Developmental Genetics and Birth Defects

Julie Désir et Aude Tessier

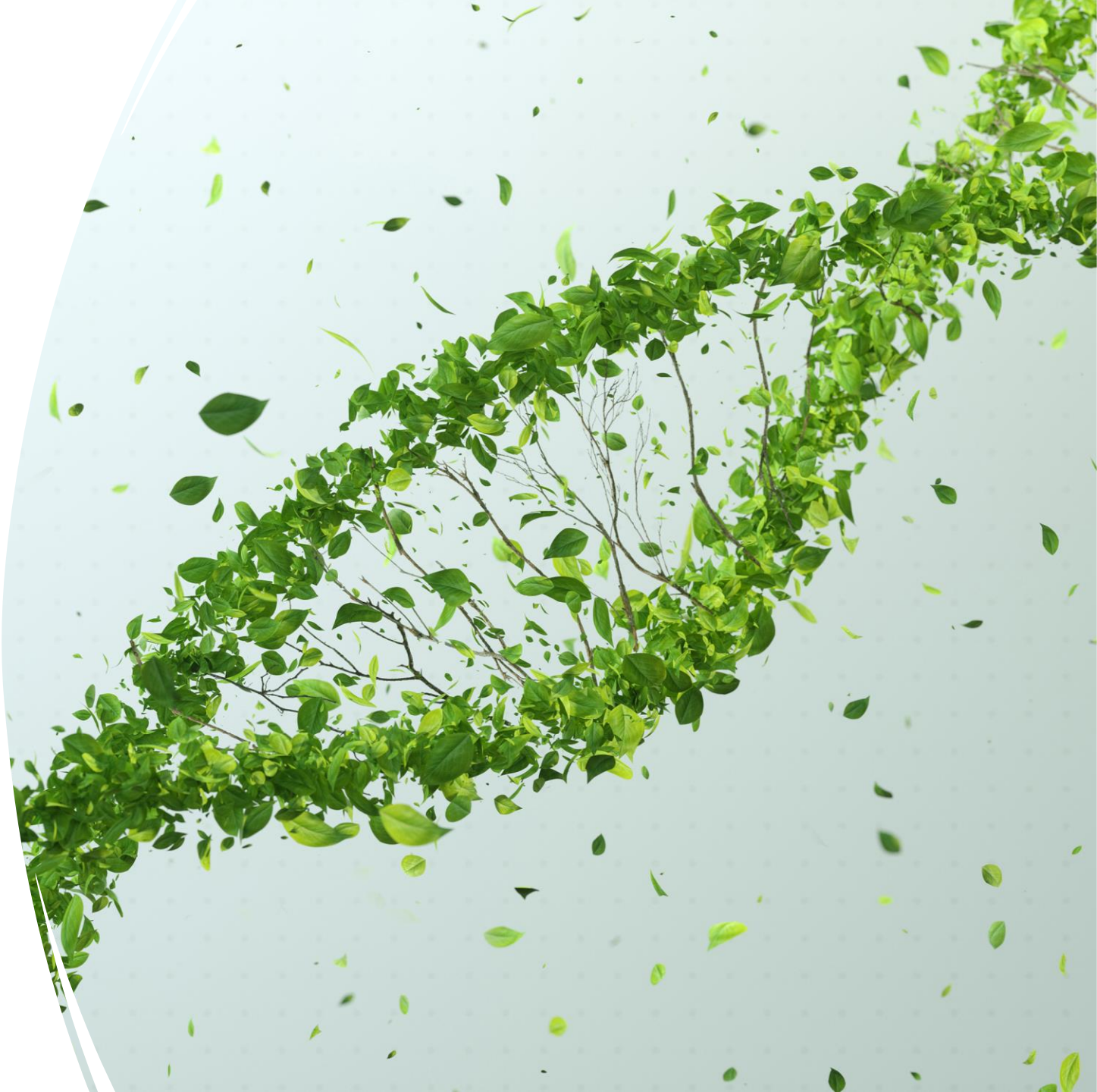
Institut de Pathologie et de Génétique
25, avenue Georges Lemaître B6041 Gosselies
Tél : +32 (0)71 47 30 47
accueil@ipg.be

Seqalis

IPG

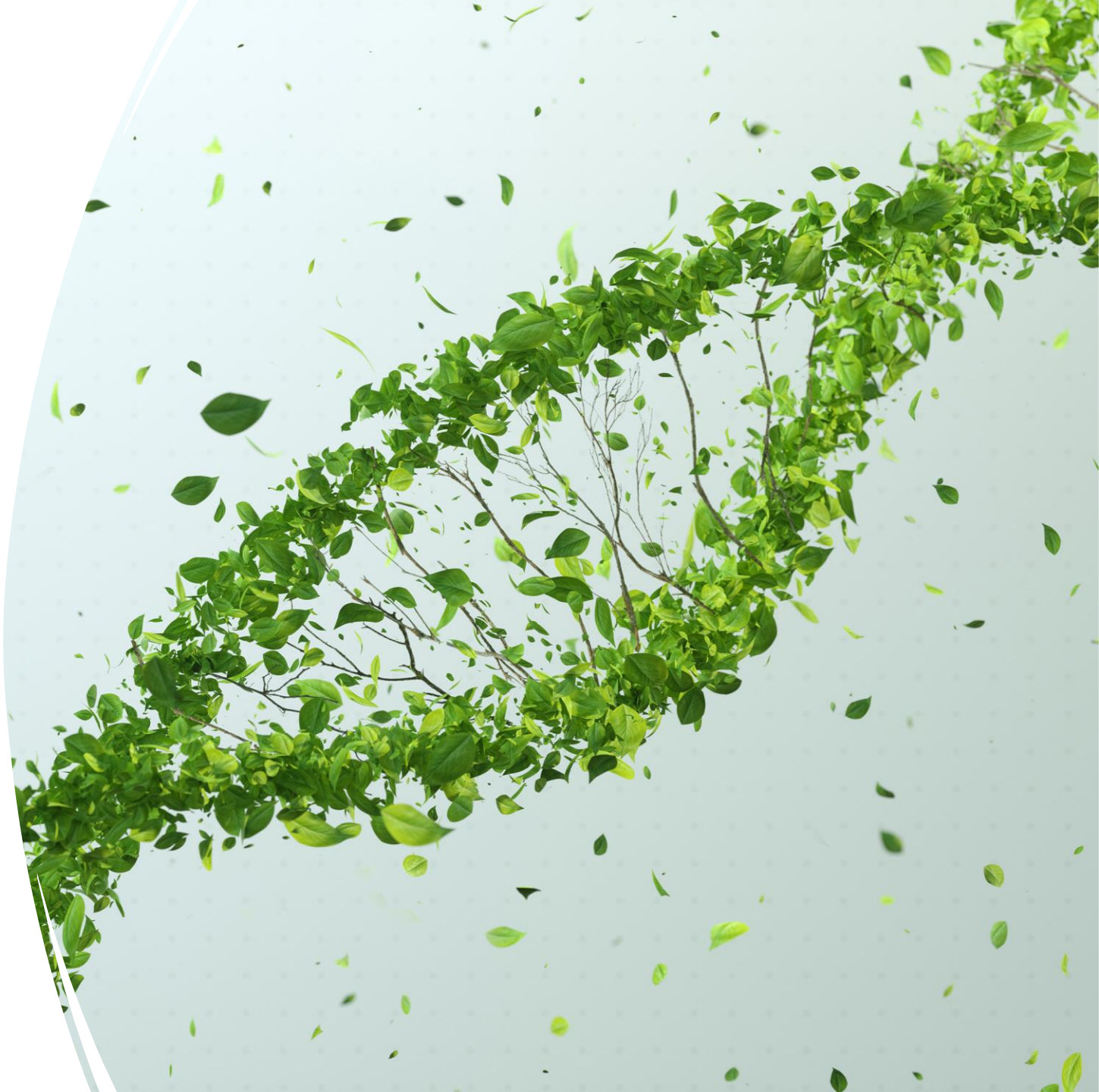
Summary

- Developmental Biology in Medicine
- Introduction to Developmental Biology
- Genes and Environment in Development



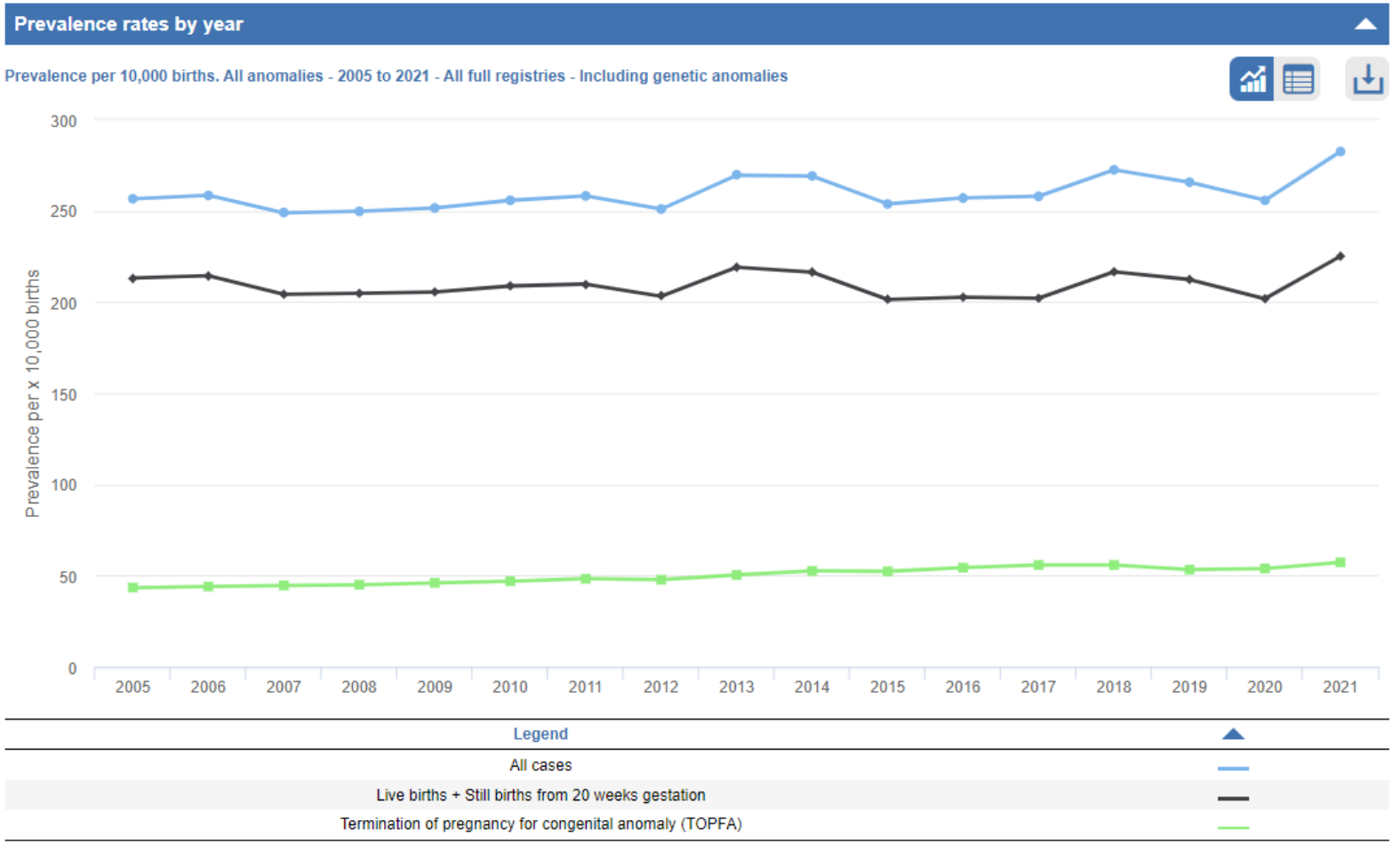
Summary

- **Developmental Biology in Medicine**
  - **Public health impact of birth defect**
  - **Clinical dysmorphology**
- Introduction to Developmental Biology
- Genes and Environment in Development

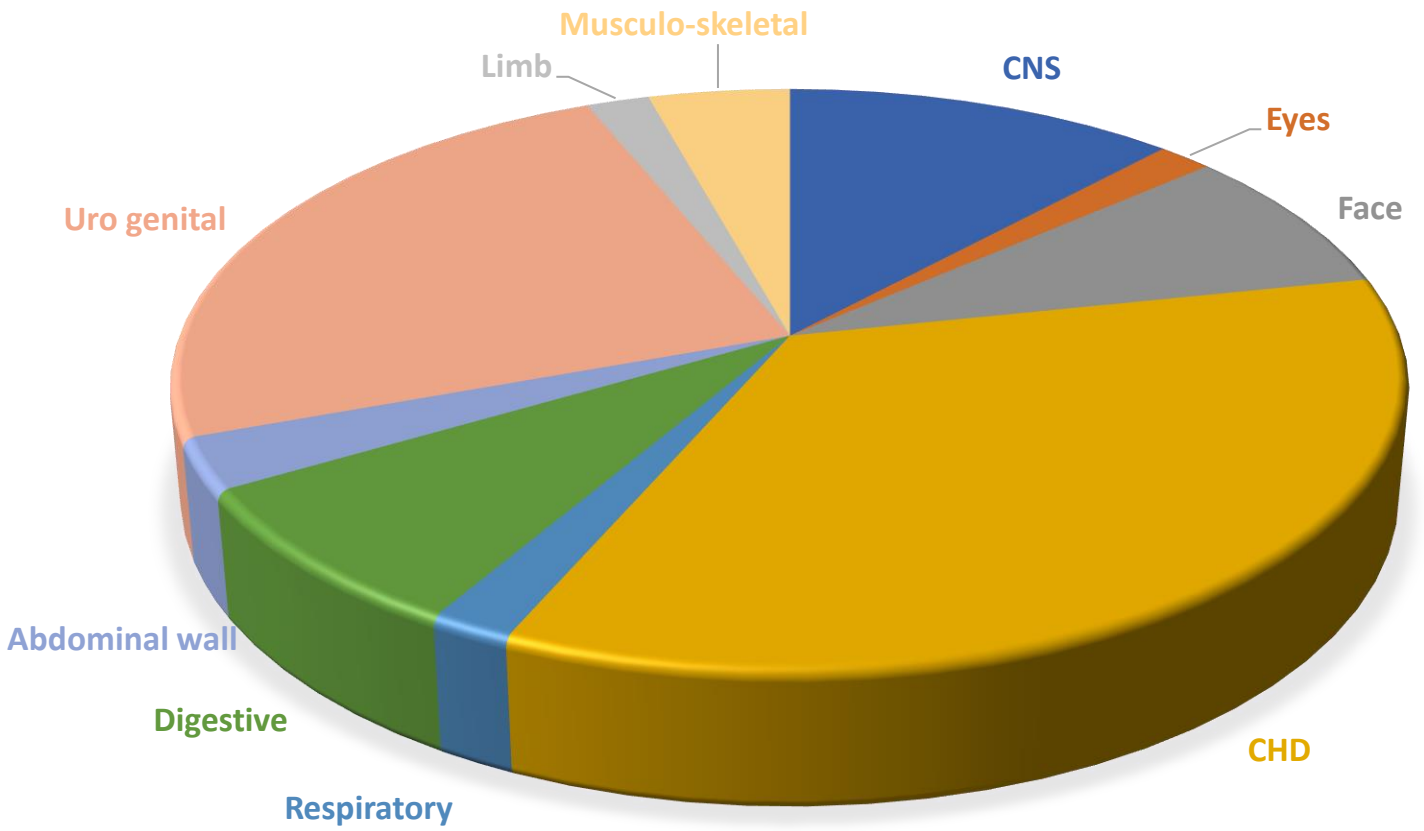


Public health impact of birth defect

- Prevalence of major congenital anomalies = 2,5%
- 80% are livebirth child
- Considerable country variations



Repartition by congenital anomaly subgroup

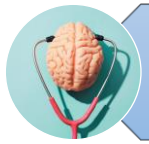


Complications due to malformations

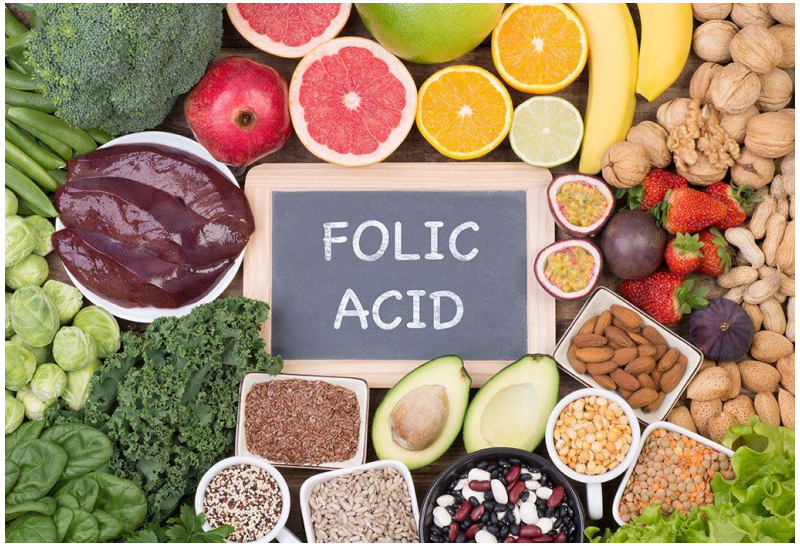
Infant death

Prematurity

Long term morbidity



Intelectual disability



Primary prevention in pregnancy

Policy of prenatal screening

Prenatal screening reduce mortality and morbidity

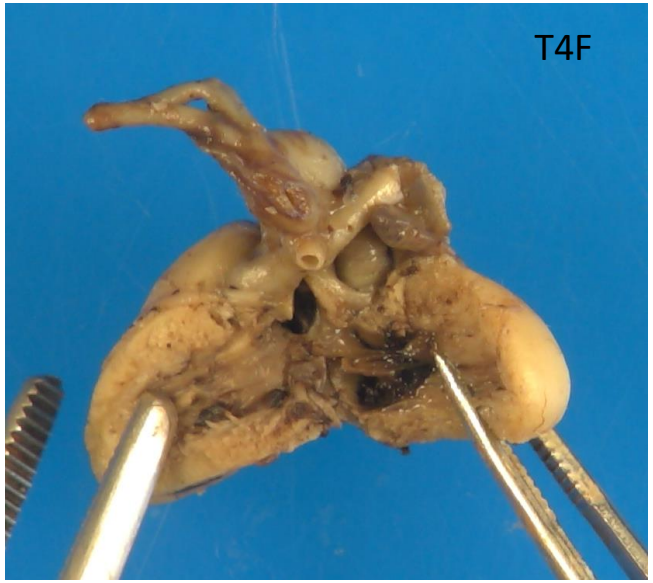
- optimize the timing of delivery,
- plan the birth in a maternity unit with specialist care,
- provide parents information to decide about termination of pregnancy
- Still, 30% of anomalies are detected postnatally

Clinical dysmorphology

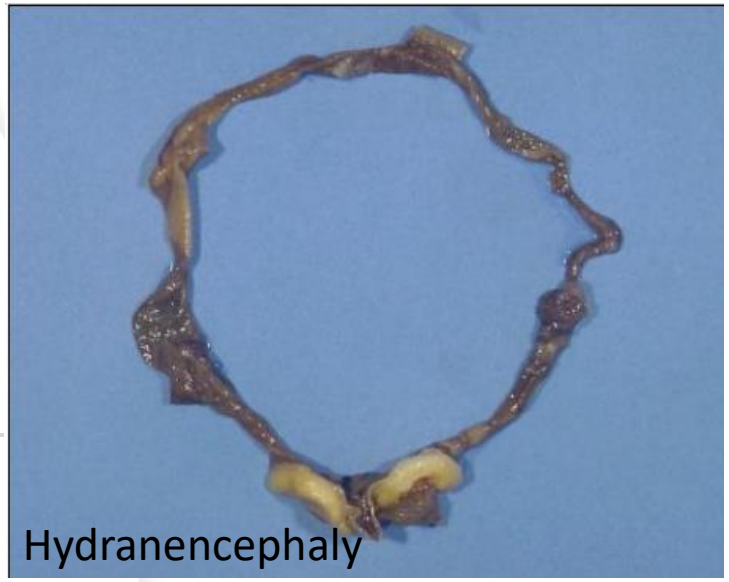
Definition :	Dysmorphology is the study of congenital birth defects
Purpose :	Understand contribution of genetic and non genetic on embryonic development
Requires :	Patient data Family history Science and literature data

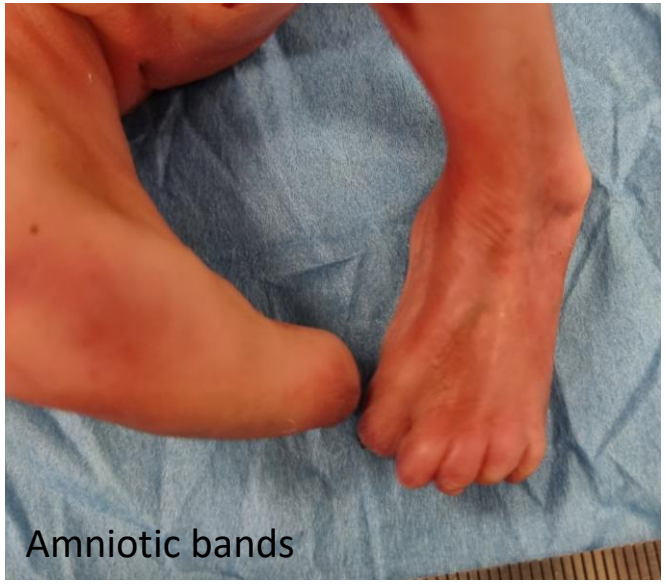
Elemental anomalies : malformation

Morphological defect of an organ, part of an organ or a larger region, resulting from an **intrinsically** abnormal developmental process.



