

Skeletal and Limb Syndromes

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Outline

- Epidemiology and phenotypic spectrum
- 2023 Revision of the International Nosology of genetic skeletal disorders
- Diagnostic approach
- Diagnostic radiological signs
- Skeletal dysplasia families
- Limb anomalies and syndromes
- Quiz

Epidemiology and Phenotypic Spectrum

- Incidence 1 in 5000 live births
- Variable age at onset
 - Lethal → Early onset → Late onset → Asymptomatic
- Broad and diverse phenotypic spectrum
- Affect bone, cartilage and other connective tissues
- Pleiotropic gene effects on other organs
- Significant burden of morbidity
 - Chronic pain
 - Impaired mobility
 - Reduced QoL
 - Reduced life expectancy

- Achondroplasia
- Hypochondroplasia
- Stickler syndrome
- SEDC
- OI
- MED

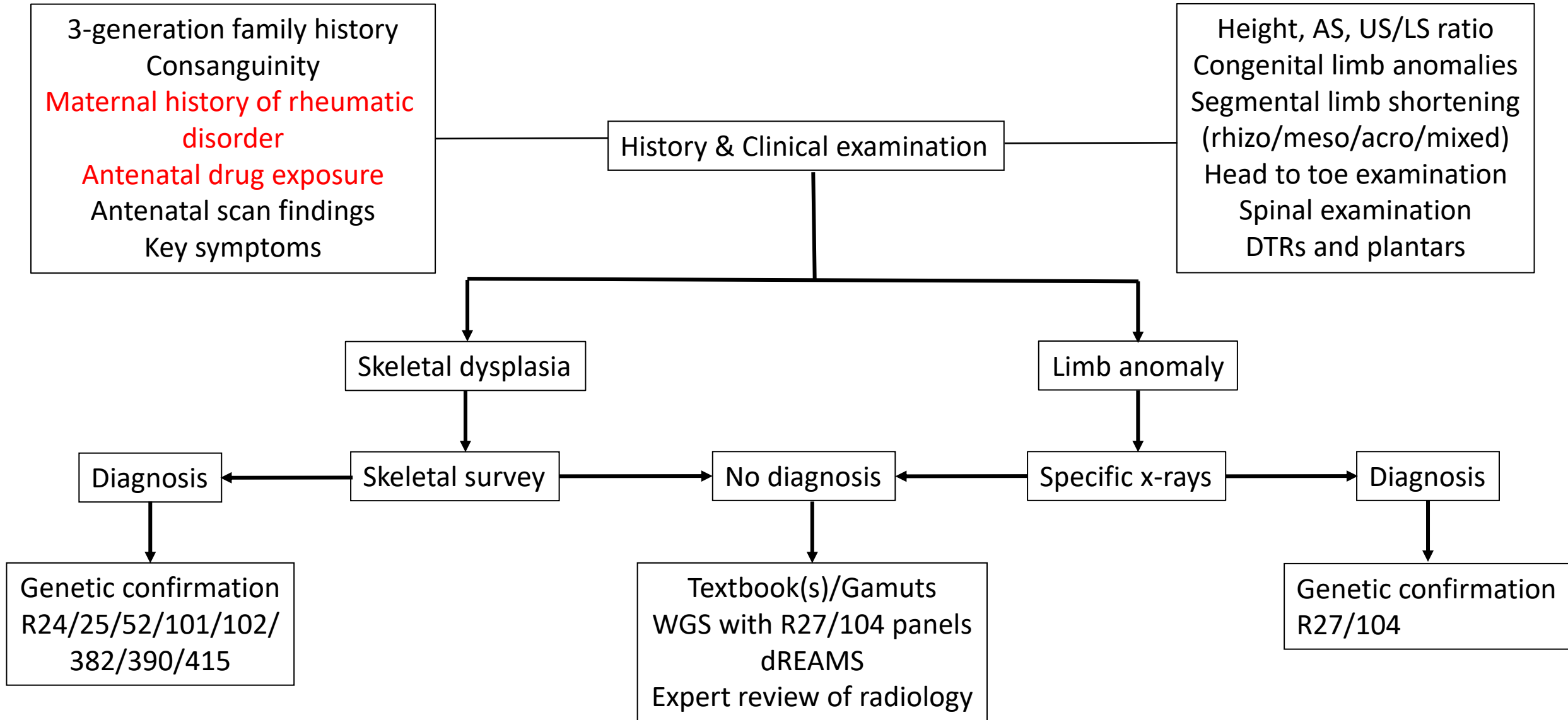
International Nosology

- Revised 2023
- 41 diagnostic groups (771 conditions; 552 genes)
- 5 gene-based groups (FGFR3 chondrodysplasias)
- 7 mechanism-based groups (sulphation disorders)
- 9 groups based on clinical features (dysplasias with multiple joint dislocations)
- 20 groups based on radiological features (metaphyseal dysplasias)
- Useful for differential diagnosis, delineation of new syndromes, research, and registeries

Clinical Clues to Skeletal Disorders

- Congenital limb anomalies
- Proportionate or disproportionate short stature
- Pathological fractures
- Cranial nerve palsies
- Non-inflammatory joint pain
- Limb deformities and bowing
- Limb asymmetry and bony lumps
- Severe (and early-onset) kyphoscoliosis
- Decreased or increased joint mobility
- Multiple joint dislocations
- Abnormal gait

Diagnostic Approach to Skeletal Disorders



Radiological Assessment

Skeletal Survey (before skeletal maturation)

1. Skull: Lateral view
2. ***Spine (T1-L5)***: AP and ***Lateral*** views
3. Chest (including shoulders)
4. ***Pelvis/Hips***
5. One Leg (including knee and ankle): AP view
6. One Forearm: AP view
7. ***Hands/Wrists (on one film)***: ***PA view***
8. Feet (only if CDP suspected)

- Skull
- Clavicles
- Ribs
- Long bones
- Short long bones
- **Carpus/tarsus**
- Pelvis
- Spine
- **Bone mineralisation**
- **Unusual calcification**
- **Specific skeletal features**

