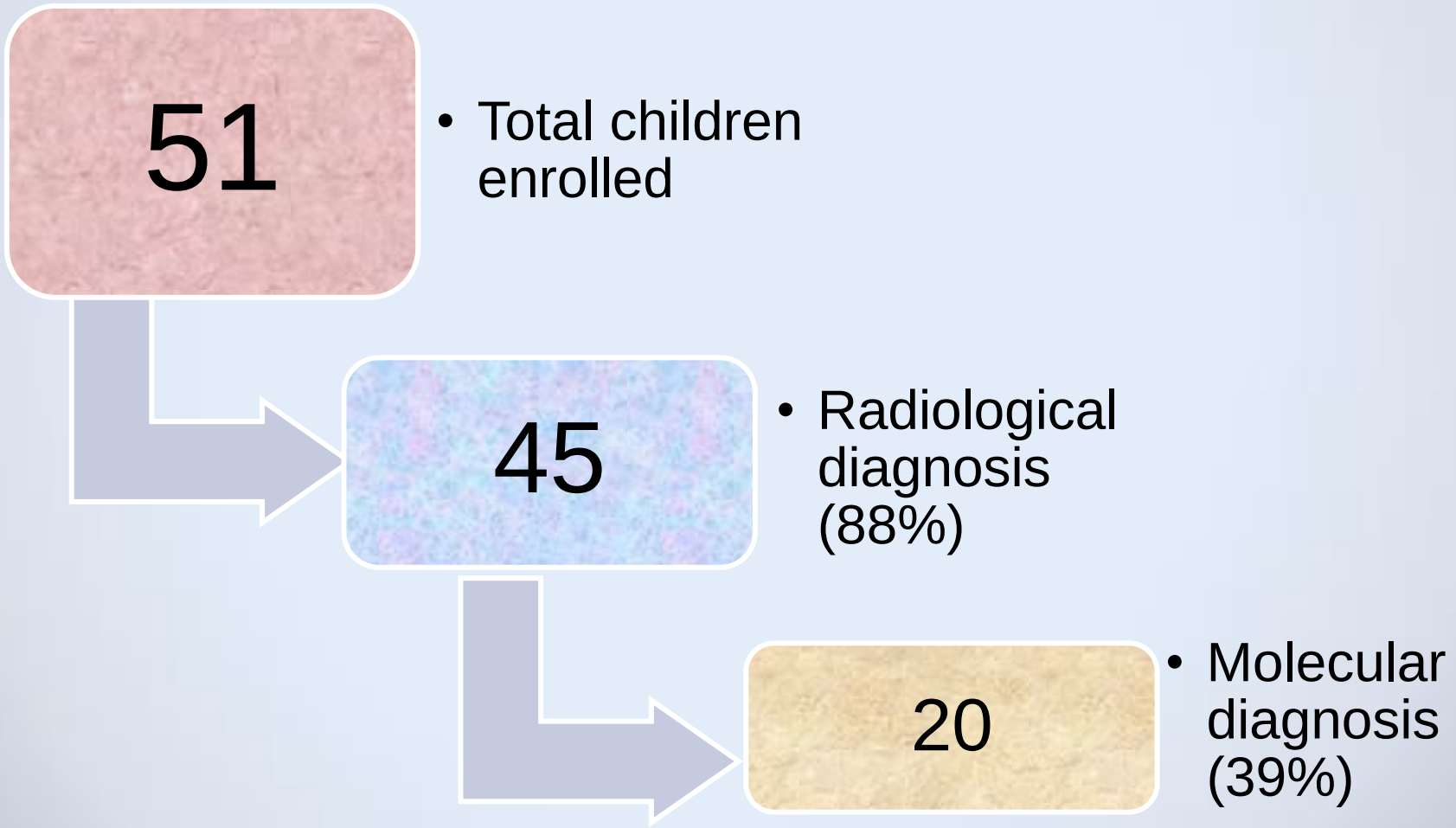


PCR-RFLP of achondroplasia patients
(164bp→154bp & 55bp) and controls

Algorithm

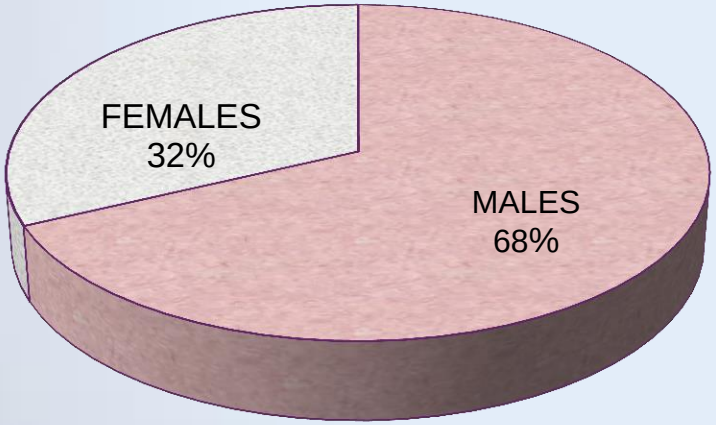

Children 0-18 years with height <-2SD
or obvious skeletal deformities
Altered US:LS ratio or arm span-
height difference
Detailed clinical examination
Radiological assessment
Molecular diagnosis

