

# Developmental Genetics and Birth Defects

Permanent Education Course in Human  
Genetics

BESHG

Dr Julie Désir  
Clinical Genetics



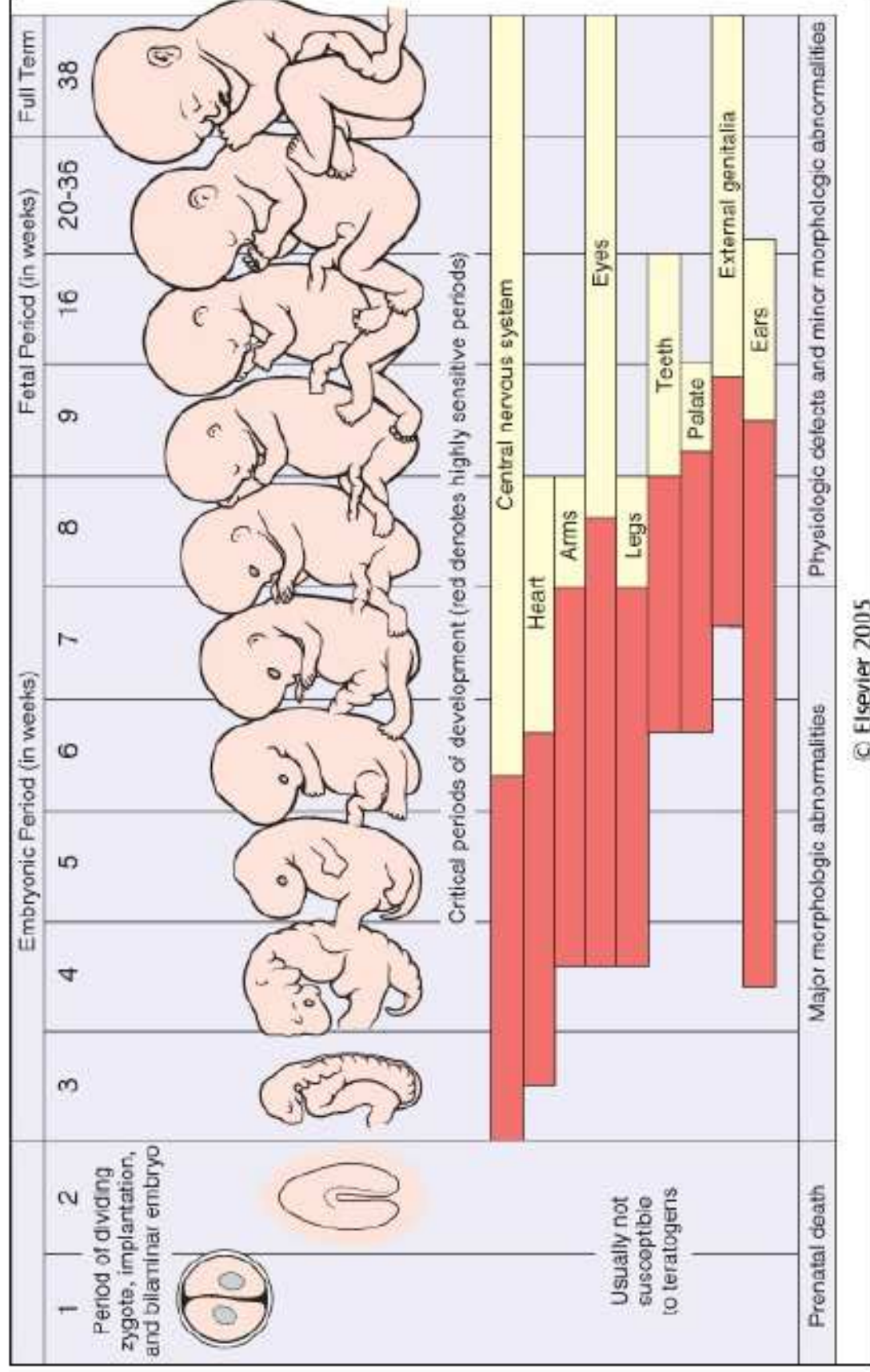
# Chapters

- ❑ **Basic Concepts of Developmental Biology**
  - Overview of Embryological Development
  - Fate, Specification, and Determination
  - Axis Specification and Pattern Formation
- ❑ **Cellular and Molecular Mechanisms in Development**
  - Gene Regulation by Transcription Factors
  - Morphogens and Cell to Cell Signaling
  - Cell Shape and Organization
  - Cell Migration
  - Programmed Cell Death
- ❑ **Interaction of Developmental Mechanisms in Embryogenesis**
  - The Limb as a Model of Organogenesis

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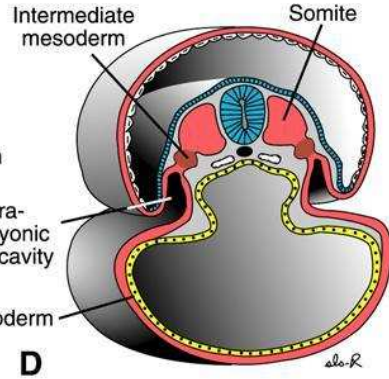
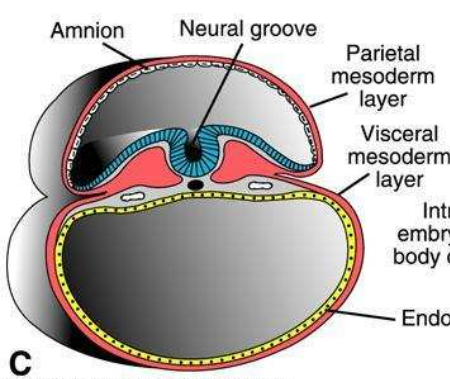
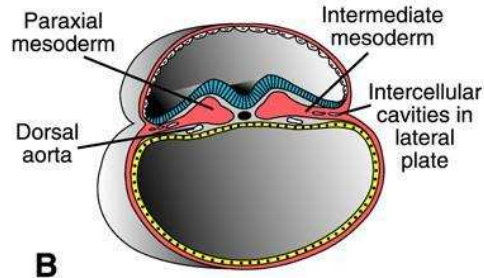
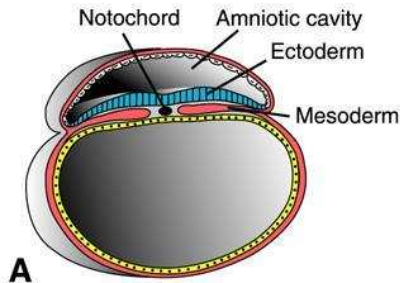
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# Critical periods of development for various organ systems and the resultant malformations







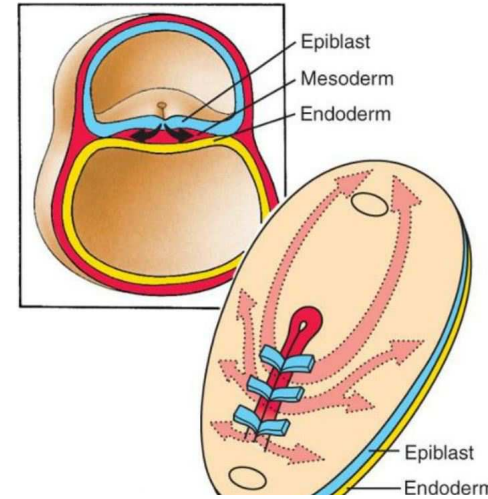


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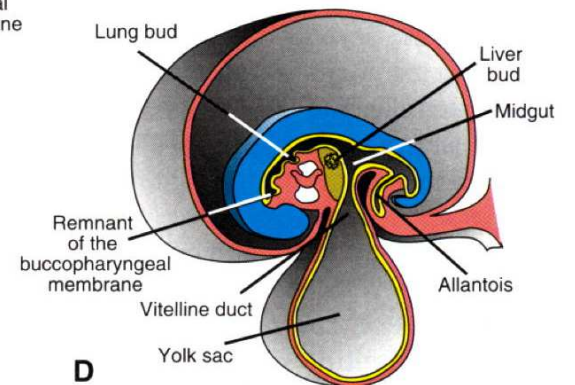
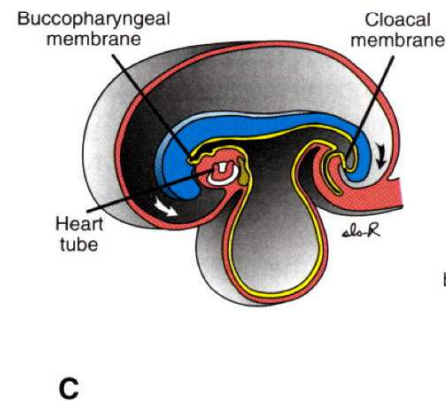
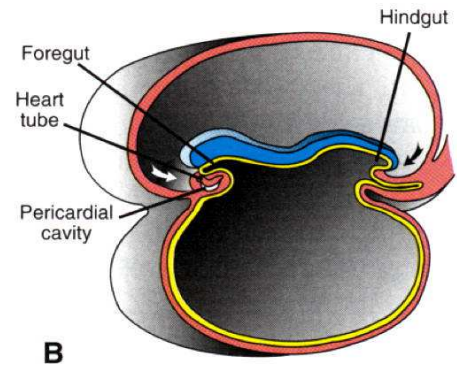
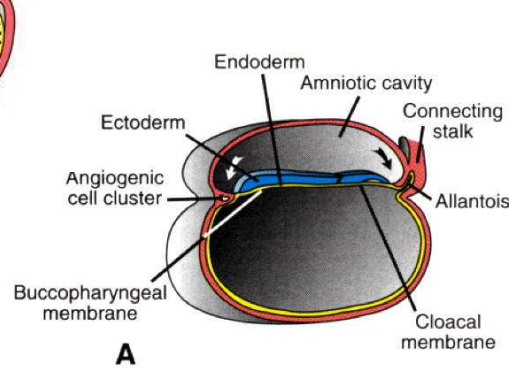
Transversal view

# Gastrulation

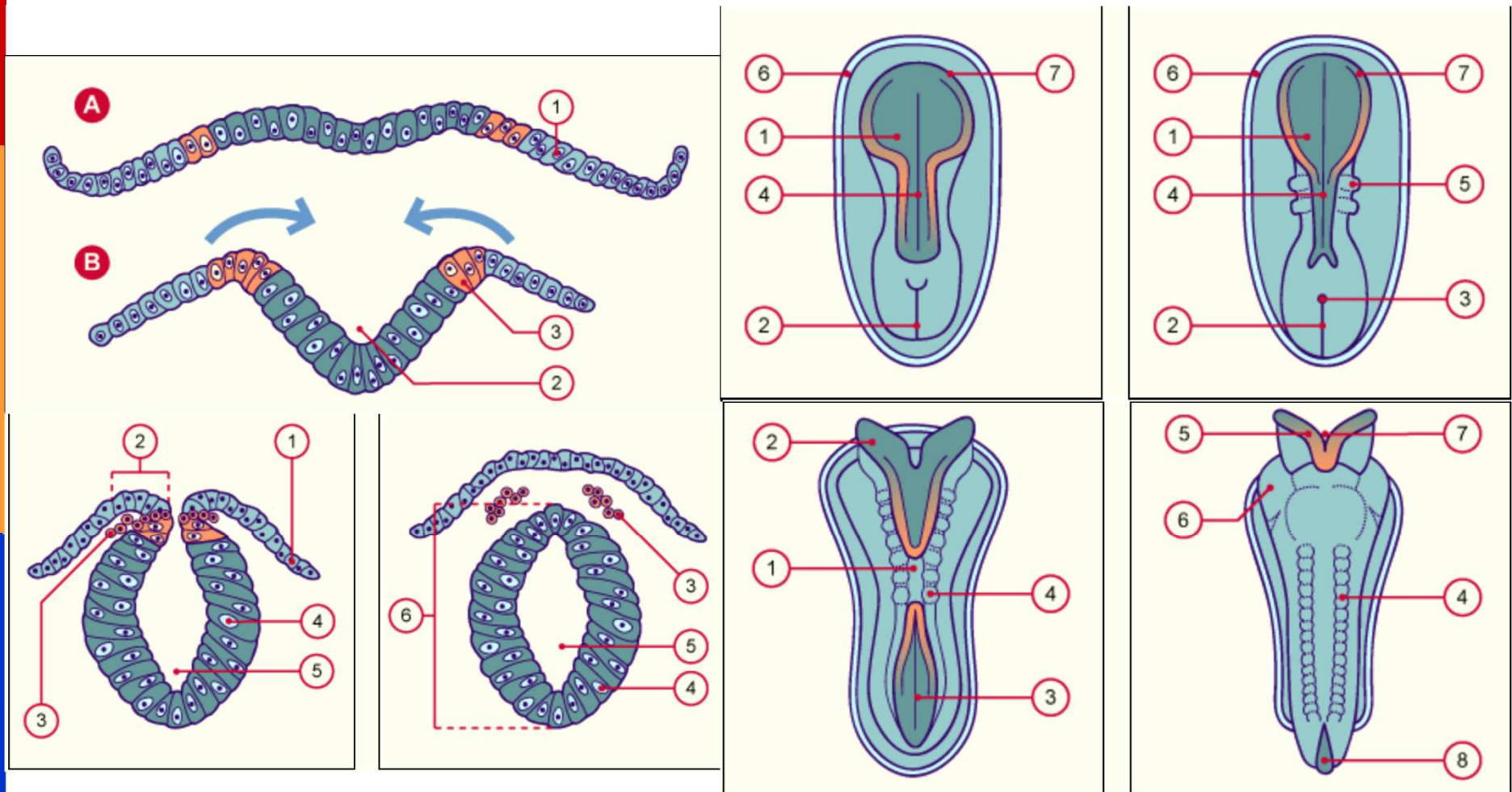
Sagittal view



Dorsal view



# Neurulation



Transversal view

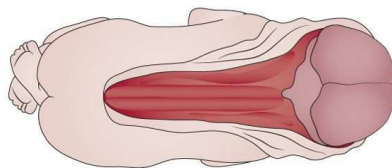
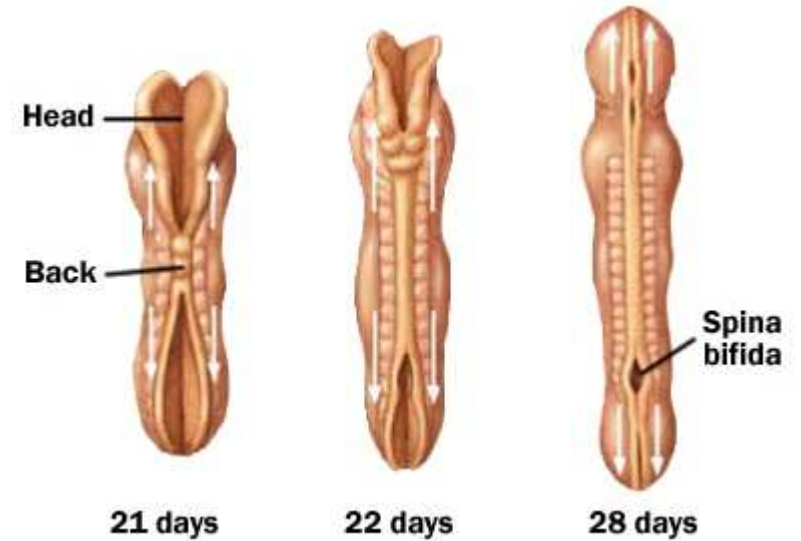
Dorsal view



# Neural tube defects



If all women that could become pregnant took the recommended amount of #folicacid BEFORE and during the first 3 months of pregnancy, we could reduce the incidence of #NTDs by up to 72%  
 #IFGPI #WFAAW



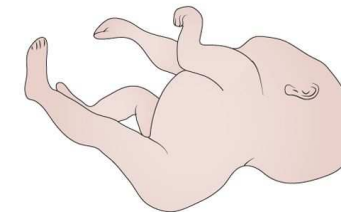
**Craniorachischisis**  
 Completely open brain and spinal cord



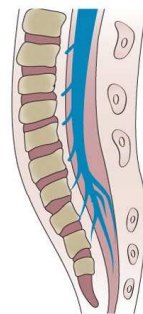
**Anencephaly**  
 Open brain and lack of skull vault



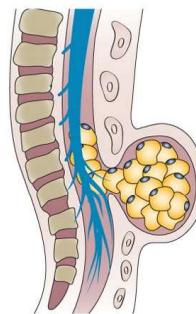
**Encephalocele**  
 Herniation of the meninges (and brain)



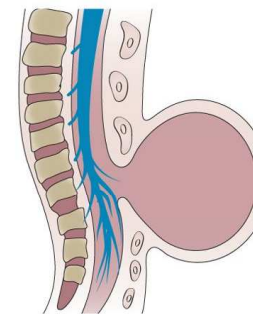
**Iniencephaly**  
 Occipital skull and spine defects with extreme retroflexion of the head



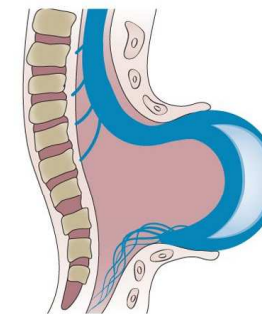
**Spina bifida occulta**  
 Closed asymptomatic NTD in which some of the vertebrae are not completely closed



**Closed spinal dysraphism**  
 Deficiency of at least two vertebral arches, here covered with a lipoma



**Meningocele**  
 Protrusion of the meninges (filled with CSF) through a defect in the skull or spine



**Myelomeningocele**  
 Open spinal cord (with a meningeal cyst)



# Cellular Processes during Development

During development, cells

- ❑ **Proliferate** (divide)
- ❑ **Differentiate** (acquire novel functions or structures)
- ❑ **Migrate** (move within the embryo)
- ❑ **Undergo apoptosis** (programmed cell death)

These four basic cellular processes act in various combinations and in different ways to allow