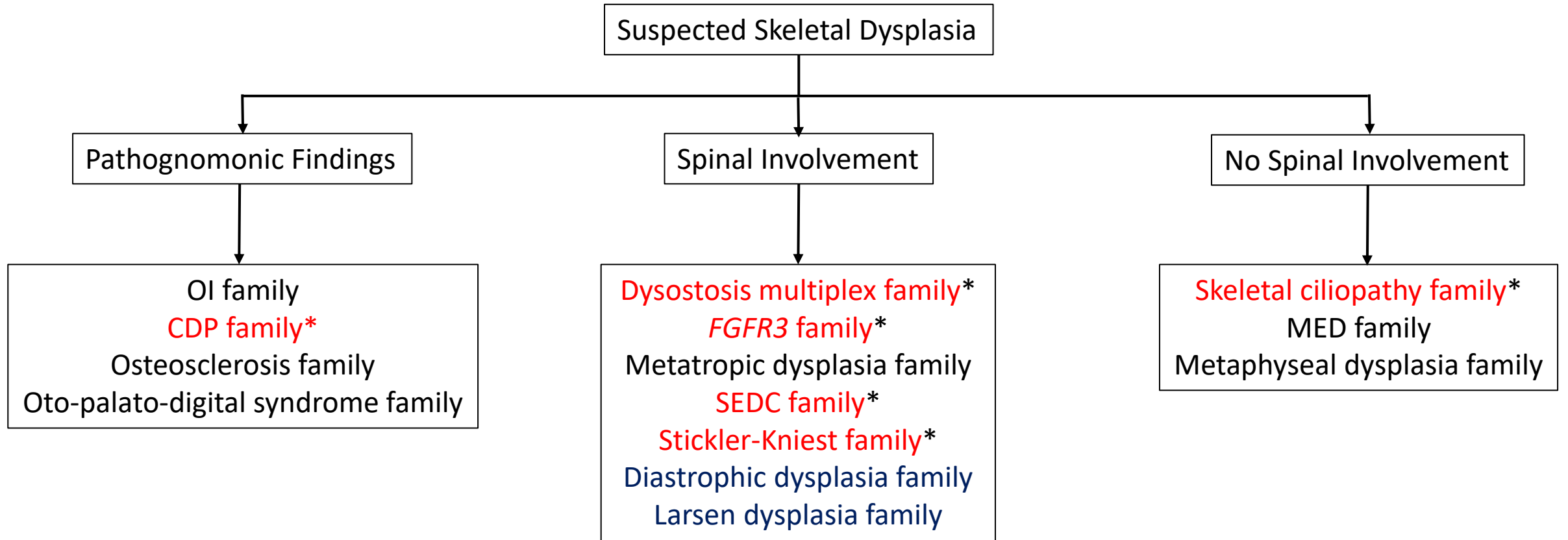
Generalised

- ED
- SED
- SEMD
- MD
- Spinal
- Reduced mineralisation
- Sclerosing
- “Weird”

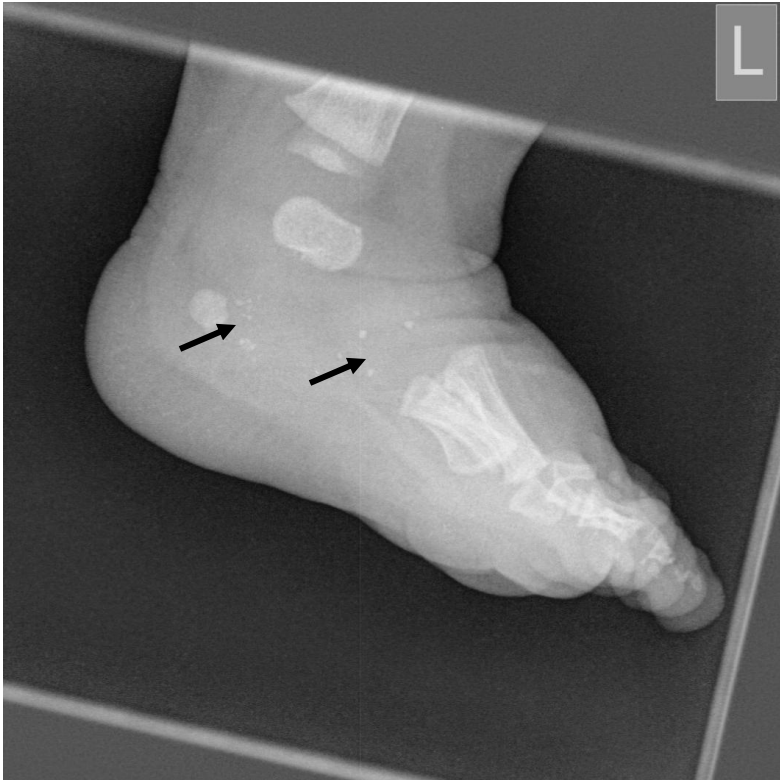
Localised

- Brachydactyly
- Limb reduction defect(s)
- Ectrodactyly
- Polysyndactyly

Skeletal Dysplasia Families

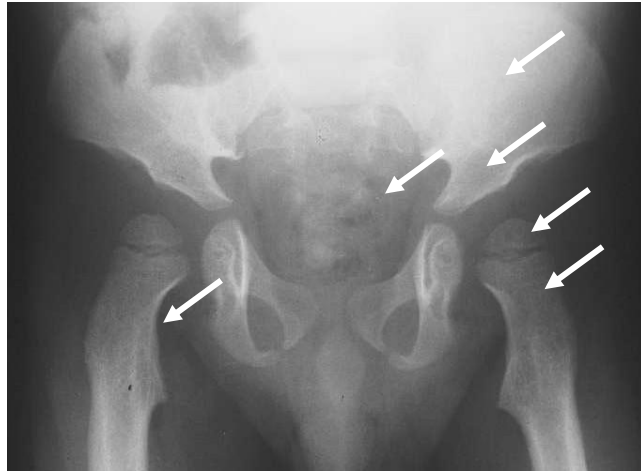


CDP Family



- Conradi-Hunermann syndrome
- Rhizomelic CDP
- Brachytelephalangic CDP
- Phenocopies
 - Warfarin embryopathy
 - Maternal rheumatic illness

