Musculoskeletal System Development

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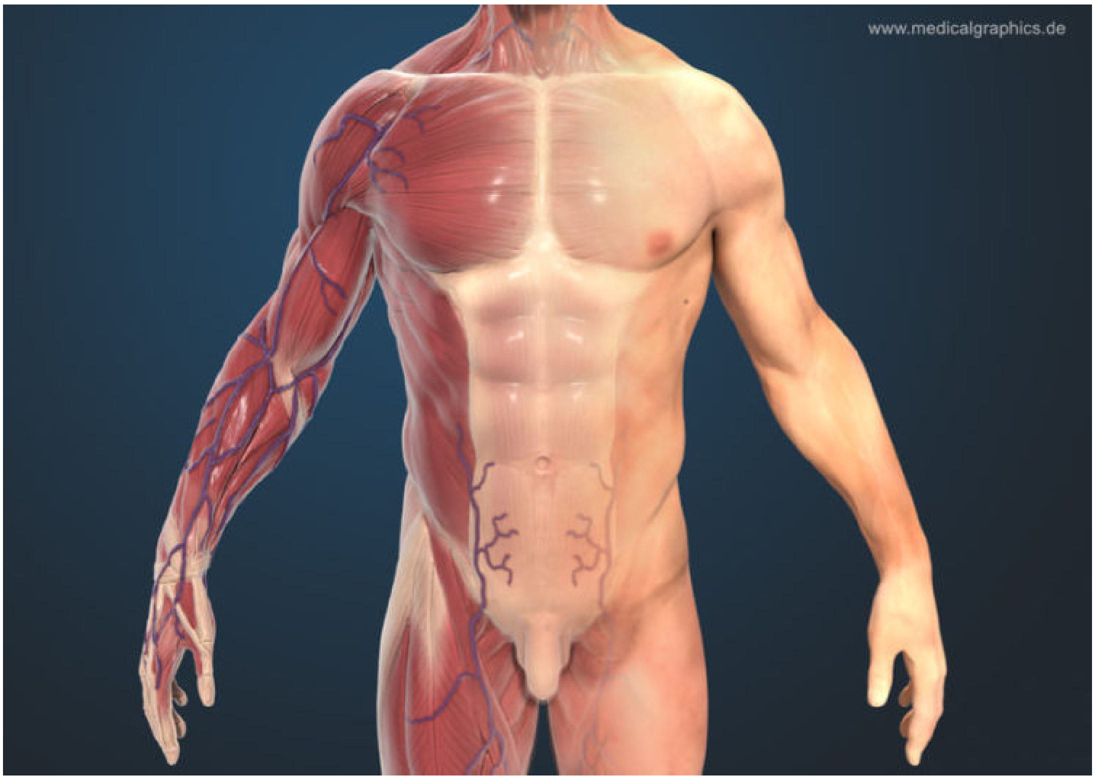
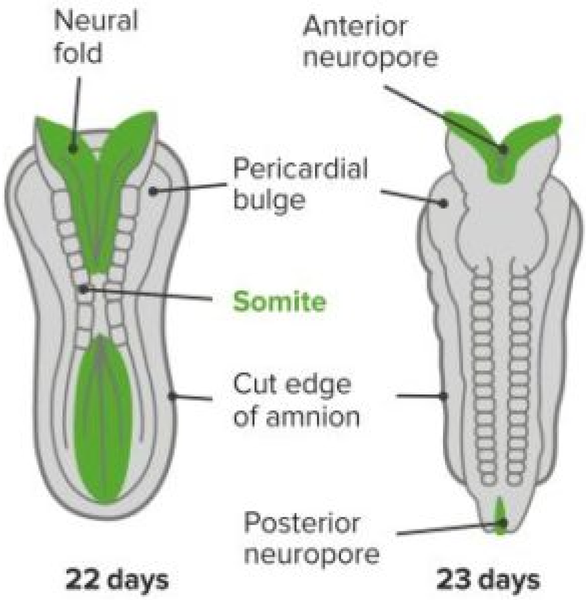
This article aims to provide an overview of the development of the musculoskeletal system, including the processes of somite formation, limb forming and limb outgrowth, genes that control limb development, and the development of complex bones. Finally, it will describe major limb abnormalities, which are caused by a combination of genetic and environmental factors (multifactorial inheritance). Another complementary article deals with the topic of skull and brain development. The musculoskeletal system comprises of bone, cartilage, and muscle all which arise from the mesodermal layer via various mechanisms of development.