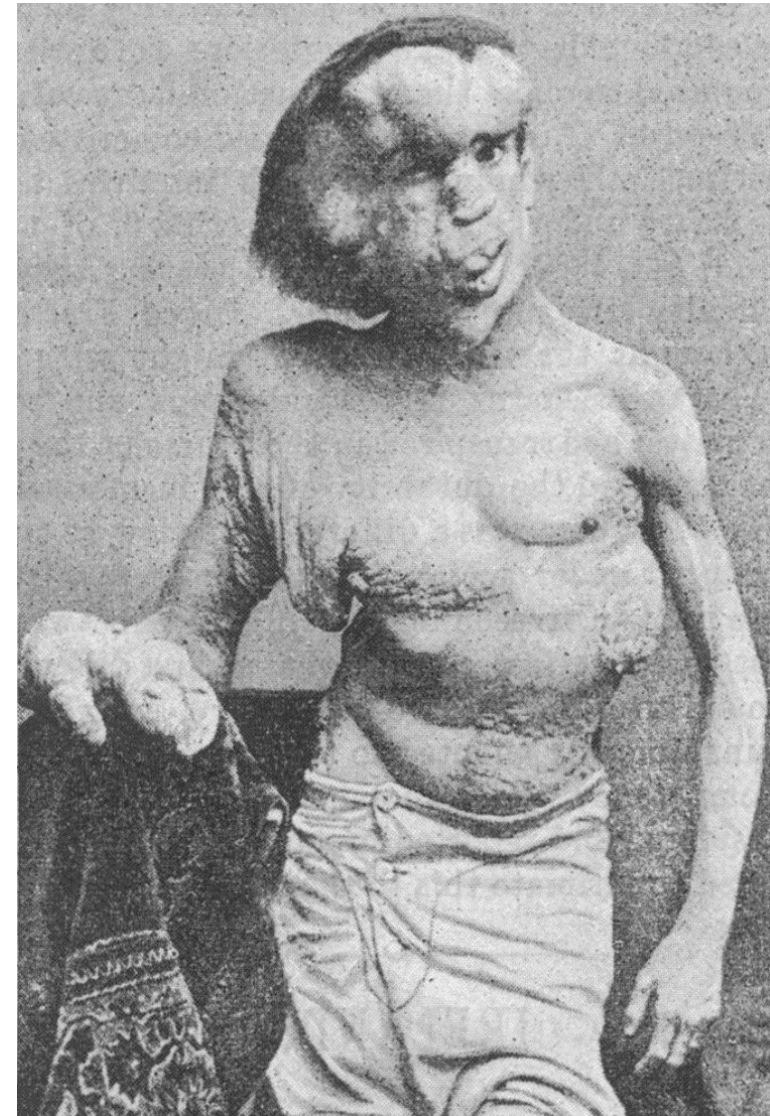
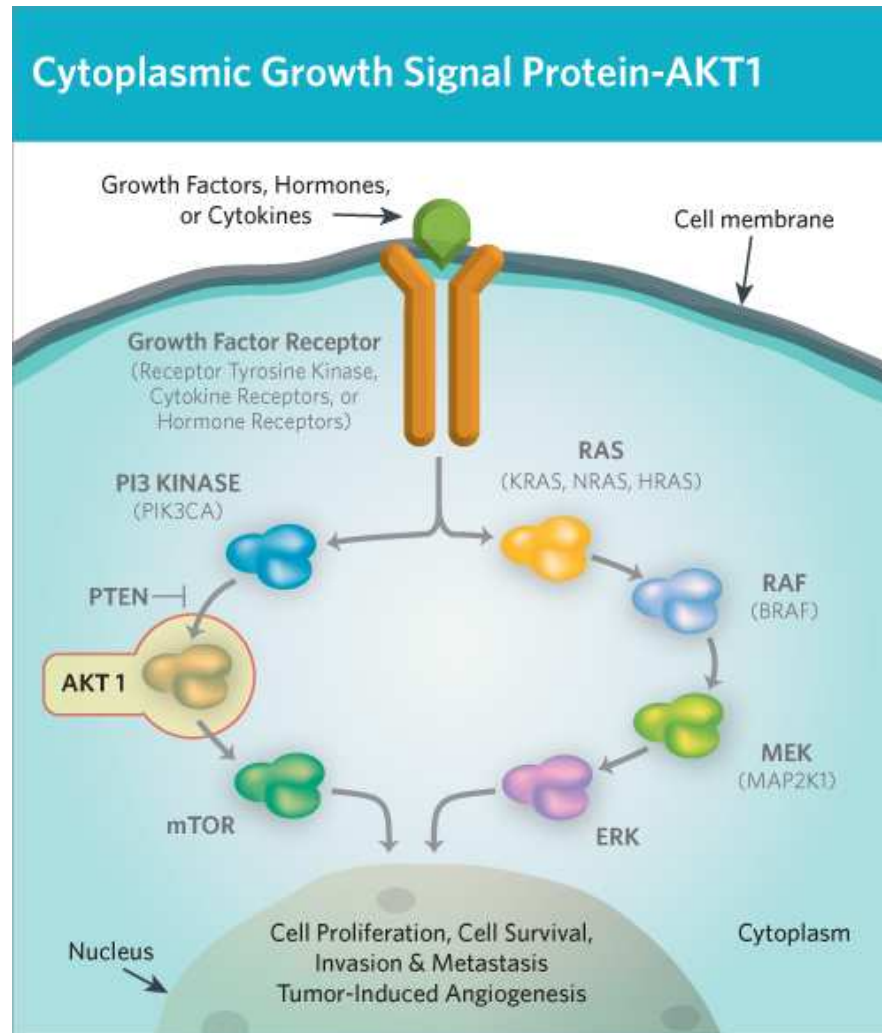
- ❑ **Growth**
- ❑ **Morphogenesis** (literally, the “creation of form”)

Thereby creating an embryo of normal size and shape, containing organs of the appropriate size, shape, and location, and consisting of tissues and cells with the correct architecture, structure, and function.



# Dysregulation of growth

Mutations AKT1  
Proteus syndrome







Mutations PIK3CA



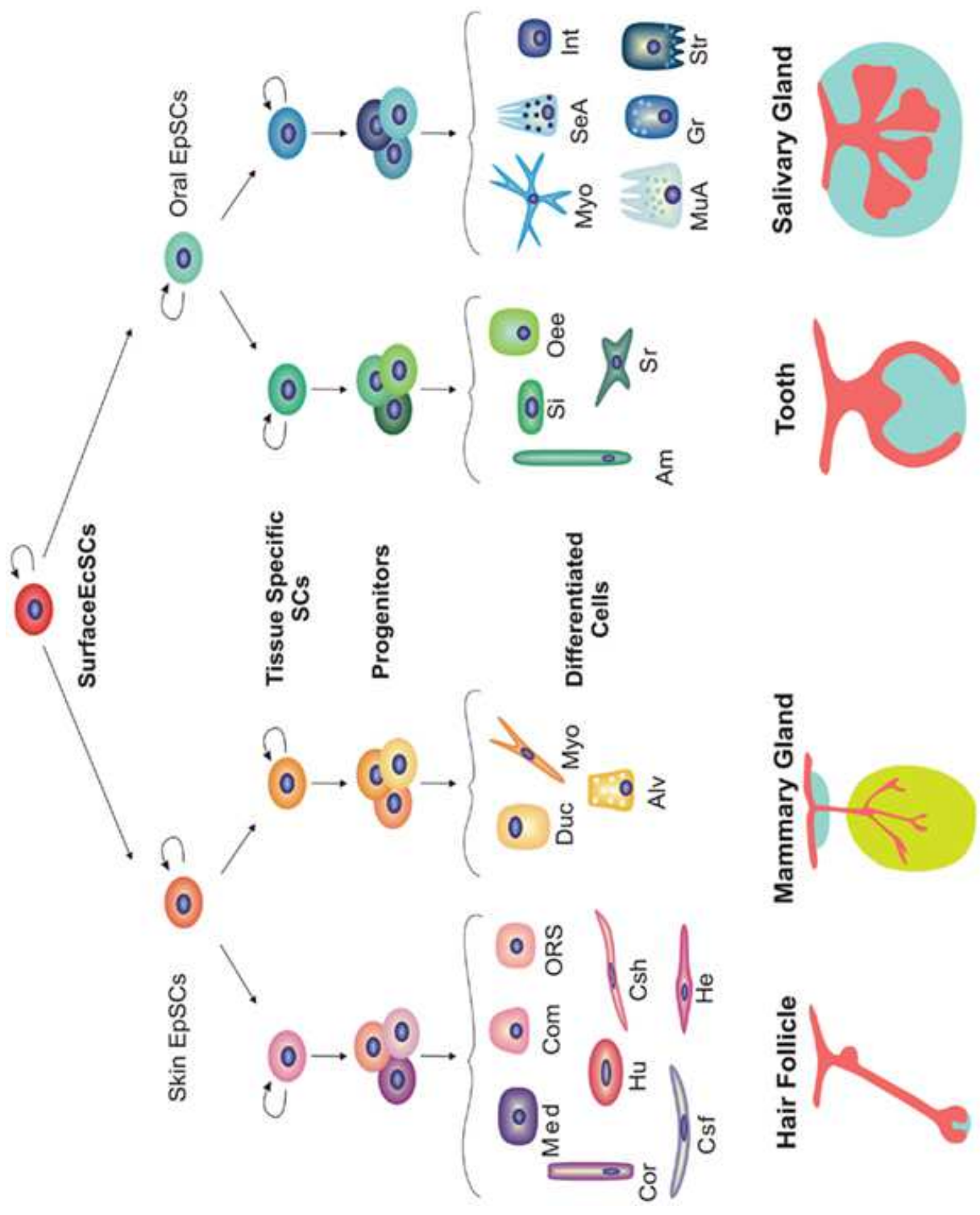
Mutations mTOR



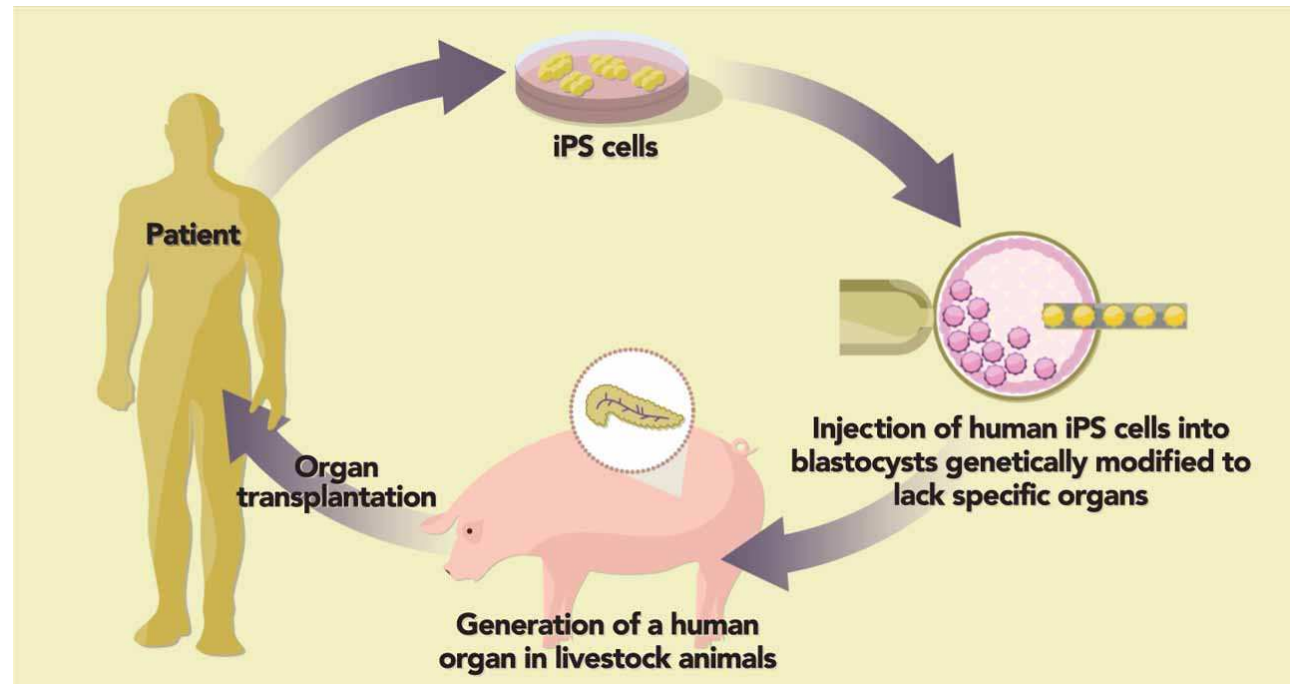
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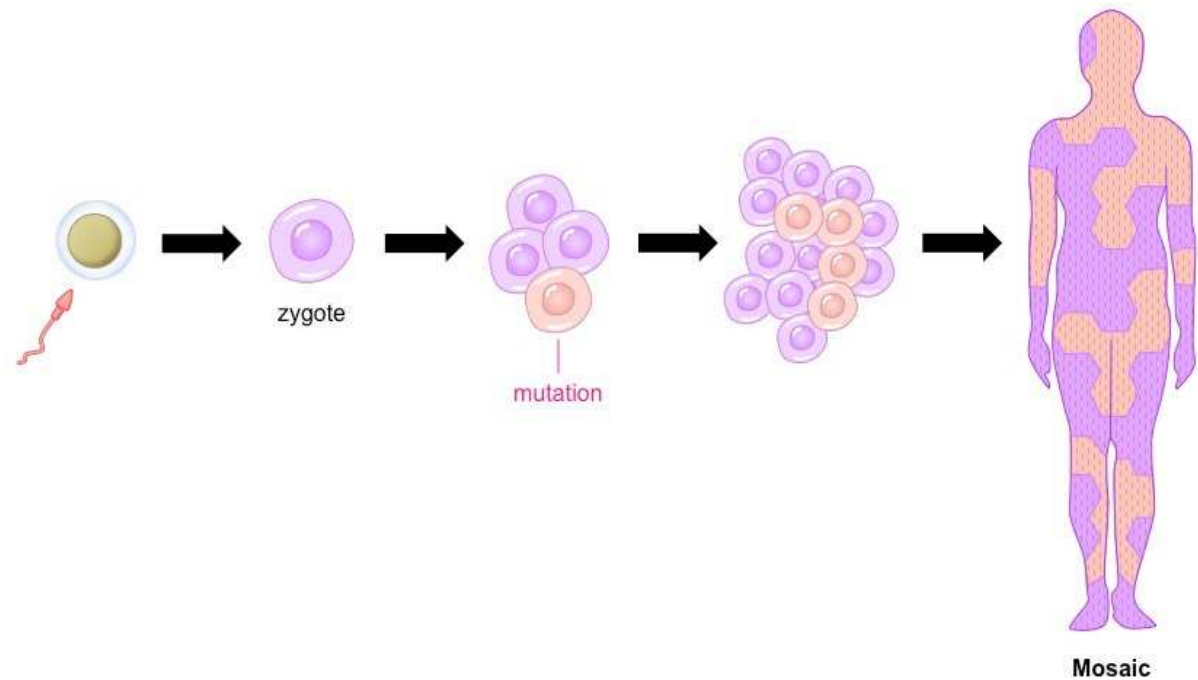
- ❑ **Undifferentiated cell** undergoes the **process of differentiation**, through a series of discrete steps in which it manifests various distinct functions or attributes until it reaches its **ultimate destination**, referred to as its **fate**
- ❑ **Early during differentiation**, a cell undergoes **specification** when it acquires **specific characteristics** but **can still be influenced by environmental** cues (signaling molecules, positional information) to change its ultimate fate
- ❑ A cell either irreversibly acquires attributes or has irreversibly been committed to acquire those attributes, referred to as **determination**
- ❑ With the exception of the germ cell and stem cell compartments, all cells undergo specification and determination to their ultimate developmental fate



