

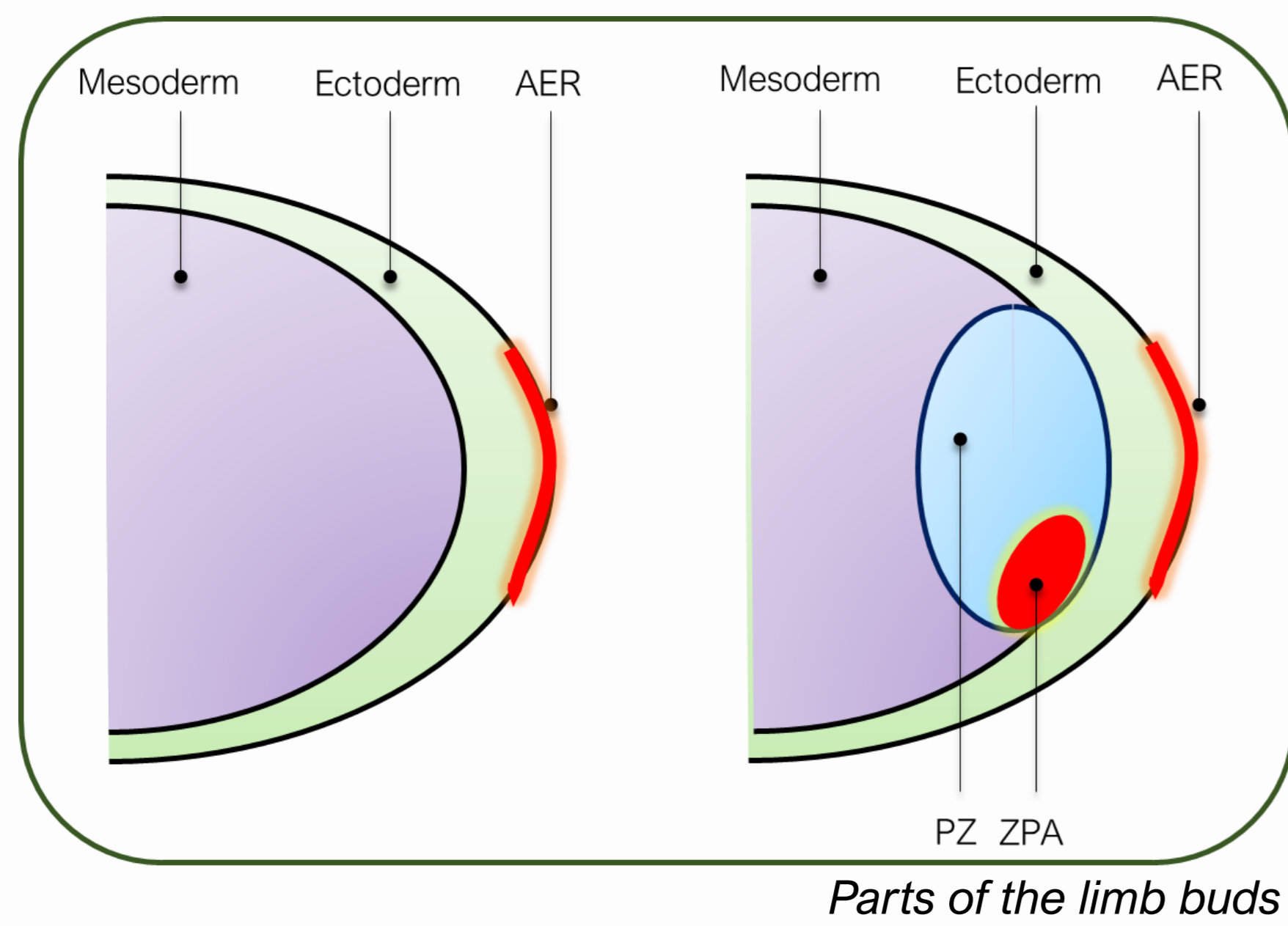
## CONGENITAL MALFORMATIONS

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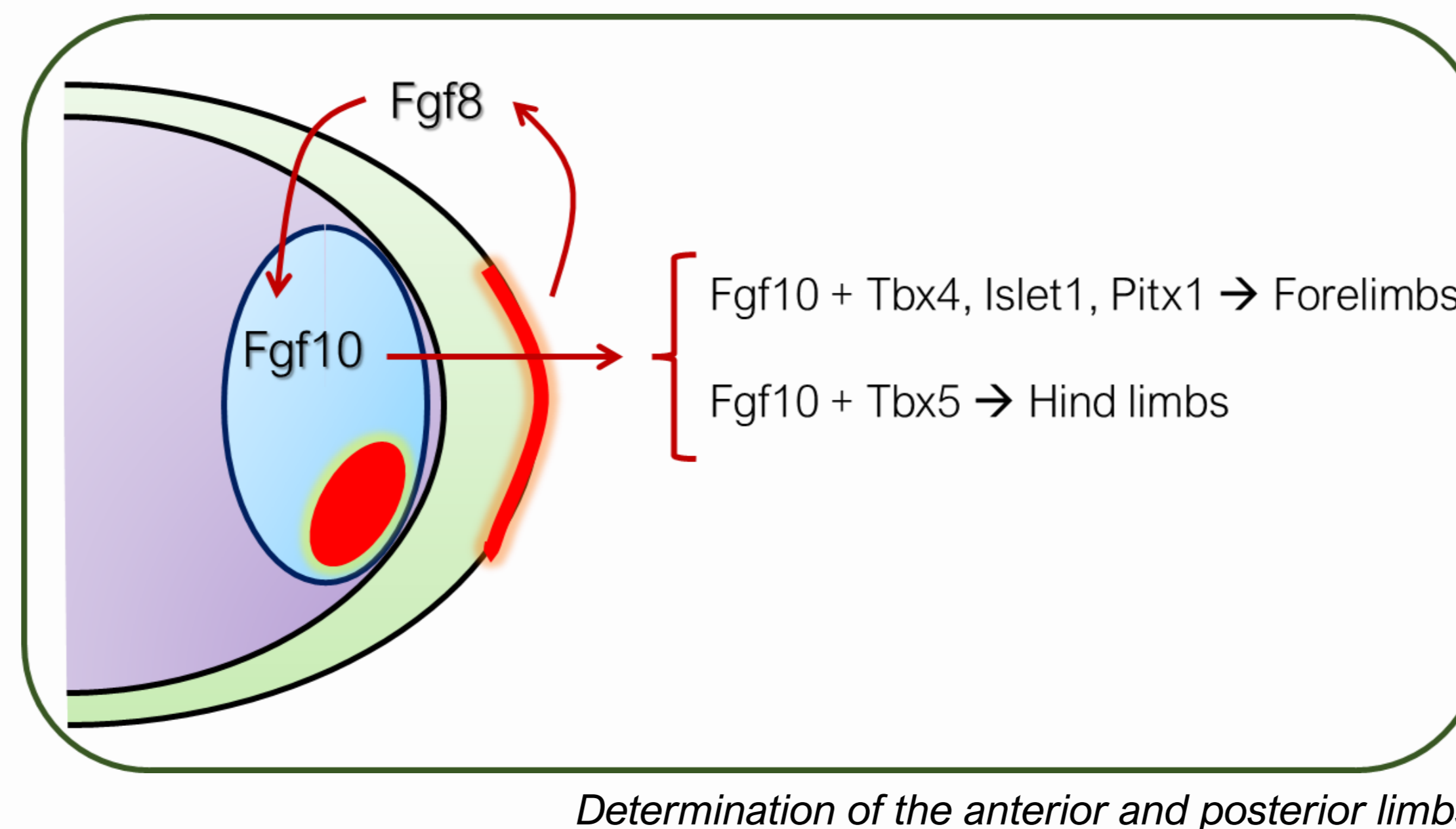
### 1. OBJECTIVES

- Collect the data provided by the most current studies to explain how embryonic structures and tissues interact with each other to form the limbs of tetrapod mammals.
- See which are the moments when developmental defects appear and how these lead to congenital malformations of the limbs.