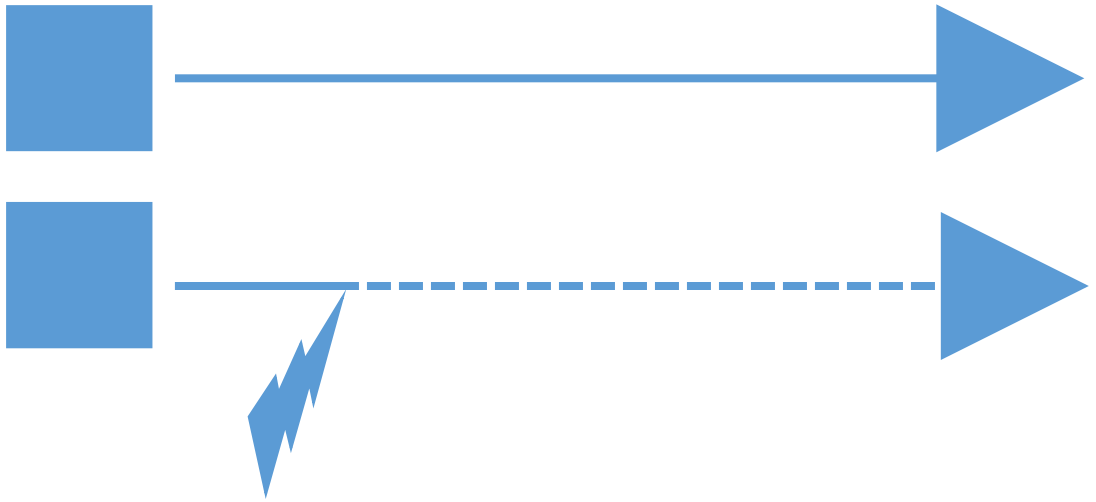
Elemental anomalies : disruption


Hydranencephaly


Amniotic bands

Morphological defect of an organ, part of an organ or a larger region, resulting from the **extrinsic** breakdown of, or interference with, an originally normal developmental process.

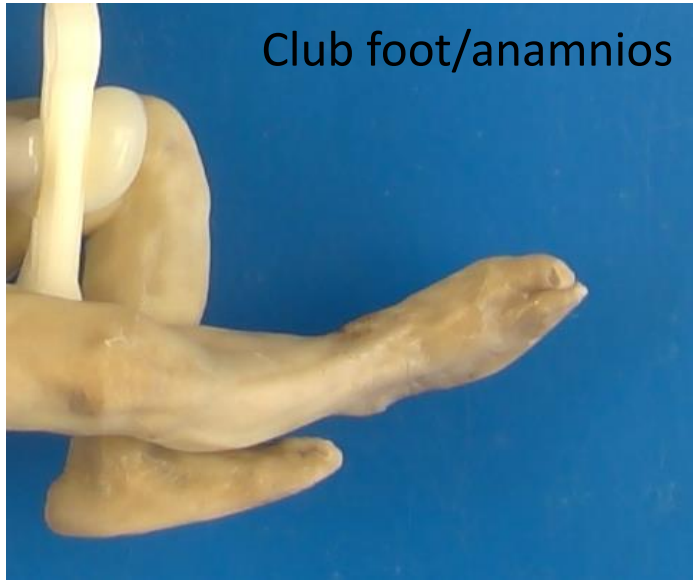
Ex : amniotic band, thrombosis

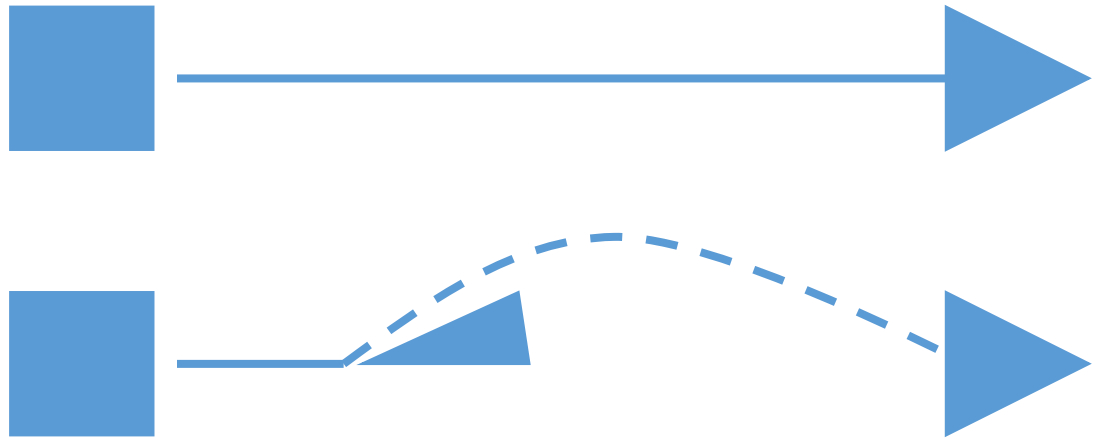


Elemental anomalies : deformation

Anomaly of shape, size or position of a body part, caused by **mechanical** phenomena.

Ex : joints contractions in multiple gestation or oligoamnios.

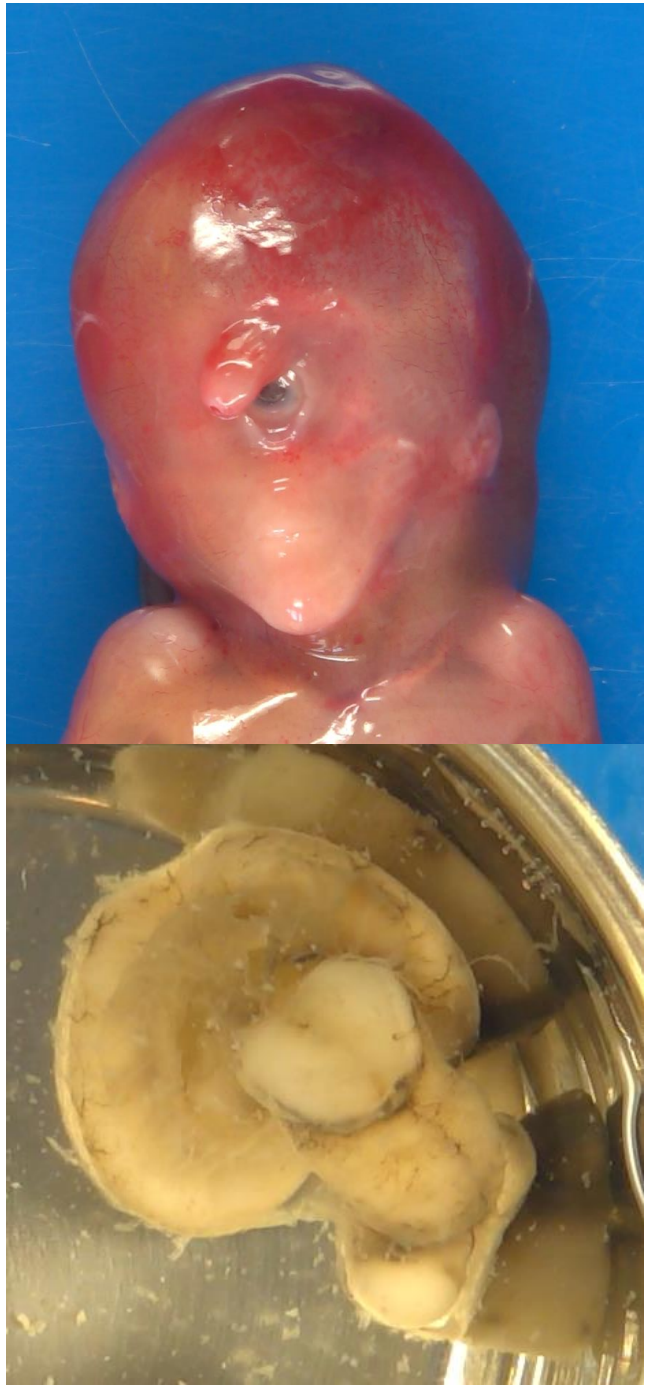




Grouping of anomalies : Morphogenetic field

A group of anomalies deriving of a single morphogenetic field.

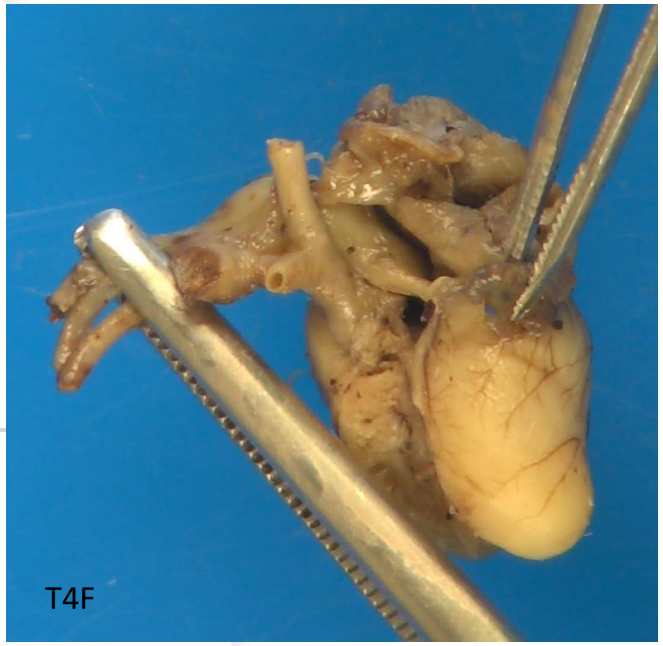
Ex : holoprosencephaly

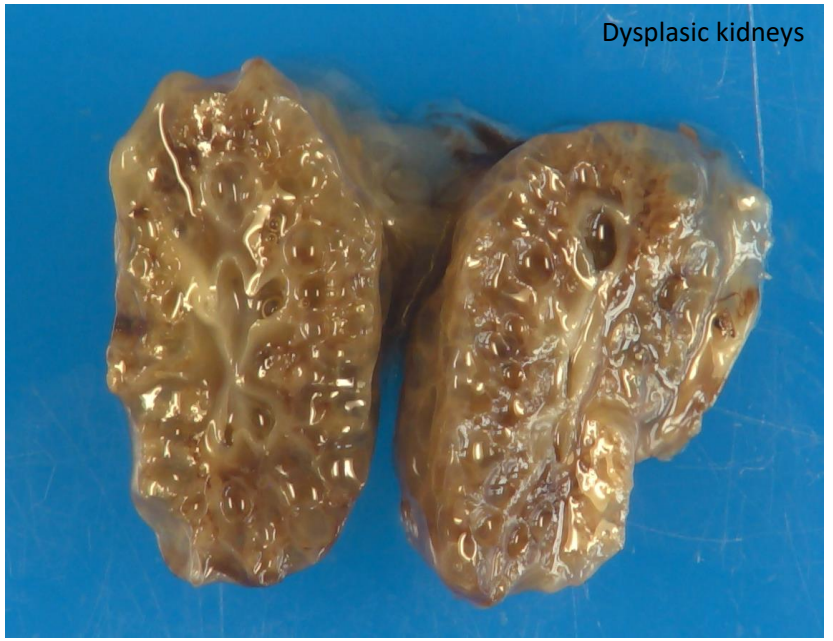


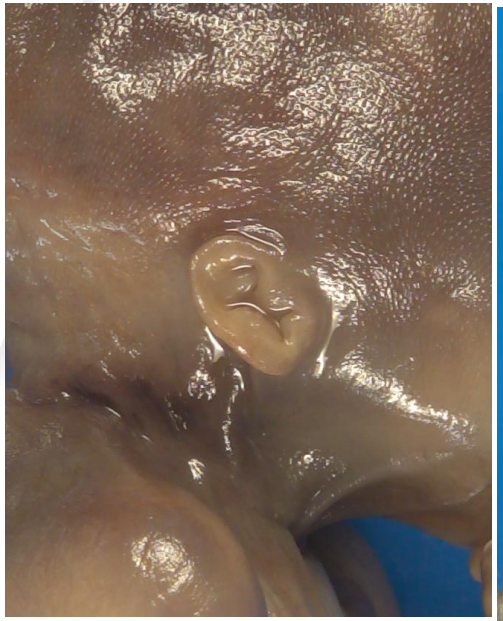
Grouping of anomalies : Syndrome

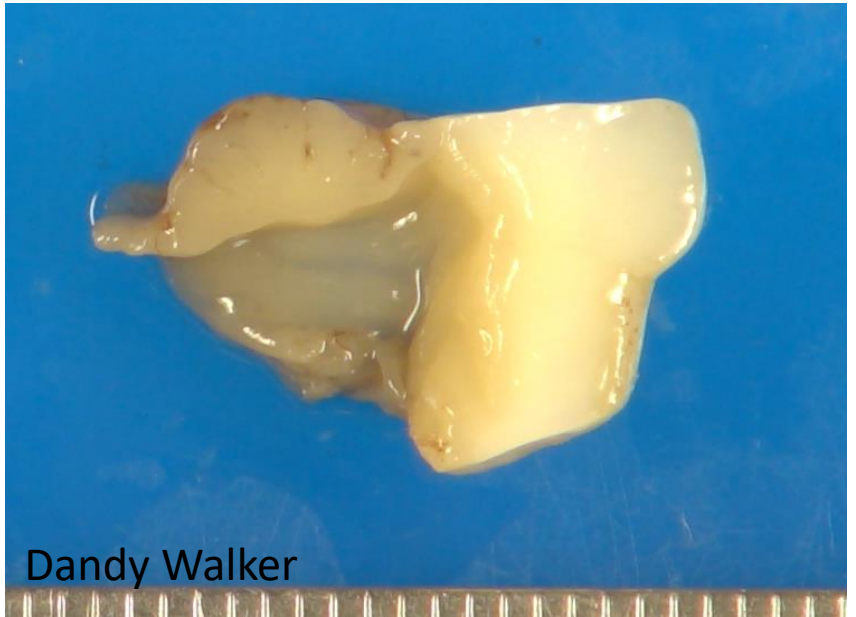
Primary defect cause multiples abnormalities in parallel.

Ex: CHARGE syndrome







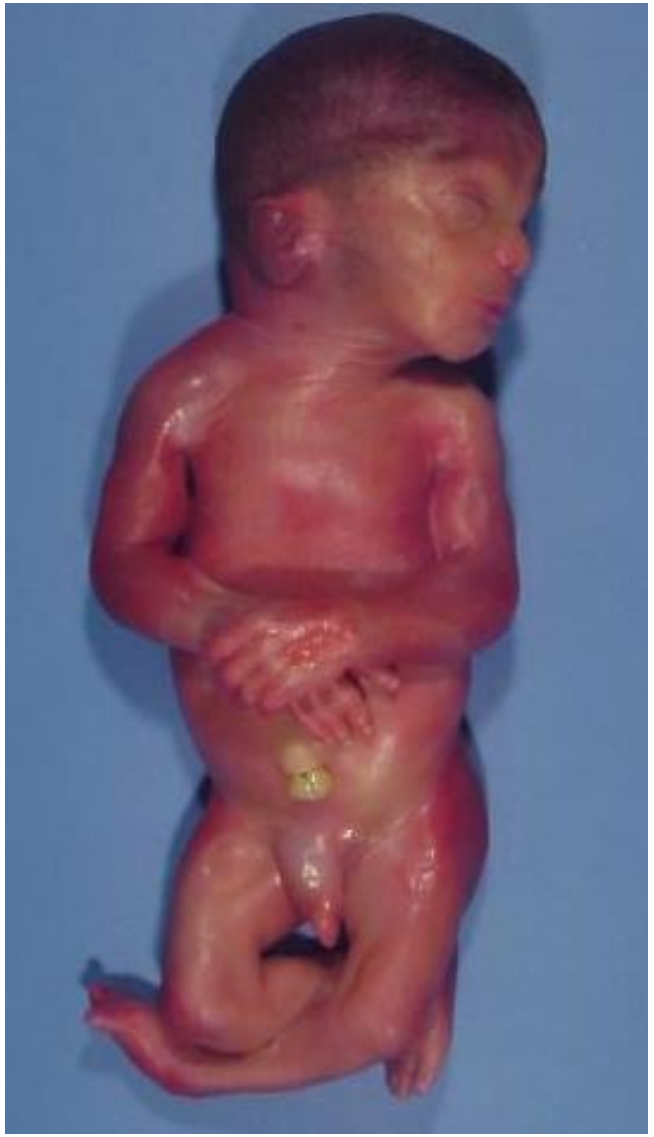


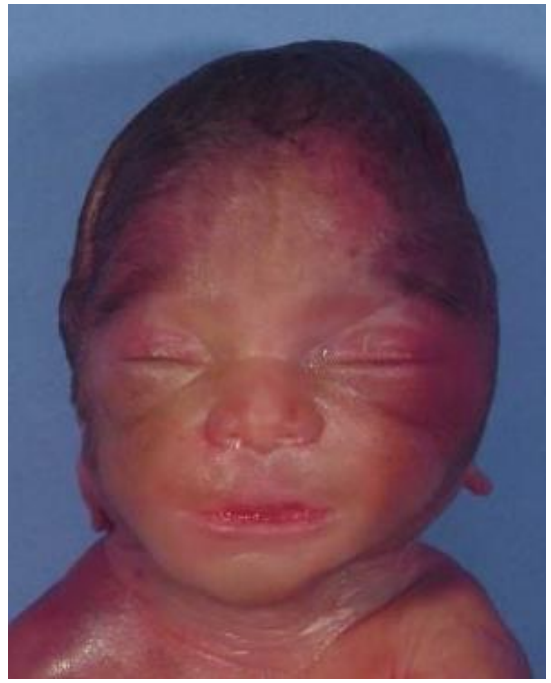
Grouping of anomalies : Sequence

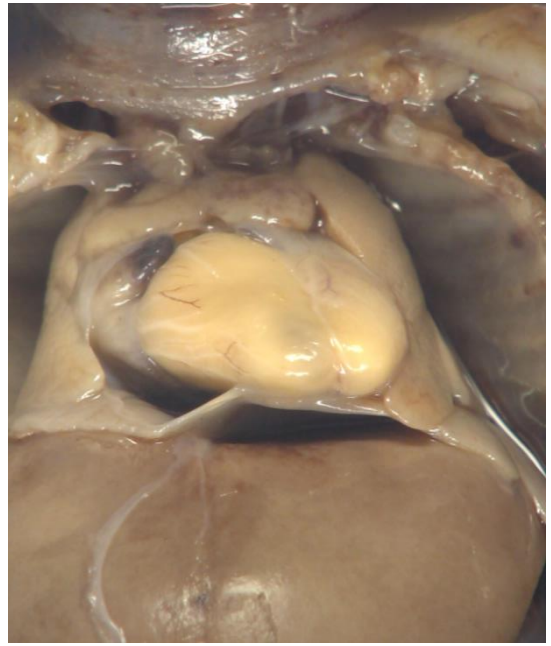
Initial isolated defect or malformation cause a cascade of secondary effects.

Ex: Potter's Sequence = anamnios sequence.

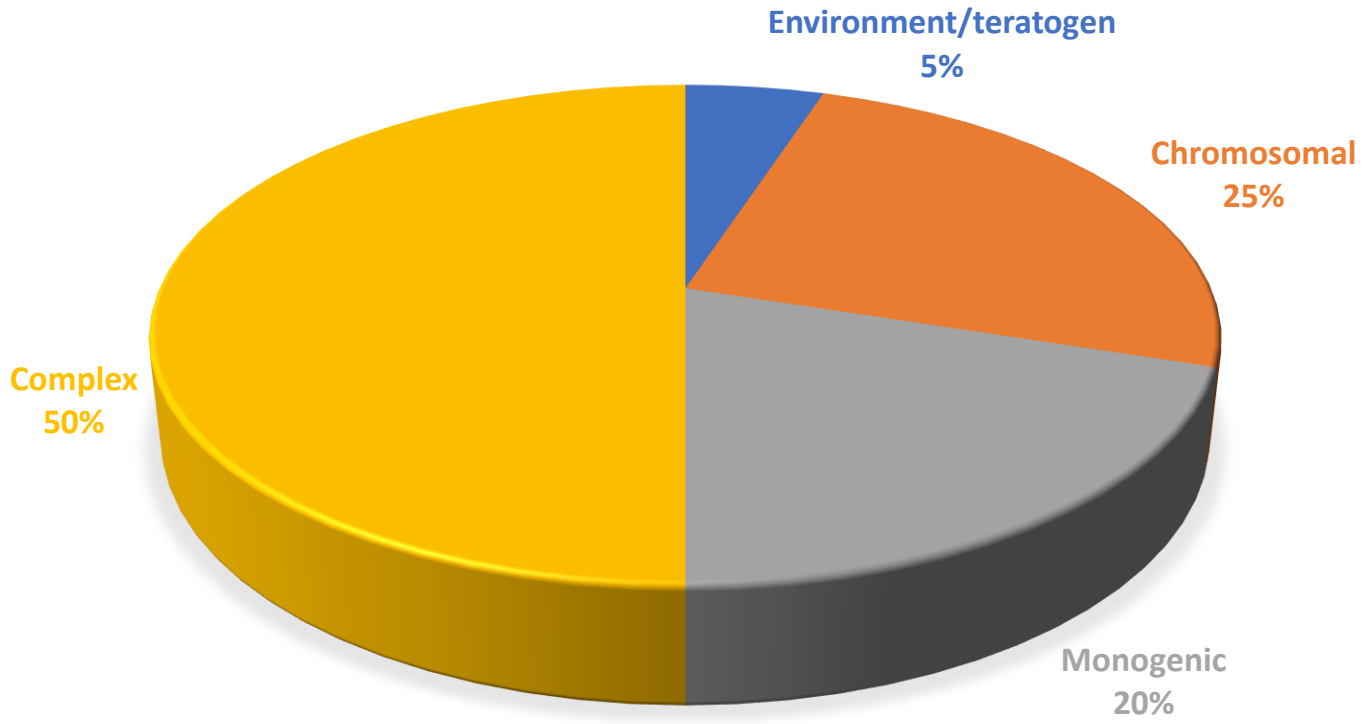
- Flat face
- Sub orbital folds
- Micrognathia
- Low set ears
- Joint contractures
- Pulmonary hypoplasia