Somite Formation

Somites are pieces of **mesoderm tissues** found on either side of the **neural tube** of the embryo. **Somitogenesis** starts at the anterior part of the embryo, adjacent to the **notochord** – a median cellular cord that is developed by the migration of mesenchymal cells from the cranial aspect of the **primitive node**. Primitive node is the proliferation of the cells on the cranial aspect of the primitive streak.



"Somite formation" Image created by Lecturio

Aside from giving rise to the notochord, mesenchymal cells from the primitive node also contribute to the formation of the **paraxial mesoderm**, also known as somatic mesoderm.

Paraxial mesoderm is segmented into **somitomeres**, which initially appear in the occipital region and later acquire a craniocaudal sequence on either side of the developing embryo. Somitomeres develop into **somites**. The first pair of somites forms on the 20th day, followed by new pairs of somites emerging at the rate of 3 per day.

There are initially 42 – 44 pairs of somites all together, out of which the first 7 pairs make up the mesoderm of the **pharyngeal arches** (that develop into head and neck structures). When the caudal most somites dissolve, the eventual number of somites is 35.

On the lateral side of each column of somites, we find the **intermediate mesoderm**, a longitudinal ridge which separates the paraxial mesoderm and the lateral mesoderm. The **lateral mesoderm** joins the **extraembryonic mesoderm** that covers the **amnion**. Intermediate mesoderm also gives rise to the urogenital ridge which forms the kidneys and genitals.

Due to their prominence, especially during the 4th-5th week, somites are utilized for determining the embryo's age.

Genes and signaling molecules involved in the somitogenesis

There is an involvement of **forkhead transcription factors FoxC1 and FoxC2** before somites are derived from the paraxial mesoderm.

Hox genes and **Notch way signaling pathway genes** are involved in the formation of somites from the paraxial mesoderm.

Delta-Notch signaling is said to be involved in the segmentation of somites, as well as their craniocaudal sequencing along the embryo.

Structures that the somites give rise to

- **Sclerotome** – makes up the bones and cartilages of the axial skeleton including the vertebral column.
- **Myotome** – makes up skeletal muscles. Motor axons attached to the spinal cord innervate the muscles cells that are derived from somites.
- **Dermatome** – makes up the dermis, as well as skeletal muscles.
- **Syndotome** – makes up tendons.

