Limbs

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✅ Limb Development

◈ Introduction

- The limbs (along with shoulder & pelvic girdles) form the appendicular skeleton.
- Appearance of limb buds:
  - Forelimb appears end of 4th week.
  - Hindlimb appears 1–2 days later.
  - Limb buds = mesenchymal core (from *parietal layer of lateral plate mesoderm*) + ectoderm covering.

◈ Apical Ectodermal Ridge (AER) – Key Inductive Structure

Feature	Description
Position	Distal border of limb bud
Structure	Thickened ectoderm
Function	Produces signals → keeps adjacent mesenchyme undifferentiated & rapidly proliferating → forms progress zone

👉 Proximodistal outgrowth occurs because cells closer to AER remain undifferentiated, while cells farther start differentiating into cartilage + muscle.

◈ Formation of Limb Segments and Digits

- 6 weeks → hand- and footplates appear (flattened distal ends).
- First constriction → separates proximal and distal segment.
- Second constriction → defines further segments → arm > forearm > hand; thigh > leg > foot.
- Digits (fingers/toes) formed due to:
    - Apoptosis in AER → splits it into 5 segments.
    - Condensation of mesenchyme → cartilaginous digital rays.
    - Apoptosis of tissue between digital rays.

◈ Upper vs Lower Limb

Feature	Upper Limb	Lower Limb
Timing	Earlier	1–2 days behind

Rotation (7th week)	90° laterally → extensor muscles → lateral/posterior side; thumbs → laterally	~90° medially → extensor muscles → anterior side; big toe → medially

◈ Cartilage Formation and Ossification

- Mesenchymal condensations → differentiate into chondrocytes.
- 6th week → hyaline cartilage models appear.
- Joint Formation:
  - Appears in cartilaginous condensations (interzone region).
  - Cell death → joint cavity.
  - Surrounding cells → joint capsule.
  - *WNT14* → important inductive signal.
- Endochondral Ossification:
  - Begins end of embryonic period.
  - By week 12 → all long bones have primary ossification centers (diaphysis).
  - At birth → diaphysis ossified; epiphyses still

cartilaginous.
    - Secondary ossification centers appear in epiphyses shortly after birth.
    - Epiphyseal plate remains between epiphysis & diaphysis → responsible for bone lengthening.
    - Plate disappears once full length is achieved.

◈ Epiphyseal Plate Summary

Bone Type	Number of Epiphyseal Plates
Long bones	One at each end
Small bones (e.g., phalanges)	One only
Irregular bones (e.g., vertebrae)	One or more primary centers & several secondary centers

◈ Synovial & Fibrous Joint Formation

- Occurs alongside cartilage formation.
- Interzone (between chondrifying bone primordia):
    - Differentiates into dense fibrous tissue →
        - Articular cartilage on bone ends
        - Synovial membranes

        - Ligaments + menisci (e.g., cruciate ligaments in the knee)
    - Surrounding mesenchyme → joint capsule.

- Fibrous joints (e.g., skull sutures) also arise from interzone but remain as dense fibrous tissue (no cavity forms).

✅ Limb Musculature

🔶 Origin of Limb Muscles

- Muscle precursor cells originate from dorsolateral region of somites.

- These cells migrate into limb buds.

- Initially, muscle masses are segmental, corresponding to their somitic origin.

🔶 Patterning of Muscle Masses

Stage	Description
Early limb bud	Muscle masses migrate and remain segmentally arranged
With limb	Muscle tissue splits into: → Flexor

elongation	compartment (ventral) → Extensor compartment (dorsal)
Later	Additional splittings + fusions occur → individual muscles may be formed from more than one segment

👉 Important:

The final pattern of muscles is defined by connective tissue derived from lateral plate mesoderm (acts as a template).

◈ Innervation – Entry of Spinal Nerves

Limb	Spinal Levels
Upper limb	Lower CS–T1
Lower limb	L4–S2

- Ventral primary rami from these segments grow into the mesenchyme of the limb bud.
- Each ramus divides into dorsal and ventral branches, which later unite to form large peripheral nerves.

Compartment	Formed from	Examples

Extensor (dorsal)	Dorsal segmental branches	Radial nerve
Flexor (ventral)	Ventral branches	Ulnar & Median nerves

🔔 *Key Point:* Contact between nerves and developing muscle cells is essential for full muscle differentiation (motor influence).

🔹 Sensory Innervation (Dermatomes)

- Spinal nerves also supply sensory innervation.
- Original dermatomal pattern is established early and modified by limb growth & rotation, but
  ☞ an orderly segmental pattern can still be identified in adults.

(e.g., thumb = C6, big toe = L4)

✅ Clinical Correlates – Limb Development

🔹 Bone Age

- Radiological evaluation of ossification centers is used to assess maturational age.
- Hands & wrists are most commonly studied

(postnatal).

- Prenatal ultrasonography of fetal long bones → estimates fetal growth & gestational age.

◈ Limb Reduction Defects

Term	Meaning
Amelia	Complete absence of limb
Meromelia	Partial absence of limb
Phocomelia	Absence of long bones → hands/feet attached close to trunk
Micromelia	All limb segments present but abnormally short

✅ Cause: Mostly genetic, but classic teratogen = thalidomide (used 1957–1962).
→ Most sensitive period: 4th–5th week.

◈ Digit Abnormalities

Condition	Description

Brachydactyly	Short digits
Syndactyly	Fusion of digits (failure of apoptosis between digital rays)
Polydactyly	Extra digits (often bilateral, with incomplete muscle connections)
Ectrodactyly	Absence of a digit (usually unilateral)
Cleft hand/foot	Absence of 3rd digit (central) → deep cleft + fusion of remaining medial/lateral digits

◈ Gene Mutations Affecting Limb Development

Gene	Syndrome	Main Features
HOXA13	Hand-Foot-Genital Syndrome	→ Fusion of carpal bones + short digits → Urogenital defects (bicornuate uterus, hypospadias etc.)
HOXD13	Synpolydactyly	Combination of syndactyly + polydactyly

TBX5	Holt-Oram Syndrome	Upper limb defects (absent radius, polydactyly, hypoplastic hand) + cardiac defects (ASD, VSD, conduction defects)
COL1A1 / COL1A2	Osteogenesis Imperfecta	Short, bowed, fragile bones + blue sclera
FBN1	Marfan Syndrome	Tall thin individuals, long limbs, pectus deformity, aortic dilation, lens dislocation

◈ Congenital Deformities (Non-Genetic / Mechanical)

Condition	Cause / Features
Arthrogryposis	Congenital joint contractures → caused by ↓ fetal movement → neurological, muscular or structural defects
Clubfoot	Often due to fetal constraint (e.g., oligohydramnios)
Radial aplasia	Genetic (e.g., craniosynostosis-

	radial aplasia / Baller-Gerold syndrome)
Amniotic bands	Bands from damaged amnion → wrap around limbs → ring constrictions / amputations
Transverse limb deficiencies	Distal parts missing while proximal are intact → results from AER disruption or vascular deficiency
Congenital hip dislocation	Underdeveloped acetabulum + femoral head → more common in female newborns (breech presentation & joint laxity are risk factors)