Dysostosis Multiplex Family



- Mucopolysaccharidoses
- Mucolipidoses



FGFR3 Family



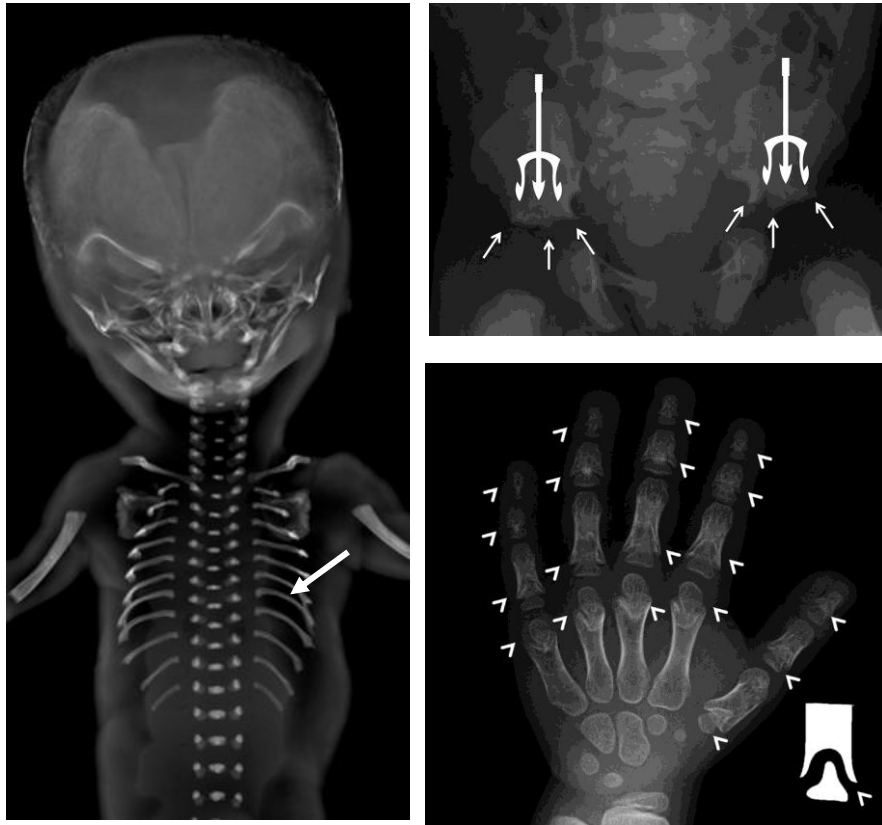
- Thanatophoric dysplasia 1
- Thanatophoric dysplasia 2
- Homozygous achondroplasia
- Severe achondroplasia, developmental delay, and acanthosis nigricans (SADDAN)
- Achondroplasia
- Hypochondroplasia

SEDC-Kniest-Stickler Family



- Achondrogenesis type 2 (type 2=COL2A1)
- Hypochondrogenesis
- SEDC
- SEMD type Strudwick
- Kniest dysplasia
- Stickler syndrome

Skeletal Ciliopathies



Handa A, et al. *Jpn J Radiol* 2020

- Ellis-van Creveld syndrome
- Jeune asphyxiating thoracic dystrophy
- Sensenbrenner syndrome
- Short-rib polydactyly syndromes

Other Selected Skeletal Dysplasias

- Cleidocranial dysplasia
- Campomelic dysplasia

Limb Anomaly Groups in 2023 Nosology

- Group 18: Isolated brachydactyly
 - Brachydactyly Type C*
- Group 19: Syndromic brachydactyly
 - Syndromes with brachydactyly and hyperphalangy*
 - Tricho-rhino-phalangeal syndrome (TRPS) *
 - Langer-Giedion syndrome *
- Group 38: Limb hypoplasia – reduction defects
 - Cornelia de Lange syndrome (CdLS)
- Group 39: Split hand/foot with or without other manifestation
 - Ectrodactyly-Ectodermal dysplasia-Clefting (EEC) syndrome
- Group 40: Polydactyly – Syndactyly – Triphalangism group
 - Townes-Brocks syndrome

Conclusions

- Skeletal disorders are individually rare but collectively quite common
- Diagnosis requires an amalgamation of clinical and radiological features
- A ‘family’ based approach can help with radiological diagnosis of skeletal dysplasias
- Accurate diagnosis is essential for appropriate management, providing genetic advice and accessing targeted treatments