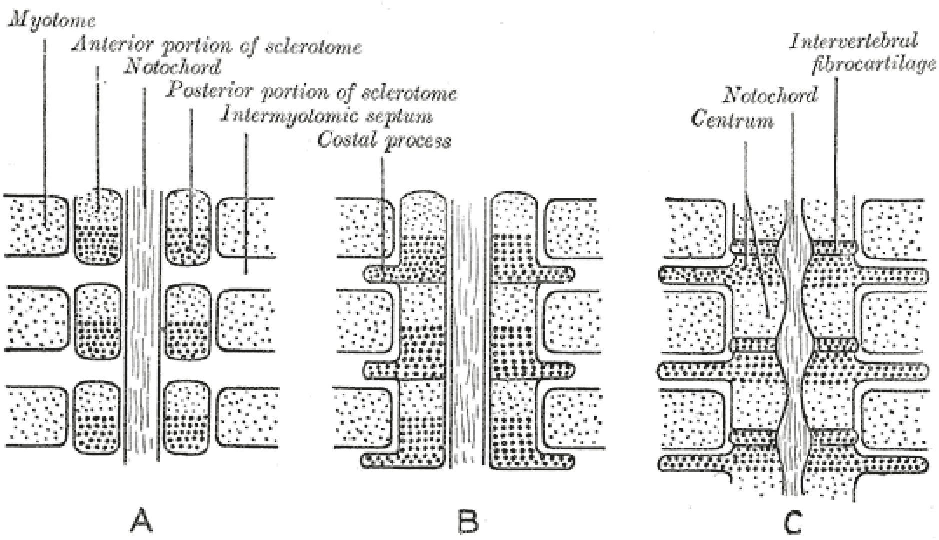
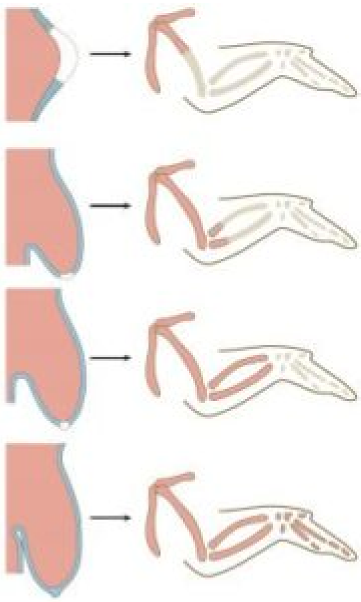


Image: "Scheme showing the differentiation of somites; how each vertebral centrum is developed from portions of two adjacent segments. (Myotome labeled in the upper left.)" by Henry Vandyke Carter, Henry Gray (1918) Anatomy of the Human Body. Bartleby.com: Gray's Anatomy, Plate 65. License: Public Domain

Limb Formation

Development starts around the end of the 4th week of embryonic life. Lateral plate mesoderm (outer most layer of the mesoderm) and somatic mesoderm migrate to the developing limb bud. Lateral plate mesoderm condenses to make up the vasculature and skeletal parts, whereas the somatic mesoderm gives rise to the musculature component.

Limb buds



“Outgrowth of the limb” Image created by Lecturio

Limb buds appear on the 24th – 26th day of embryonic life. The formation of limb buds takes place in the ventrolateral aspect of the body, under a band of ectoderm known as an **apical ectodermal ridge** (AER). Underneath the AER, the core of the limb buds consists of mesenchymal tissues derived from the mesoderm. It is the proliferation of the mesenchymal core that causes the limb buds to elongate and take form.

The position of limb buds:

- **Upper limb buds**: opposite to caudal cervical segment
- **Lower limb buds**: opposite to lumbar and sacral segments

Genes that Control Limb Development

Apical ectodermal ridge, a thick multi-layered ectodermal ridge found covering the mesenchymal core of the limb buds also produces paracrine factor **Fibroblast Growth Factor-10 (FGF-10)**. FGF works to stimulate the growth of mesenchyme cells in the limb buds. FGF-10 also activates the zone of polarizing activity, which is a group of mesenchymal cells forming a signaling center found on the base of limbs.

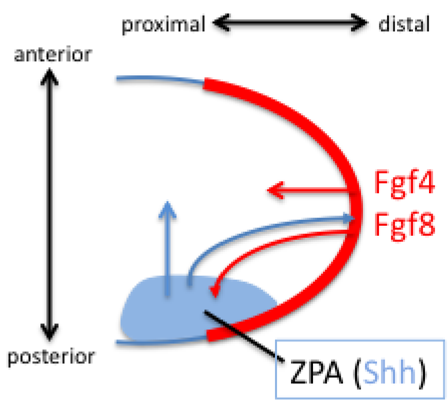


Image: “Early signals that define the anterior-posterior and proximal-distal axis in vertebrate limb development.” by Peteruetz – PPT Previously

Zone of polarizing activity is responsible for causing the expression of the **Sonic hedgehog gene (Shh)**. Sonic hedgehog proteins are mainly involved in the development of the limbs along the anterior-posterior polar axis, as well as the patterning of the digits. Shh is a **morphogen** and it brings about these changes in the limbs by activating genes such as BMP (one morphogenetic protein) as well as Hoxd-9, Hoxd-10, Hoxd-11, Hoxd-12, and Hoxd-13 genes.