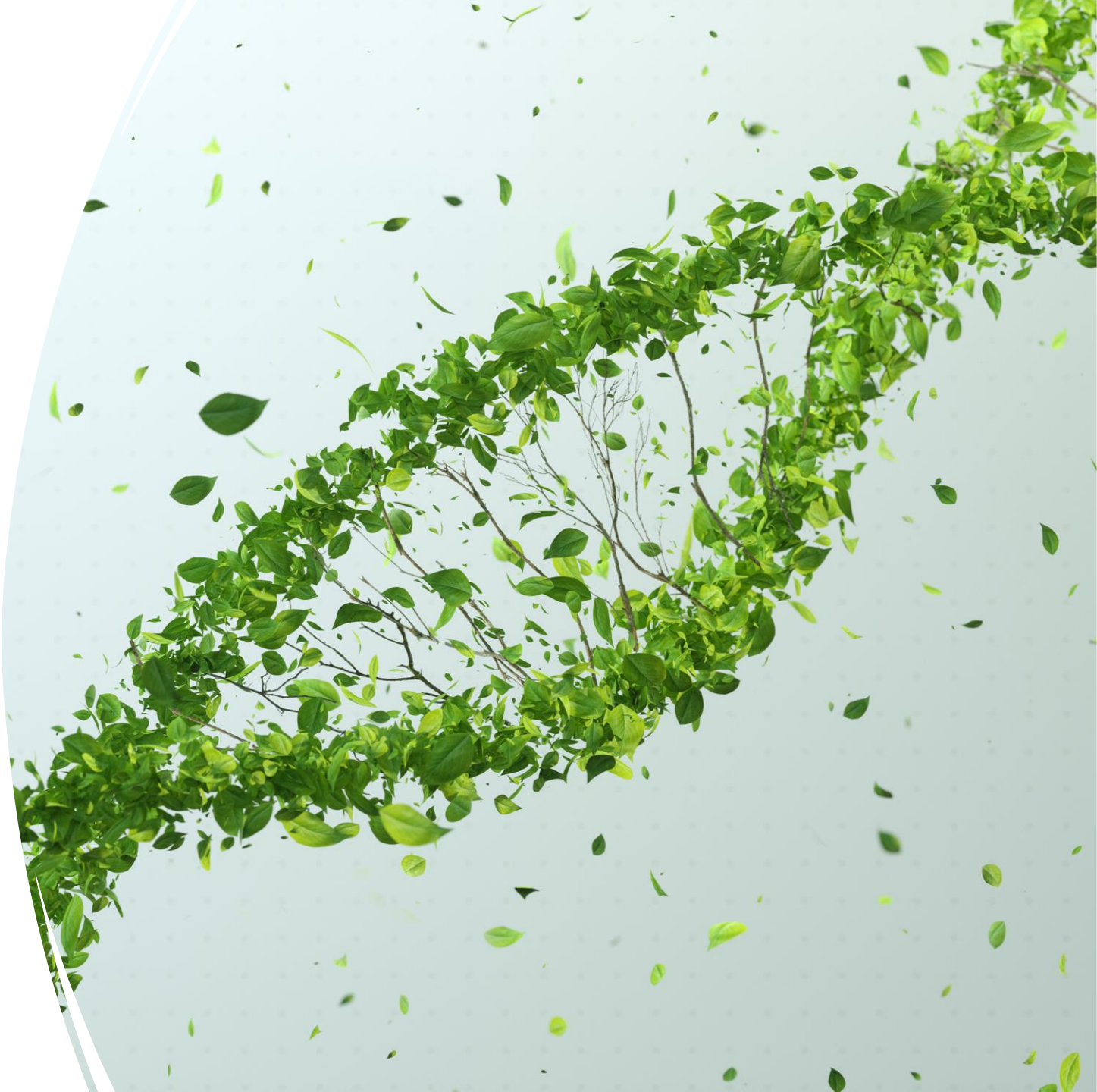


Causes of malformations



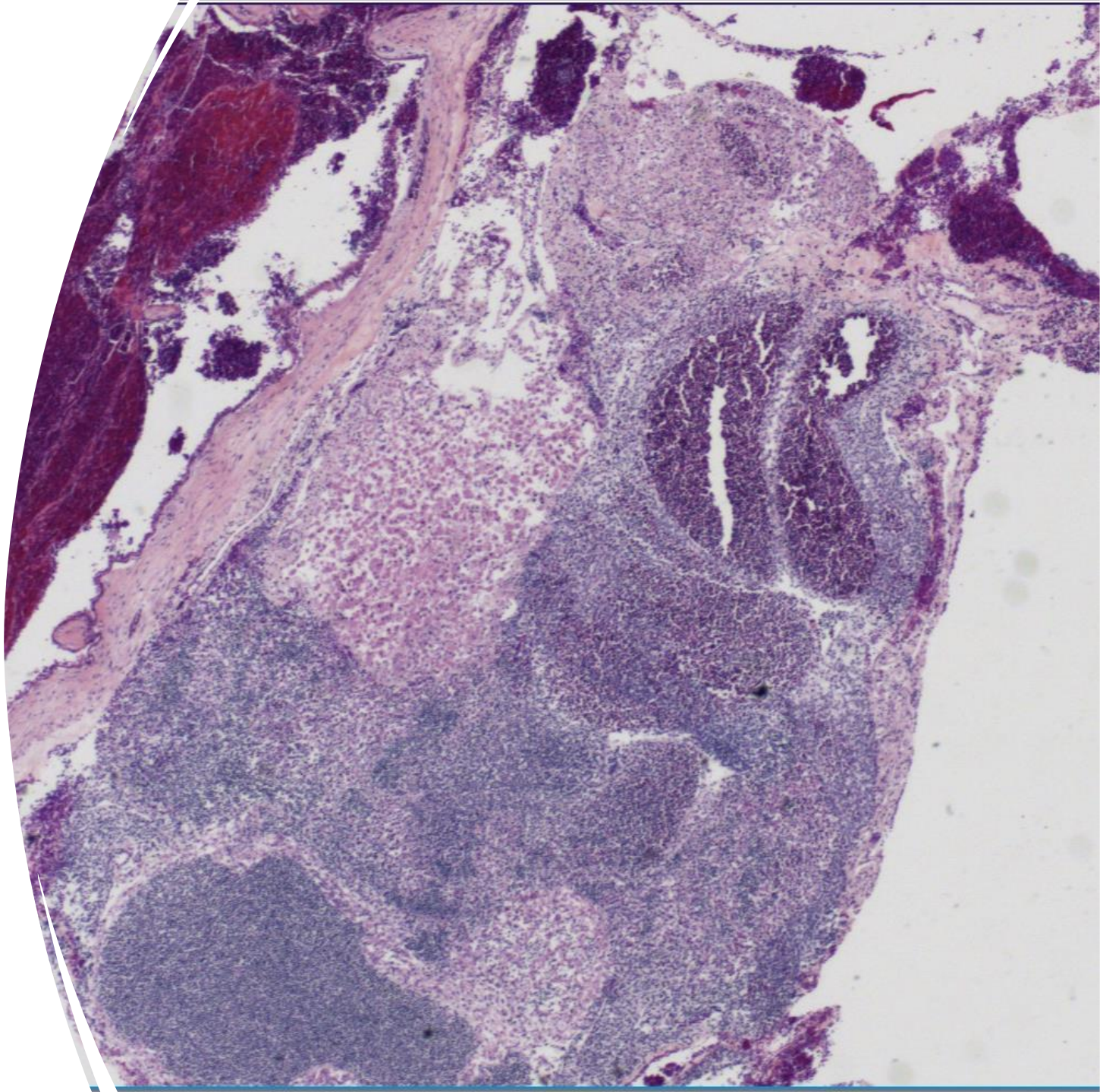
Summary

- Developmental Biology in Medicine
- **Introduction to Developmental Biology**
- Genes and Environment in Development

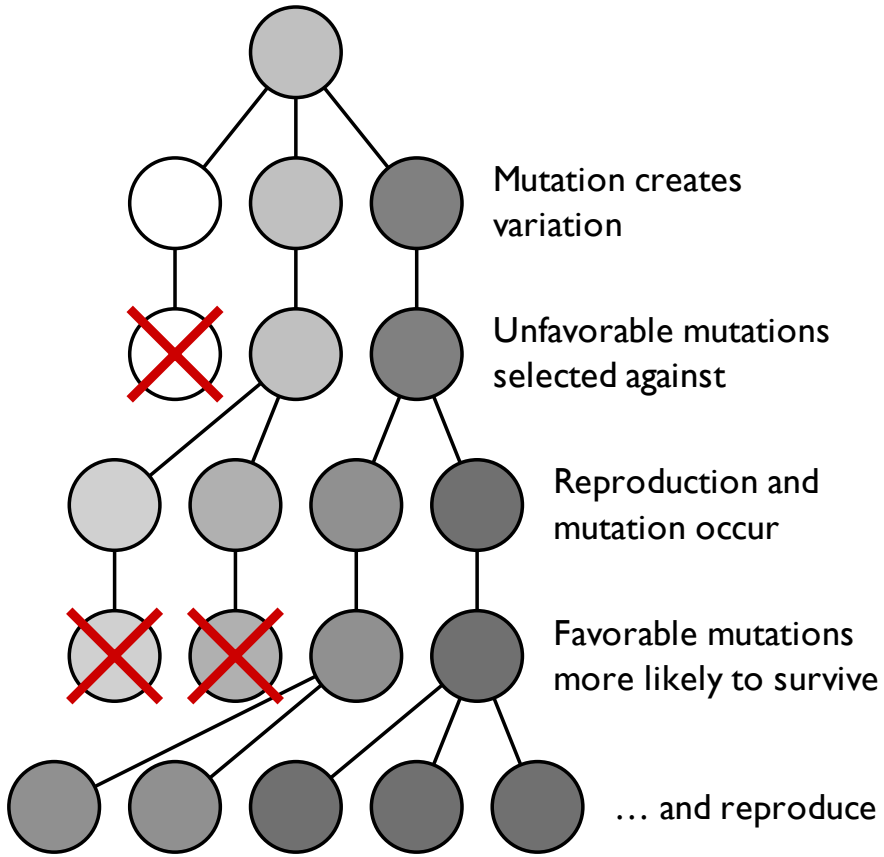


Definition

- “Developmental biology is the science that investigates how a variety of interacting processes generate an organism’s heterogeneous shapes, size, and structural features that arise on the trajectory from embryo to adult, or more generally throughout a life cycle.” Stanford Encyclopedia of Philosophy

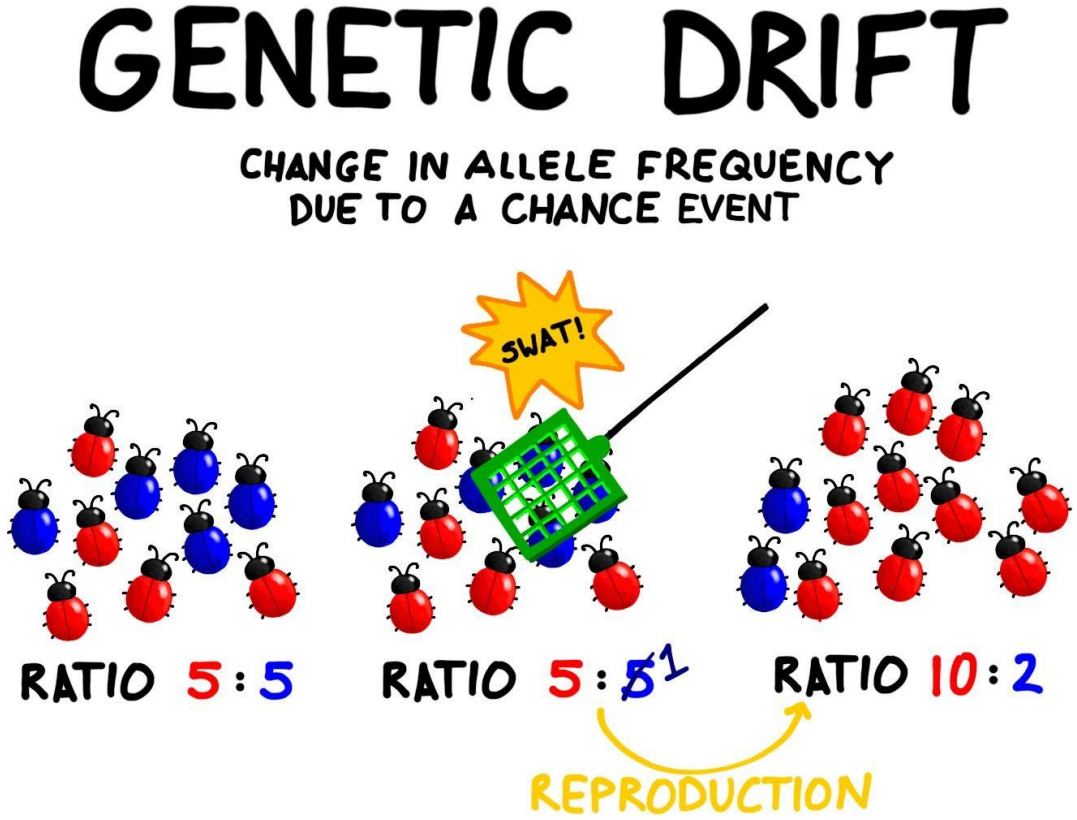


Evolution



- Definition : Change in the heritable characteristics of biological populations over successive generations.
- Need genetic variation within a population.
- Variation comes from mutations, reshuffling of genes through sexual reproduction and migration between populations (gene flow).
- Natural selection is the process by which traits that enhance survival and reproduction become more common in successive generations of a population.
- Phenotypic variation : variation in morphology, physiology and behaviour.
- Differential fitness : Different traits confer different rates of survival and reproduction.
- Heritability of fitness : These traits can be passed from generation to generation.

Genetic drift



- =Wright effect
- Definition : change in the frequency of an existing gene variant (allele) in a population due to random chance
- May cause gene variants to disappear completely and thereby reduce genetic variation. It can also cause initially rare alleles to become much more frequent and even fixed.
- When few copies of an allele exist, the effect of genetic drift is more notable, and when many copies exist, the effect is less notable (due to the law of large numbers).
- neutral theory of molecular evolution : (Motoo Kimura, 1968) : most instances where a genetic change spreads across a population (although not necessarily changes in phenotypes) are caused by genetic drift acting on neutral mutations. In the 1990s, constructive neutral evolution was proposed which seeks to explain how complex systems emerge through neutral transitions.

Convergent evolution

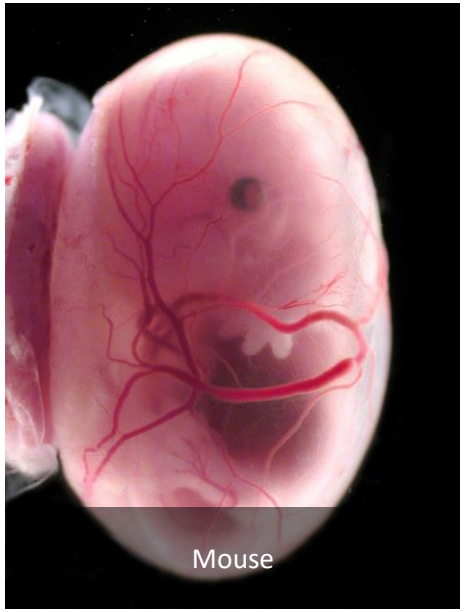
Independent evolution of similar features in species of different periods or epochs in time.

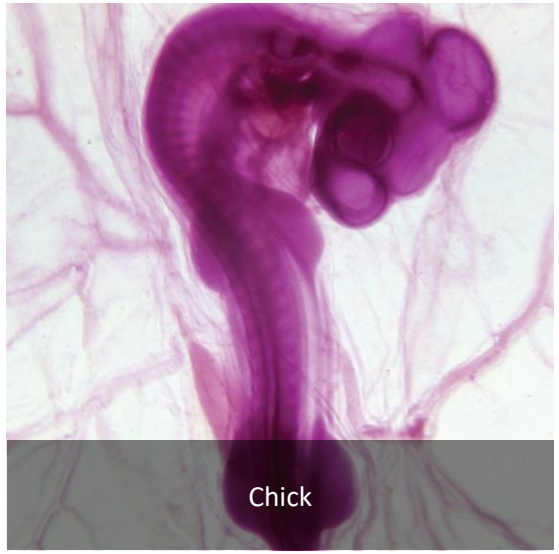
Creates analogous structures that have similar form or function but were not present in the last common ancestor of those groups.

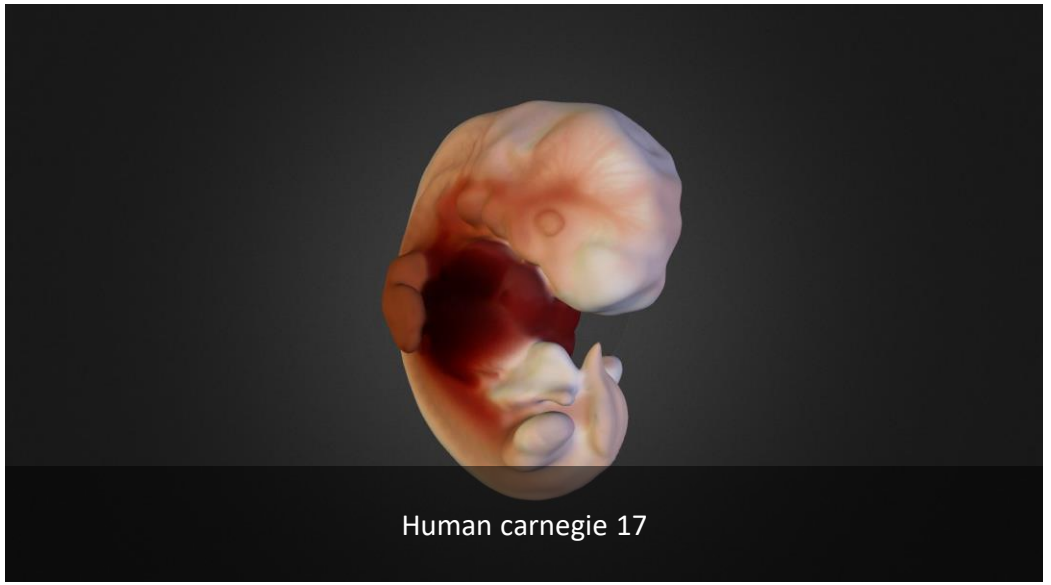
Ex : beak shape

Evo-devo

- Evolutionary developmental biology compares the developmental processes of different organisms to infer how developmental processes evolved.

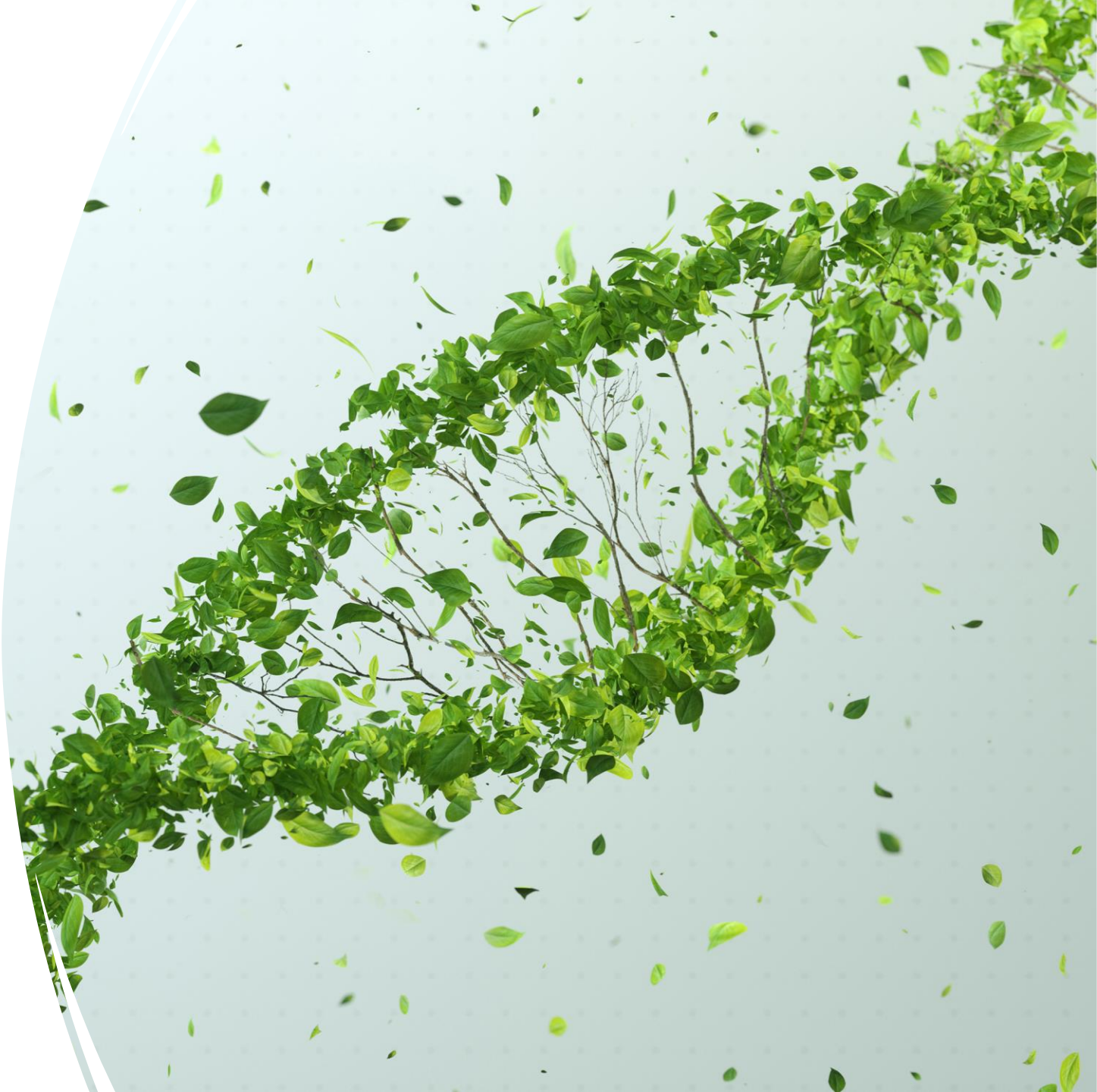






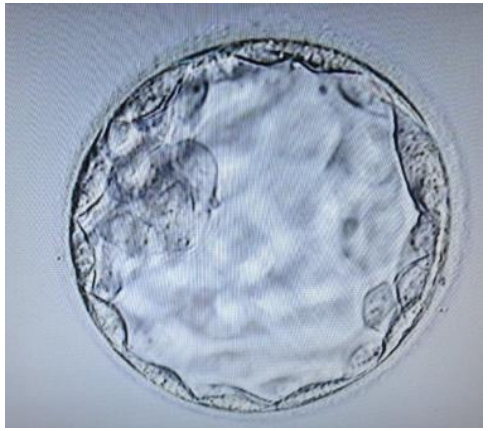
Summary

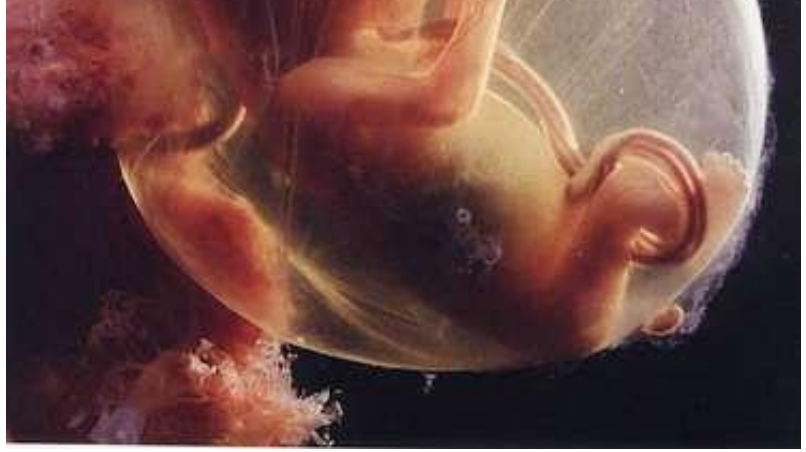
- Developmental Biology in Medicine
- Introduction to Developmental Biology
- **Genes and Environment in Development**

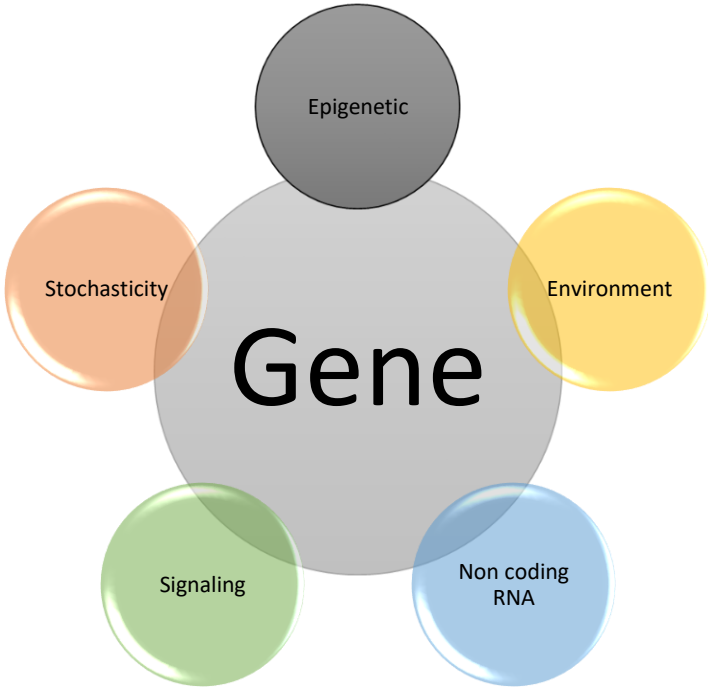


Beyond genes

- How can a single cell produce a complete fetus with specific organs and function, as all cells have the same genome?
- What determine cell fate?