# Chimerism

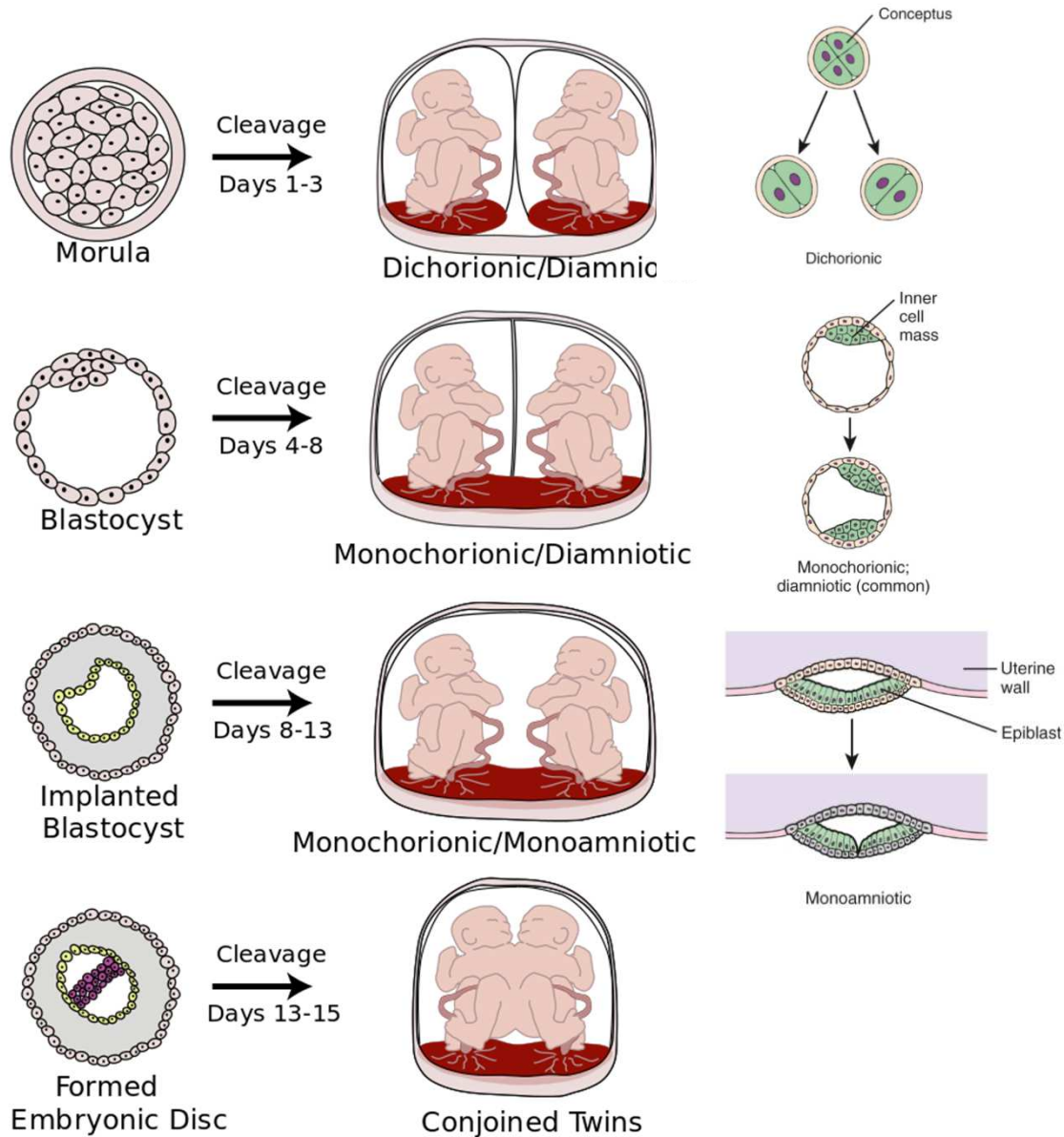


# Mosaicism





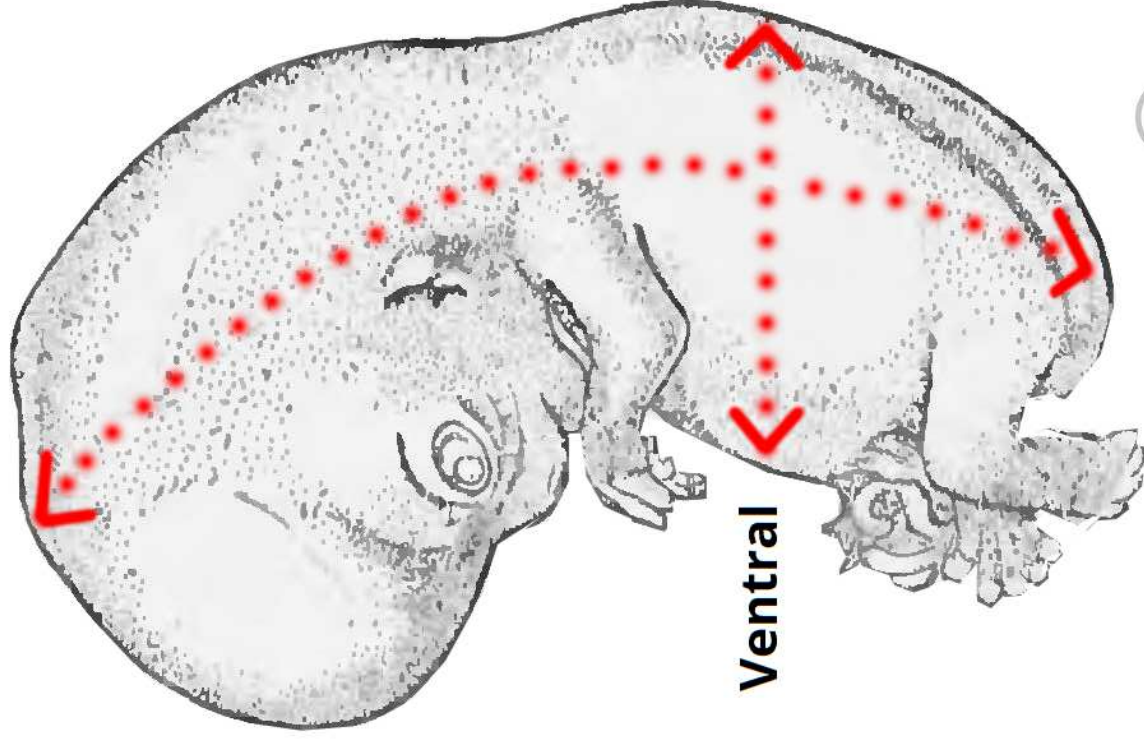
# Regulative Development and Twinning



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**Cephalic/cranial**



**Ventral**

**Dorsal**

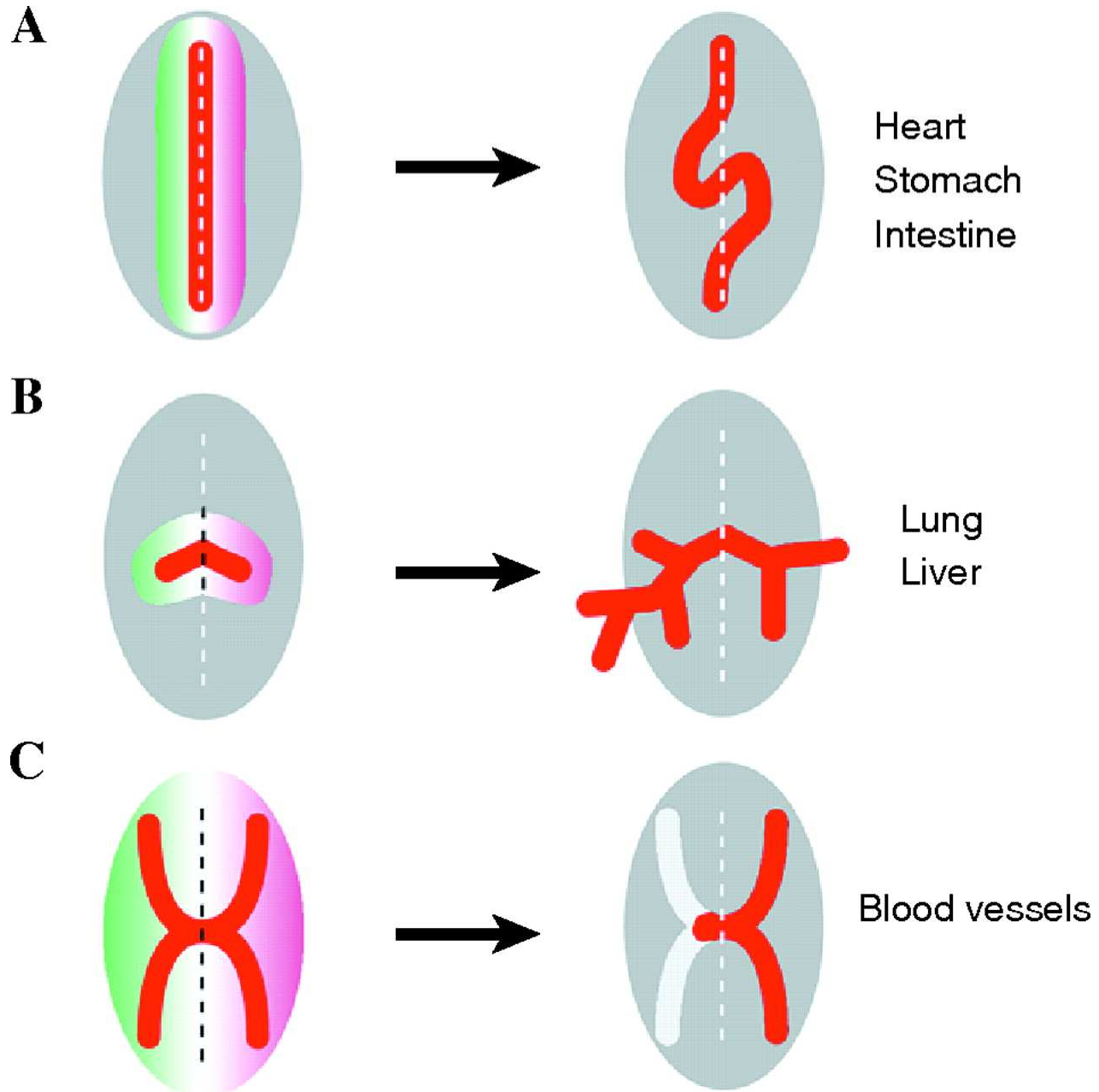
**Caudal**

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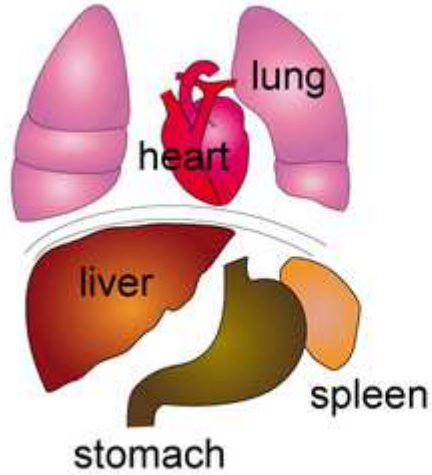


Left-Right axis

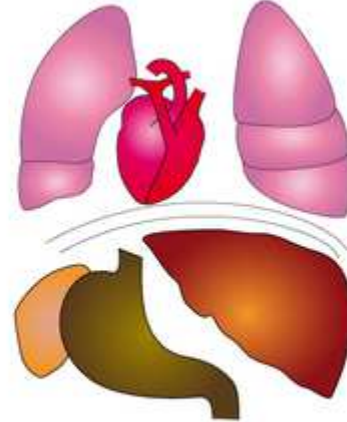




*situs solitus*



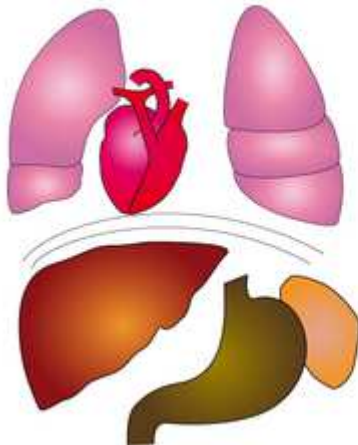
*situs inversus totalis*



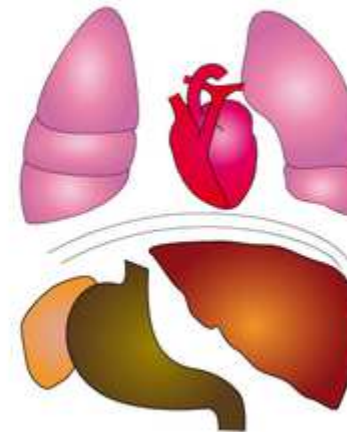
*left isomerism (polysplenia)*



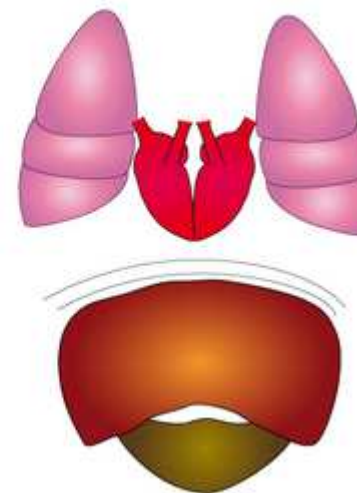
*situs inversus thoracalis*



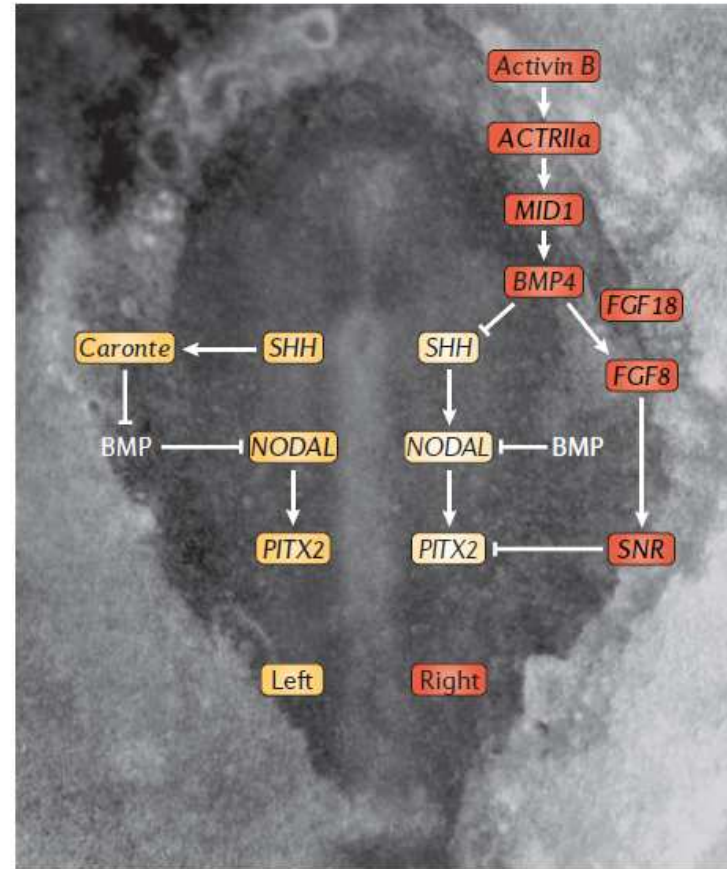
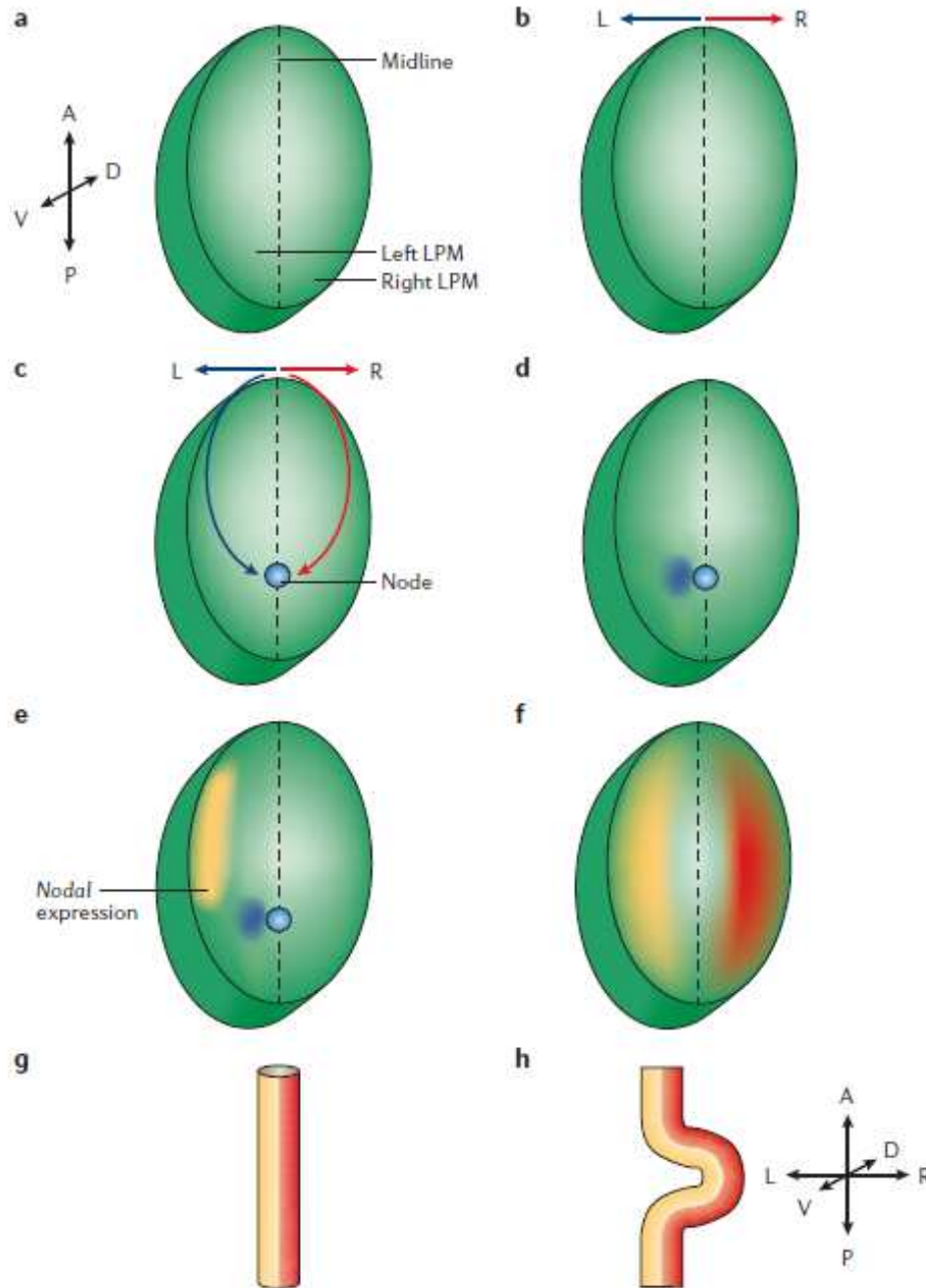
*situs inversus abdominalis*



*right isomerism (asplenia)*



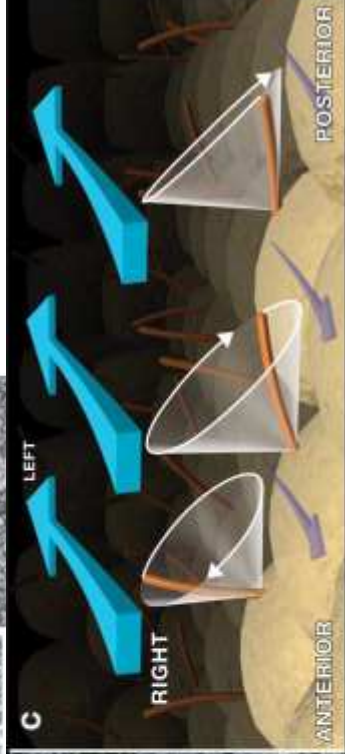
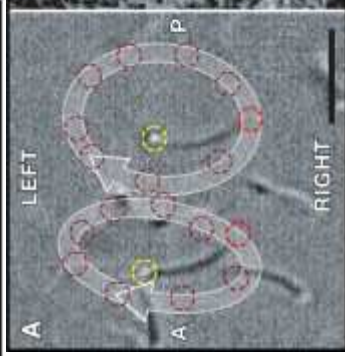
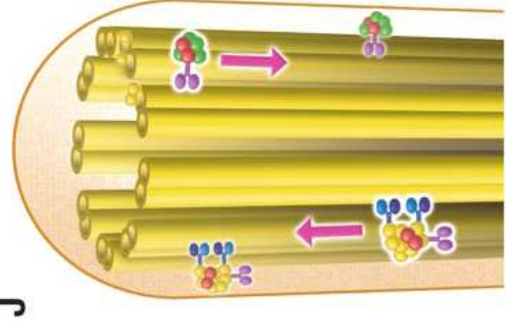
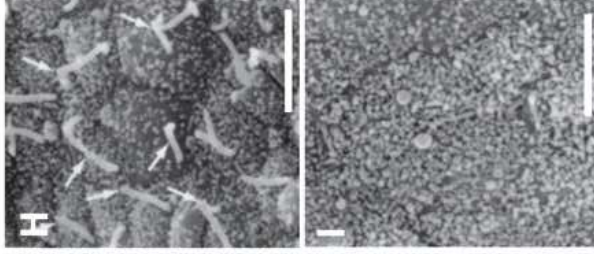
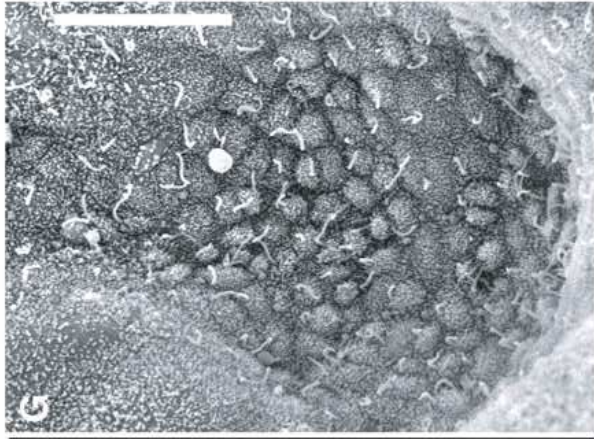
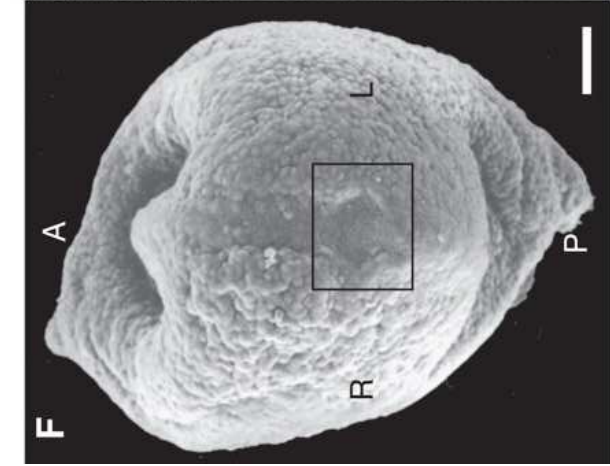
Heterotaxy is defined as an abnormality where the internal thoraco-abdominal organs demonstrate abnormal arrangement across the left-right axis of the body.



