Skeletal Dysplasia Need-to-Knows

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Fundamentals of Skeletal Dysplasias (Osteochondrodysplasias)

Bone Development

- Bones develop in 2 ways:
  - Direct - Membranous ossification
    - Mesenchymal cells \( \rightarrow \) osteoblasts \( \rightarrow \) bone
    - Flat bones of skull, pelvis, terminal aspects of clavicles
  - Indirect - Endochondral ossification
    - Mesenchymal cells \( \rightarrow \) chondrocytes \( \rightarrow \) cartilage \( \rightarrow \) bone
    - Most mammalian bones

Human Bones

- 206 bones
  - 126 appendicular
  - 74 axial
  - 6 cranial

Disorders of Bones

- Molecular basis established for ~350 of the ~450 known disorders
- Distinctions blurry (clinical, radiological & molecular overlap)
  - Mutations in the same gene cause different disorders
  - Mutations in different genes cause similar disorders
  - Ex: Atelosteogenesis (AO)
    - FLNB: AO type I, AO type III, Boomerang dysplasia, Larsen syndrome
    - SLC26A2: AO type II, A chondrogenesis IB, Diastrophic dysplasia
    - FBN1: Otopalatodigital dysplasia type II, can resemble AO type III

Disclosures

- None
Disorders of Bones

- Multiple phenotypes
  - Affects bone & cartilage (also muscle, tendons, ligaments)
  - Chest predicts lethality
    - Heart circumference/chest circumference > 50%
    - Thoracic circumference/abdominal circumference < 0.6

- Multiple classification schemes
  - Genotype, phenotype, lethal vs nonlethal, etc

- Multiple inheritance patterns
  - Autosomal recessive or dominant, X-linked recessive or dominant, Y-linked, mosaicism (somatic or gonadal), imprinting

Simple Steps

- Scan
  - Mineralization
  - Shape of bones
  - Size of bones
  - Alignment/deviation of joints
  - Too many or too few bones
  - Movement of limbs
  - Other (heart, kidneys, genitalia)

- Connect
  - Findings
  - Genes
    - Genetic bone reference [genetonline.org]
    - [OMIM](https://www.ncbi.nlm.nih.gov/omim)

Helpful Hints

- 1st trimester
  - CRL and NT
    - Think skeletal if less than expected CRL + increased nuchal

- 2nd/3rd trimester
  - How do bones look (size, shape, mineralization)?
  - How does fetus move (contractures)?
  - How do other structures look (face, genitalia, heart, kidneys)?
  - Think skeletal if any of the above are abnormal, or if midtrimester survey was normal but long bones lag in 3T

Quick Scan

- Head
  - Brachycephaly
  - Dolicocephaly
  - Macrocephaly
  - Plagiocephaly
  - Craniosynostosis
  - Cloverleaf skull
**Face**
- Bossing
- Micrognathia
- Other

**Face**
- Midface hypoplasia
- Cleft palate
- Cleft lip

**Spine**
- Abnormal vertebrae
  - Hemivertebra
  - Klippel-Feil
- Abnormal caudal eminence
- Abnormal mineralization
- Abnormal curvature
  - Scoliosis (lateral)
  - Kyphosis (outward)
  - Lordosis (inward)

**Chest**
- Bell-shaped
- Small/bent ribs

**Limbs**
- Bent, bowed
- Absent/hypoplastic radius (+/- thumb)
- Short
  - Mesomelia (short middle)
  - Rhizomelia (short proximal)
  - Micromelia (both)

**Hands**
- Sydactyly
  - Clubbed/Clenched
- Oligodactyly
  - Mitten/Trident
- Polydactyly
  - Hitchhiker thumb
Feet

- Syndactyly
- Clipped
- Oligodactyly
- Rocker bottom
- Polydactyly
- Sandal gap

Genes (very, very oversimplified)

**Short-limb skeletal dysplasias**
- **FGFR3** mutations cause short bones, brachydactyly (trident) hands, flat face, abnormal cranium (frontal bossing, cloverleaf skull)
  - **Achondroplasia.** Macrosephaly, frontal bossing, midface hypoplasia, trident hands.
  - **Hypochondroplasia.** Macrosephaly, short hands/feet, taller than achondroplasia.
  - **Thanatophoric dysplasia.** Narrow chest, short ribs, severely short bones, midface hypoplasia, trident hands, cloverleaf skull.