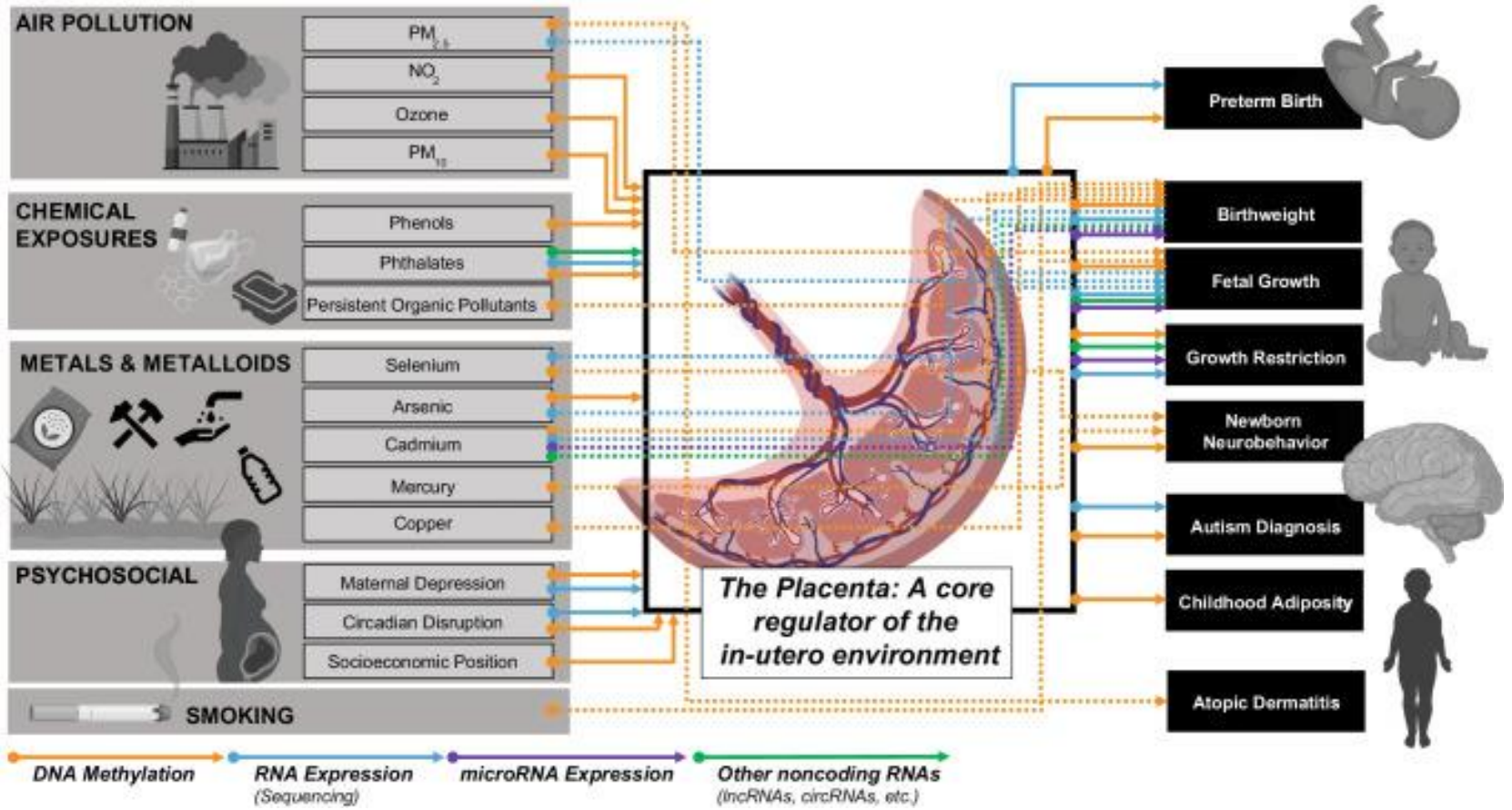


An exemple of interaction between gene expression and environment : siamese cat!

- Mutation in *tyrosinase*
- Heat-sensitive enzyme
- No production of melanin in warm body parts

Concept of DOHaD

- Developmental origins of health and disease (DOHaD) is the study of how the early life environment can impact the risk of chronic diseases from childhood to adulthood and the mechanisms involved.
- Epigenomic modification of the placenta during pregnancy.
- Relationships between the prenatal environment and perinatal complications.



Lapehn S, Paquette AG. The Placental Epigenome as a Molecular Link Between Prenatal Exposures and Fetal Health Outcomes Through the DOHaD Hypothesis. Curr Environ Health Rep. 2022 Sep;9(3):490-501

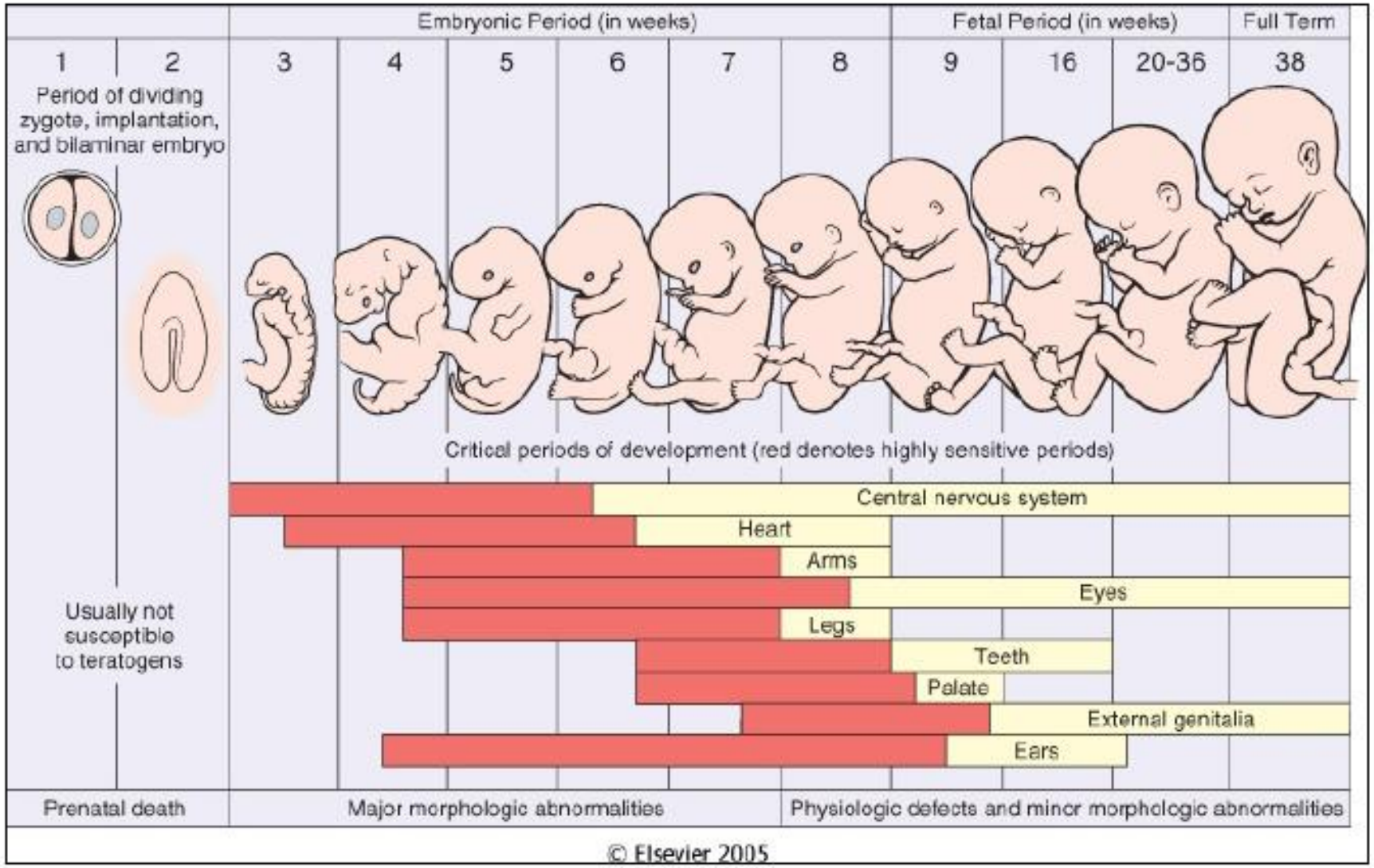
Chapters

- **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

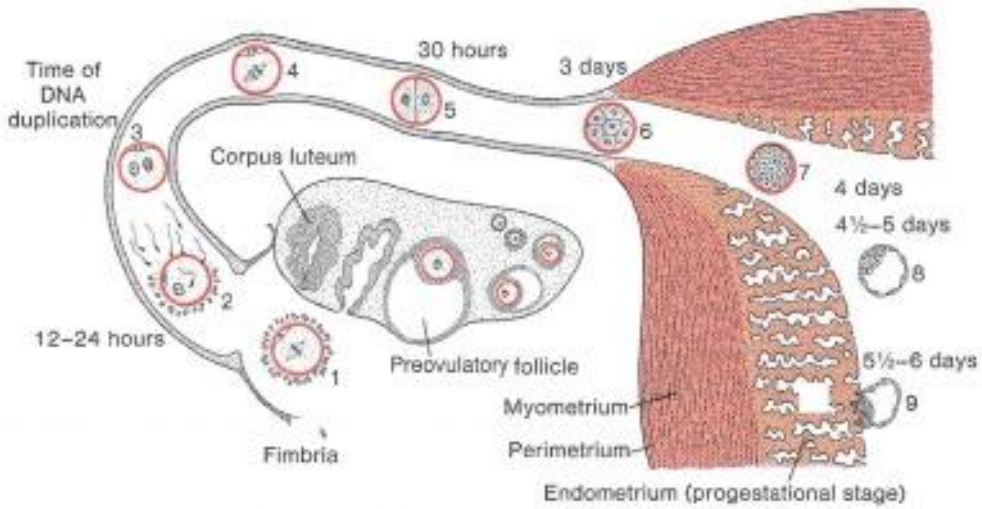
Chapters

- **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

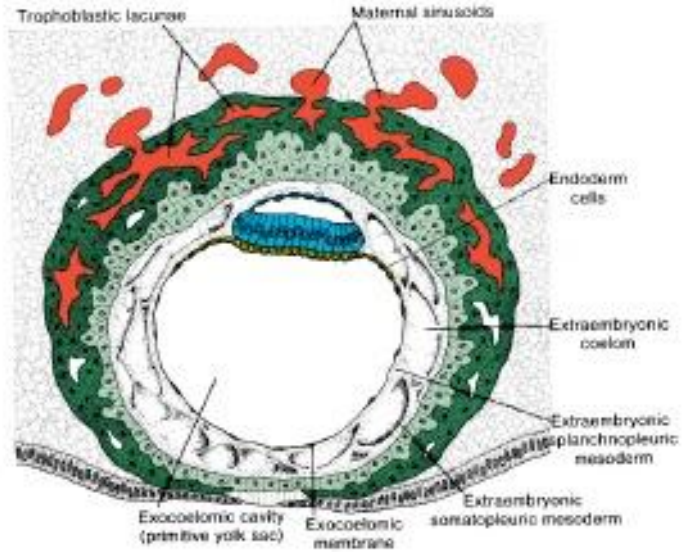
Critical periods of development for various organ systems and the resultant malformations



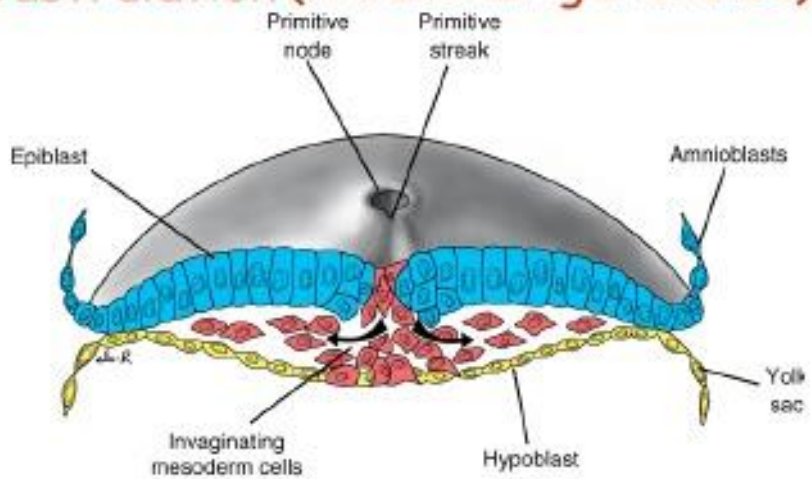
First week of development: Ovulation to implantation

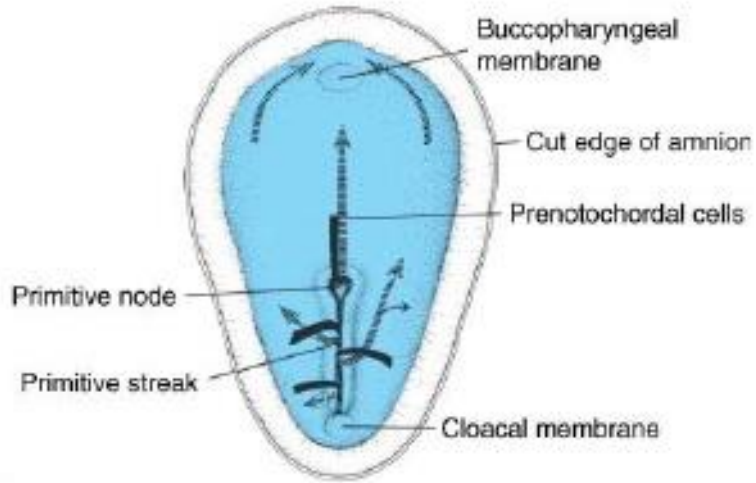


Second week of development: Bilaminar germ disc

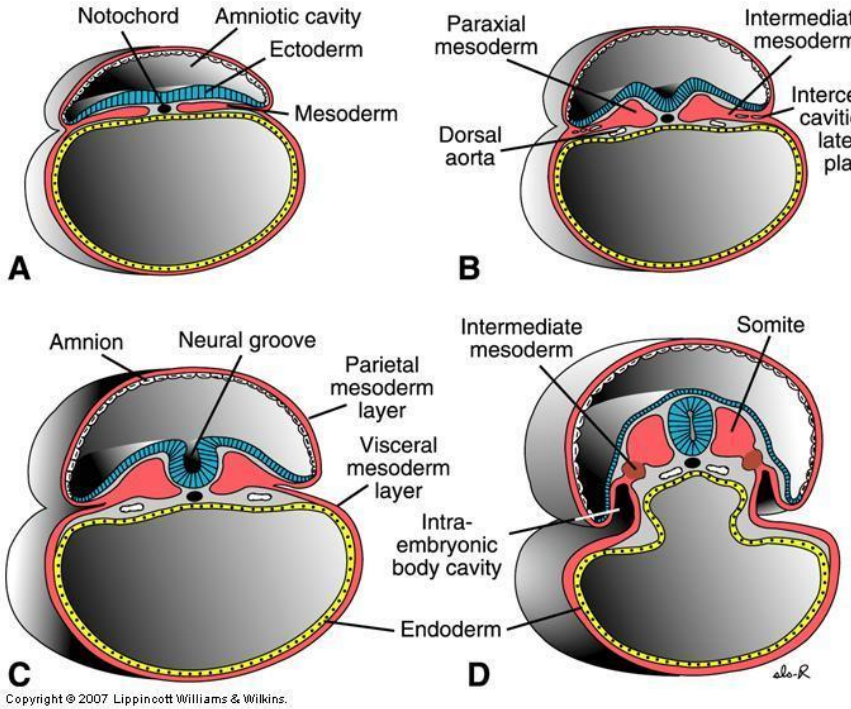


Third week of development: Gastrulation (trilaminar germ disc)