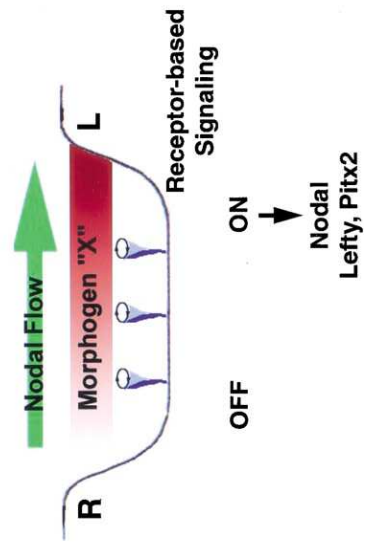
Raya and Belmonte, Nature Reviews Genetics, 2006



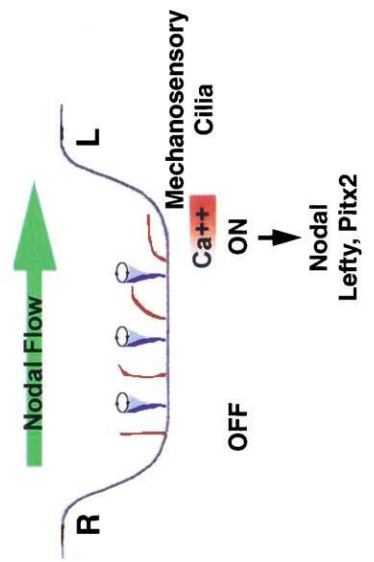


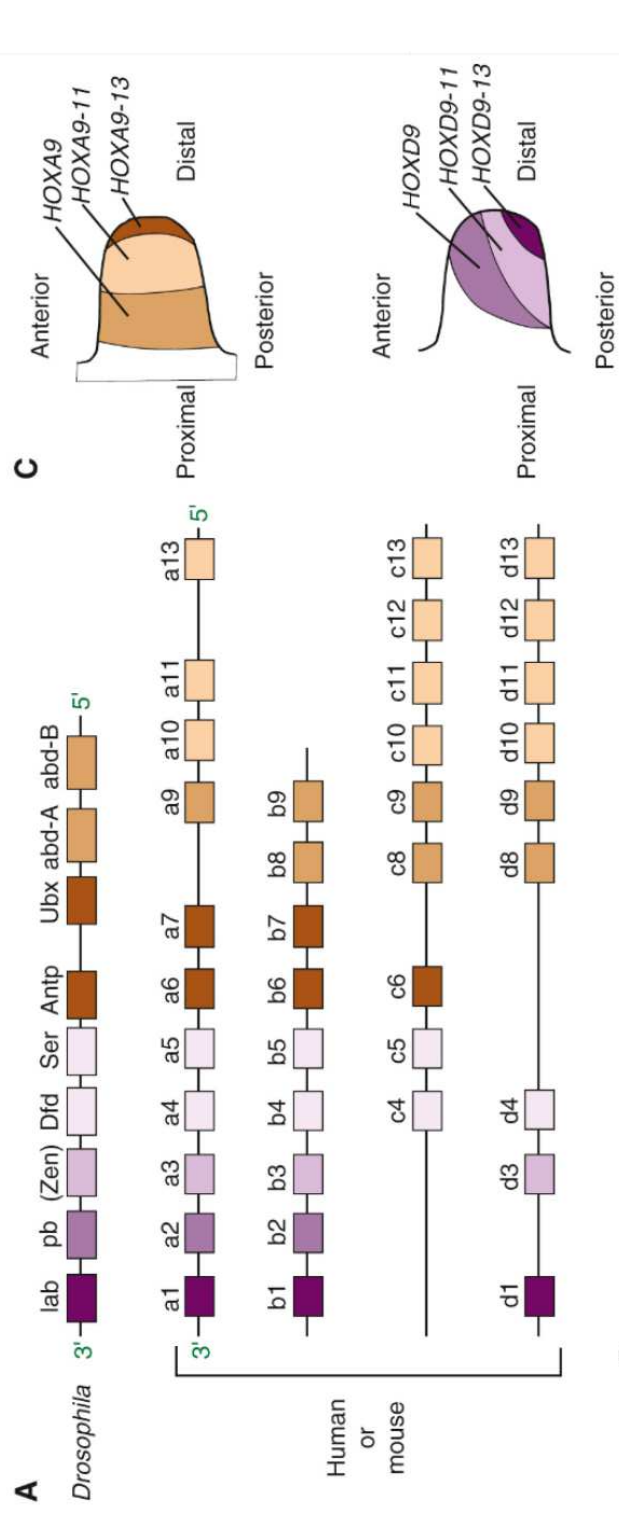
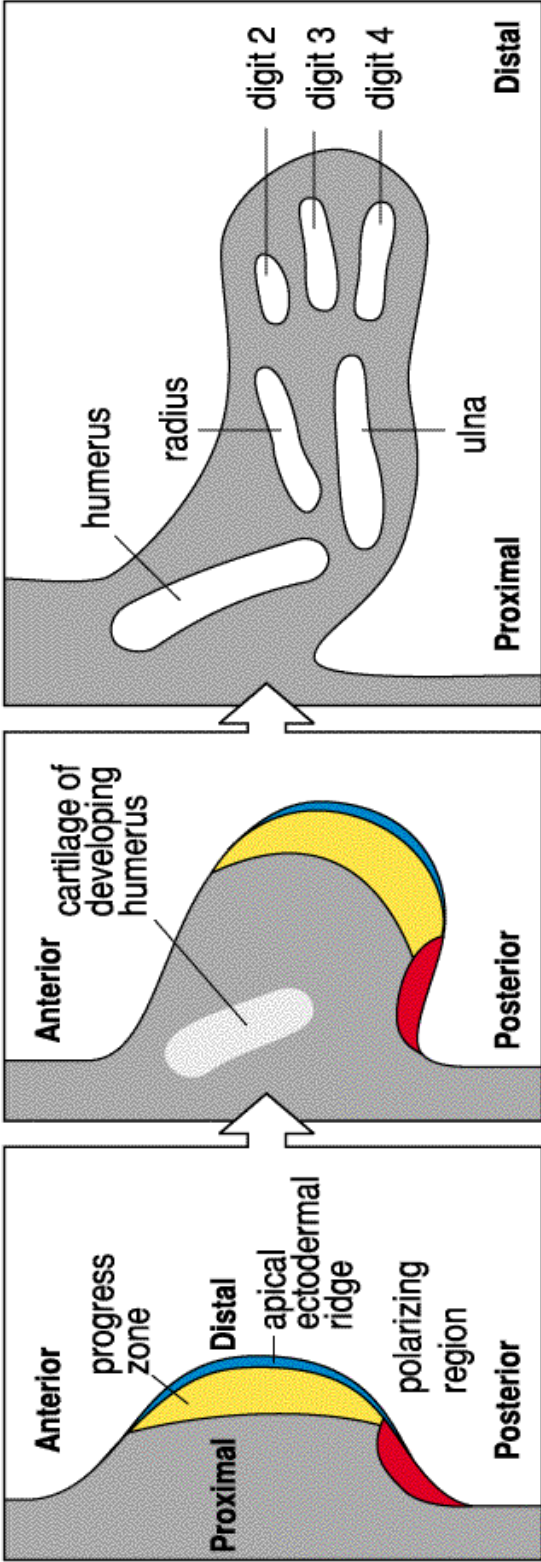


**A**



**B**





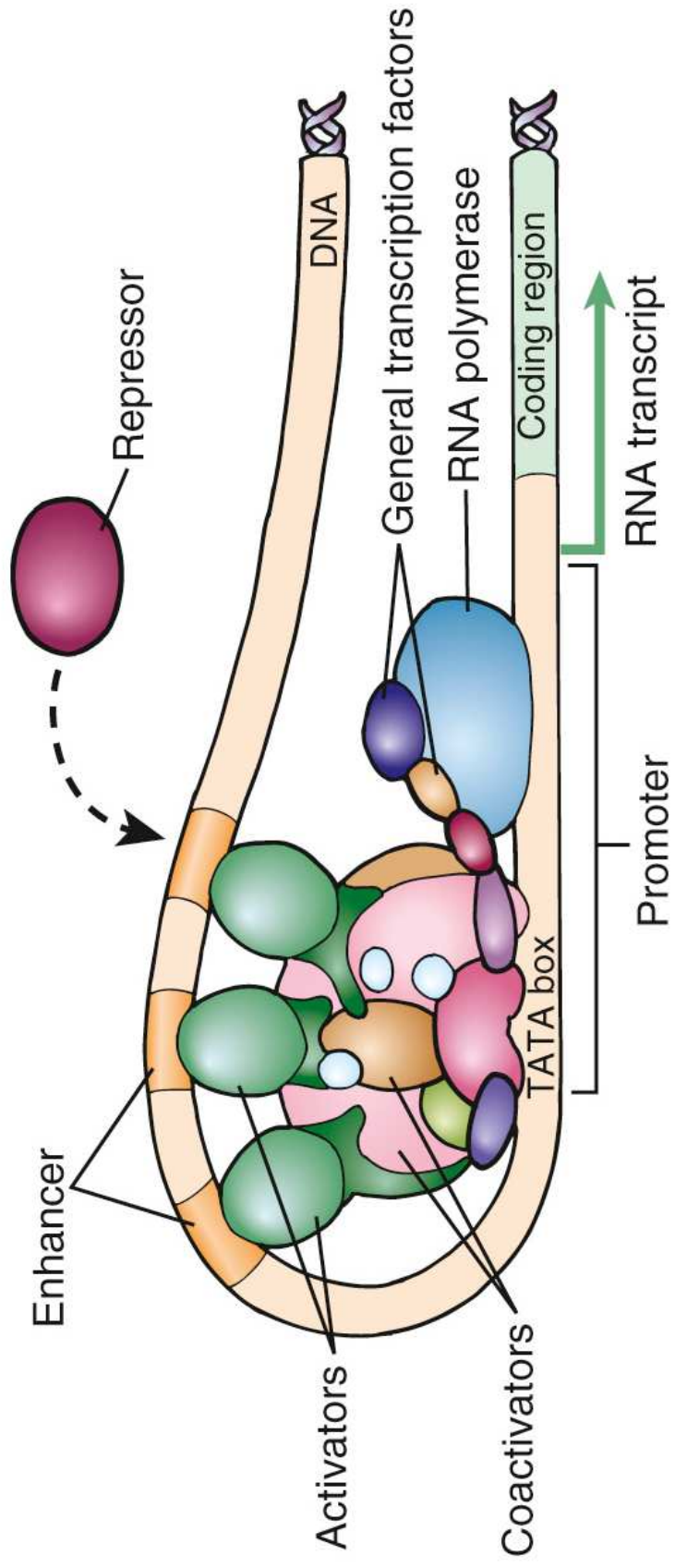


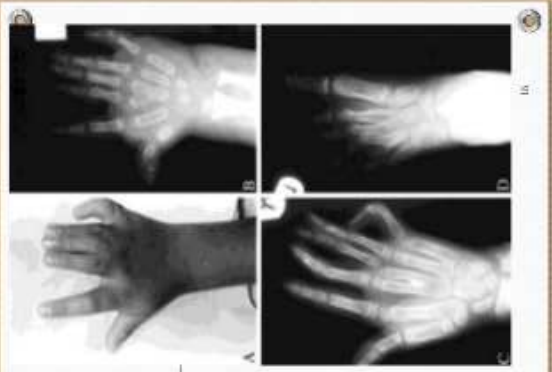
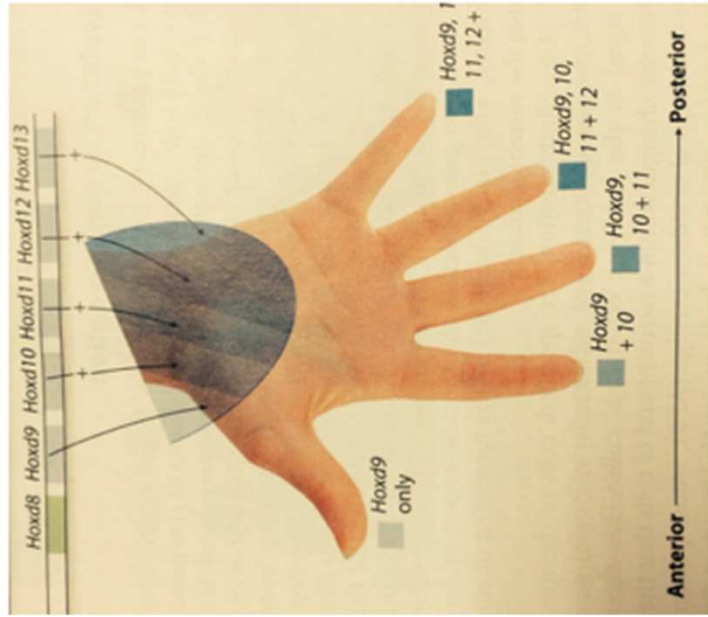
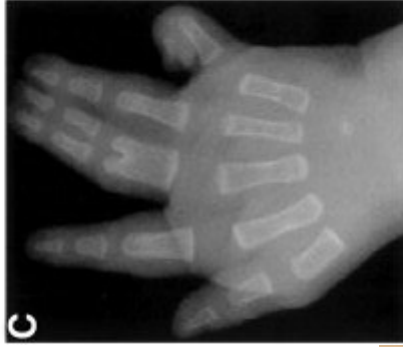
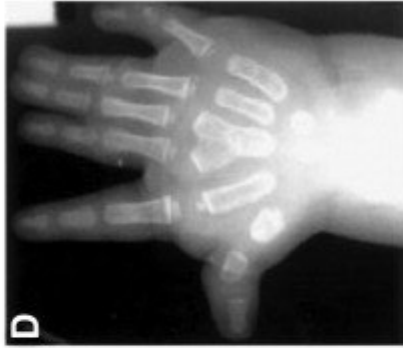
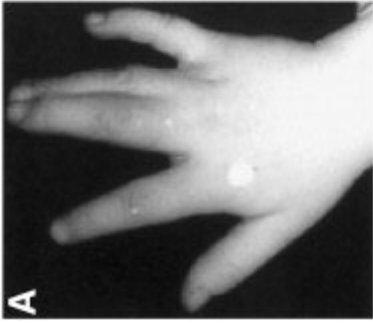


Ulnar dimelia or mirror hand syndrome

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Synpolydactyly

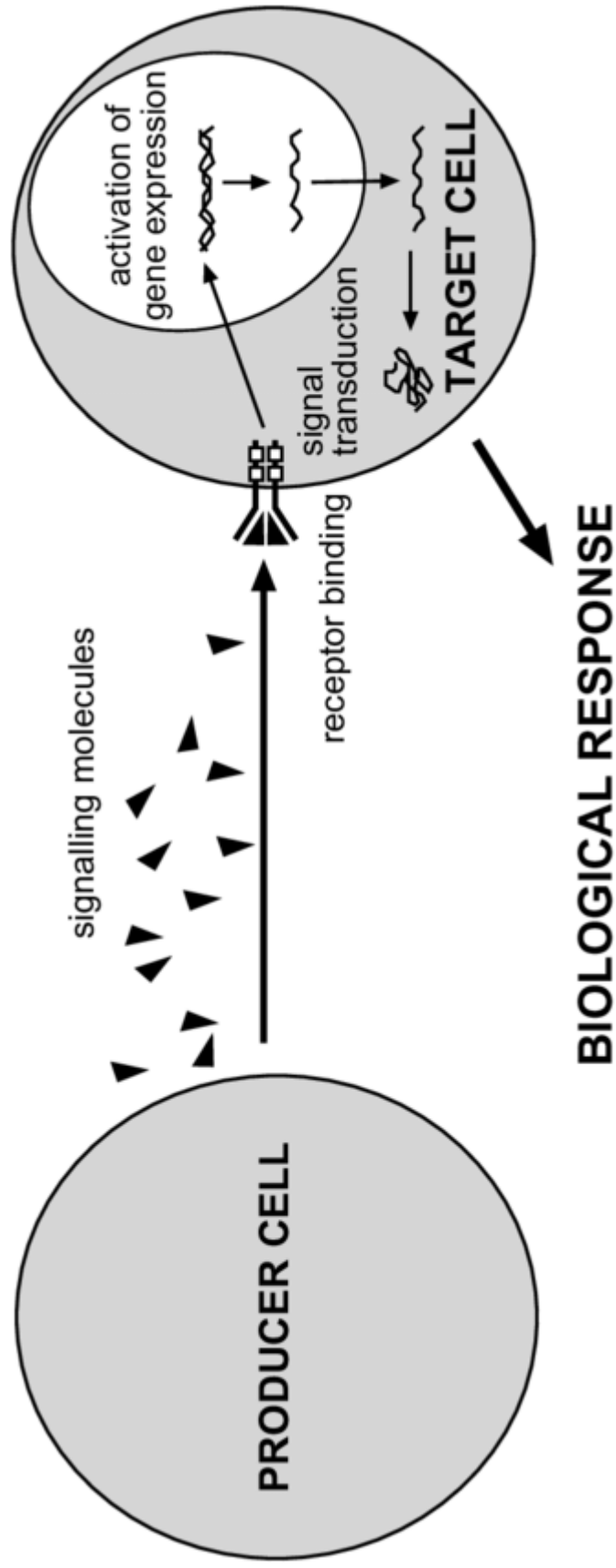


Mutation in the HOXD13 gene.

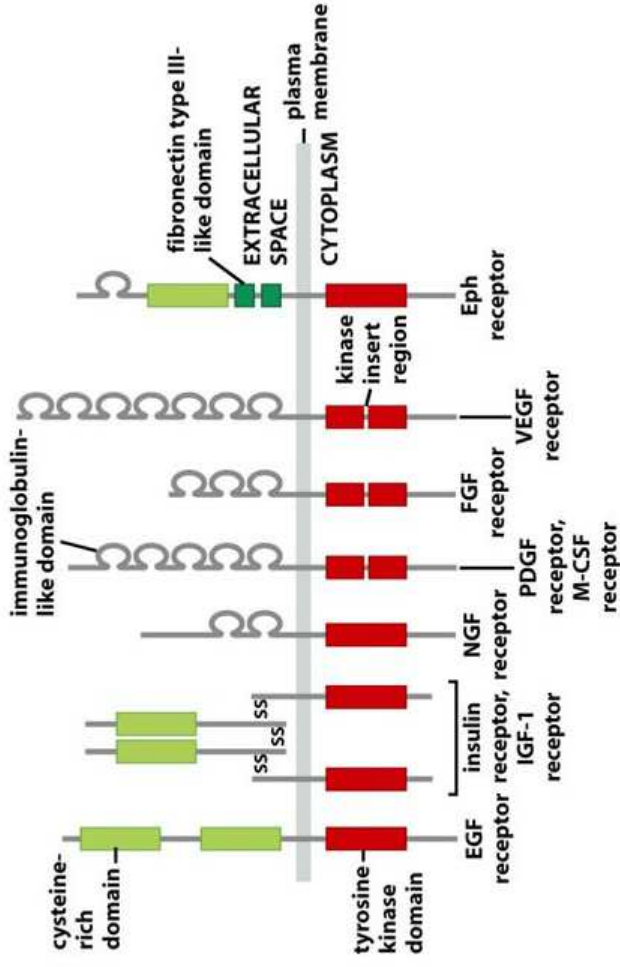


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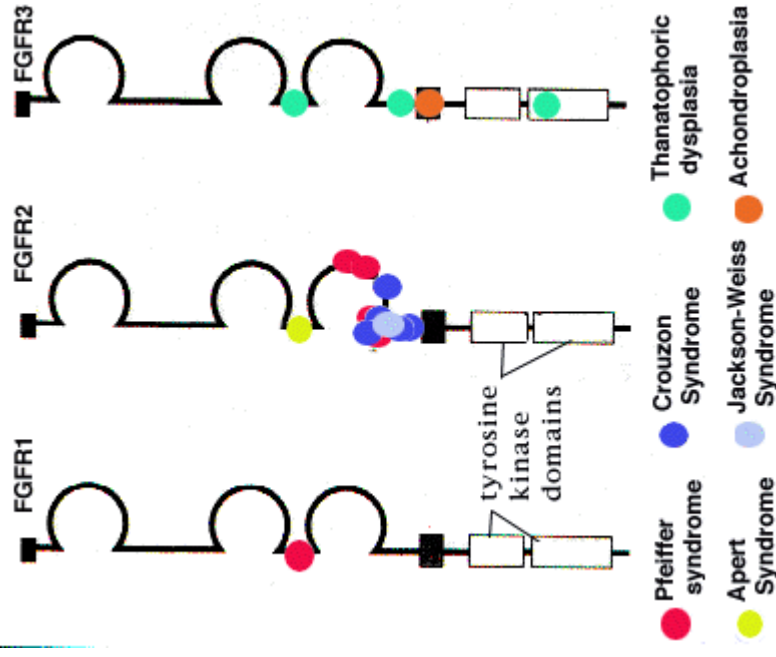
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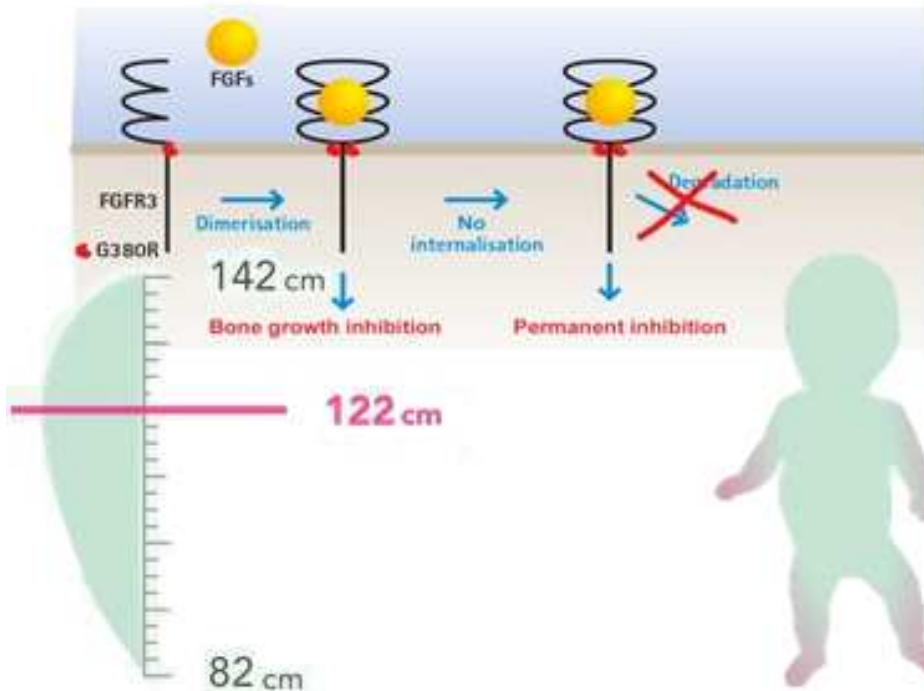
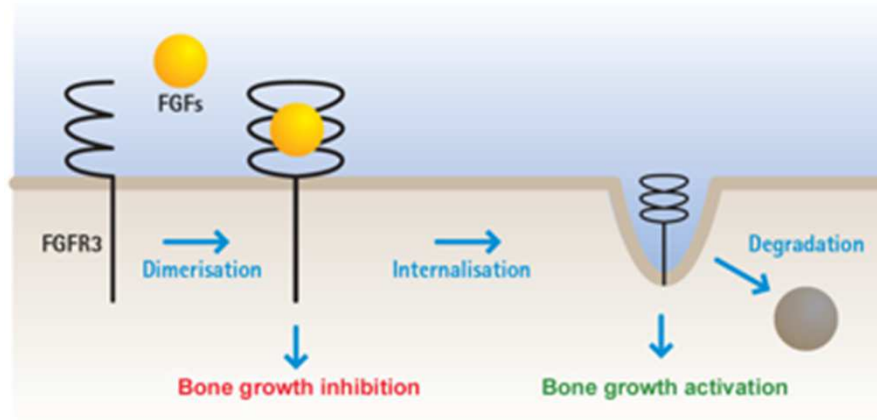
# Structure of tyrosine kinase receptors