**Short-Limb Skeletal Dysplasias**

- **FNLB** mutations cause short (or absent) bones, abnormal mineralization, joint dislocations, flat face, hands, clubfeet
  - **Atelosteogenesis type I.** Encephalocele, synpolydactyly, omphalocele, poor ossification, small chest, short broad hands, clubfeet, micrognathia, cleft palate
  - **Atelosteogenesis type II.** Multiple joint dislocations, small chest, short broad hands, broad forehead, hypertelorism.
  - **Boomerang dysplasia.** Clubfeet, hypoplasic/absent ribs, spine, long bones, severely bent femurs (boomerang appearance), encephalocele, omphalocele.
  - **Larsen syndrome.** Clubfeet, extra bones in wrists, ankles, joint contractures, frontal bossing, midface hypoplasia, hypertelorism.

- **SLC26A2** mutations cause short limbs, normal size skull, joint contractures, spinal curvature abnormalities, cleft palate, clubfeet, hitchhiker thumb.
  - **Atelosteogenesis type III.** Severely short bones, small chest, cleft palate, clubfeet, hitchhiker thumb (similar to diastrophic dysplasia but more severe).
  - **Diastrophic dysplasia.** Hitchhiker thumbs, clubfeet, scoliosis, cleft palate.
  - **Achondrogenesis type II.** Severely short bones, small chest, brachydactly, clubfeet, umbilical or groin hernia.
Short-Limb Skeletal Dysplasias

- **SOX9** mutations cause midface hypoplasia, cleft palate, micrognathia, macrocephaly, clubfeet, dolicocephaly, hypoplastic scapulae, bowed bones, small chest, ambiguous genitalia
  - Campomelic dysplasia

- **COL2A1** mutations cause abnormal ossification, short bones, micrognathia, cleft palate
  - Achondrogenesis type II. Abnormal ossification in spine and pelvis, small chest, short ribs, micrognathia, cleft palate, hydrops.
  - Hypochondrogenesis. Abnormal ossification in spine and pelvis, micrognathia, hypertelorism, cleft palate
  - Spondyloepiphyseal dysplasia congenita. Similar features but less severe than hypochondrogenesis. (Newborns who survive reclassified as SED.)

- **COL1A1, COL1A2, P3H1, CRTAP** mutations cause weak bones that fracture easily (90% of OI is caused by COL1A1 or COL1A2 mutations) and weak connective tissues
  - Osteogenesis imperfecta. Several types (I-VIII), also called mild (Type I), severe deforming (Types II, IV, VII), perinatal lethal (Type II). Bones appear bent, bowed, broken, and short, and may be compressible (eg cranium)
  - Ehlers-Danlos Syndrome. Variable presentation. Mutations in not only COL1A1 or COL1A2 but also COL5A1, COL5A2, TNR, others

- **DYNC2H1** mutations cause short ribs, short long bones, polydactyly, and nearly anything else (renal, heart)
  - Short Rib Polydactyly Syndromes
    - SRPS I (Saldino-Noonan)
    - SRPS II (Majewski)
    - SRPS III (Verma-Naumoff)
    - SRPS IV (Beemer-Lamer)
    - Asphyxiating thoracic dystrophy (Jeune)

- **EVC, EVC2** mutations cause very short forearms, polydactyly, heart defects (50% of EVC caused by one of these mutations)
  - Ellis van Creveld (chondroectodermal dysplasia)

  - Other ciliopathies include Bardet-Biedel, Meckel-Gruber, etc

Ciliopathies

Cases

- Scan
  - Head:
  - Face:
  - Bones:
  - Chest
  - Hands:
  - Connect
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**Eight**

**Nine**

• Surprise!

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**Thank you and Good Luck**

![Ultrasound Image]