Results

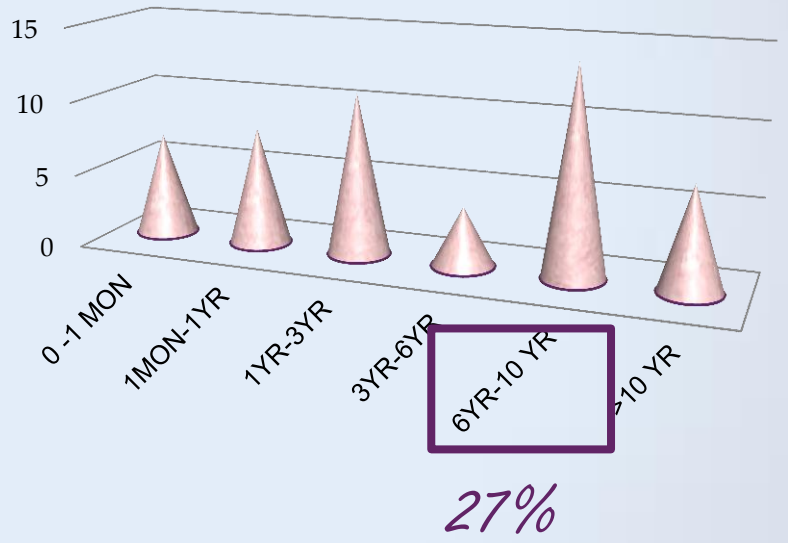

51
Total children enrolled
45
Radiological diagnosis (88%)
20
Molecular diagnosis (39%)

Results

Sex distribution

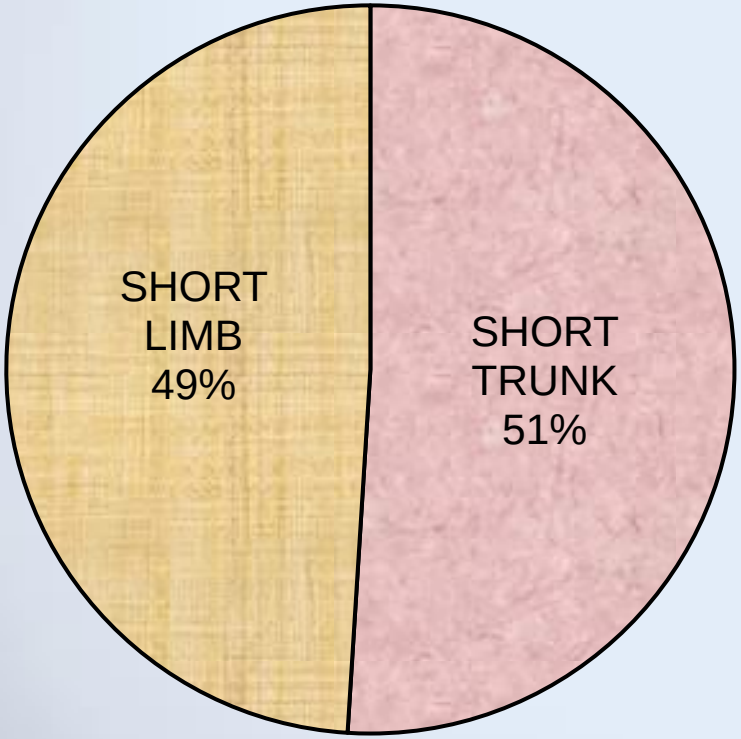


Age distribution

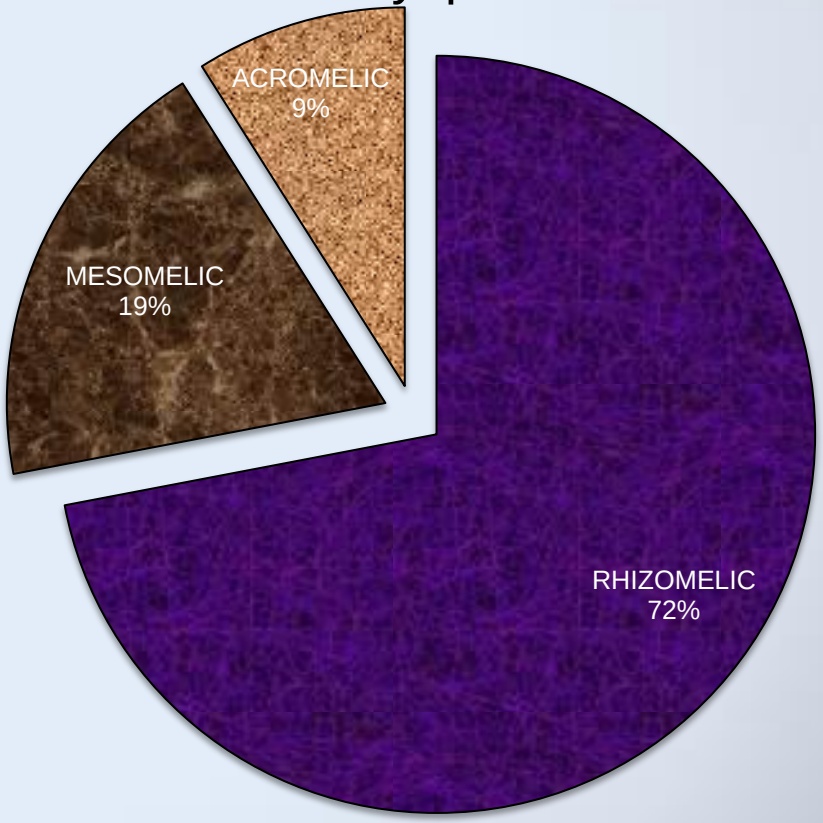


Results

SKELETAL DYSPLASIA



Short limb dysplasia



Clinical details

- Parental consanguinity was present in 23.5% of skeletal dysplasias
- Abnormal antenatal ultrasonography was found in 3 cases