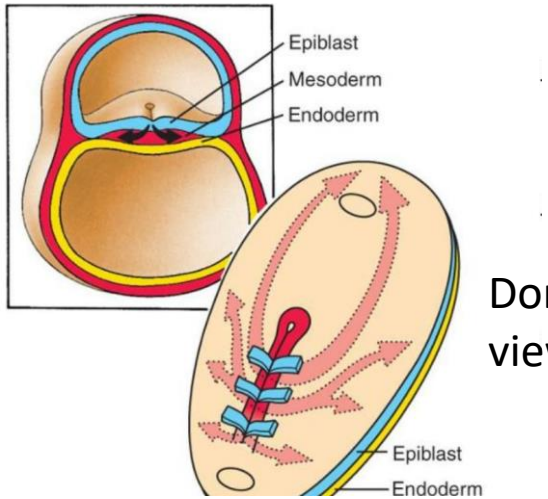




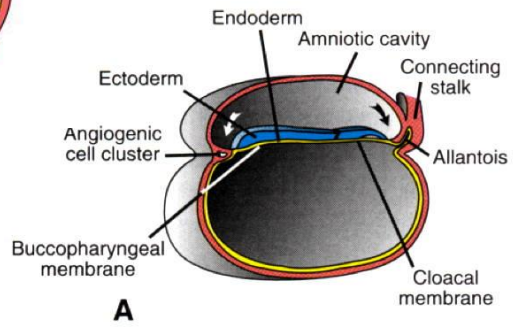
Gastrulation

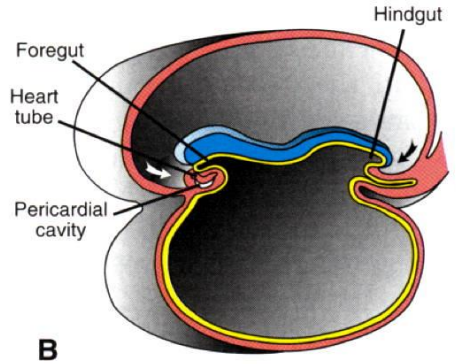


Transversal view

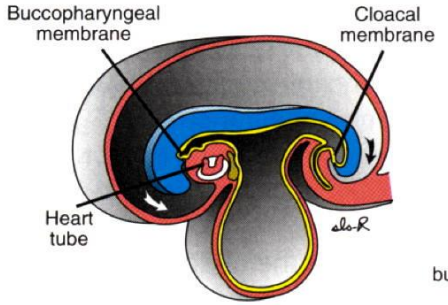


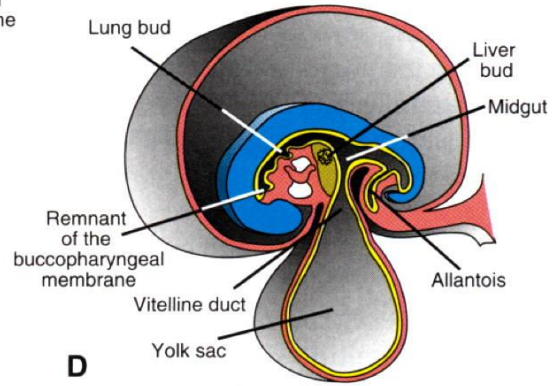
Dorsal view



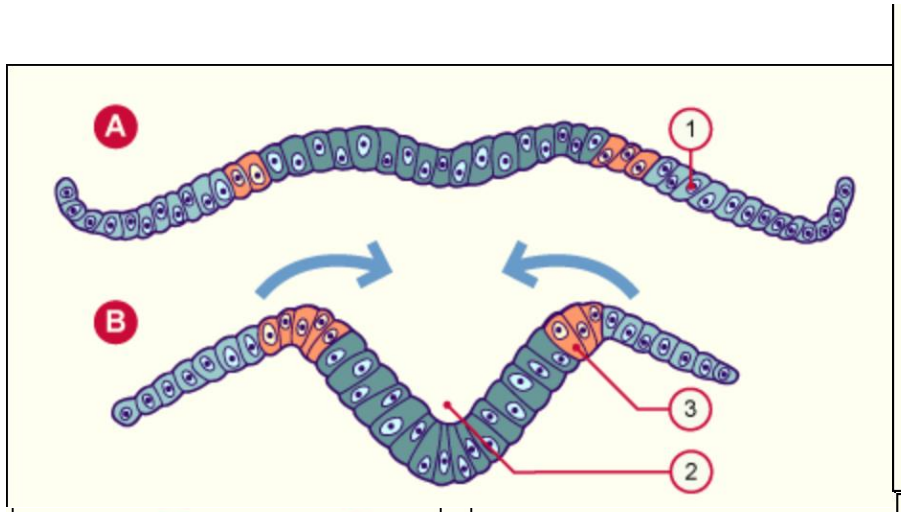


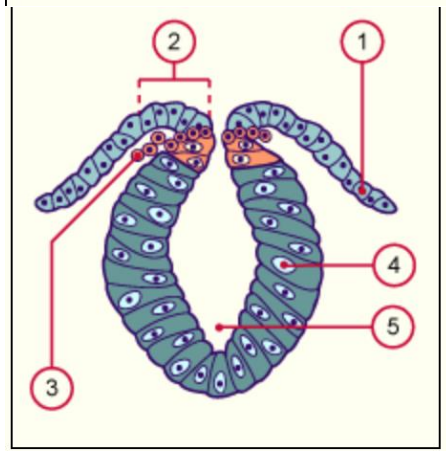
Sagittal view

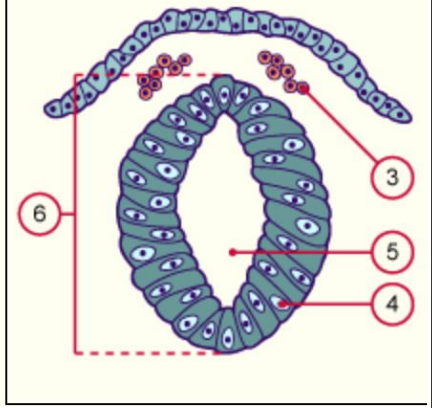




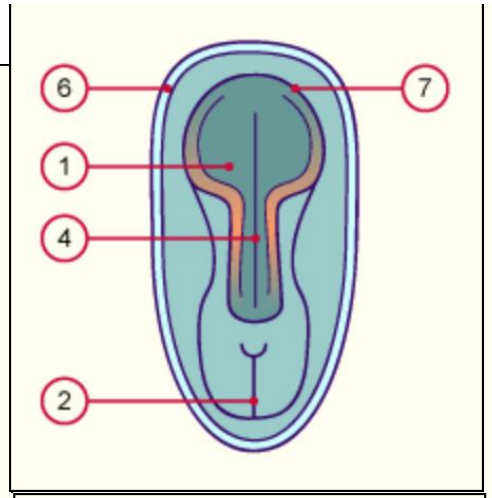
Neurulation

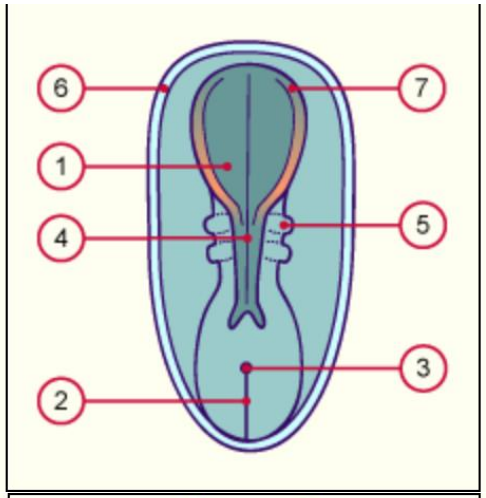


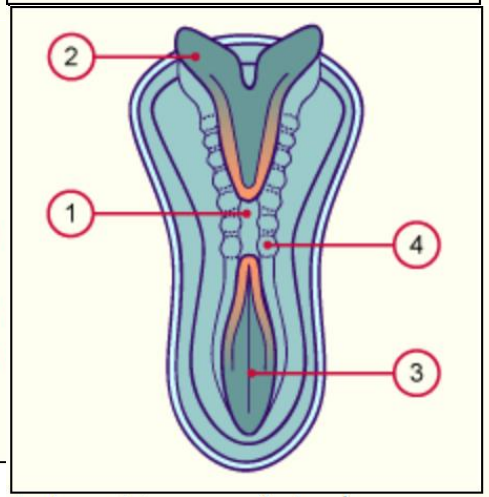


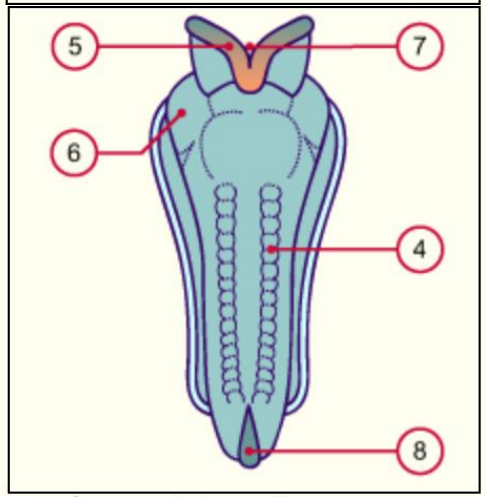


Transversal view



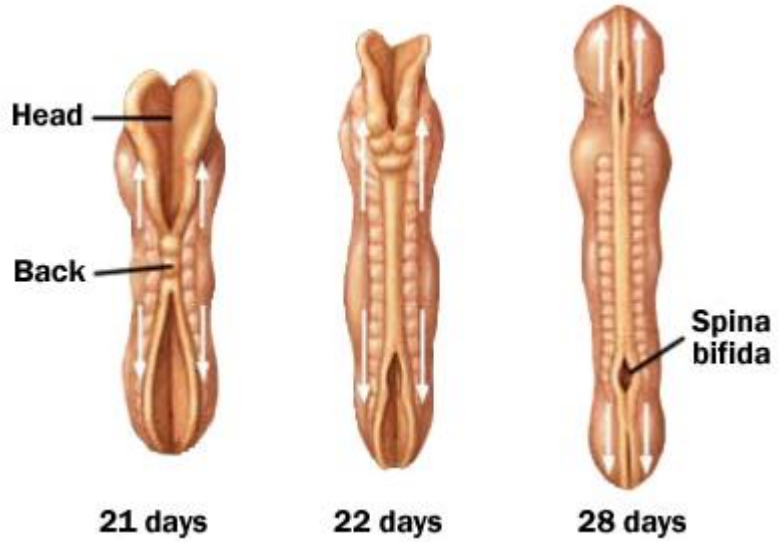


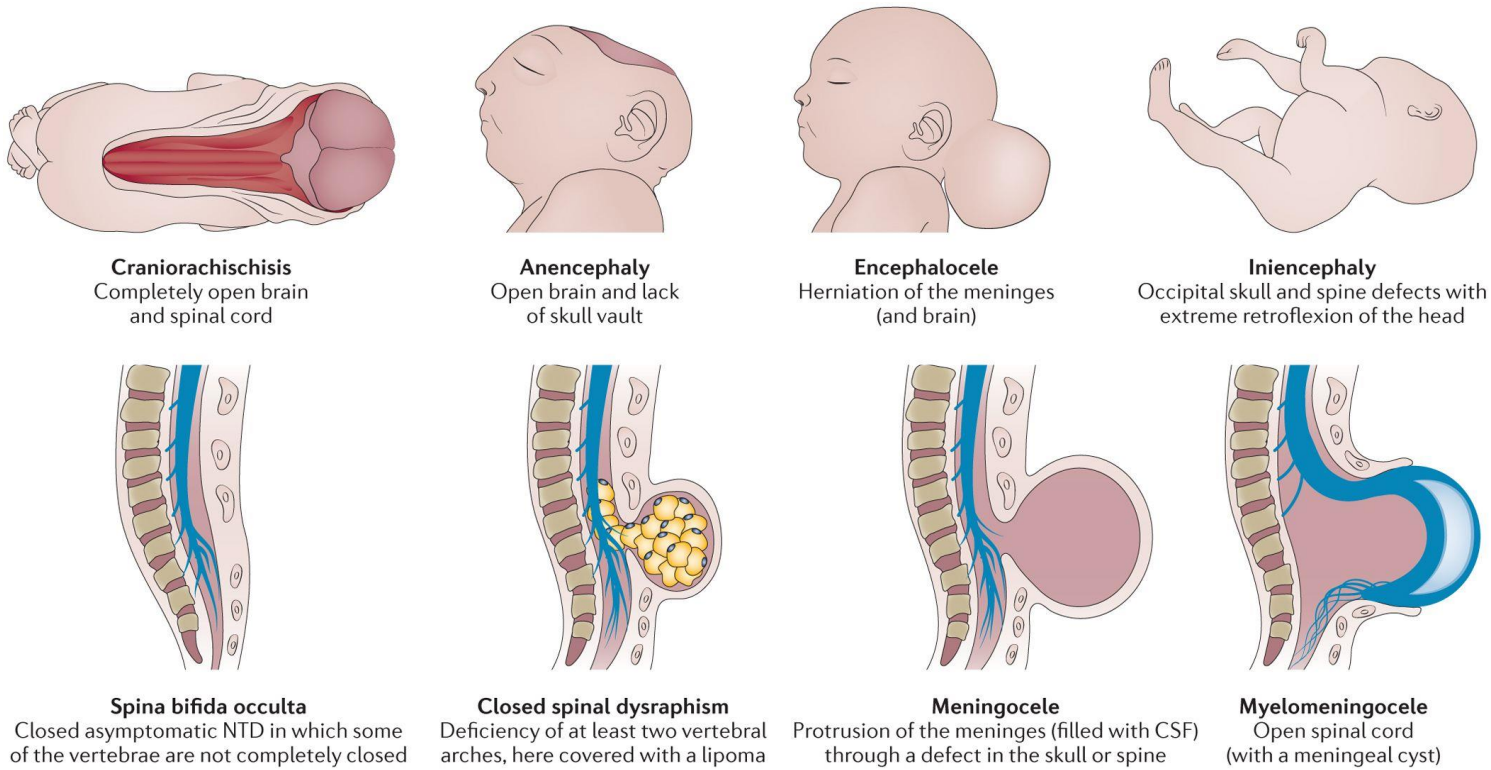




Dorsal view

Neural tube defects





Cellular Processes during Development

During development, cells

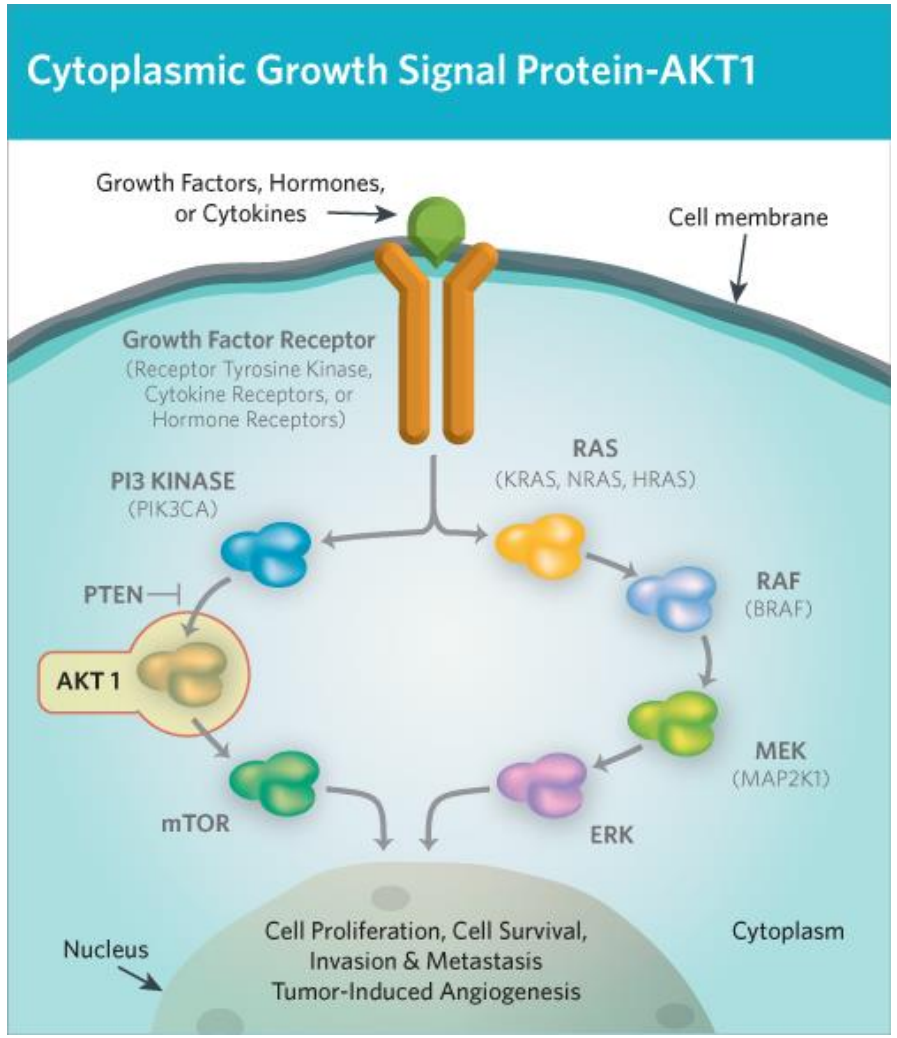
- **Proliferate** (divide)
- **Differentiate** (acquire novel functions or structures)
- **Migrate** (move within the embryo)
- **Undergo apoptosis** (programmed cell death)

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

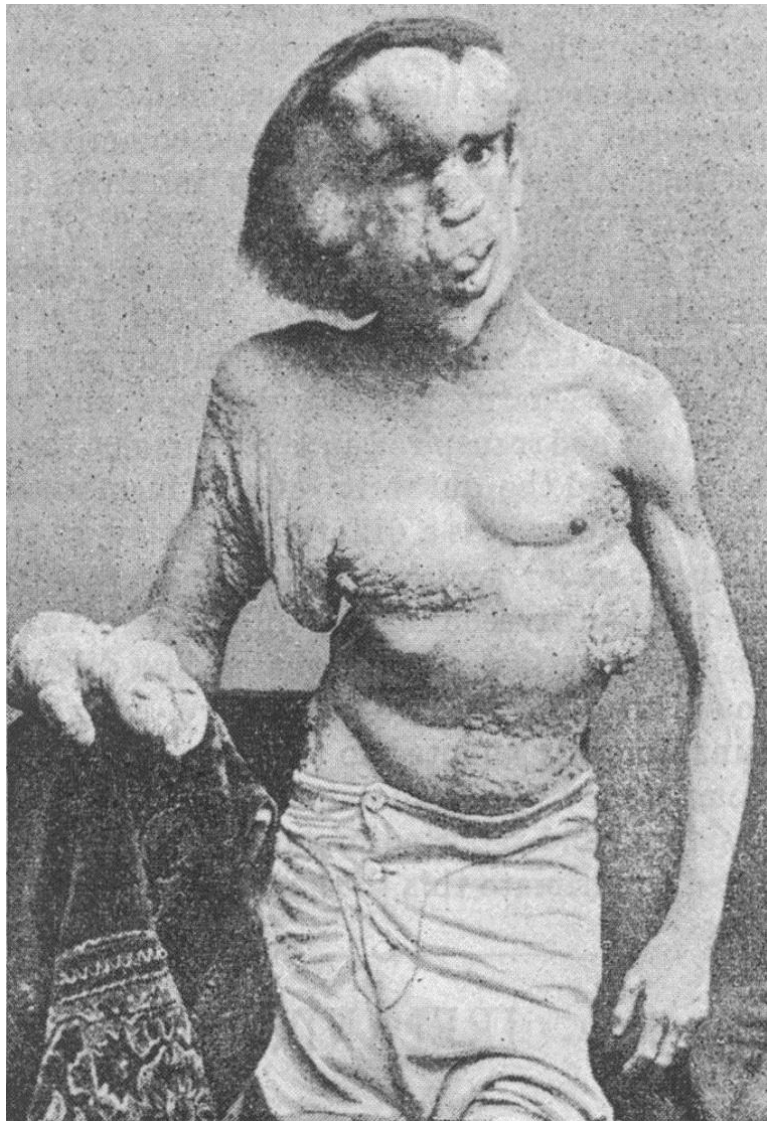
- **Growth**
- **Morphogenesis** (literally, the “creation of form”)

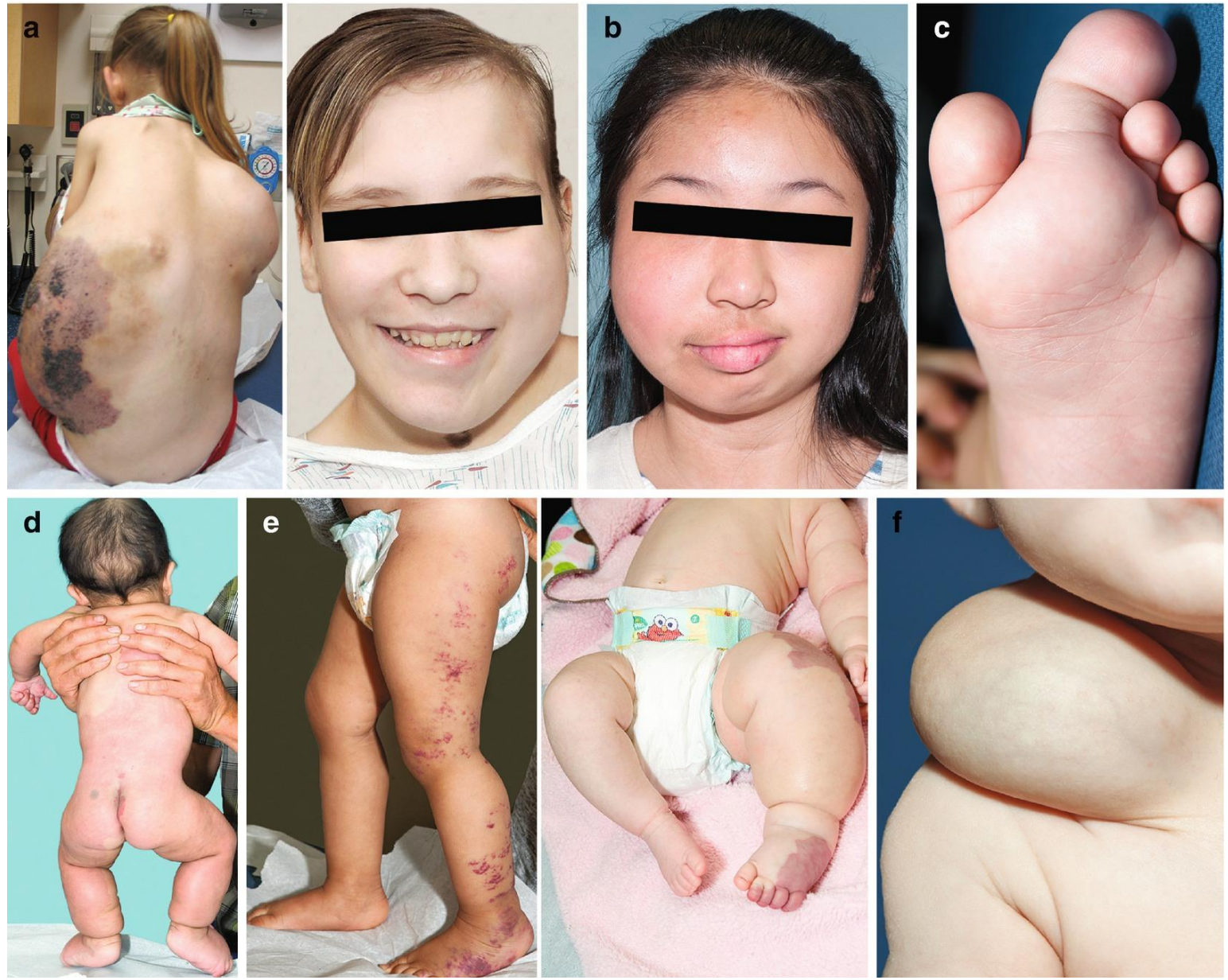
Thereby creating an embryo of normal size and shape, containing organs of the appropriate size, shape, and location, and consisting of tissues and cells with the correct architecture, structure, and function.