The dorsal-ventral axis growth of the limbs depends on the activation of **Wnt7a gene**. AER is said to be involved in the expression of this gene.

Endogenous **retinoic acid**, **BMP** and **Msx-1** are said to play a role in digit formation. This is brought about by the selective apoptosis of the AER, giving rise to five separate segments that will give rise to future digits.

Rotations of the Limbs

Upper limb

Week 4: limb buds emerge in the coronal plane.

Week 6: limb buds go through horizontal mobility and come on the sagittal plane.

Week 6-8: elbows and extensor compartment are moved posteriorly due to the 90° rotation laterally. This causes the flexor compartment to be shifted anteriorly. This rotation also results in the proper allocation of the dermatomes innervation.

Lower limb

The first two changes of the lower limb formation are similar to the upper limb. However, during week 6-8, lower limb experienced 90° rotation medially, resulting in the flexor compartment being situated posteriorly, whereas the extensor compartment is located anteriorly.

Formation of Musculature

Muscles are derived from somites. Mesodermal cells of the somites travel to the limb buds to form muscles at **week 5**.

Upper limbs

Somites that give rise to the musculature of the upper limb include **C4-C8** as well as **T1-T2**. Muscle cells, i.e., **myoblasts,** are derived from anterior and posterior condensations that are formed by the mesodermal cells of the somites (i.e., **myotomes**).

The extensor and supinator muscles of the upper limb, for example, muscles of the rotator cuff, brachioradialis, and extensors of the fingers, are derived from the **posterior condensation**.

Flexor and pronator muscles of the upper limbs are derived from the **anterior condensation**. This includes biceps brachii, pronator teres, flexor carpool ulnaris and various muscles of the fingers.

Lower limbs

Somites that give rise to the musculature of the lower limb include **L1-L5** and **S1-S2**.

The extensor and abductor muscles of the lower limb, for example, gluteus maximus, piriformis, tibialis anterior and extensor digitorium, are derived from the posterior condensation.

Flexor and adductor muscles of the lower limbs are derived from the anterior condensation. This includes adductor longus, obturator externus, flexor halluces longus, tibialis posterior, adductor halluces, and flexor digitorium brevis.

Development of Complex Bones

The bones go through two types of **ossification** during fetal development:

1. **Endochondral ossification**: cartilage is already present during the ossification. This cartilage occurs due to the action and division of **chondrocytes** and extracellular matrix.
2. **Intramembranous ossification**: cartilage is not already present during intramembranous ossification. This type of ossification is initiated by the mesenchymal cells in the medullary cavity of the bones.