- 2 pairs of siblings included- MPS type IV A & Desbuquois dysplasia

Clinico radiological classification

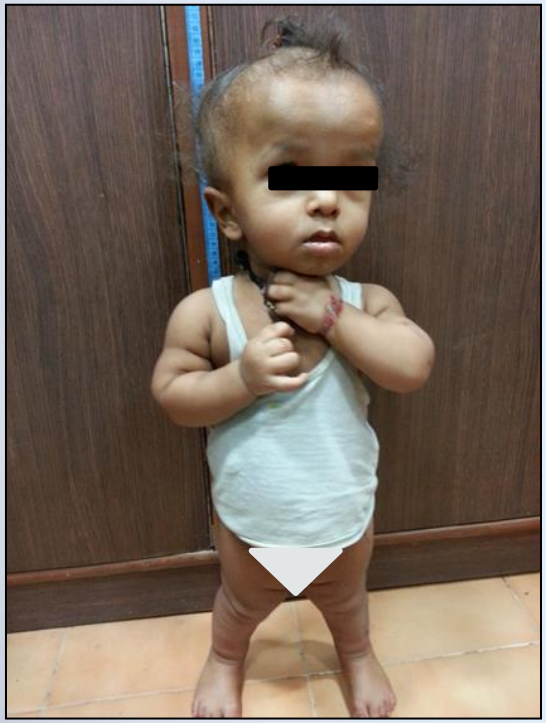
Sl no.	Group	Type	Number
I	Lethal Osteochondrodysplasias	Atelosteogenesis	1
II	Chondrodysplasia Punctata Group	Chondrodysplasia punctata, rhizomelic type	1
III	Predominant Metaphyseal involvement	Achondroplasia	8
		Hypochondroplasia	1
		Asphyxiating thoracodystrophy	1
		Cartilage -Hair- Hypoplasia	1
IV	Predominant Epiphyseal involvement	Pseudoachondroplasia	2