Dysregulation of growth

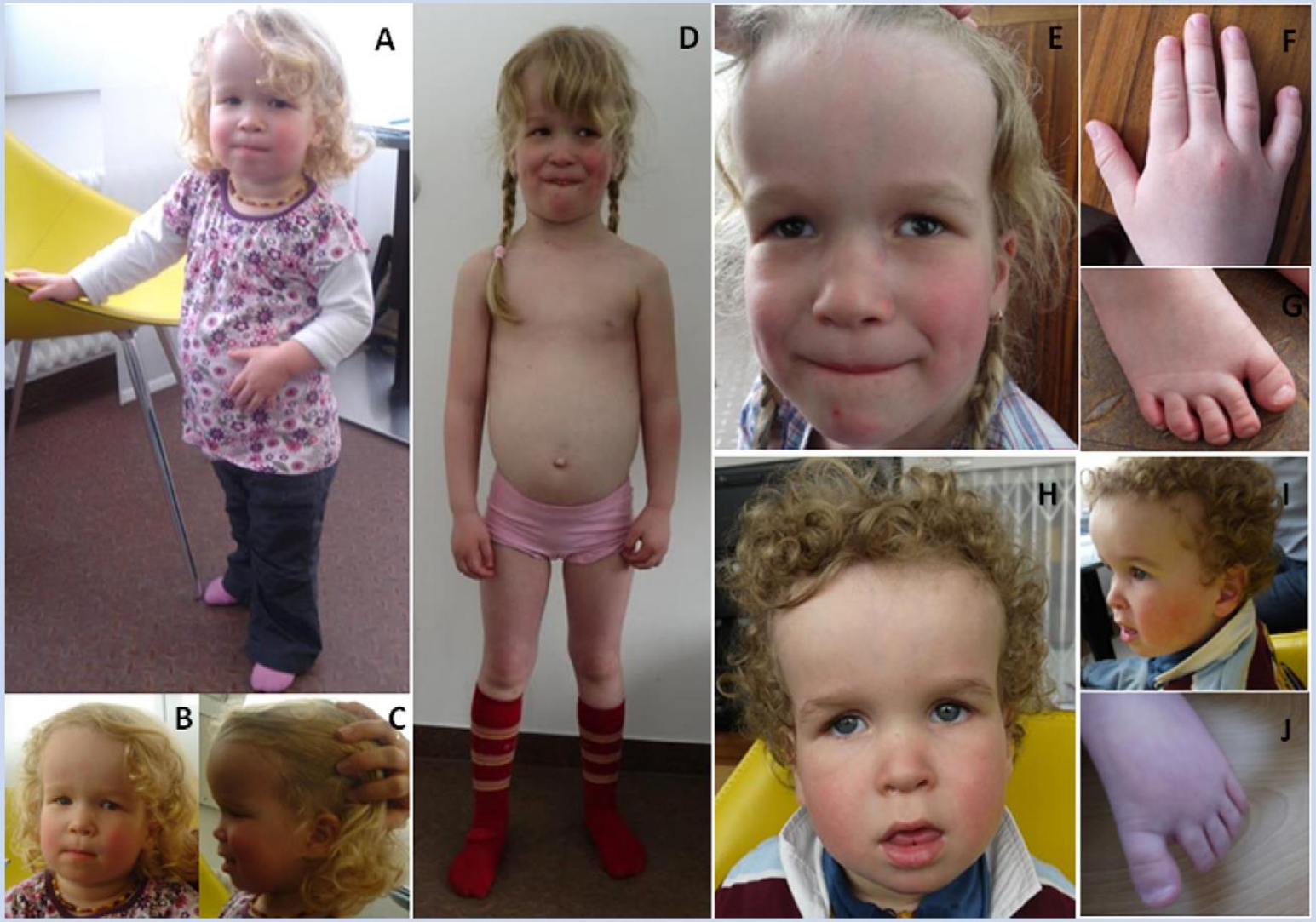


Mutations AKT1
Proteus syndrome





Mutations PIK3CA

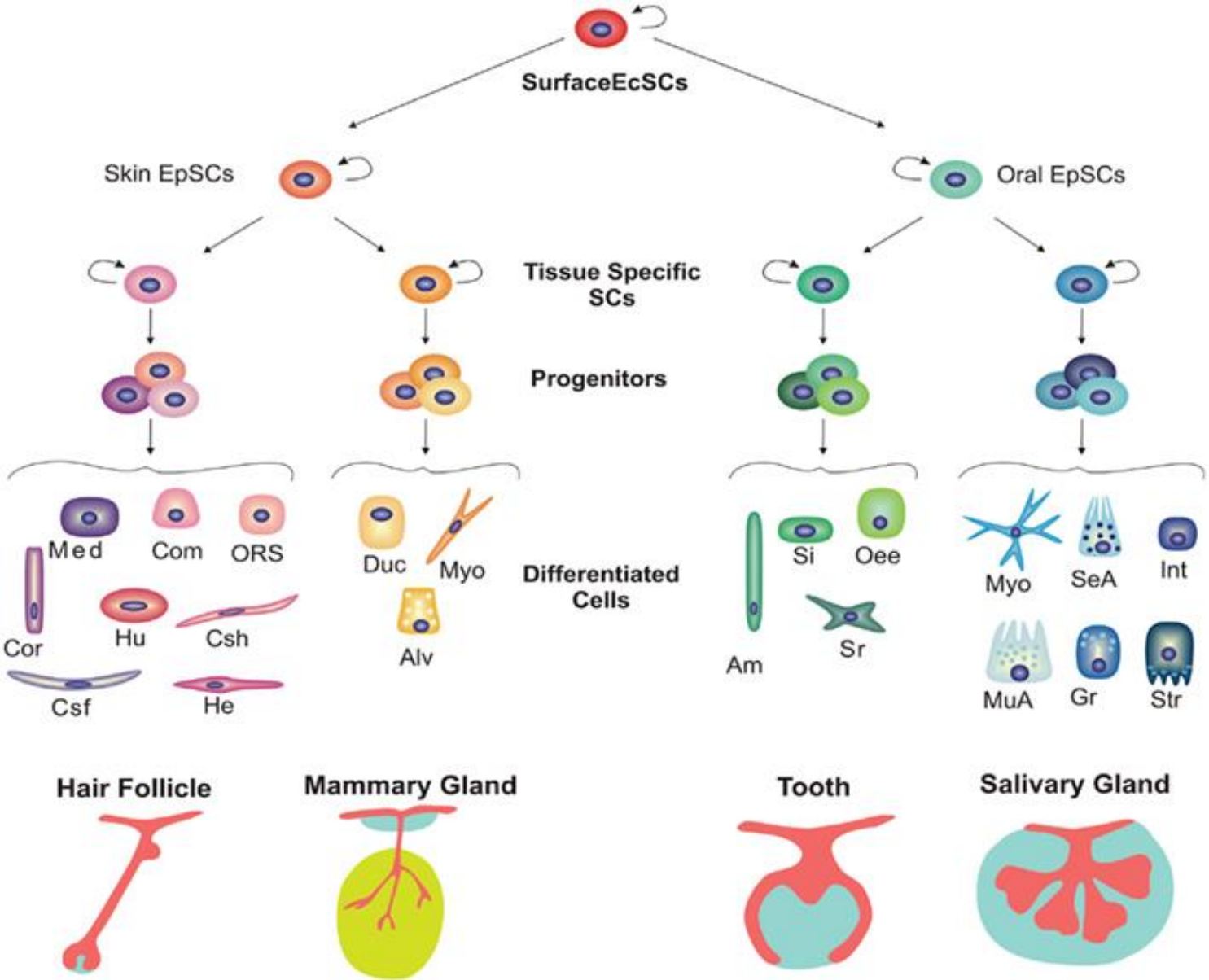


Mutations mTOR

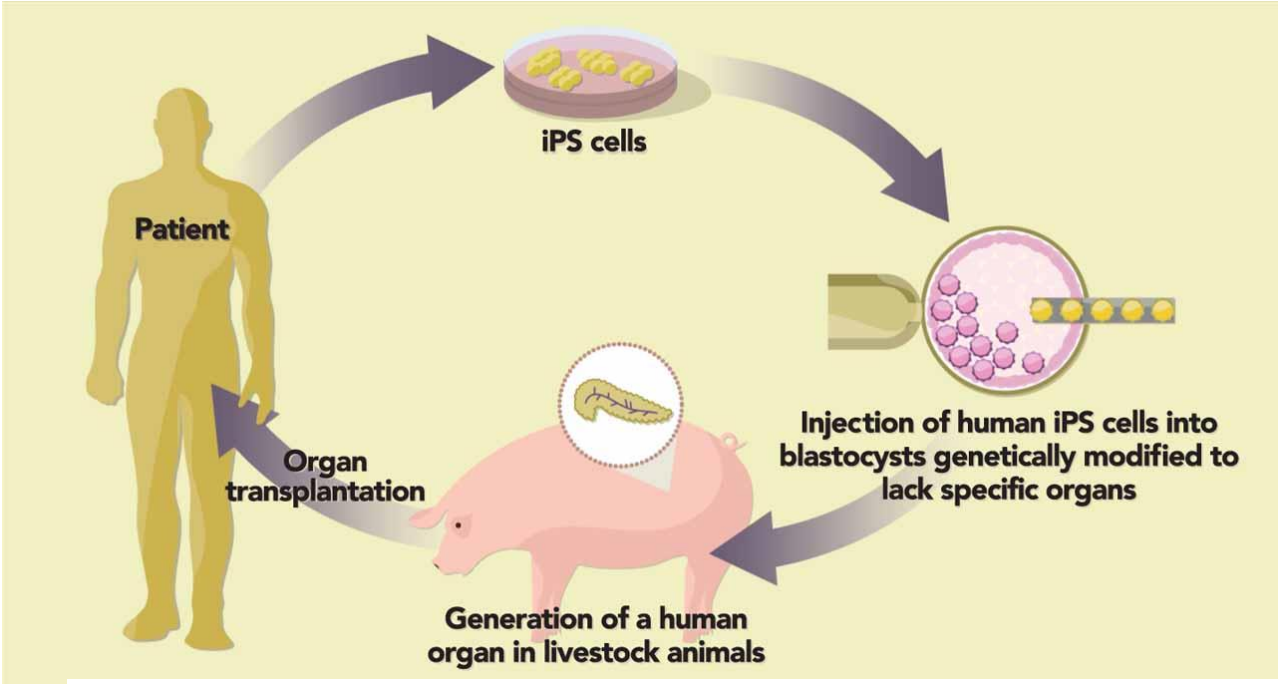
Chapters

- **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

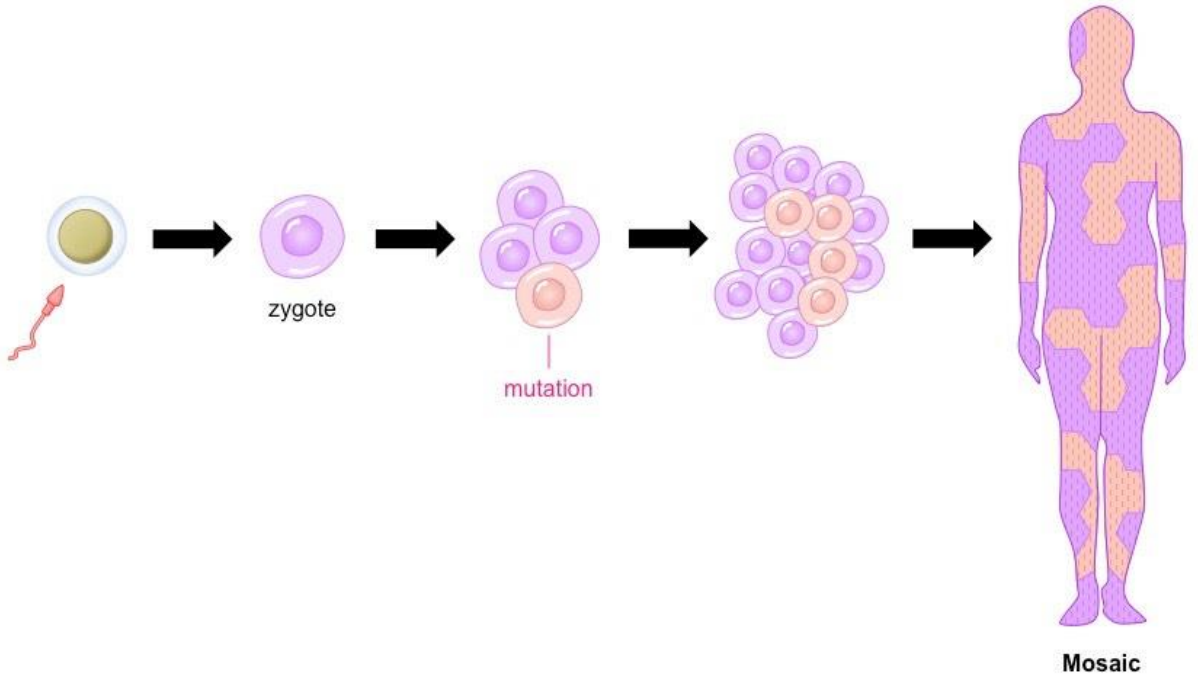
- **Undifferentiated cell** undergoes the **process of differentiation**, through a series of discrete steps in which it manifests various distinct functions or attributes until it reaches its **ultimate destination**, referred to as its **fate**
- **Early during differentiation**, a cell undergoes **specification** 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


SurfaceEcSCs
Skin EpSCs
Oral EpSCs
Tissue Specific SCs
Progenitors
Differentiated Cells
Med
Com
ORS
Cor
Hu
Csh
Csf
He
Duc
Myo
Alv
Am
Si
Oee
Sr
Myo
SeA
Int
MuA
Gr
Str
Hair Follicle
Mammary Gland
Tooth
Salivary Gland