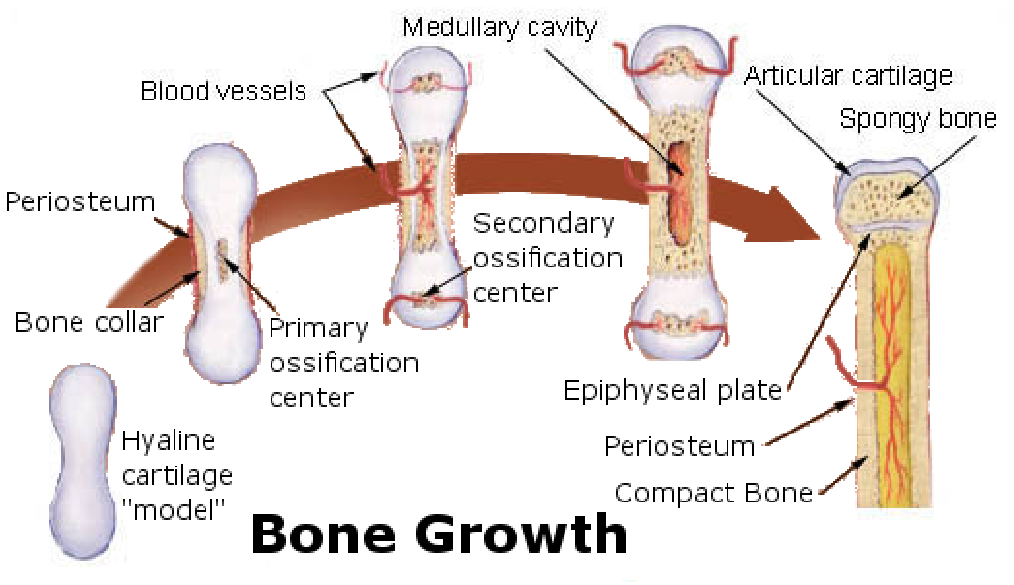


Image: "Stages of bone growth." Derivative work: Chaldor (talk) Illu_bone_growth.jpg: Fuelbottle – Illu_bone_growth.jpg. License: Public Domain

Primary ossification centers and sequence of bone formation

The primary ossification center is the location of the bone where ossification starts taking place, i.e., the shaft of the bone, also known as **diaphysis**.

- **Periosteum** forms from the **perichondrium** (a dense layer of connective tissue around the cartilage of developing bone). Periosteum consists of undifferentiated cells which later turn into **osteoblasts**.
- **Bone collar**, the layer of periosteum that surrounds the diaphysis, is formed

by the osteoid produced by the osteoblasts.
- **Calcification of the bone matrix** occurs when mature **chondrocytes** start producing the enzyme **alkaline phosphatase**, which is responsible for mineral deposition on bones.
- **The medullary cavity** is formed by the action of osteoclasts. **Osteoclasts** are derived from macrophage and they work to break down bone.

Secondary ossification centers

Secondary ossification occurs around the time of birth or after it. Secondary ossification centers are located at the end of bones, also called **epiphysis**.

Epiphyseal plate is growing cartilage between the primary and secondary ossification centers that contribute to the lengthening of the bone during body growth. Bone growth occurs until 20 years of age, after that the epiphyseal plate is replaced by bone.

Bones of the upper limb

The bones of the upper limbs are derived from the **lateral mesoderm**. It gives rise to the scapula, clavicle, humerus, radius, ulnar, carpals, metacarpals and the phalanges.

All upper limb bones go through **endochondral ossification**. The clavicle, however, goes through both endochondral and **intramembranous ossification**.

The time period of bone formation:

- Lateral mesoderm condenses **around week 5**.
- Formation of hyaline cartilage, via the condensed mesoderm, takes place **around week 6**.
- The clavicle is the first bone to ossify in the whole body. This, along with the formation of primary ossification centers in the humerus, ulnar and radius bones takes place **from week 7 to 9**.
- Remaining primary ossification centers of the scapula and carpal bones occur **from week 9 to time of birth**.
- Secondary ossification centers develop **during childhood**.