Sl no.	Group	Type	Number
V	Major involvement of the Spine	Spondylocostal dysplasia	1
		Kniest dysplasia	1
		Metatropic Dysplasia	1
		Diastrophic Dysplasia	1
		Dyggve-Melchoir-Clausen Syndrome	1
		Spondyloepiphyseal dysplasia	1
		Spondyloepimetaphyseal dysplasia	1
		Spondylothoracic dysostosis	1
VI	With Multiple Dislocations	Desbuquois dysplasia-Kim type	3
VII	Dysostosis Multiplex Complex	MPS type I	4
	Carbohydrate Storage Diseases	MPS type IV A	7
		MPS type IV B	1

Sl no.	Group	Type	Number
VIII	Predominant involvement of single sites or Segments	Rhizomelic dysplasia- Patterson Lowry type Acromesomelic Dysplasia - Maroteaux type	1 1
IX	Predominant Diaphyseal involvement		none
X	Decreased bone density	Osteogenesis imperfecta	1
XI	Increased bone density	Bent bone disease	1
XII	Disorganised development of bone constituents		none
XIII	Osteolyses		none

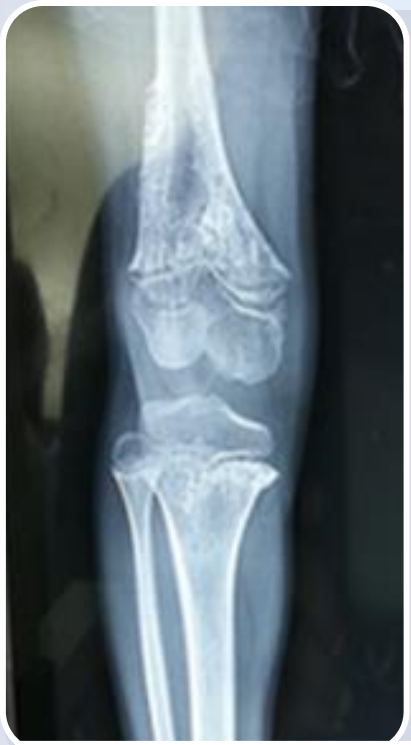
*Spranger's textbook of skeletal dysplasias

Achondroplasia

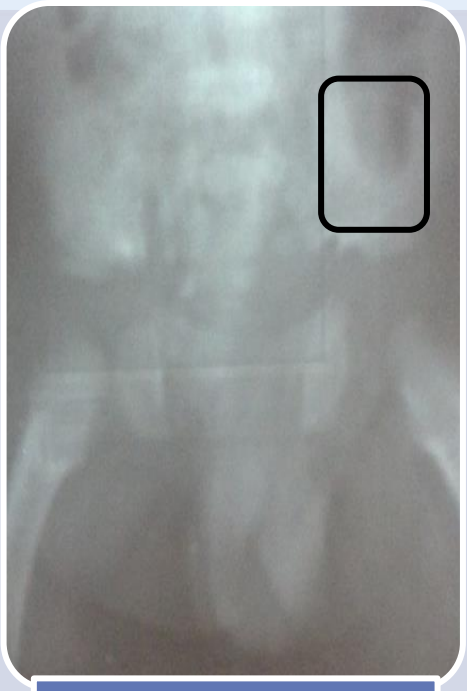


Clinical features
Rhizomelic micromelia
Disproportionately large head
Depressed nasal bridge
Trident hand with short stubby fingers