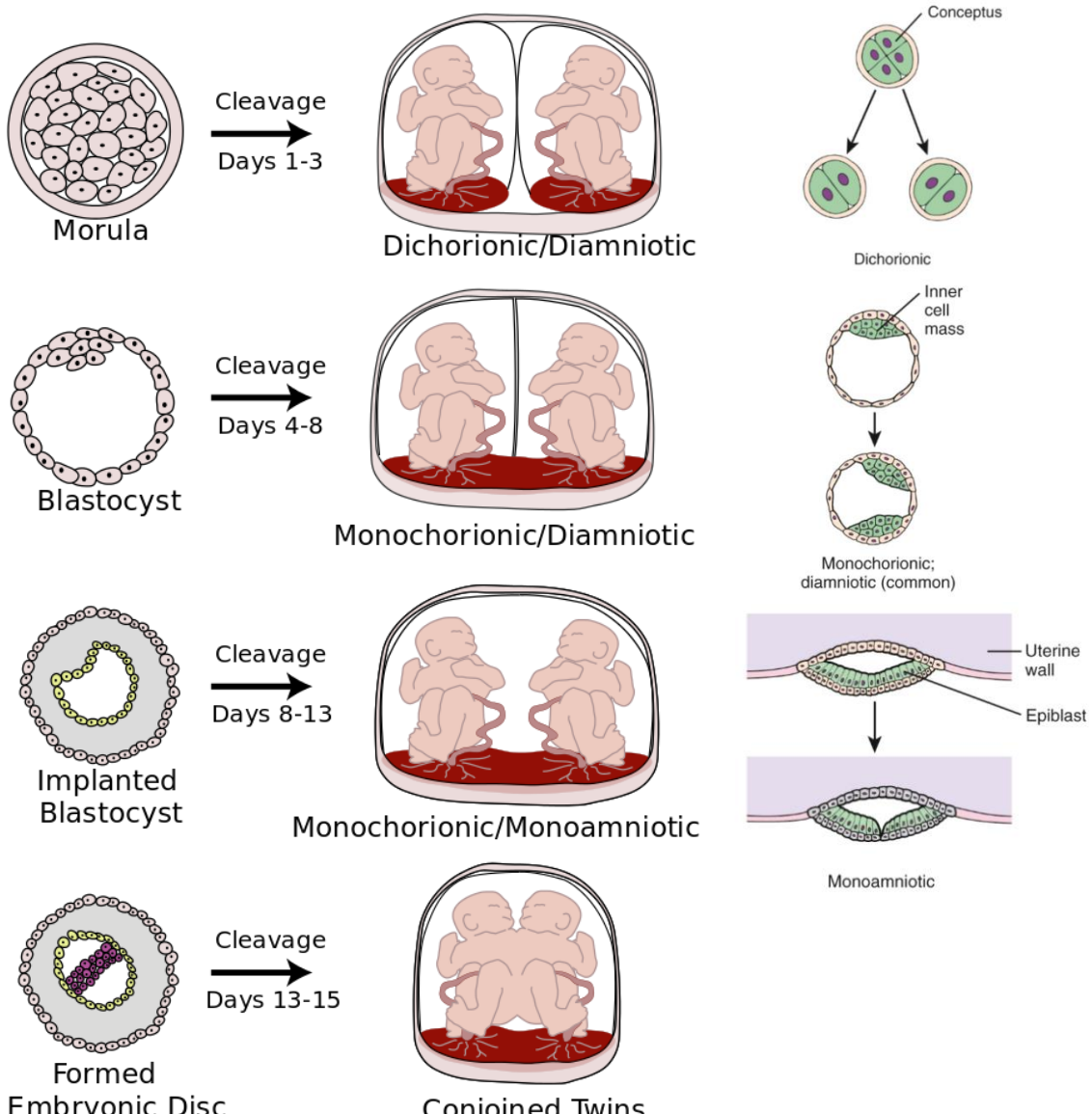
Chimerism



Mosaicism

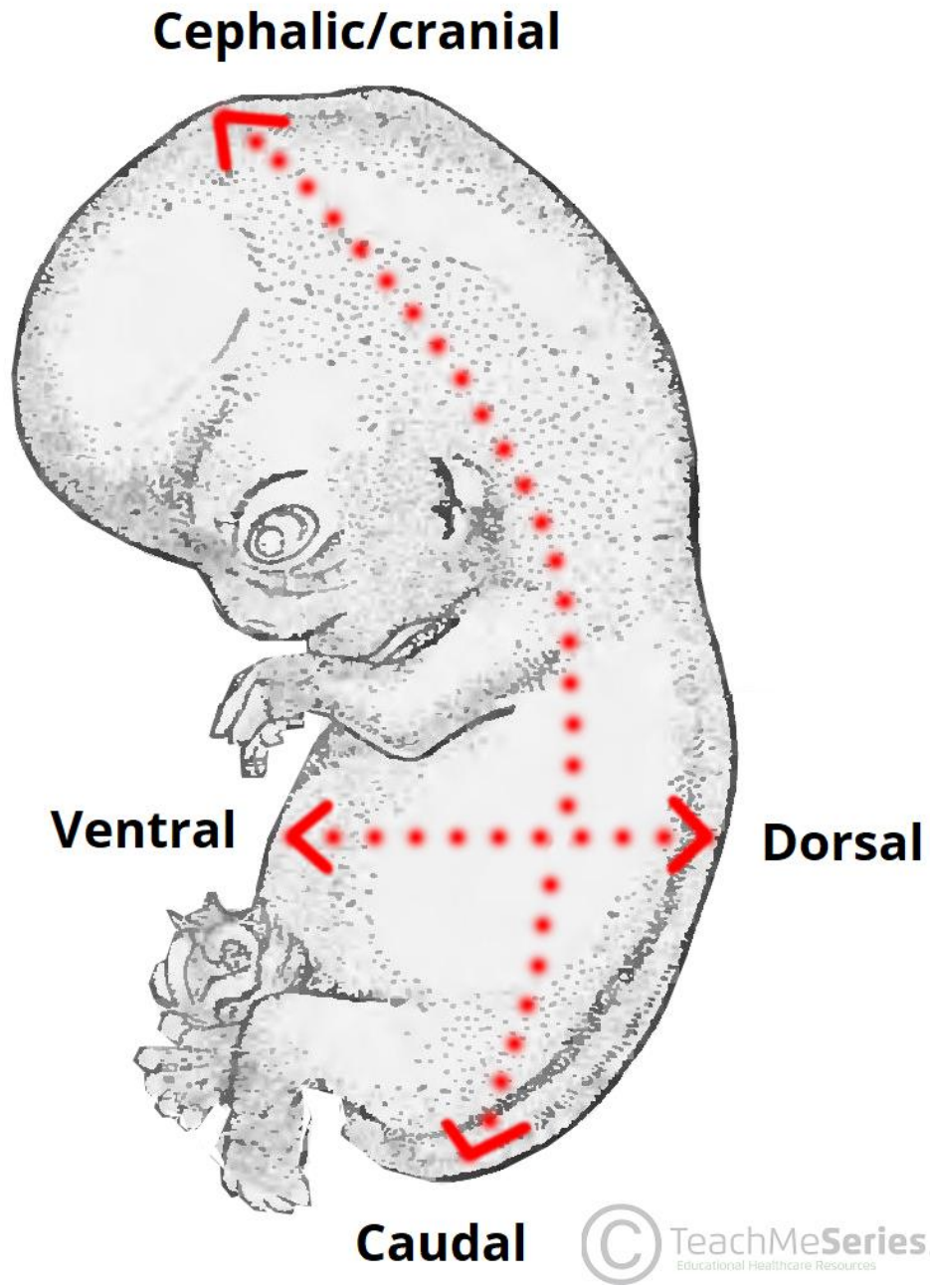


Regulative Development and Twinning

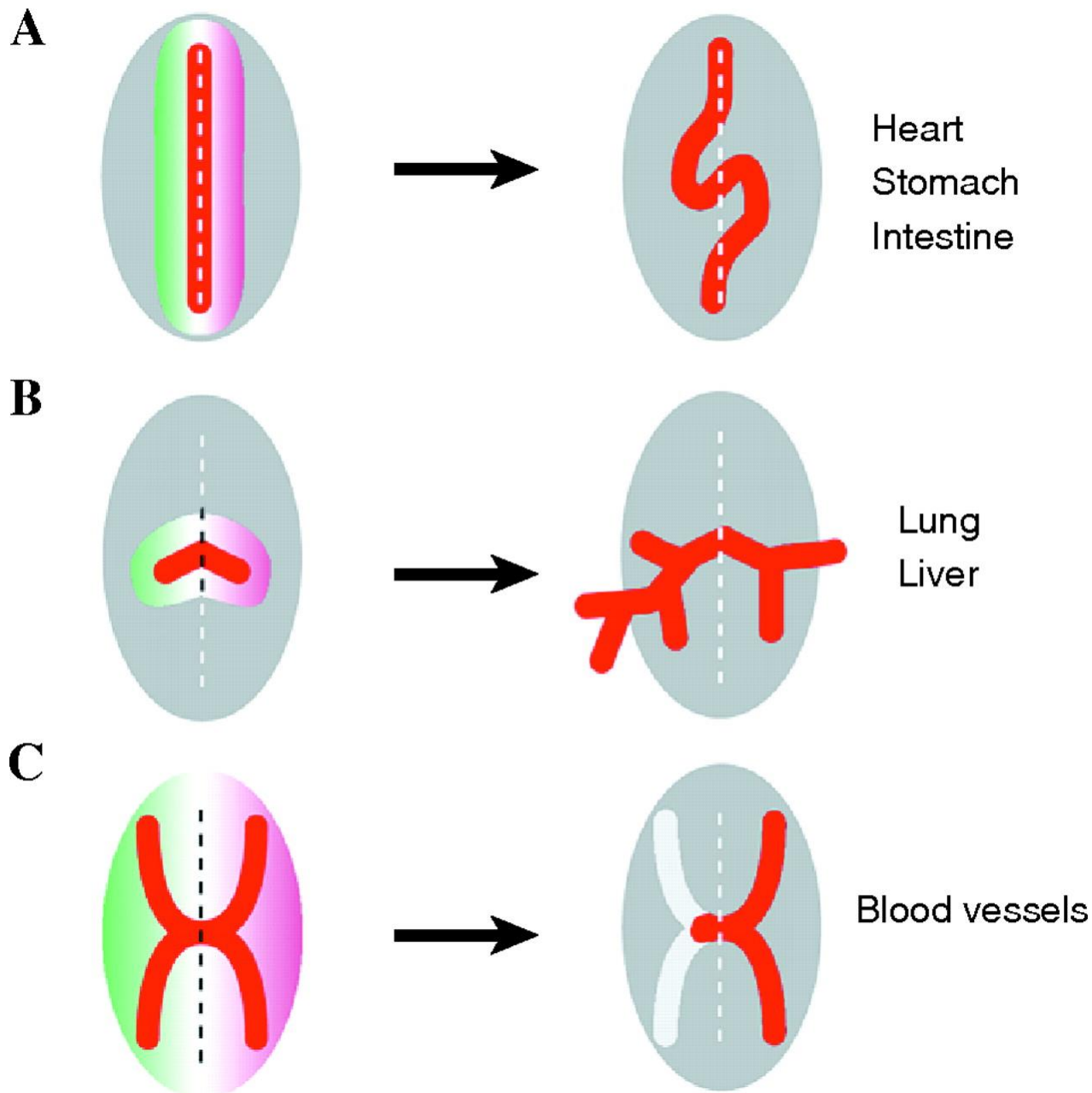


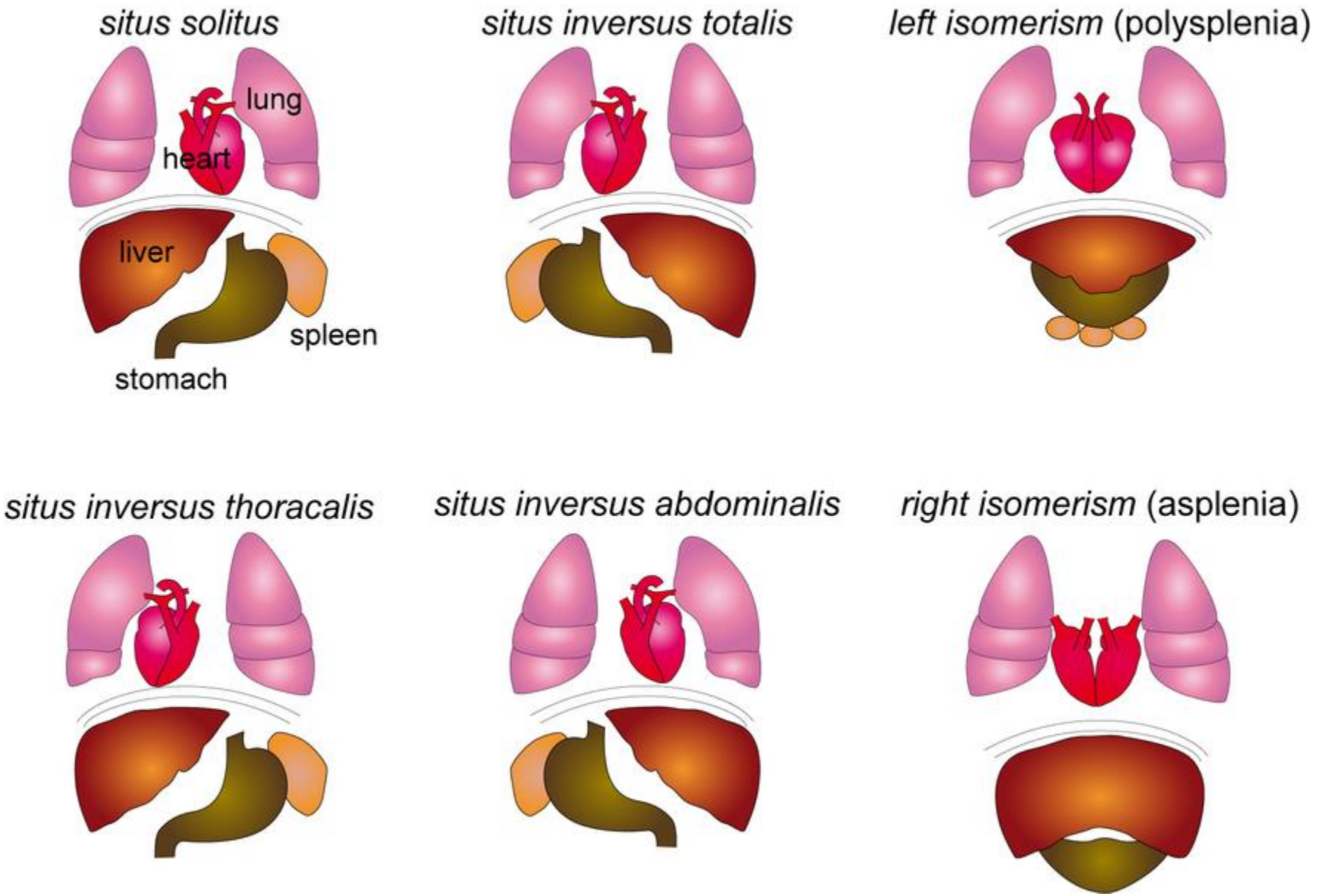
Chapters

- **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

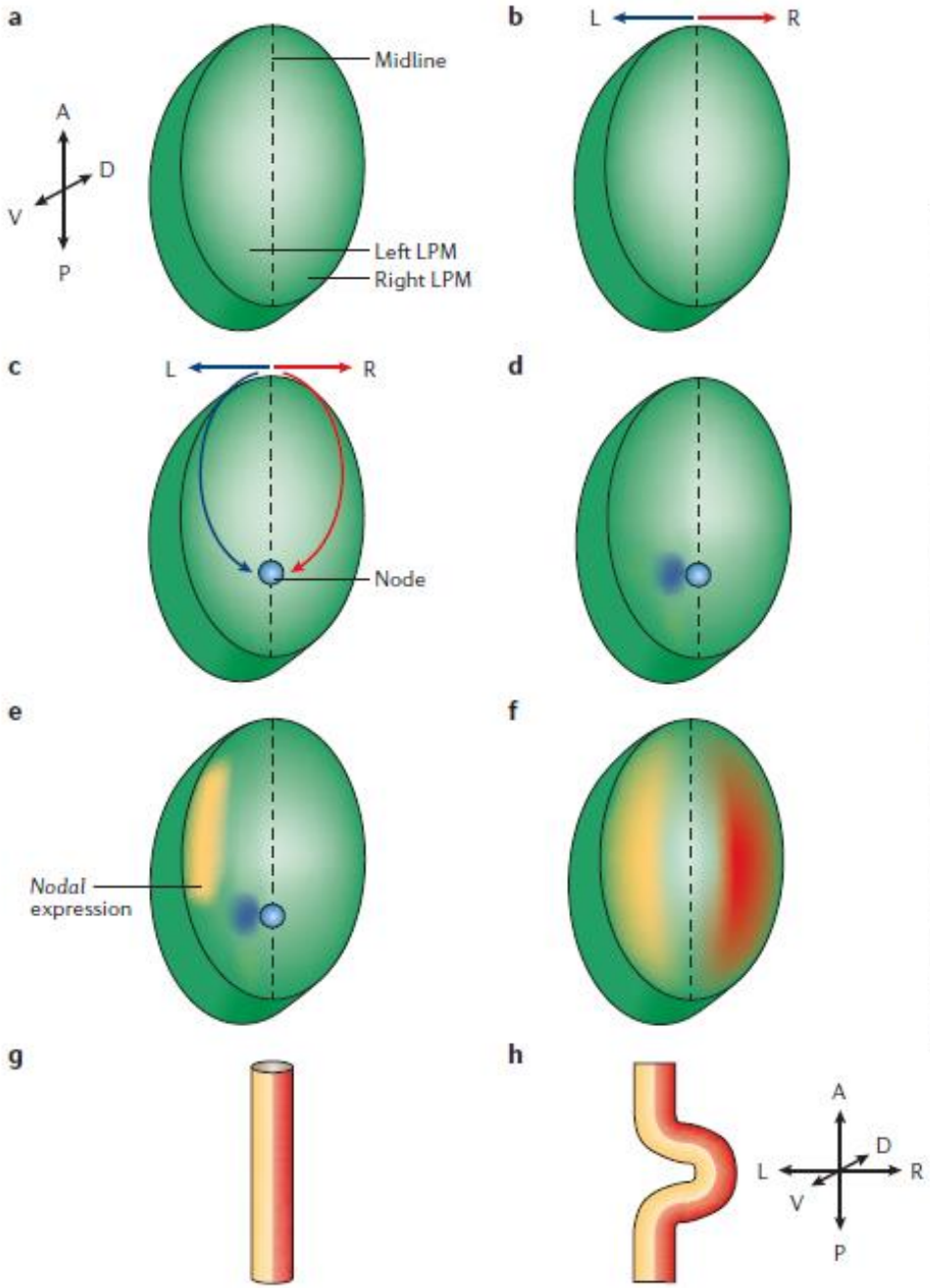


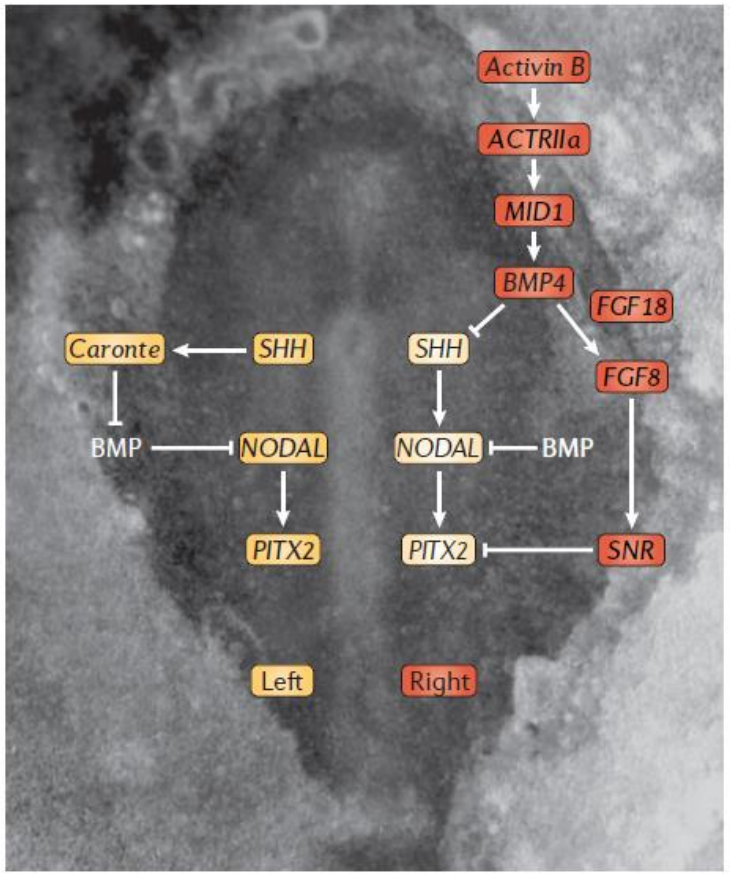
Left-Right axis



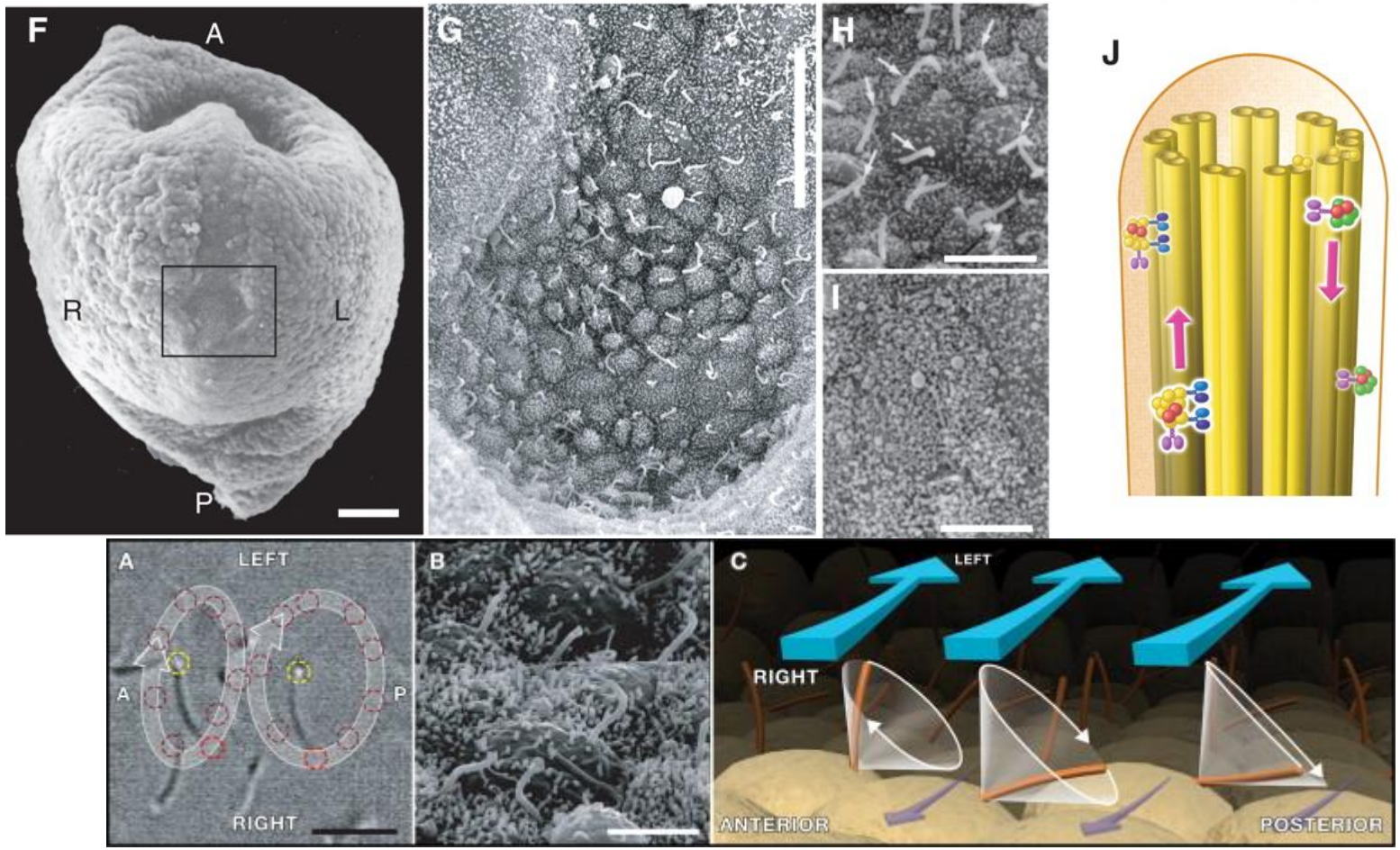


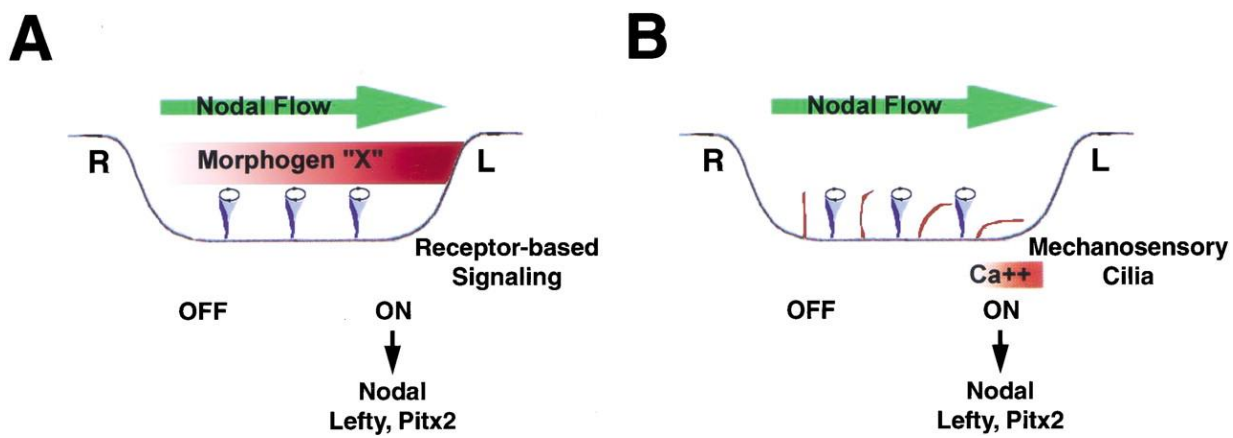
Heterotaxy is defined as an abnormality where the internal thoraco-abdominal organs demonstrate abnormal arrangement across the left-right axis of the body.

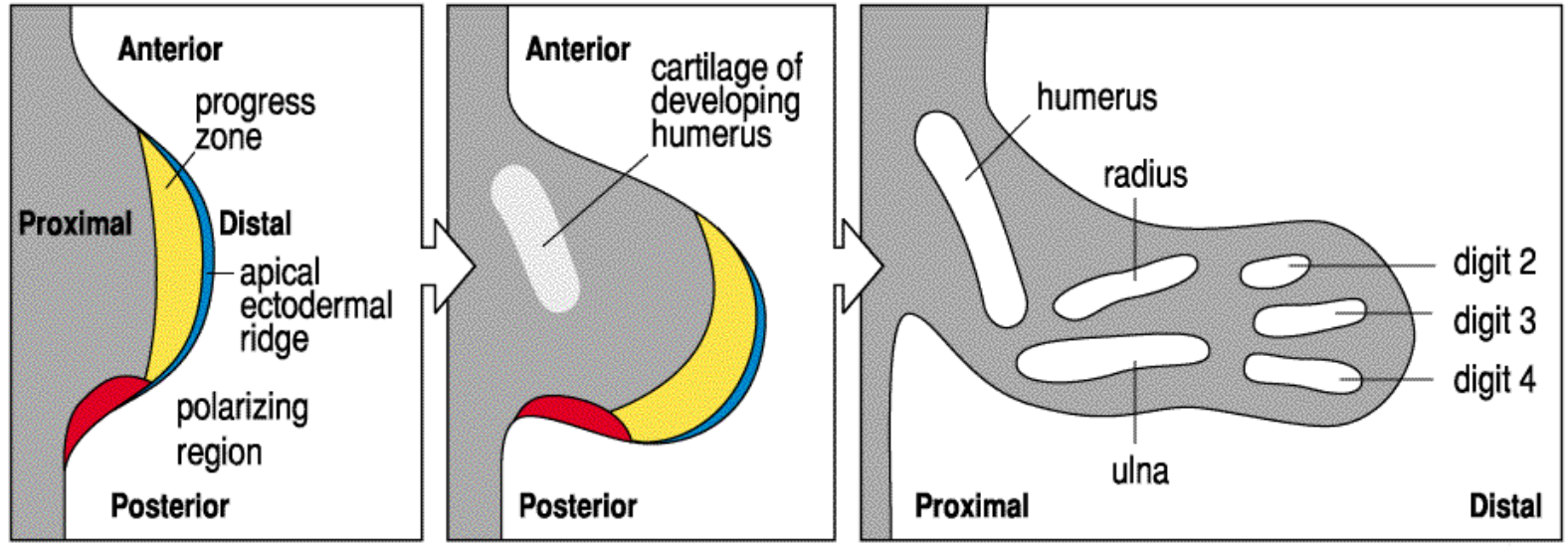


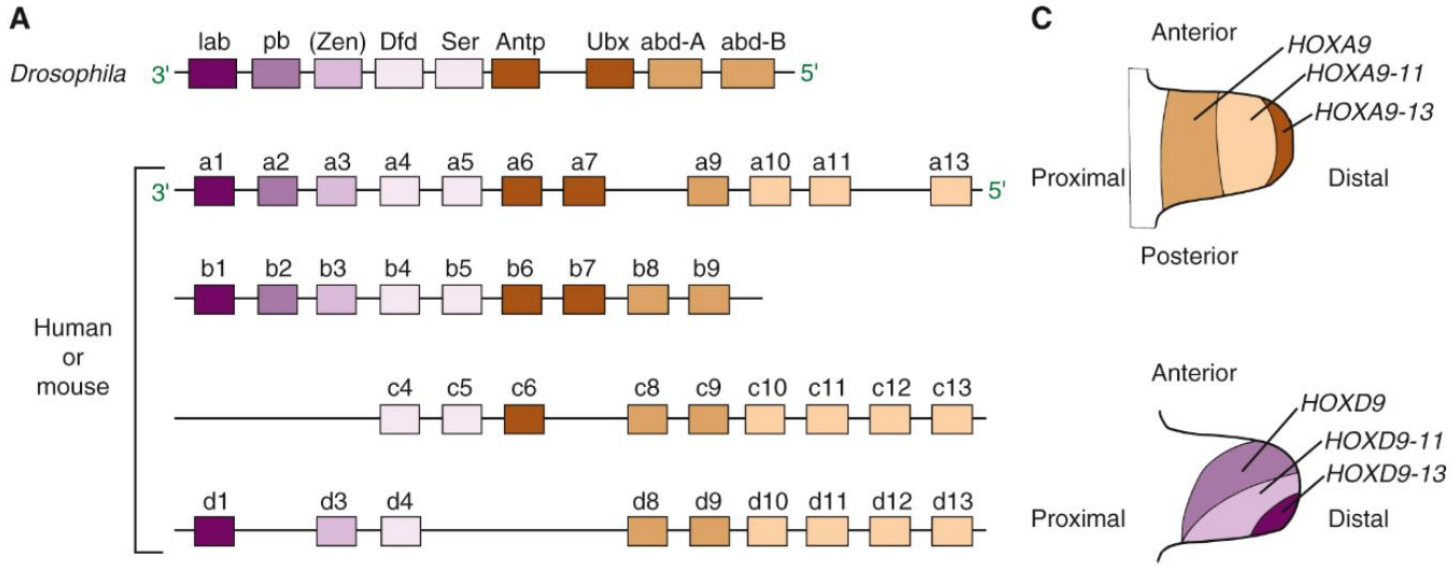


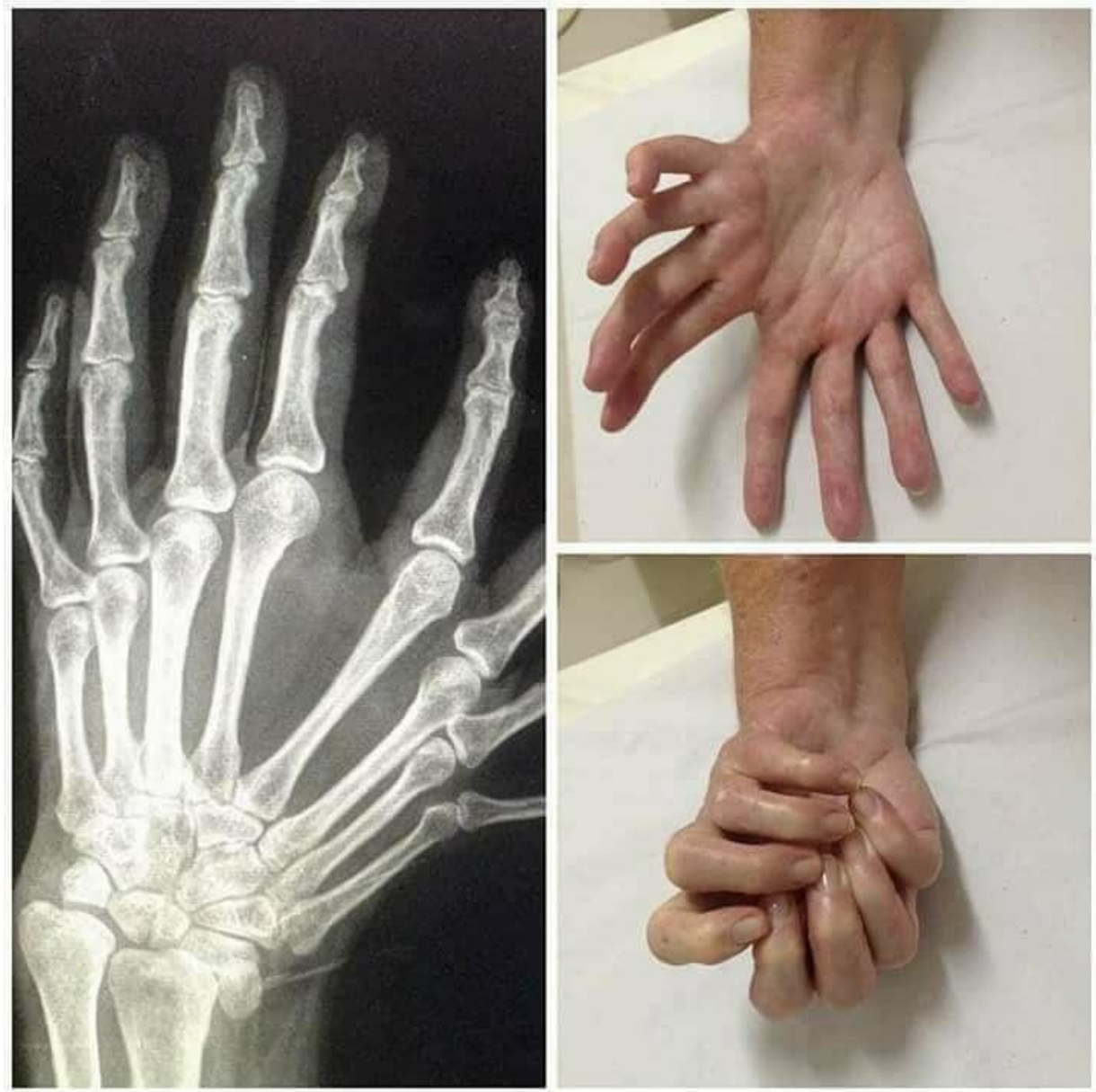
Raya and Belmonte, Nature Reviews Genetics, 2006