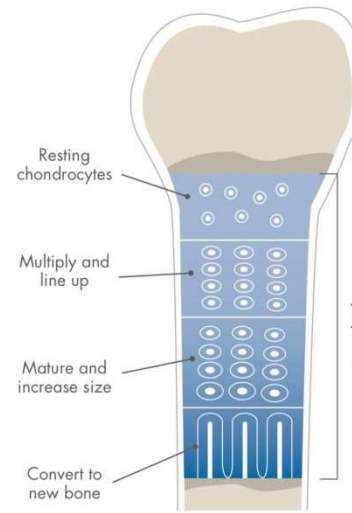
IGF-1: insulin-like growth factor-1, NGF: nerve growth factor,  
 PDGF: platelet-derived growth factor, FGF: fibroblast growth factor,  
 VEGF: vascular endothelial growth factor, Eph: ephrin



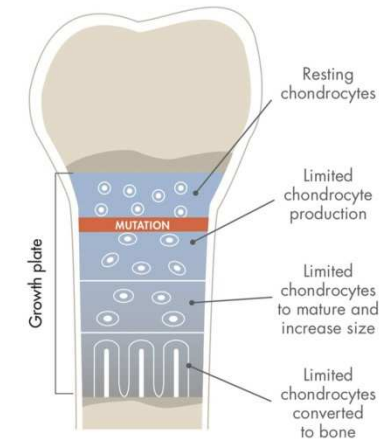
# Achondroplasia



Typical Bone Growth<sup>3</sup>



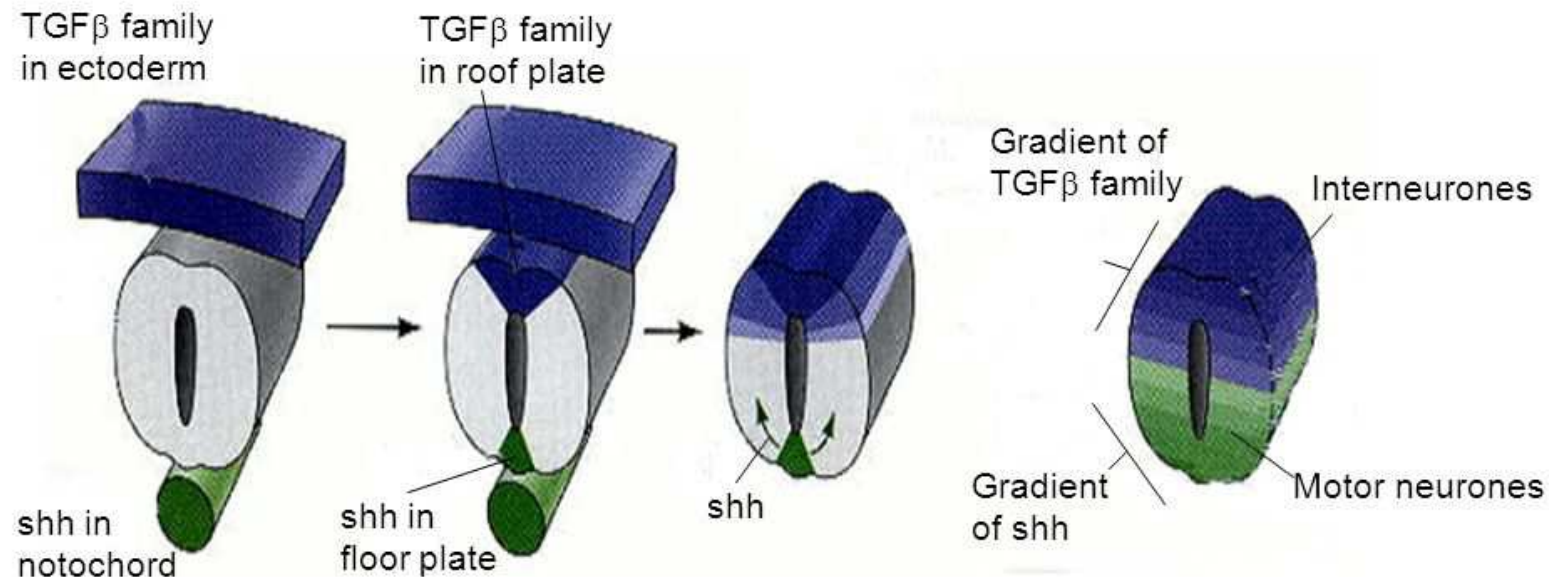
Irregular Bone Growth in Achondroplasia<sup>1,2</sup>





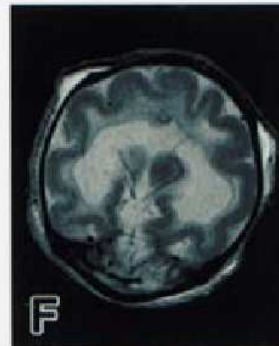
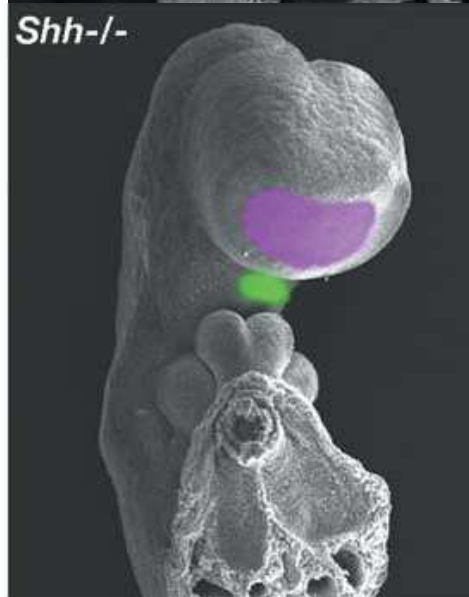
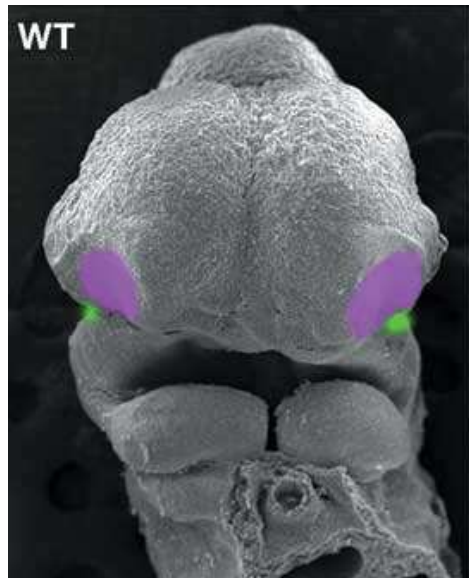
# Example of the gene sonic hedgehog (*SHH*)

## *Dorsal-ventral axis in the Neural Tube*



1. The notochord produces Sonic hedgehog (Shh) and induces the ventral neural tube to become floor plate and produce Shh
2. The ectodermal cells produce members of the Transforming growth factor (TGF-β) family and induce the dorsal neural tube to become roof plate and to start to produce the same proteins
3. Two gradients are created of TGF-β and Shh
4. Different concentrations of these proteins activate the expression of different sets of genes so that cells differentiate to become inter-neurons and motor neurones

# SHH mutations: holoprosencephaly

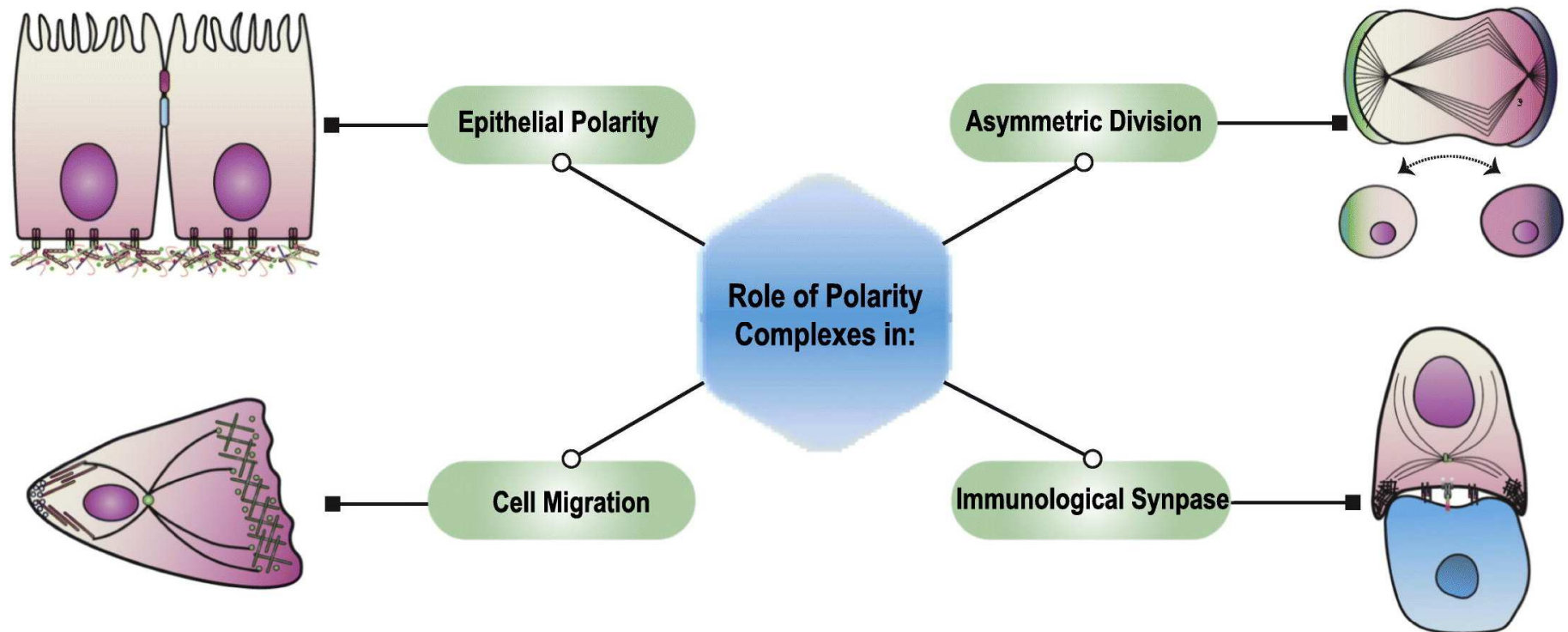
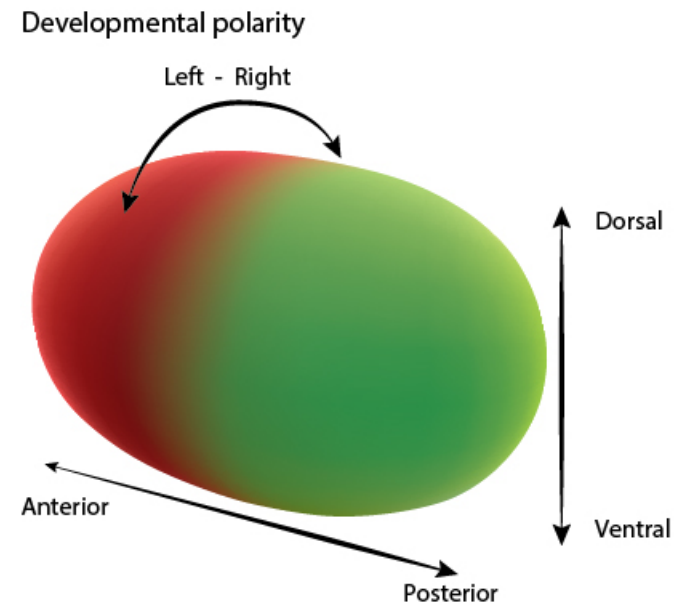


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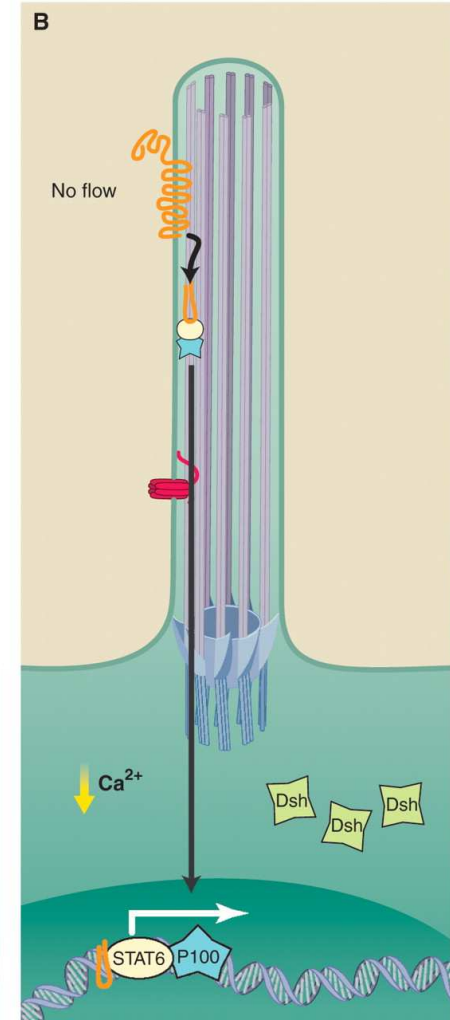
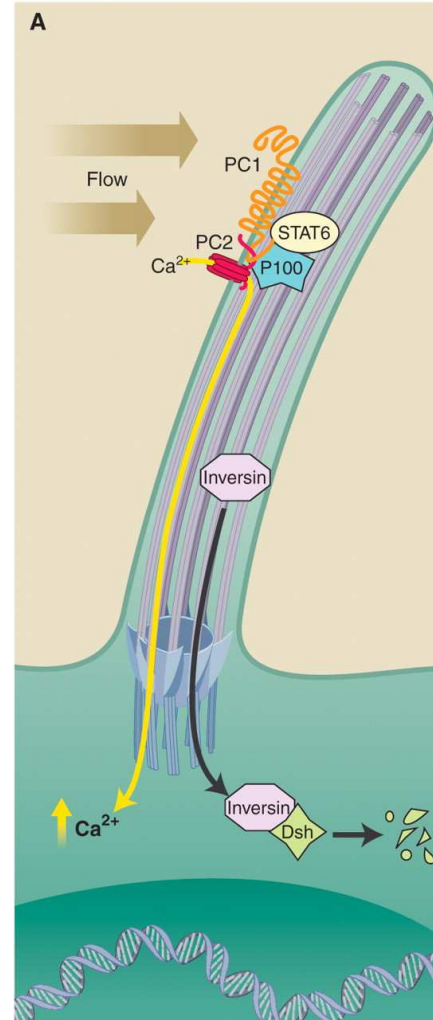
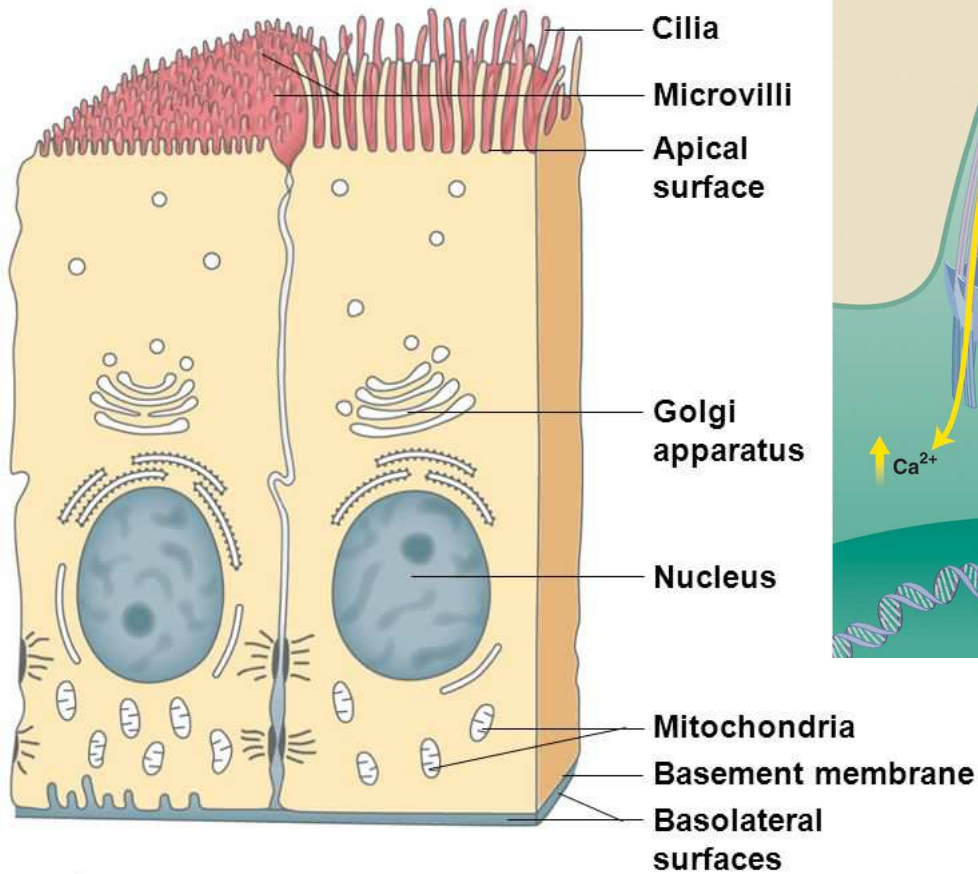
- Cells must organize themselves with respect to their position and polarity in their microenvironment
- The acquisition of polarity by a cell can be viewed as the cellular version of axis determination with respect to the development of the overall embryo