Achondroplasia

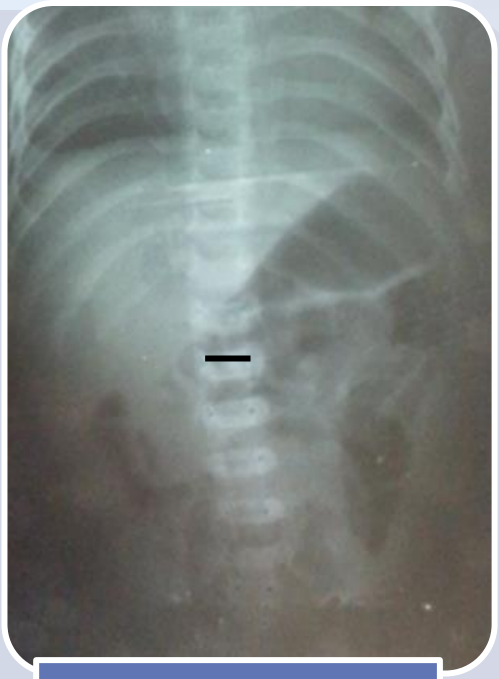


Irregular metaphysis



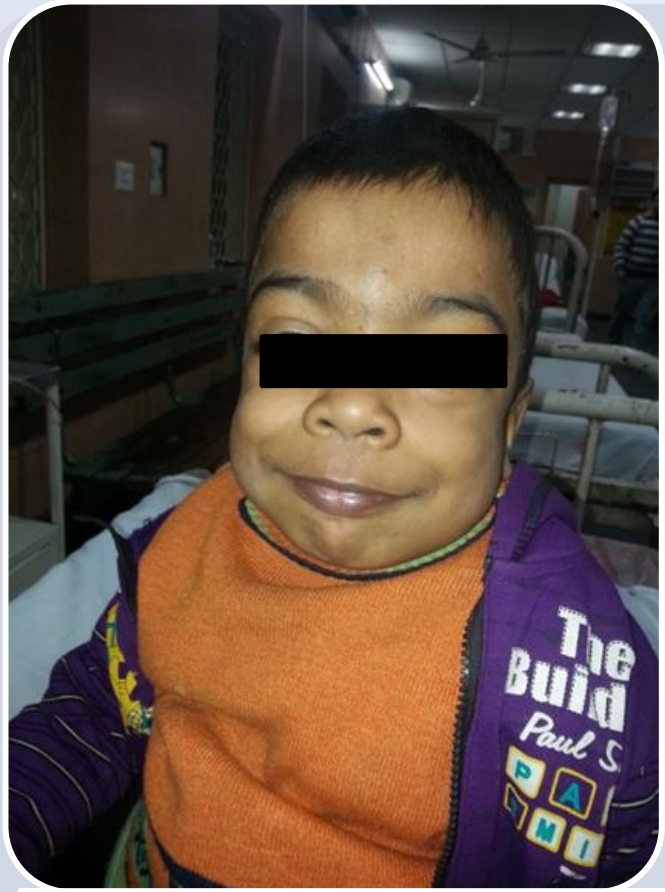
Squared ilia

Horizontal acetabular margins

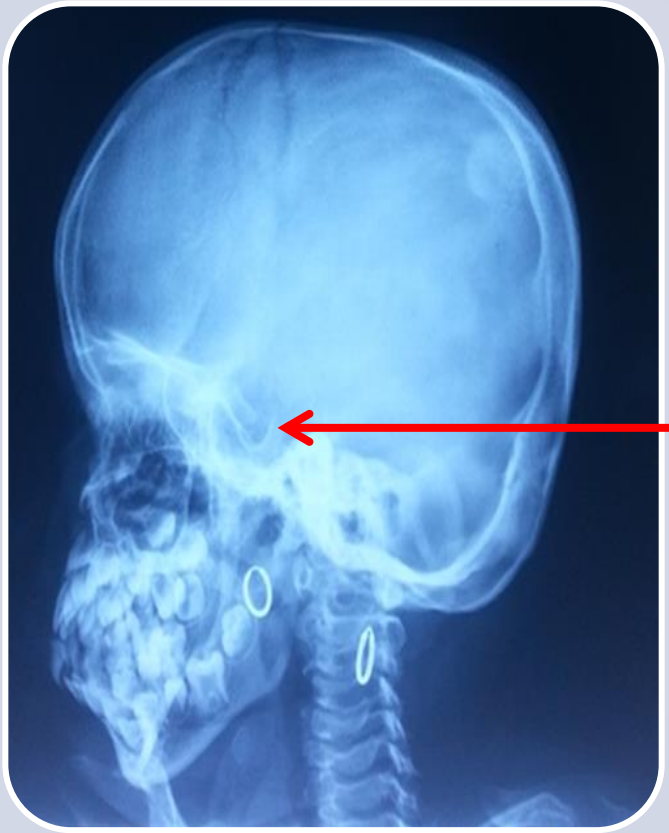


Progressive decrease in interpedicular distance

Mucopolysachharidosis

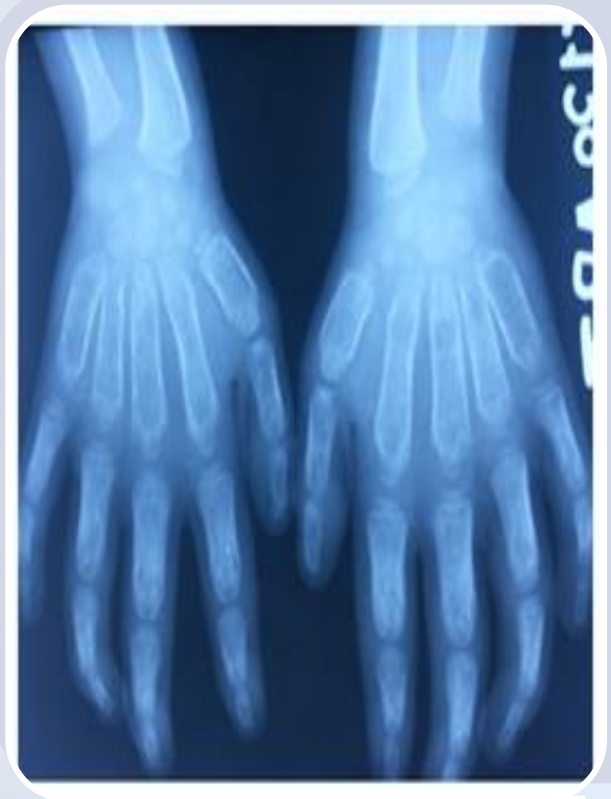


Coarse facies

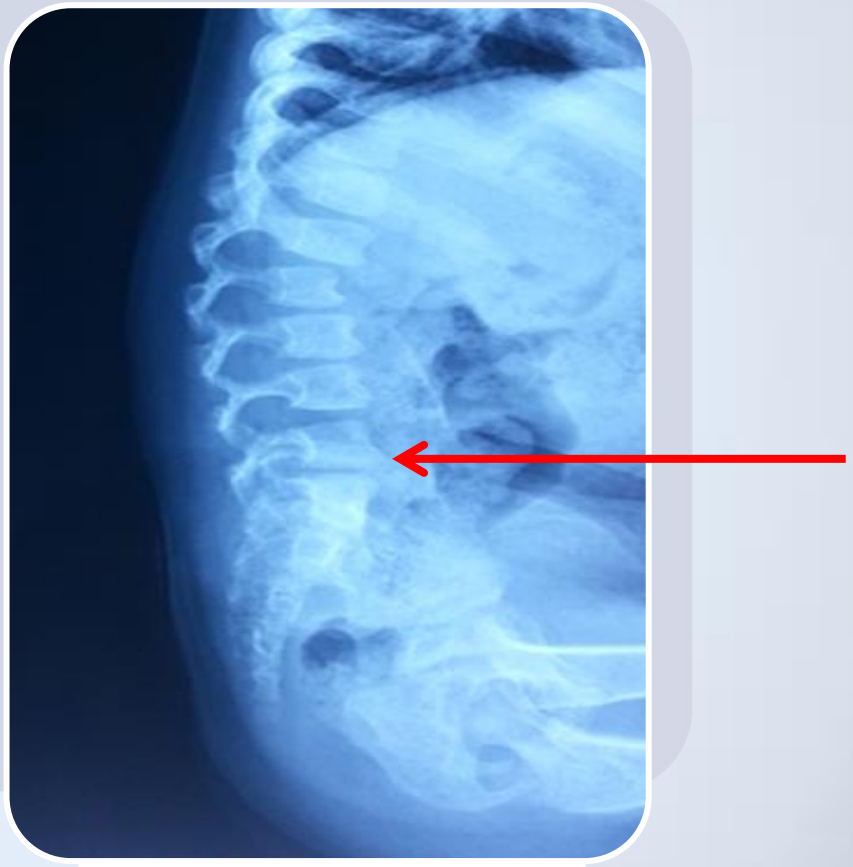


J shaped sella

Mucopolysachharidosis

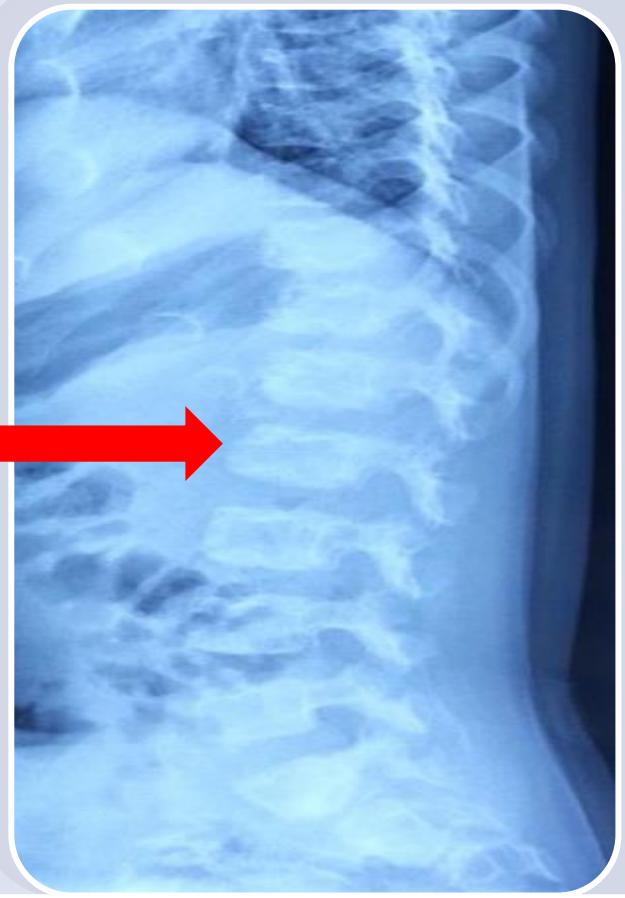


Bullet shaped metacarpals

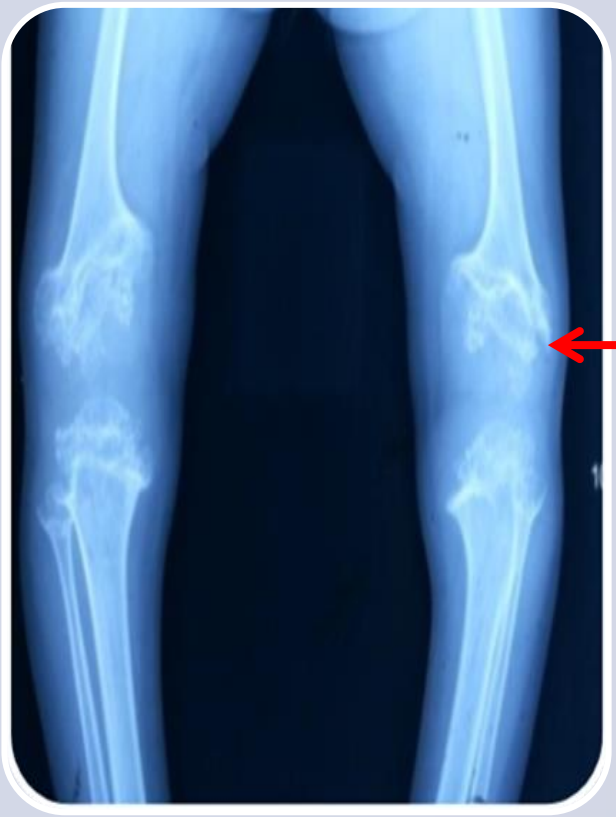


Inferior beaking

Pseudoachondroplasia

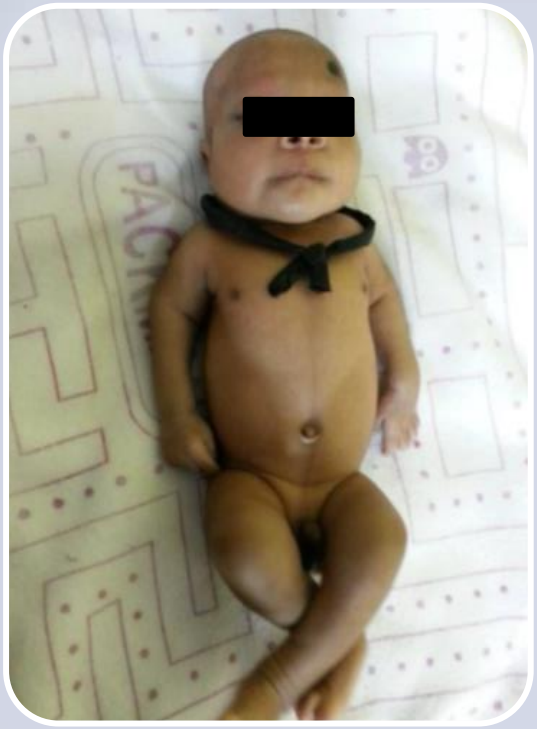


Irregularity in vertebral plates



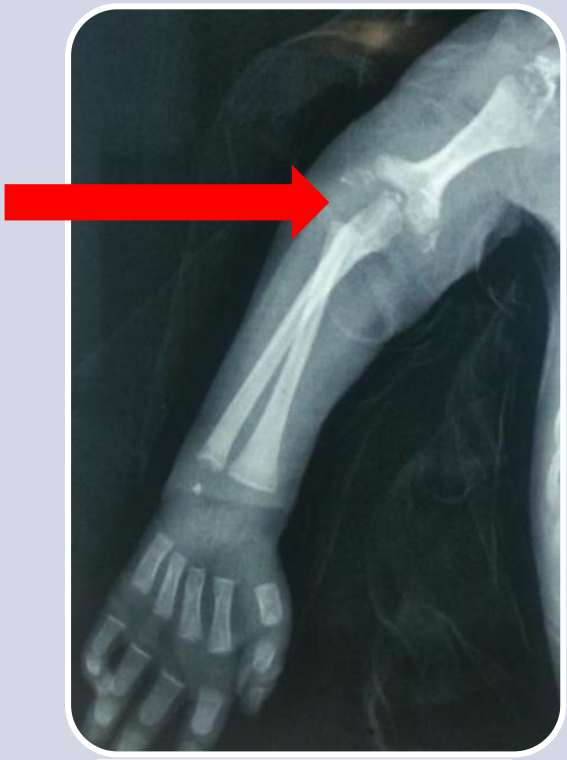
Irregular epiphysis