Bones of the lower limb

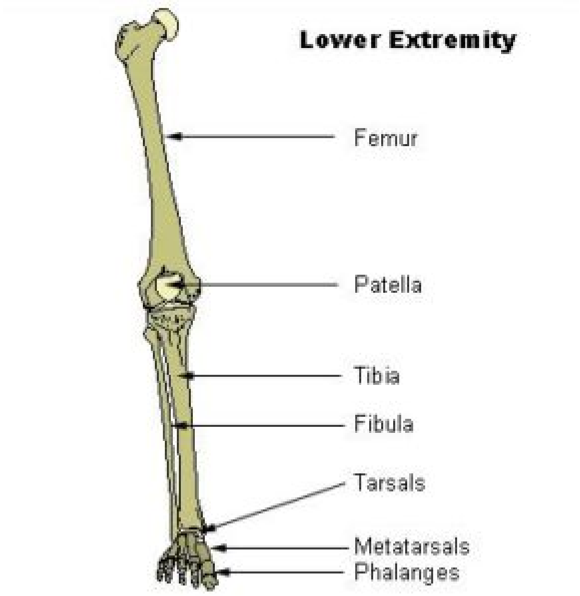


Image: "Bones of the Lower Limb." License: Public Domain

The bones of the lower limb-derived from the lateral plate mesoderm are as following: ilium, ischium, pubis, fibula, tibia, femur, tarsals, metatarsals and phalanges.

The time period of bone formation:

- Lateral mesoderm condenses **around week 5**.
- Formation of hyaline cartilage via the condensed mesoderm takes place **around week 6**.
- Primary ossification centers of tibia and femur occurs in **week 7-9**.
- Remaining primary ossification centers, i.e., that of ilium, ischium, fibula, pubis, calcaneus, talus, metatarsals and phalanges occurs from the period **between week 9 and birth**.
- Secondary ossification centers occur **during childhood**.

Major Limb Anomalies

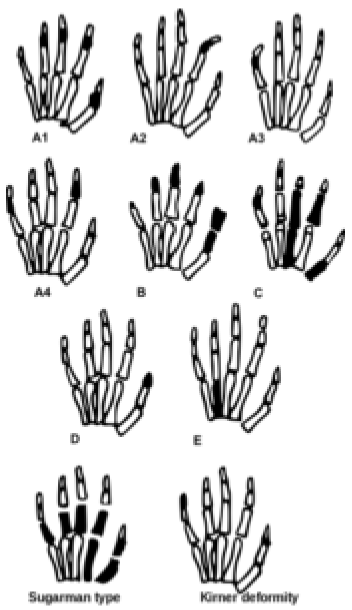


Image: "Classification of

Brachydactyly." by Samia A Temtamy; Mona S Aglan – based on: Samia A Temtamy, Mona S Aglan. Brachydactyly. Orphanet Journal of Rare Diseases. 3, 15. 2008. doi:10.1186/1750-1172-3-15. License: CC BY 2.0

Causes of limb anomalies consist of a combination of genetic and environmental (**multifactorial inheritance**) factors. They are also associated with **trisomy 18**.

Amelia is the absence of one or both limbs, which occurs due to suspension in development during the 4th week.

Meromelia is the condition when a part of the limb is missing. This occurs due to a disturbance in development during the 5th week of development. For example, **hemimelia** (absence of fibula) and **phocomelia** (hands and feet are attached directly to the body).

Split hand/foot malformations (SHFM) also known as **ectrodactyly** is a condition compromising of the absence of digits of a hand or foot giving a forked hand or cleft foot. The hand or foot is described as "claw-like" due to two separate parts that are opposed and curve inwards towards each other.

Image: "Newborn baby hand showing complete complex syndactyly of two fingers (III & IV)." by Dumplestilskin, uploaded by Gliu – en.wiki, uploaded under the same name. License: Public Domain

Brachydactyly is described as the short length of the digits (of either foot or hand). This occurs due to the shortness of phalanges. Short stature is often strongly associated with brachydactyly. There are numerous types of this disorder differentiated according to different syndromes and genetic etiologies.

Polydactyly is another limb anomaly that consists of the presence of extra digits on hands or feet. The extra digit is often inadequately formed and lacks proper musculature. This is an inherited dominant trait and the extra digit usually arises medially or laterally, rather than centrally.

Cutaneous syndactyly refers to the webbing between digits. It occurs due to the failure of apoptosis which is responsible for the separation of the digits.

Osseous syndactyly consists of fusions of the bones of the digits.

References

Keith L. Moore. (2013). The developing human. 9th edition. Philadelphia: Elsevier Inc.

Lecture – Limb Development via unsw.edu.au

Somites: Formation and Role in Developing the Body Plan via asu.edu

Notes