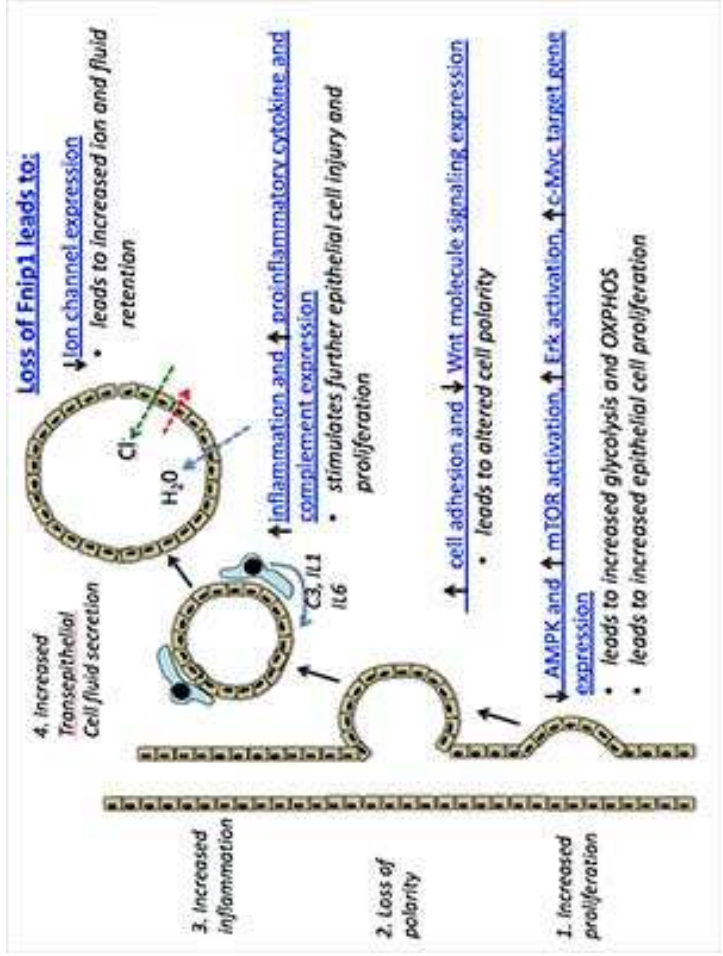
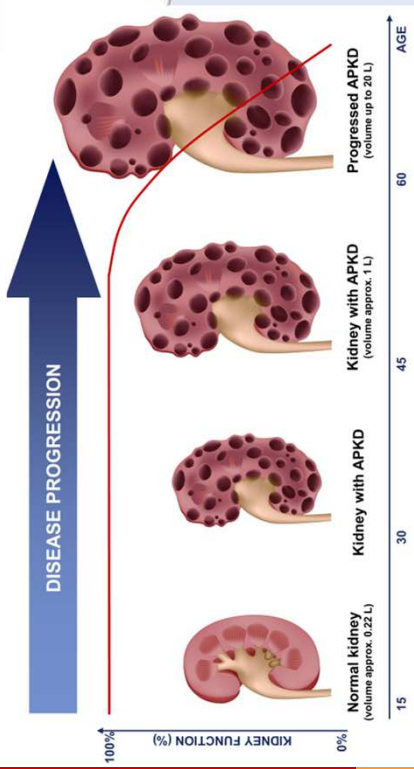
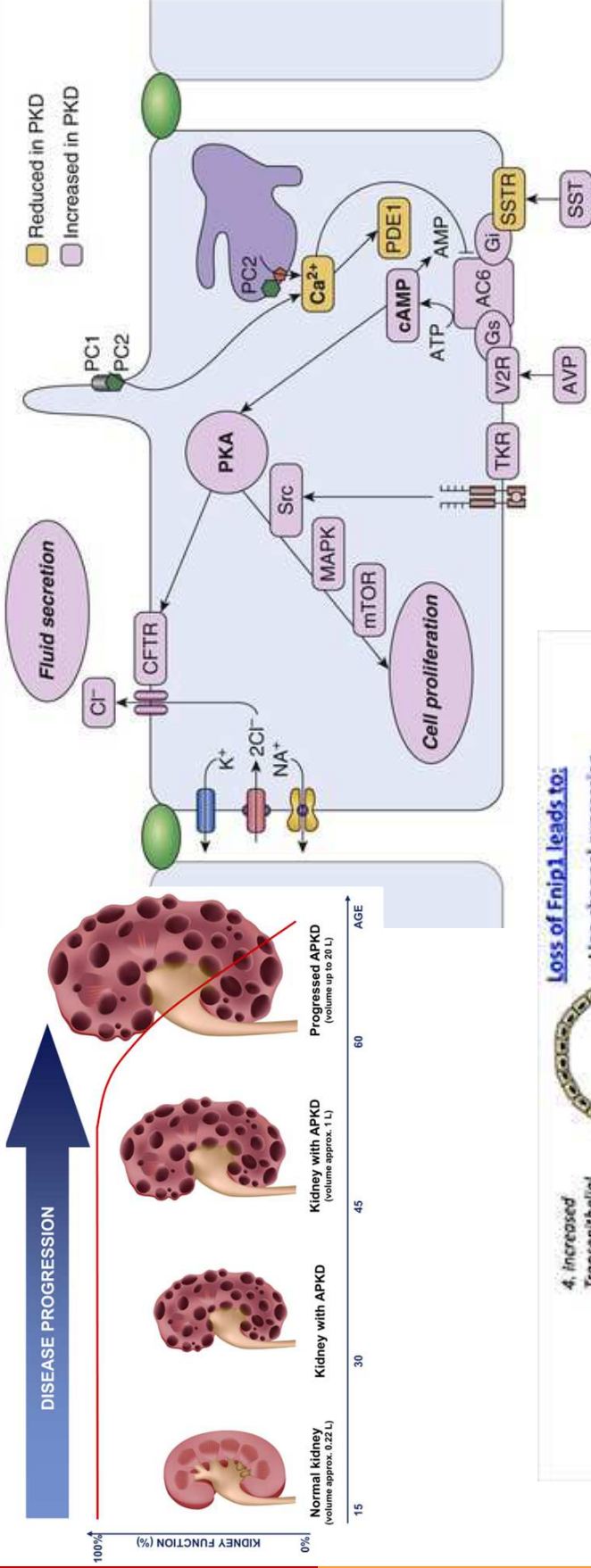


# Primary cilium

Figure 4-1 The Polarity of Epithelial Cells



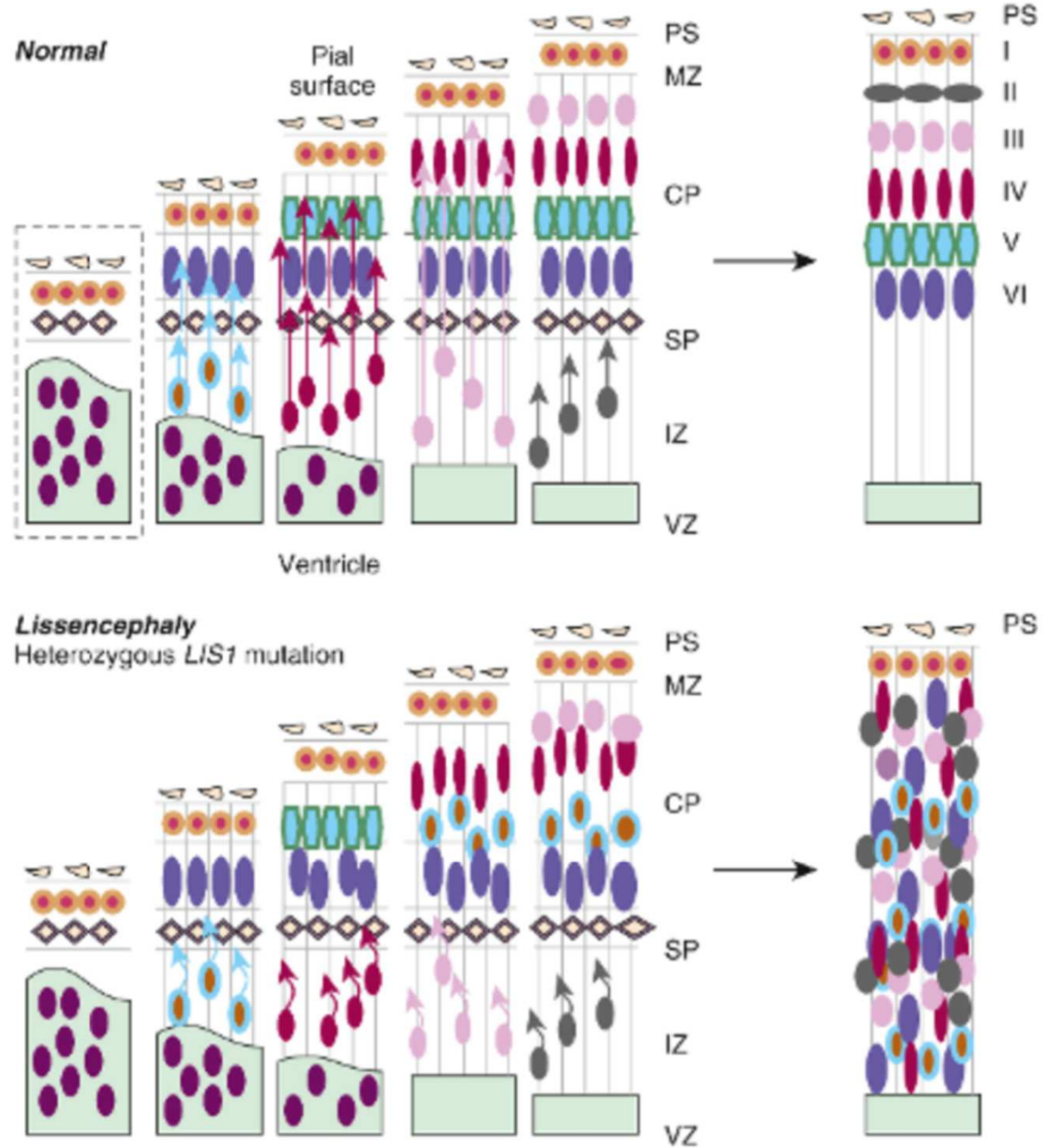
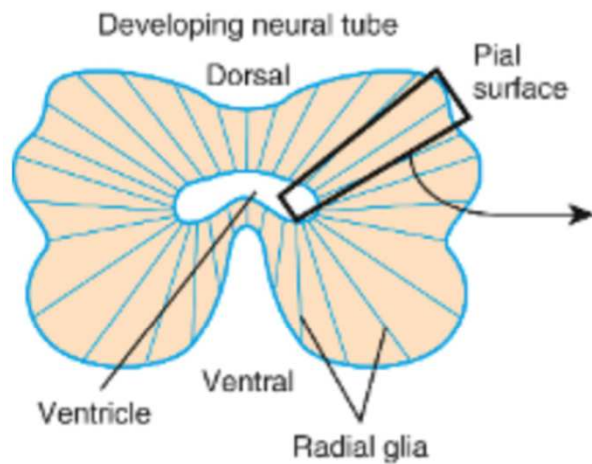
# Signaling Pathways in Polycystic Kidney Disease



# Chapters

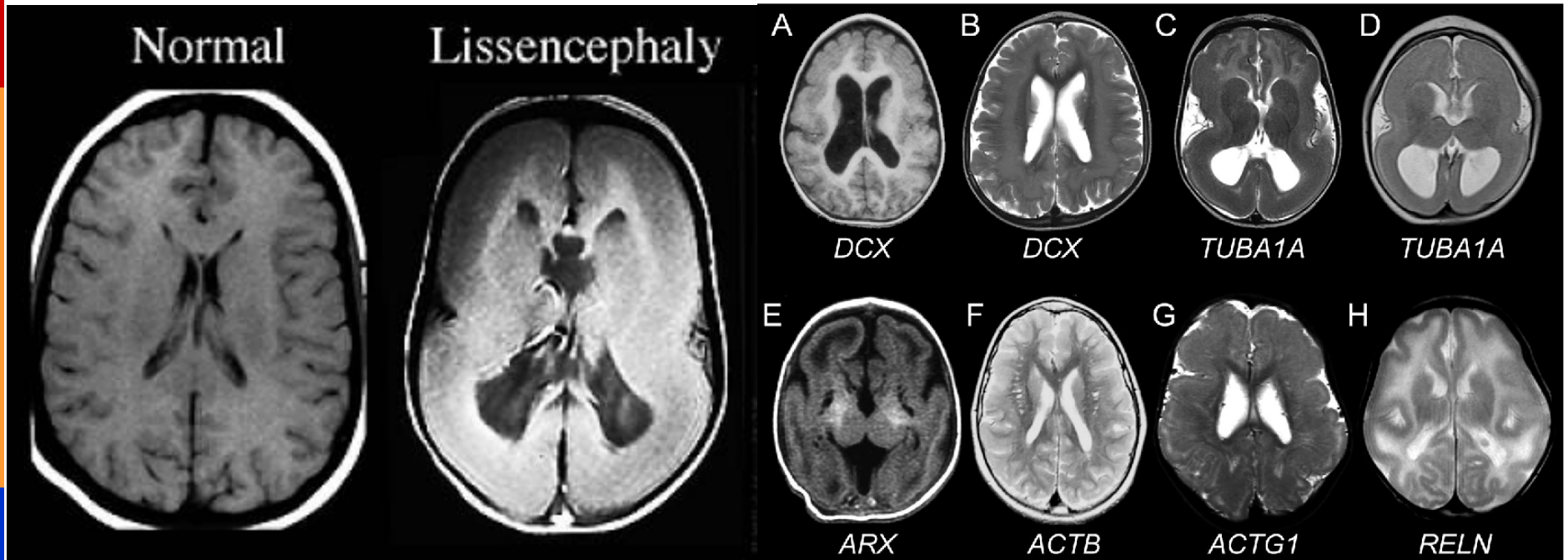
- ❑ **Basic Concepts of Developmental Biology**
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# Neuronal migration in cortex

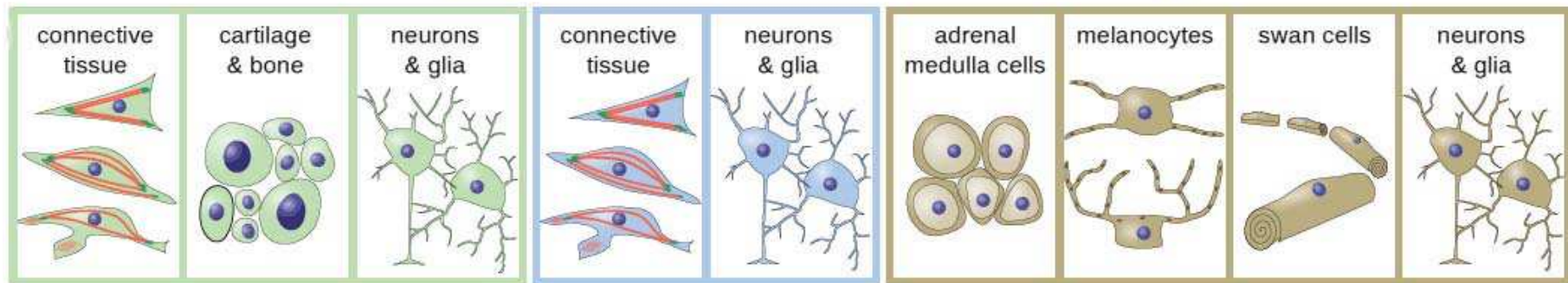
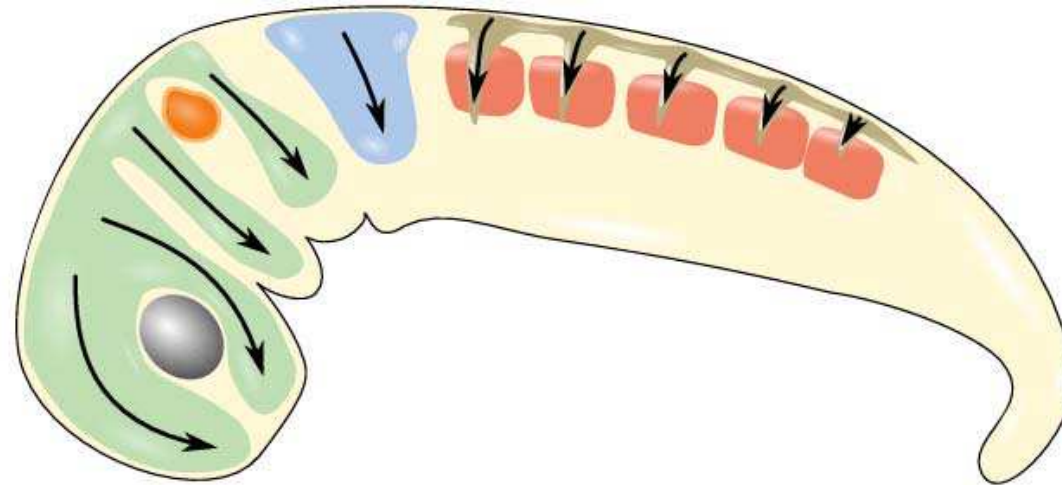




# Neuronal migration defects in cortex



# Neural crest cells



skull bones

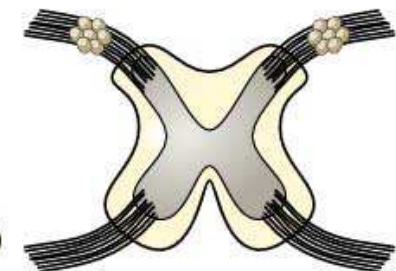
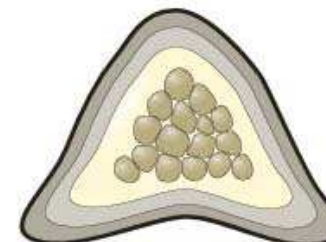
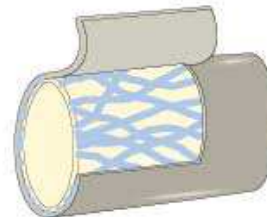
facial structures

heart outflow tract

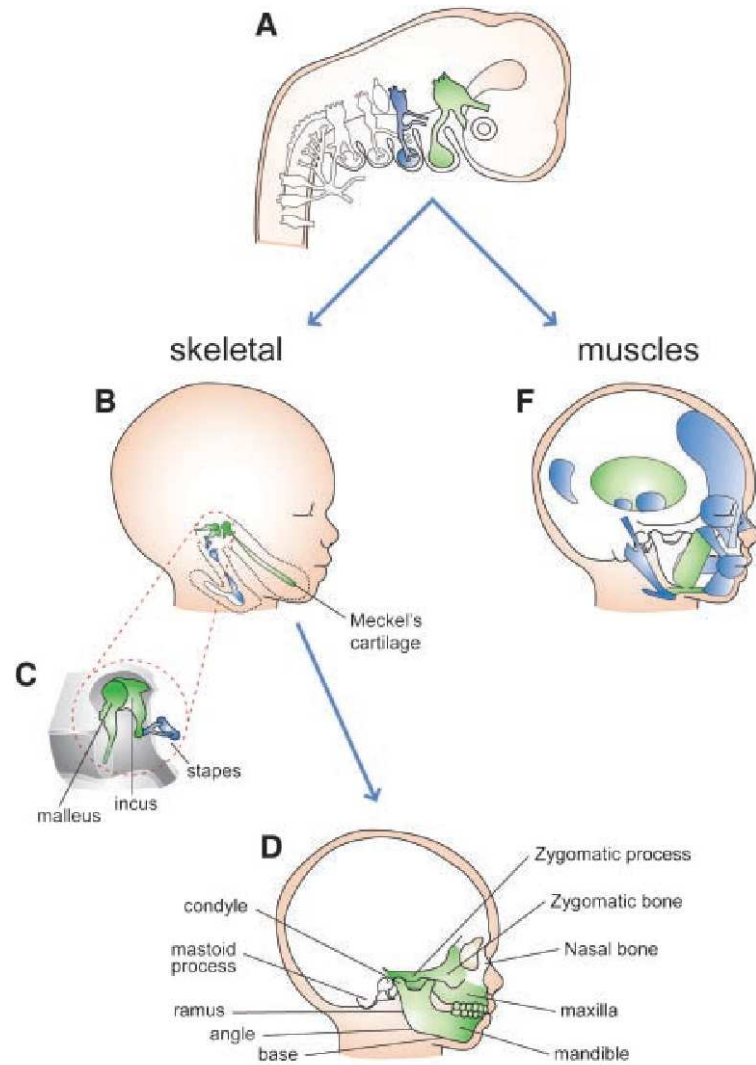
enteric nervous system

adrenal medulla

dorsal root ganglia

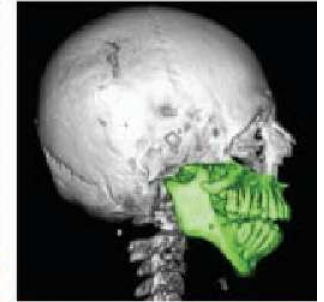
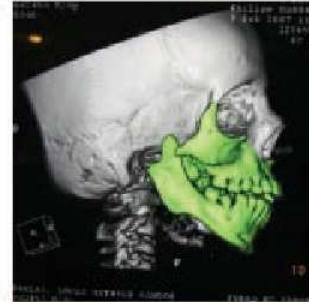
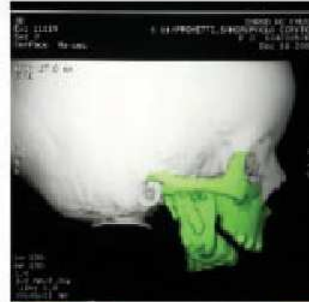