Rhizomelic Chondrodysplasia Punctata

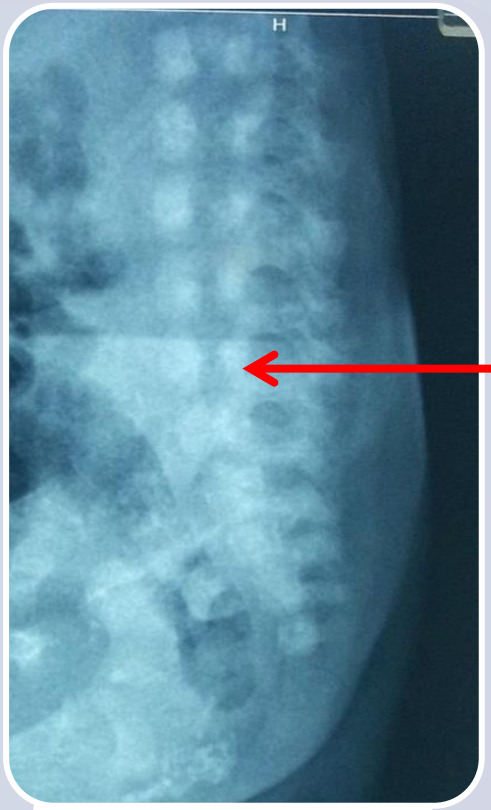


Rhizomelia

anteverted nares
midfacial hypoplasia



Punctate calcification



Coronal clefting of vertebrae

Molecular Diagnosis

Diagnosis	Type	Number	Mutation
Achondroplasia	Short limb	8	FGFR3 G-->A 1138 transition
Hypochondroplasia	Short limb	1	FGFR3 c1620C-->A heterozygous mutation
Pseudoachondroplasia	Short limb	2	c.1554C>G;p.D518E
Mps Type IV A (Morquio)	Short trunk	2	c.155C>T in exon 2 of the GALNS
		1	[c.3G>A;p.Met1] [c.452C>T;p.P151L]
Desbuquois Dysplasia - kim type	Short limb	3	c.C467T p.Ser156Ph
Cartilage Hair Hypoplasia	Short limb	1	g.69dupG,r69dupG
Dyggve-Melchoir-Clausen Dysplasia	Short trunk	1	DYM_v001):c.1923del deletion