### 2. LIMB BUDS AND PROXIMODISTAL AXIS



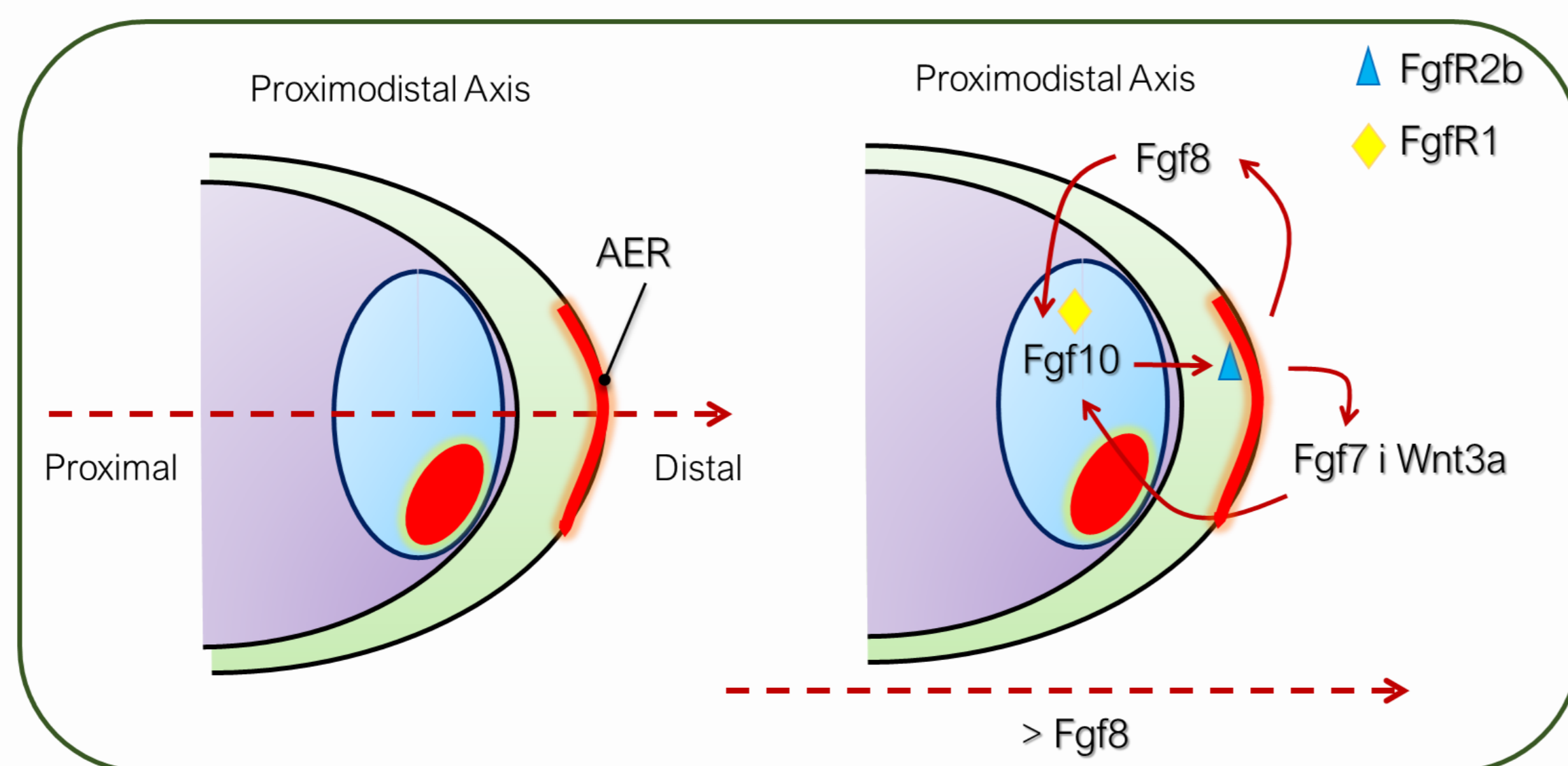
Parts of the limb buds



Determination of the anterior and posterior limbs



Amelia and tarsal Hemimelia (Whitacre et al., 2017)