# Neurocristopathies



III

Skull tomography



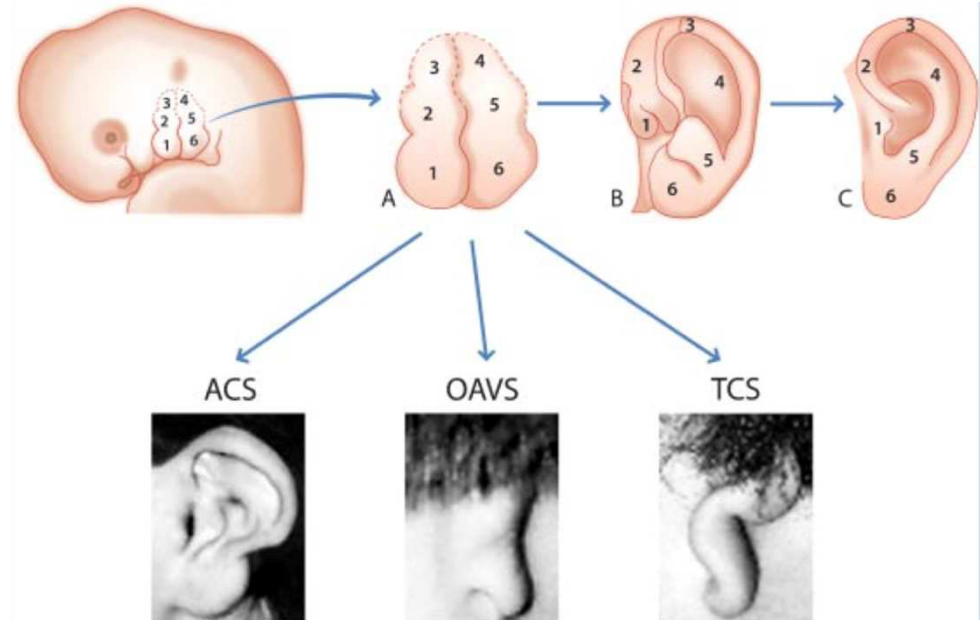
Patients



Auriculo-Condylar syndrome

Oculo-auriculo-vertebral syndrome

Treacher-Collins syndrome



III



# Waardenburg syndrome



## Symptoms:

- ▶ Cleft Lip
- ▶ Constipation
- ▶ Deafness
- ▶ Extremely pale blue eyes or eye colors that do not match
- ▶ Sometimes difficulty in completely straightening the joints
- ▶ Possible slight decrease in intellectual functions
- ▶ White patch of hair or early graying of the hair
- ▶ A wide space between the eyes

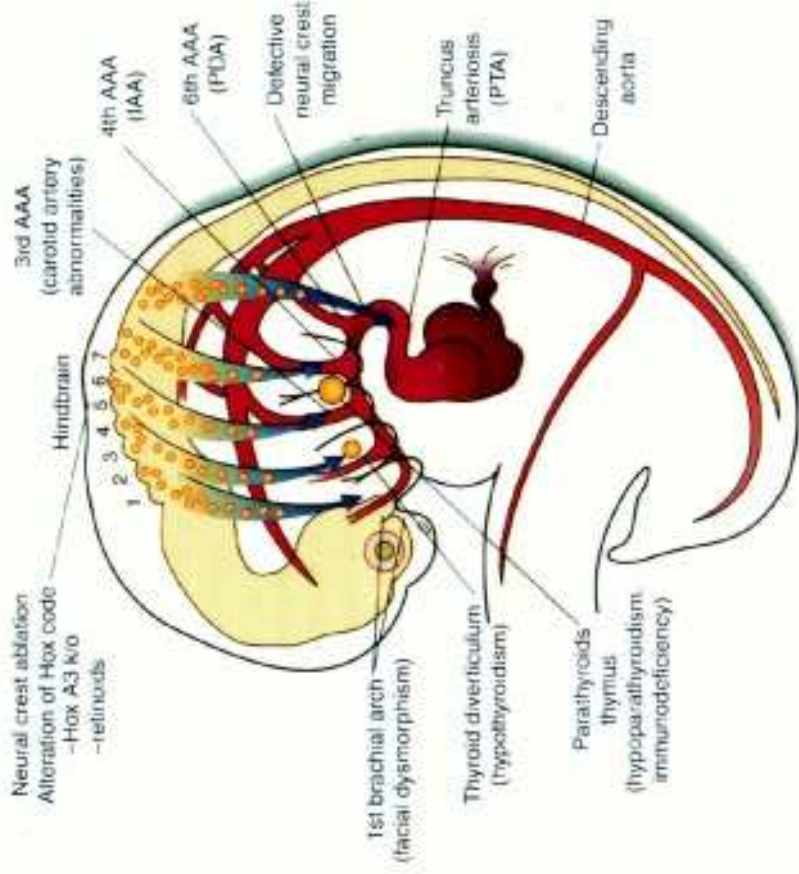




# Velocardiofacial Syndrome/DiGeorge anomaly



- 22q11.2 deletion
- "CATCH 22"
  - Cardiac defects
  - Abnormal face
  - Thymic hypoplasia
  - Cleft palate
  - Hypocalcemia
- Abnormal development of neural crest cells
- Specific facial features
  - low-set ears, wide-set eyes, a small jaw, and a short groove in the upper lip
- Etiology
  - Genetic causes, exposure to retinoic acids, alcohol, and maternal DM



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# Programmed cell death (apoptosis)

- ❑ Critical function in development, necessary for the morphological development of many structures
- ❑ It occurs wherever tissues need to be remodeled during morphogenesis
  - separation of the individual digits
  - perforation of the anal and choanal membranes
  - establishment of communication between the uterus and vagina, ...

# Importance Of Apoptosis

15

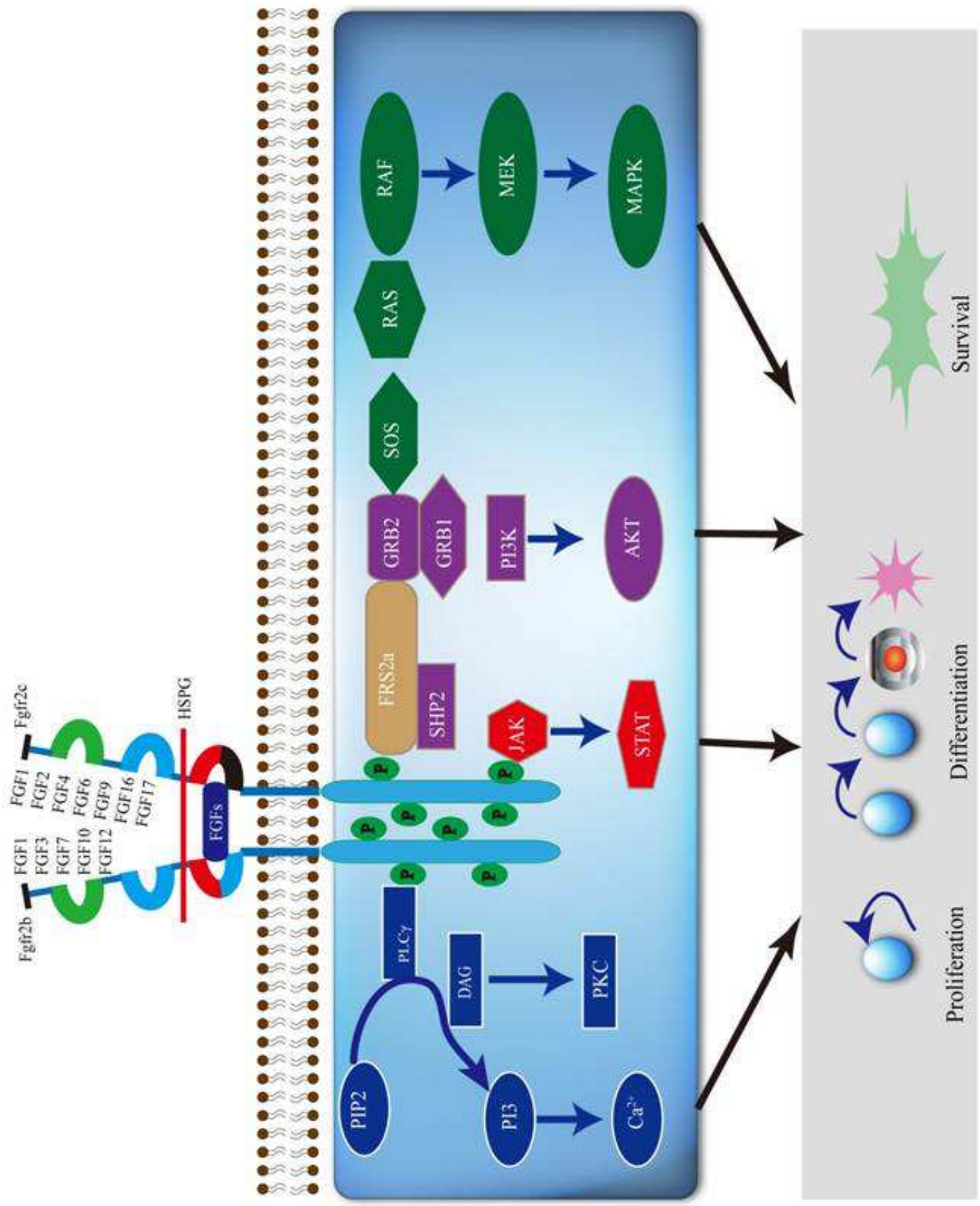
- ❖ Apoptosis is a beneficial and important phenomenon:
  - In embryo
  - 1. During embryonic development, help to digit formation.



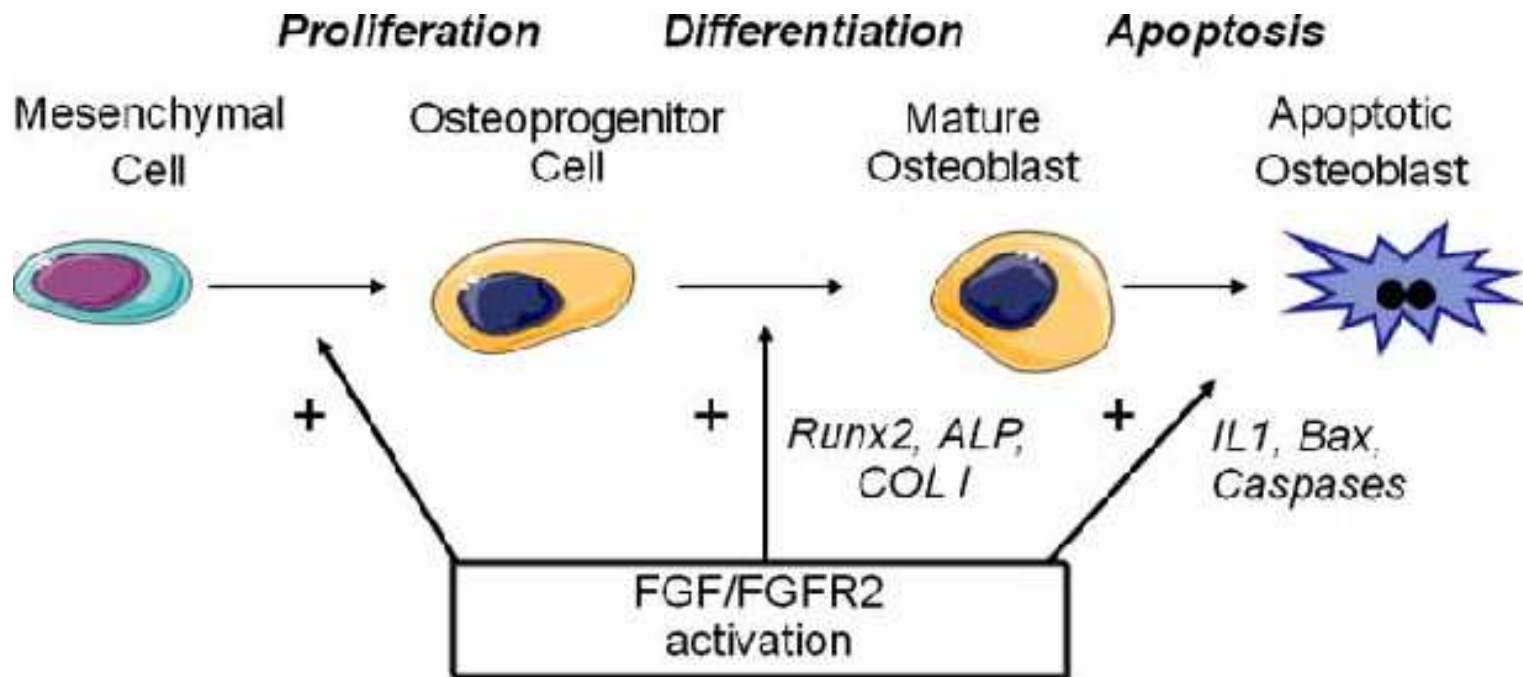
- Lack of apoptosis in humans can lead to webbed fingers called “**syndactyly**”.



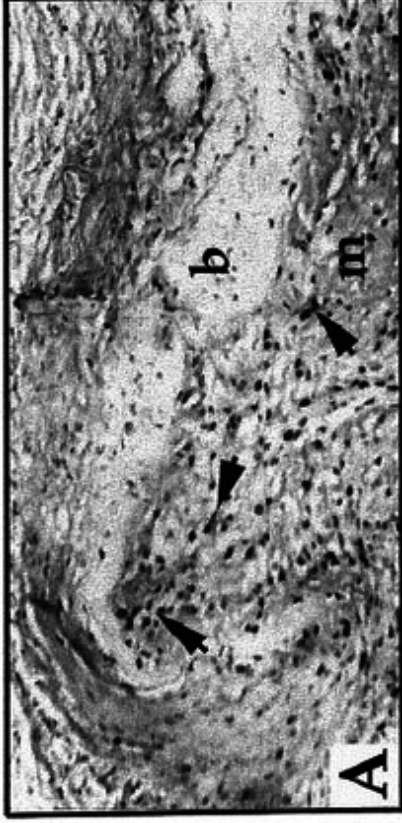




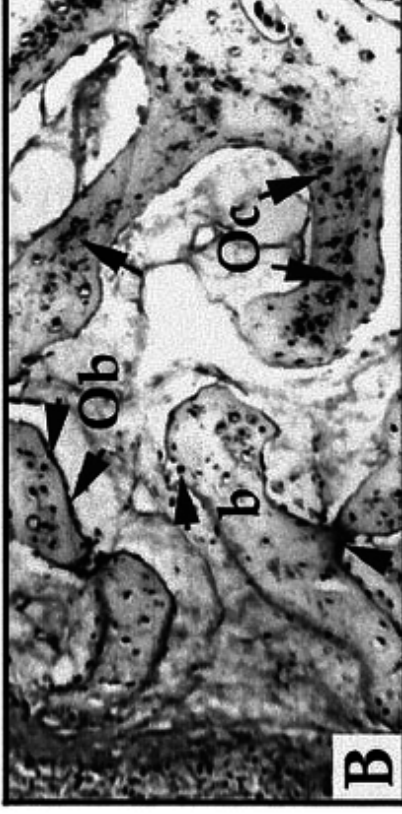
# FGFR2 mutation



## Normal Suture

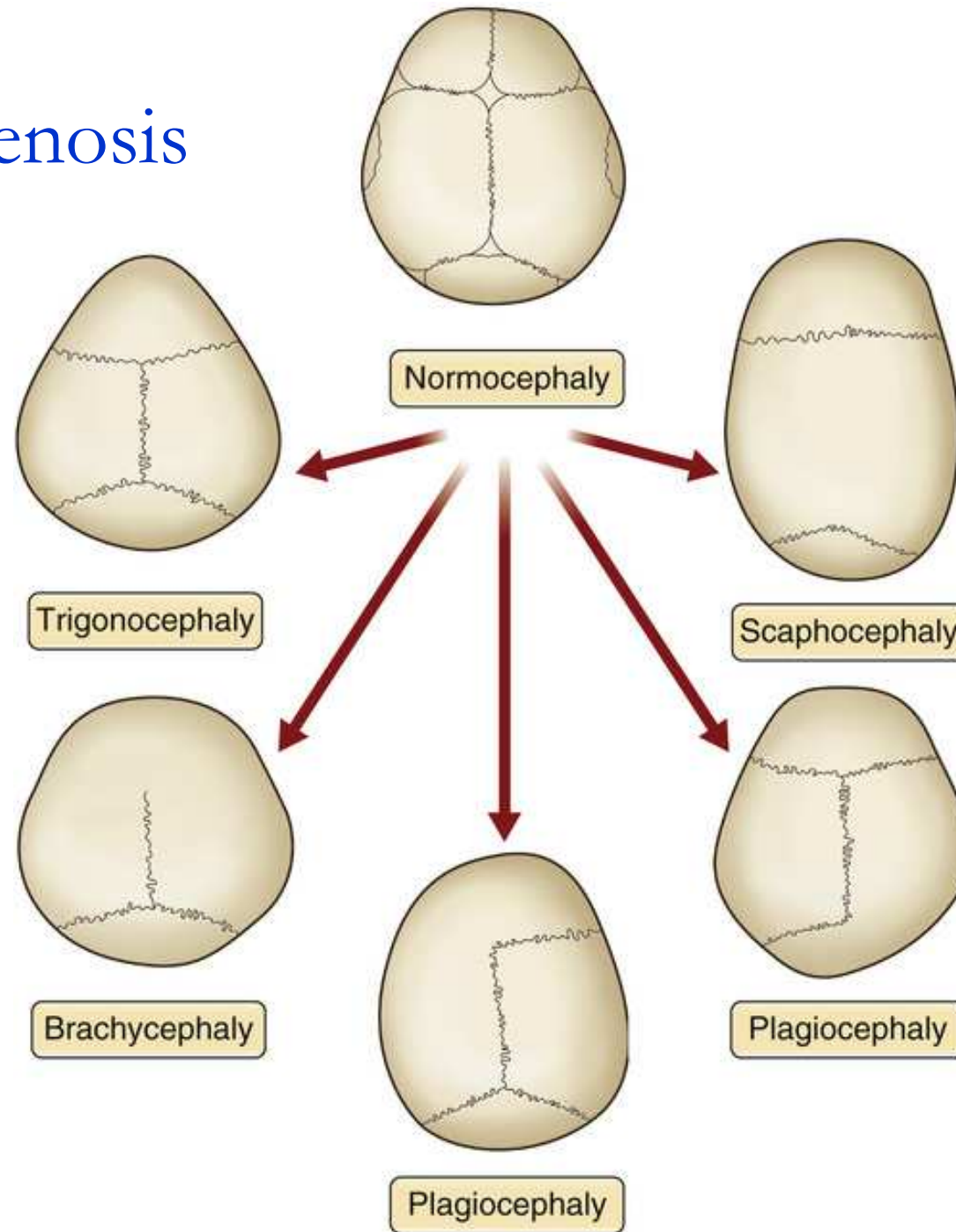


## Apert Suture



The Apert S252W FGFR-2 mutation induces premature osteoblast apoptosis in the human suture. Normal ( A ) and Apert ( B ) coronal sutures were prepared for TUNEL analysis. The Apert suture shows numerous TUNEL-positive mature osteoblasts (Ob) along the bone trabeculae and TUNEL-positive osteocytes (Oc) in the bone (b) matrix ( arrows ) whereas only mesenchymal (m) cells were found to be TUNEL-positive in the normal suture. Original magnification, x 125.