Rhizomelic Chondrodysplasia Punctata	Short limb	1	PEX7 mutation in the L292X allele

Conclusion

- Clinical examination & radiological assessment are sufficient to diagnose a majority of cases
- If a diagnosis made, prognosis can be explained in terms of expected complications, final adult height, intelligence & also for genetic counselling
- Emphasis on early diagnosis to prevent complications
- No definitive treatment → focus on prenatal diagnosis by ultrasonography & molecular methods

Conclusion

- Males were significantly higher probably due to gender bias in seeking medical attention
- Maximum cases belonged to the age group of 6- 10 years
  - Height compared with that of the peers
  - Home deliveries accounting for not seeking medical attention
- Limitations
  - Hospital based study
  - Still births not included

Future prospects

- Larger studies in community including still births are necessary to establish the true prevalence & spectrum of skeletal dysplasia
- Studies including cases diagnosed antenatally are essential to highlight the importance of prenatal diagnosis

Acknowledgements

- Departments of Pediatrics, Radiology & Orthopedics, Maulana Azad Medical College, New Delhi, India
- Department of Pediatrics, Indira Gandhi Institute of Child Health, Bangalore, India
- Organizers


Heck, yes I'm short.
God only lets things
grow until
they are
Perfect
some of us
didn't take as
long as others!

Thank you