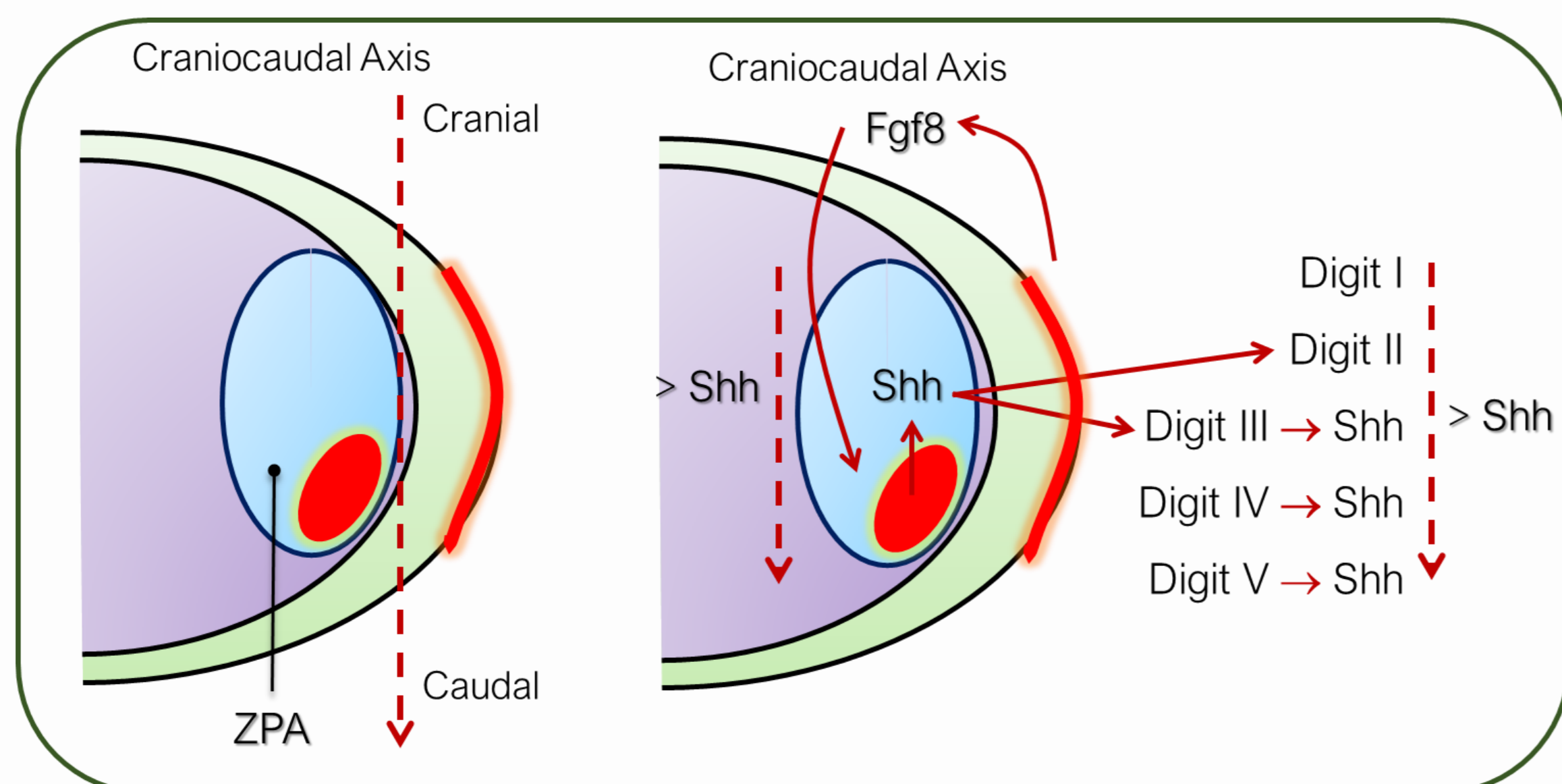


Elements that form the proximodistal axis

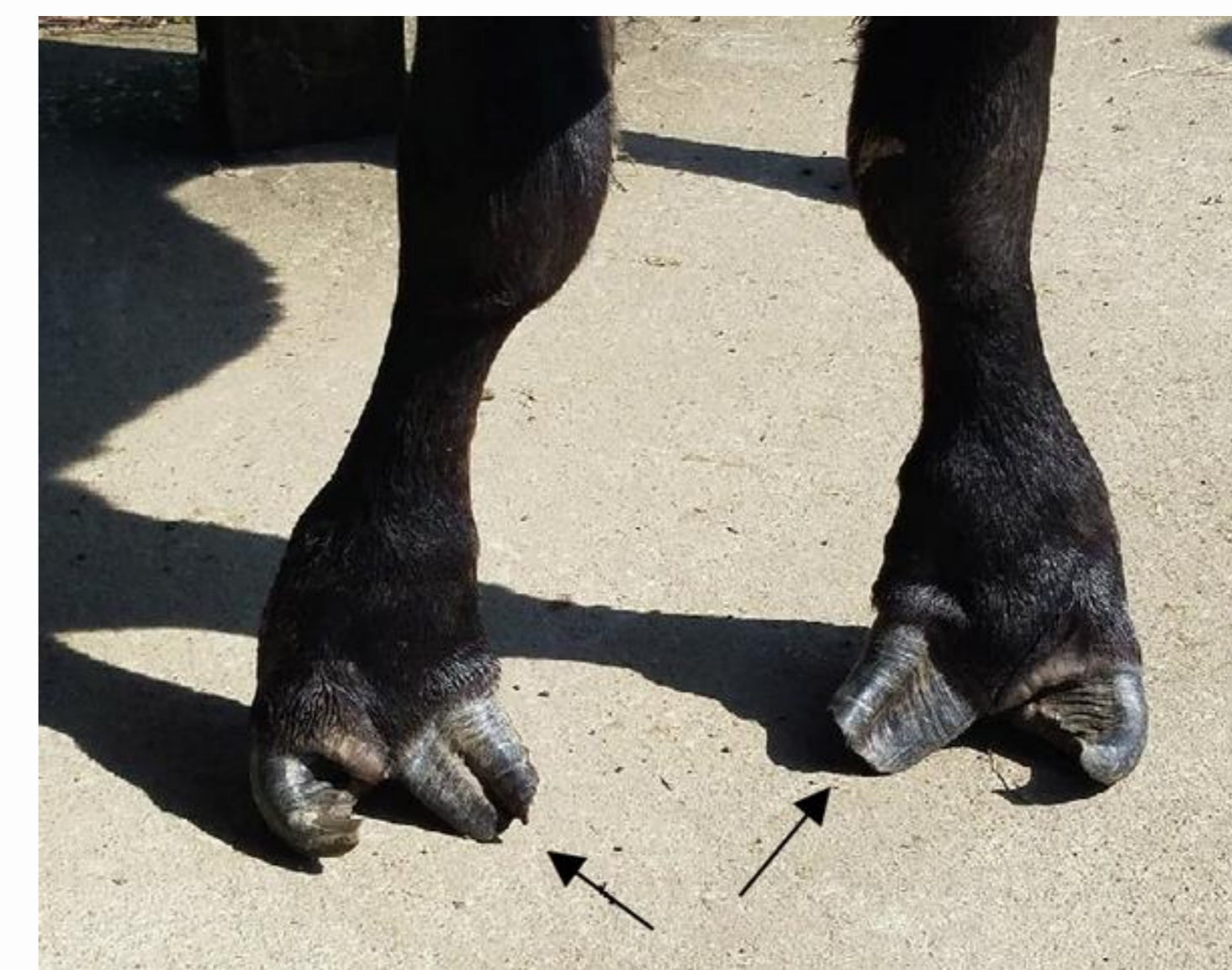


Achondroplasia: Dachshund

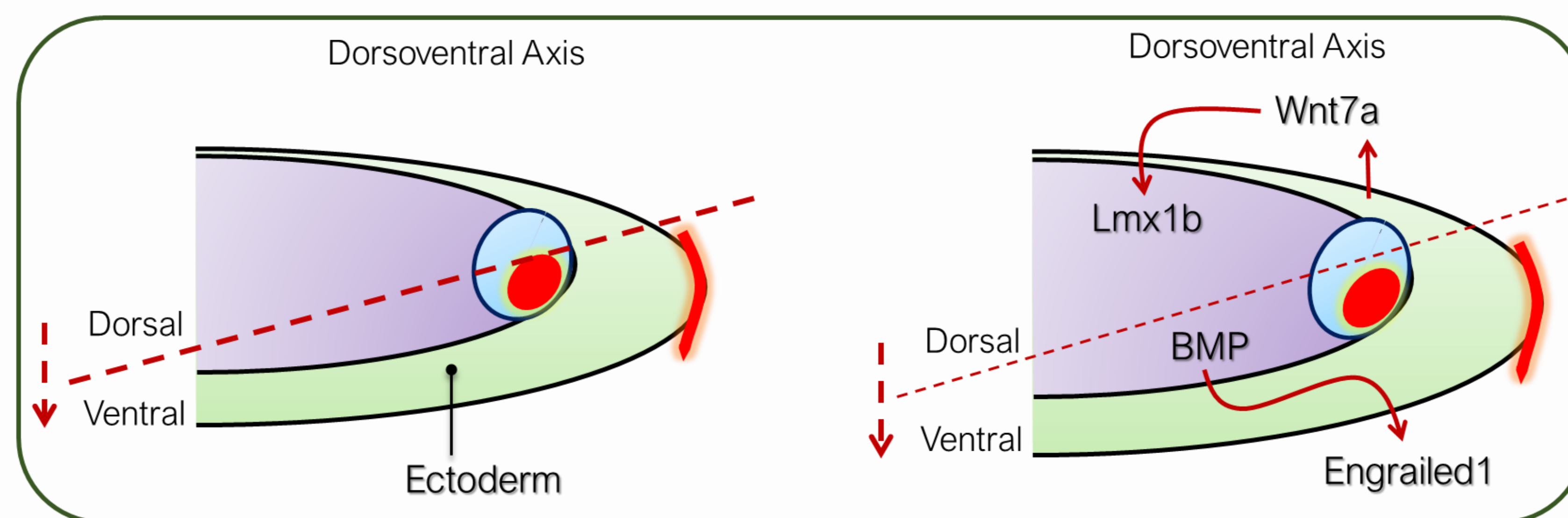
### 3. CRANIOCAUDAL AND DORSIVENTRAL AXES



Elements that form the craniocaudal axis



Polydactyly (Browning Jr. et al., 2020)



Elements that form the dorsoventral axis

### 4. CONCLUSIONS

1. The proximodistal axis is determined by the apical ectodermal ridge and the mesoderm. In the establishment of this axis, Fgf 8 and 10 are key, they are secreted simultaneously by these two signaling centers and allow the maintenance of the CEA and the longitudinal growth of the limbs. The disorganization of these elements and/or factors can cause malformations, such as amelia or micromelia.
2. During the establishment of limb buds, the fact that Fgf10 coincides with Tbx4, Islet1 and Pitx1 or Tbx5 will determine the formation of forelimbs or hindlimbs and deficits in any of these factors can also cause amelia.
3. Fgf factors are involved in the formation of cartilage and joints and, therefore, alterations in the expression of these factors can cause joint and growth alterations, such as brachydactyly or achondroplasia.
4. The craniocaudal axis is determined by the Polarizing Activity Zone and the Apical Ectodermal Ridge. These structures through the expression of Fgf8, Shh and Hox allow the determination of the identities of the fingers. Alterations in the expression of these factors can cause malformations, such as polydactyly or syndactyly.
5. The dorsoventral axis is determined by the underlying ectoderm and mesoderm, which express Wnt7a and Lmx1b, respectively and consecutively. Deficiencies of these factors can cause malformations, such as ectromelia.
6. The formation of the members is a dynamic and continuous process, in which the three axes are formed and change through processes of activation and inhibition, proliferation and apoptosis that occur at the same time and allow the coupling of the various mechanisms for the formation of all the musculoskeletal elements of the limbs.