# Craniostenosis





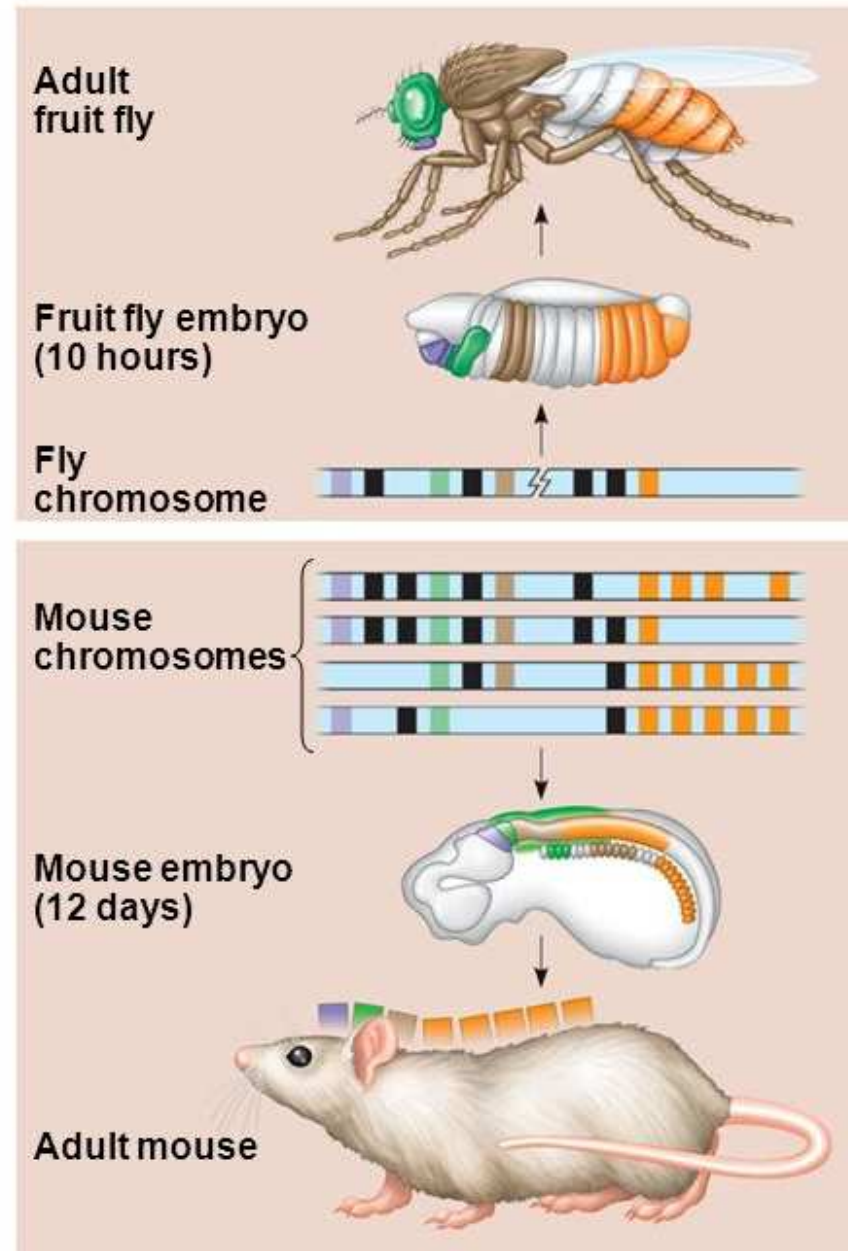
# Apert syndrome (FGFR2 mutation)

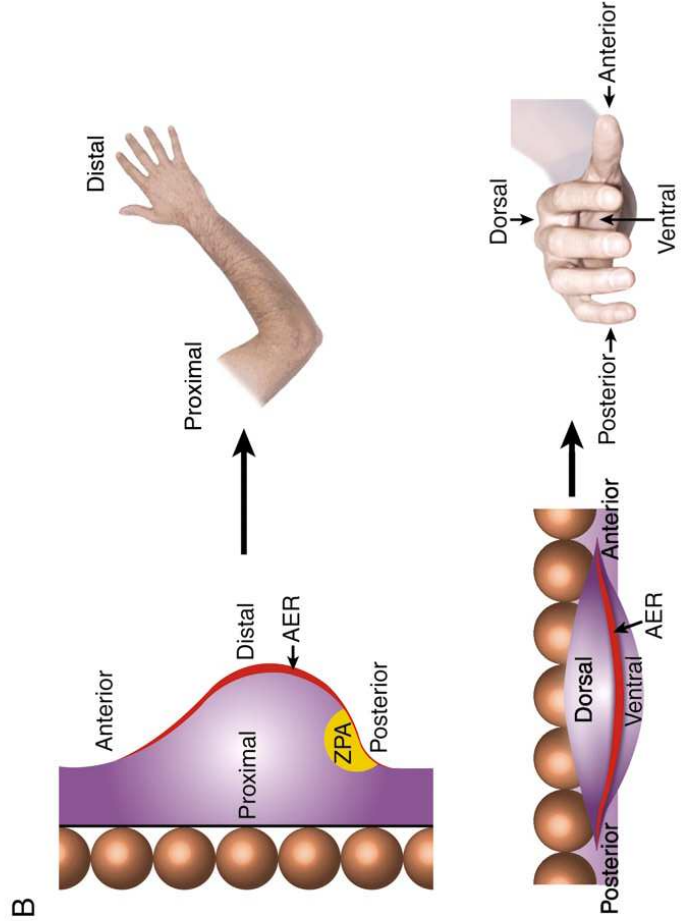
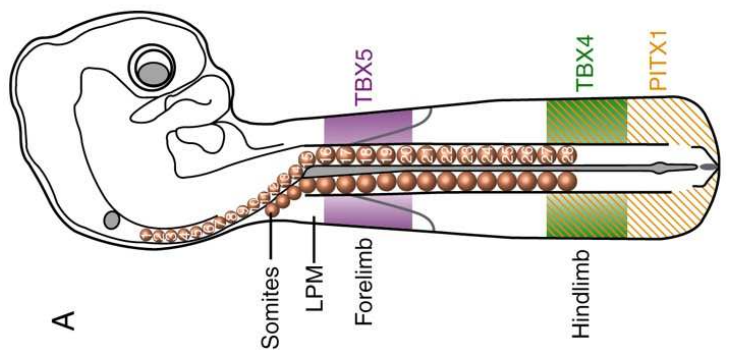
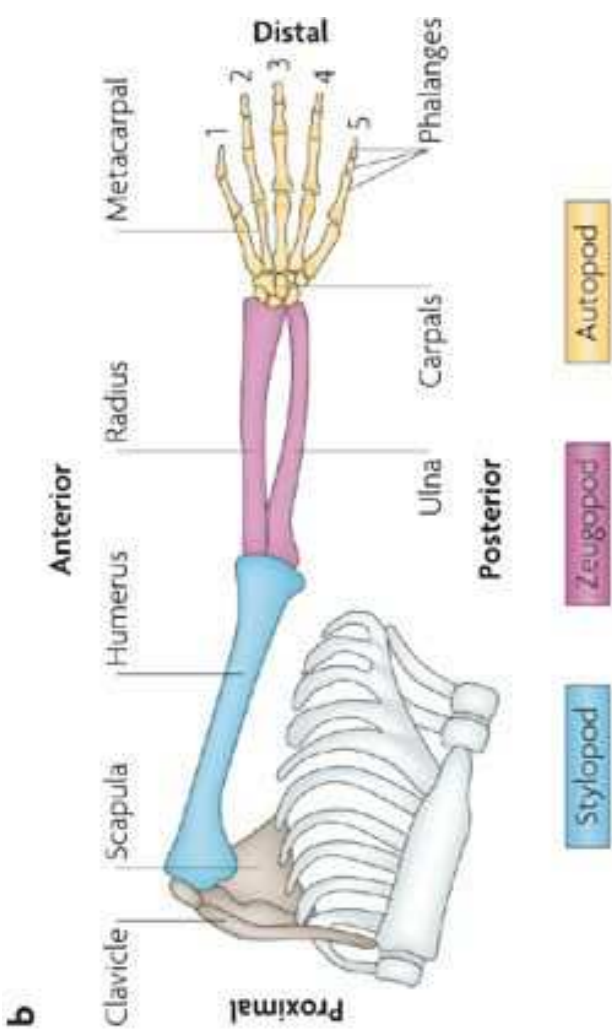
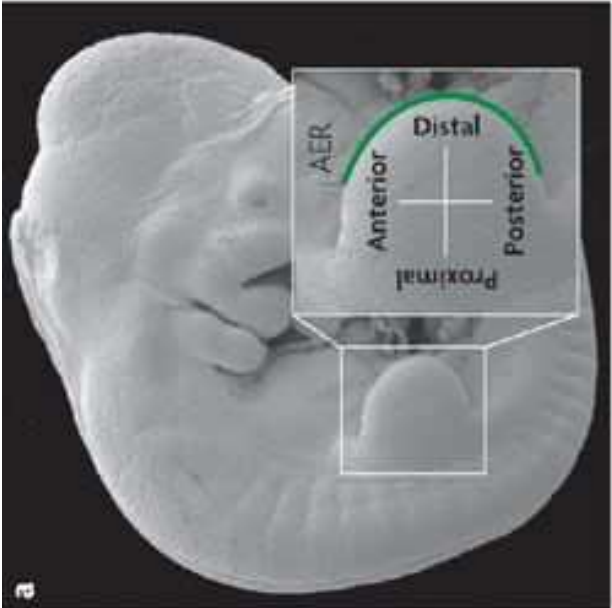


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- ❑ Organogenesis requires the coordination of multiple developmental processes
  - Proliferation
  - Differentiation
  - Migration
  - Apoptosis
- ❑ To understand how these processes interact and work together, developmental biologists typically study embryogenesis in a model organism, such as worms, flies, or mice



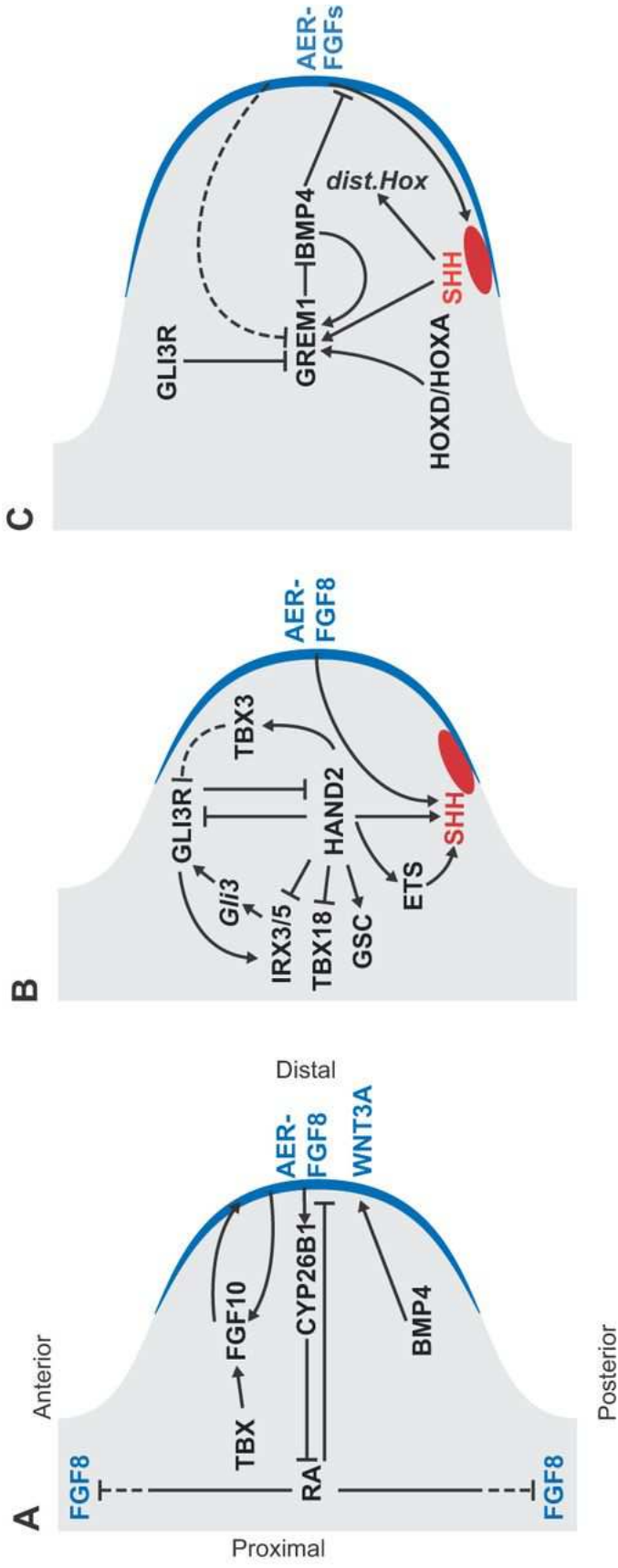


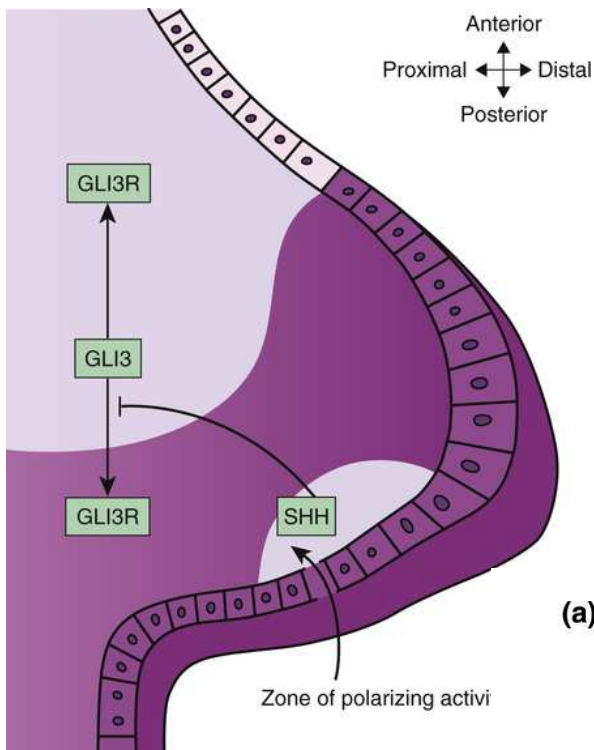
Stylopod

Zeugopod

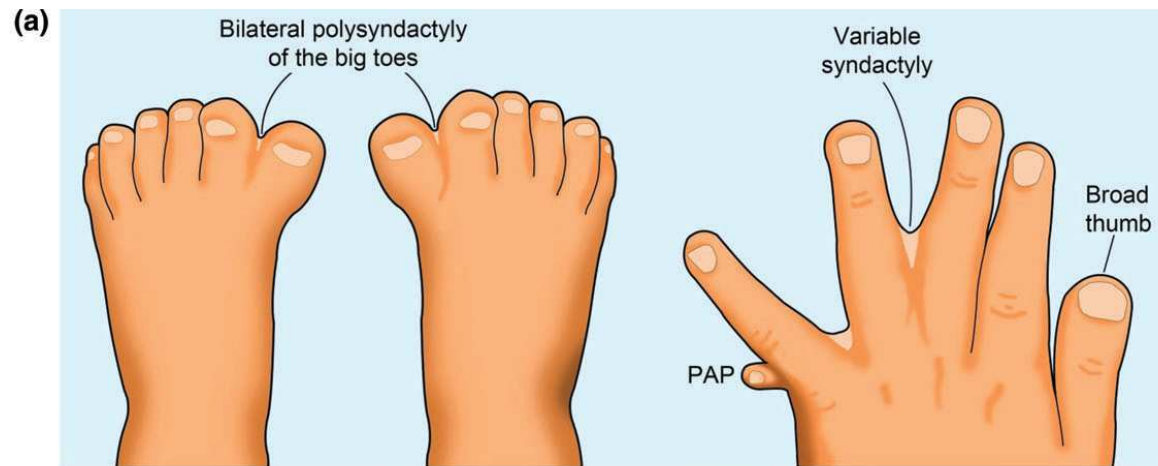
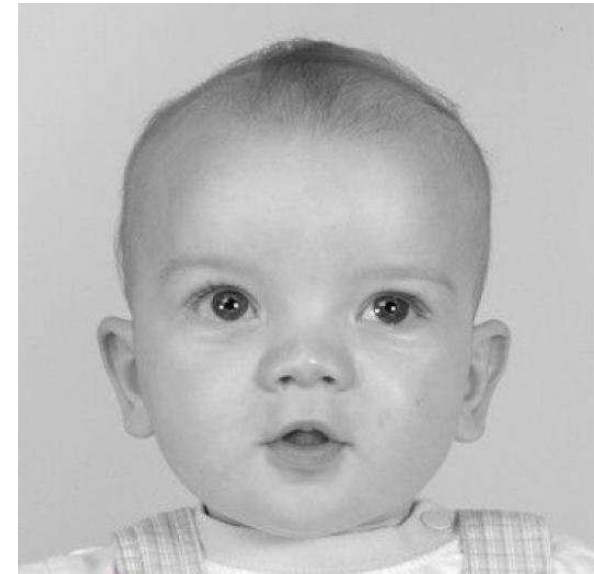
Autopod







## Greig cephalopolysyndactyly GLI3 Mutations



# Conclusions

- ❑ **Genes** are the **primary regulators of developmental processes**
- ❑ Their protein products function in developmental genetic pathways, and these pathways are employed in related developmental processes in a number of organ systems
- ❑ Understanding the molecular basis of gene function, how those functions are organized into modules, and how abnormalities in those modules cause and correlate with malformations and syndromes forms the basis of the clinical approach to human birth defects
- ❑ Understanding of these developmental pathways may also provide an avenue in the future to devise therapies that target appropriate parts of these pathways

Questions?



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