F
A
R
L
P
G
H
I
J
A
LEFT
A
P
RIGHT
B
C
LEFT
RIGHT
ANTERIOR
POSTERIOR


A
Nodal Flow
R
Morphogen "X"
L
Receptor-based
Signaling
OFF
ON
Nodal
Lefty, Pitx2
B
Nodal Flow
R
L
Mechanosensory
Cilia
Ca++
OFF
ON
Nodal
Lefty, Pitx2


Anterior
progress zone
Proximal
Distal
apical ectodermal ridge
polarizing region
Posterior
Anterior
cartilage of developing humerus
Posterior
humerus
radius
digit 2
digit 3
digit 4
ulna
Proximal
Distal

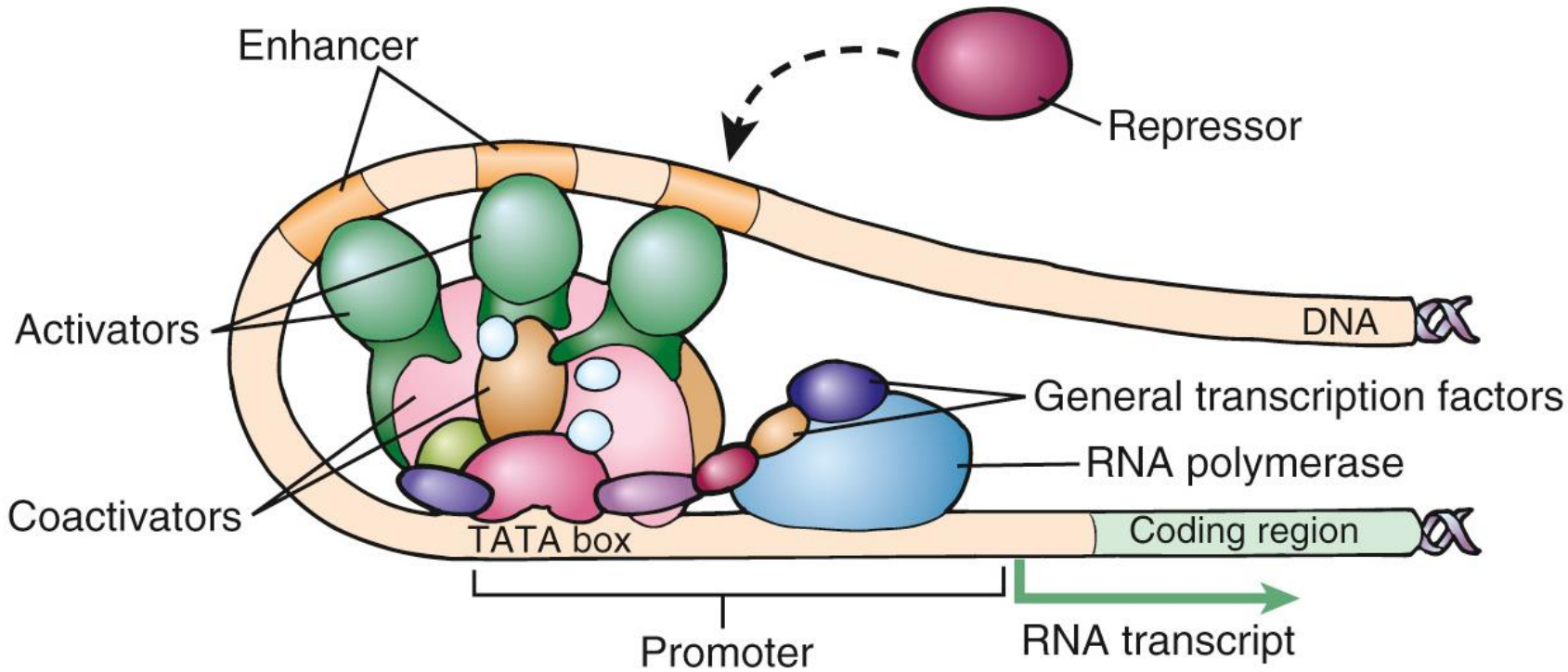

A
Drosophila
3'
lab pb (Zen) Dfd Ser Antp Ubx abd-A abd-B
5'
Human or mouse
a1 a2 a3 a4 a5 a6 a7 a9 a10 a11 a13
b1 b2 b3 b4 b5 b6 b7 b8 b9
c4 c5 c6 c8 c9 c10 c11 c12 c13
d1 d3 d4 d8 d9 d10 d11 d12 d13
C
Anterior
HOXA9
HOXA9-11
HOXA9-13
Proximal
Distal
Posterior
Anterior
HOXD9
HOXD9-11
HOXD9-13
Proximal
Distal
Posterior
B

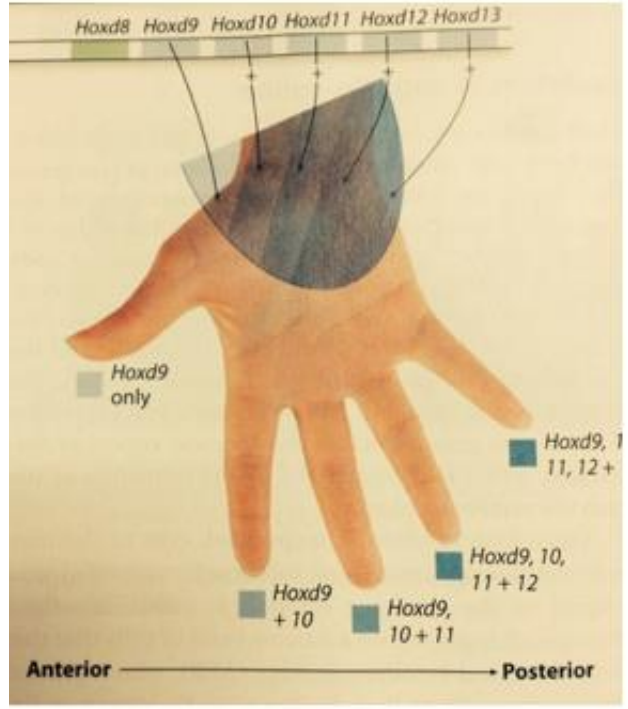


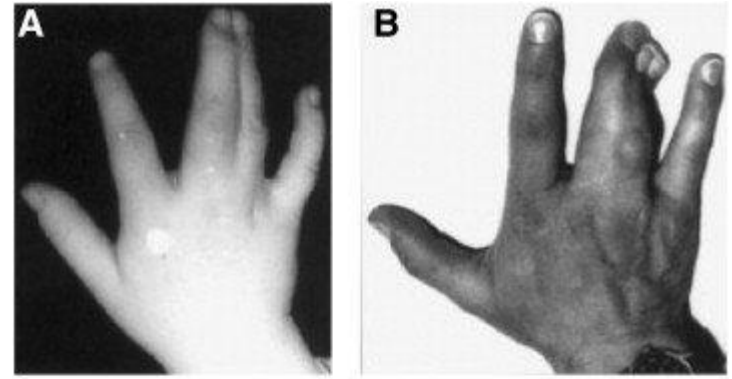
Ulnar dimelia or mirror hand syndrome

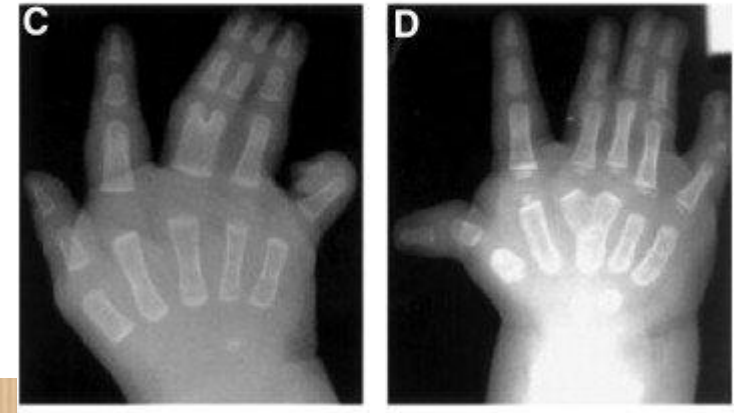
Chapters

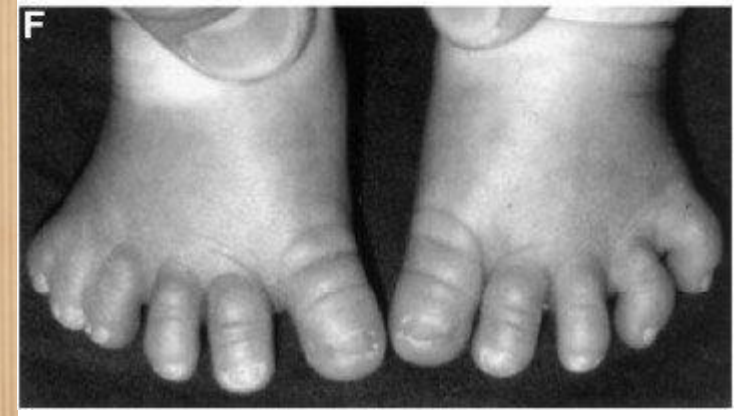
- **Basic Concepts of Developmental Biology**
  - Overview of Embryological Development
  - Fate, Specification, and Determination
  - Axis Specification and Pattern Formation
- **Cellular and Molecular Mechanisms in Development**
  - Gene Regulation by Transcription Factors
  - Morphogens and Cell to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

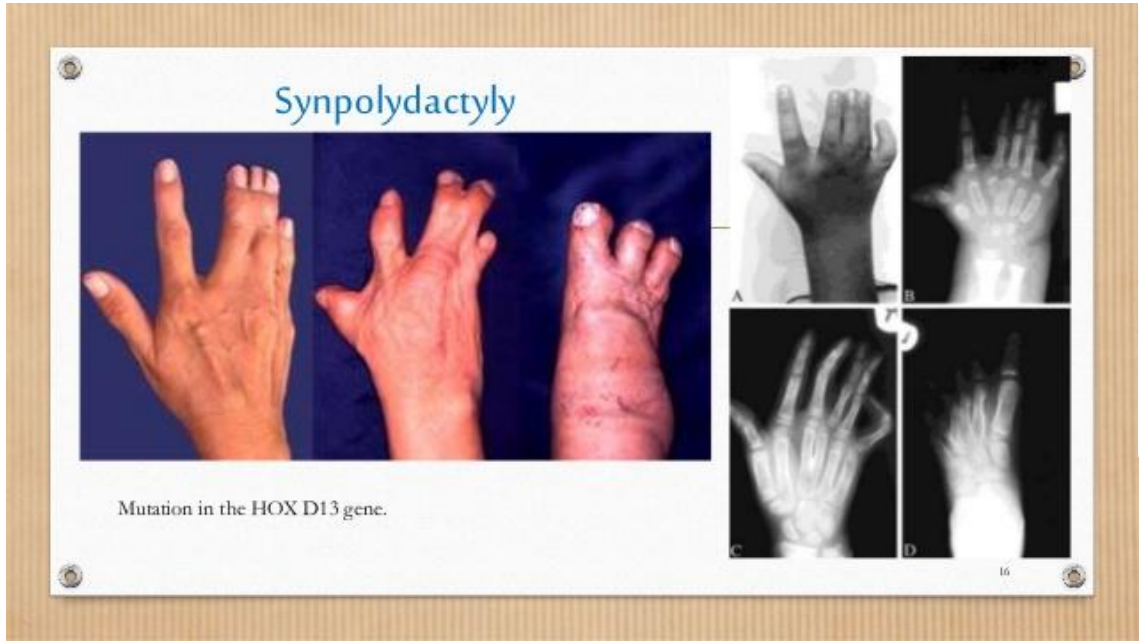

Enhancer
Repressor
Activators
DNA
General transcription factors
RNA polymerase
Coactivators
TATA box
Coding region
Promoter
RNA transcript


Hoxd8 Hoxd9 Hoxd10 Hoxd11 Hoxd12 Hoxd13
Hoxd9 only
Hoxd9, 11, 12 +
Hoxd9, 10, 11 + 12
Hoxd9 + 10
Hoxd9, 10 + 11
Anterior
Posterior


A
B

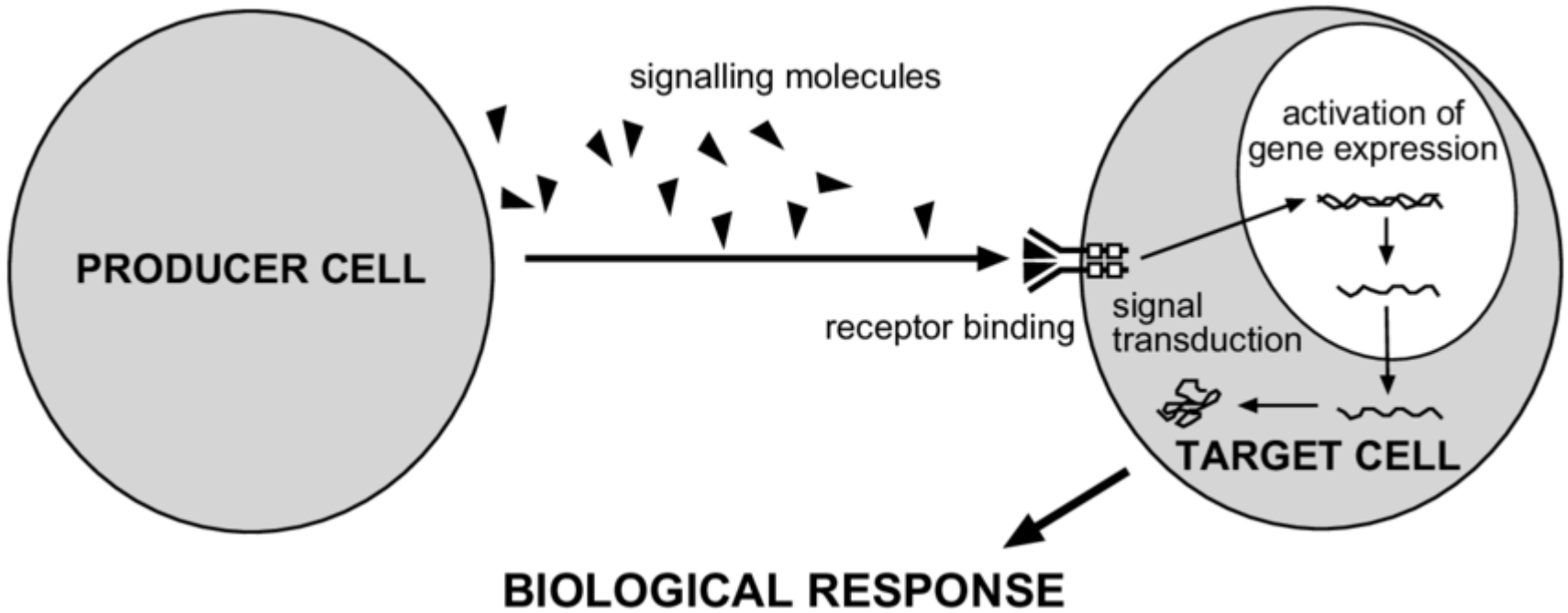

C
D


F

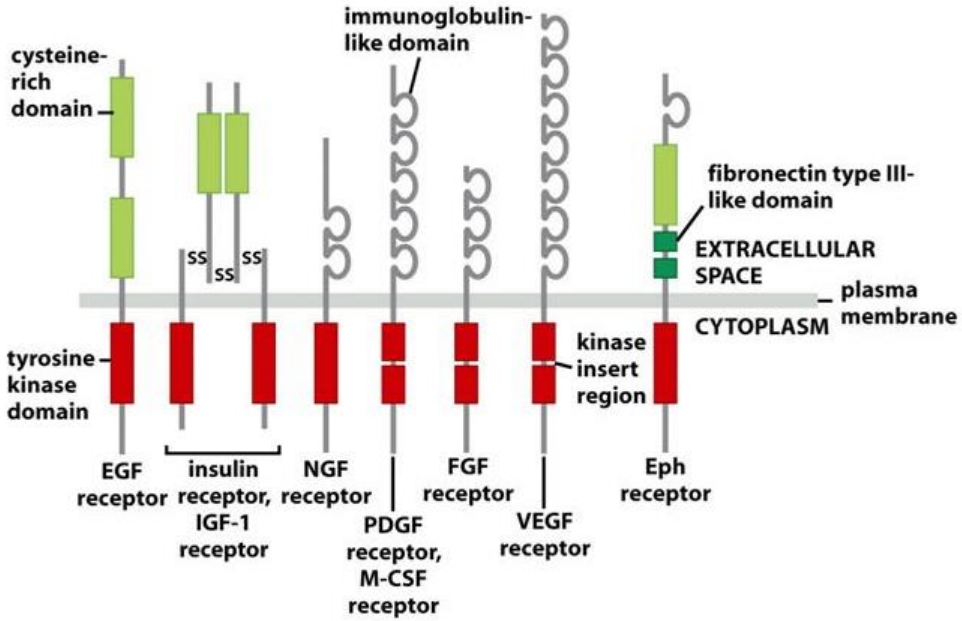

Synpolydactyly
Mutation in the HOX D13 gene.
16

Chapters

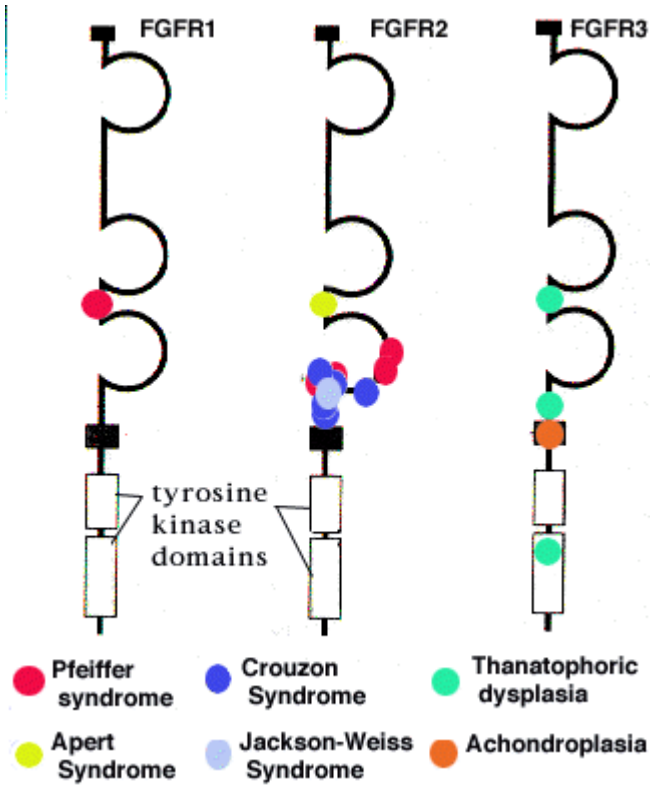
- **Basic Concepts of Developmental Biology**
  - Overview of Embryological Development
  - Fate, Specification, and Determination
  - Axis Specification and Pattern Formation
- **Cellular and Molecular Mechanisms in Development**
  - Gene Regulation by Transcription Factors
  - Morphogens and Cell to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


signalling molecules
PRODUCER CELL
receptor binding
activation of
gene expression
signal
transduction
TARGET CELL
BIOLOGICAL RESPONSE

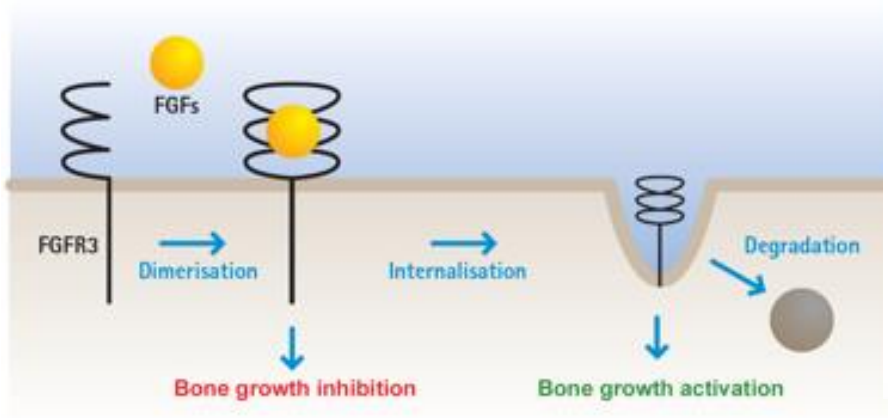
Structure of tyrosine kinase receptors

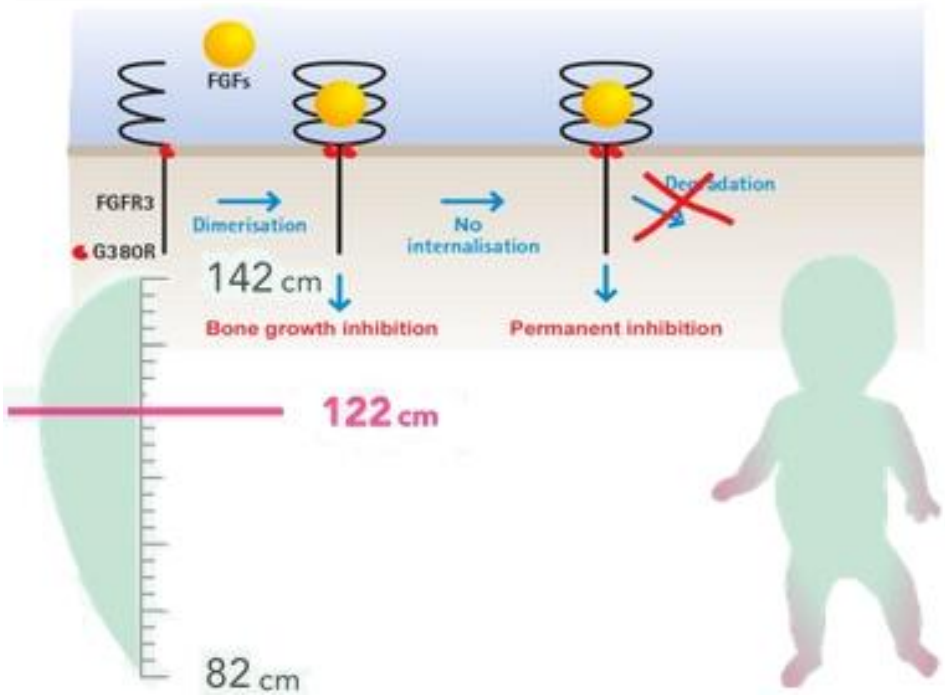


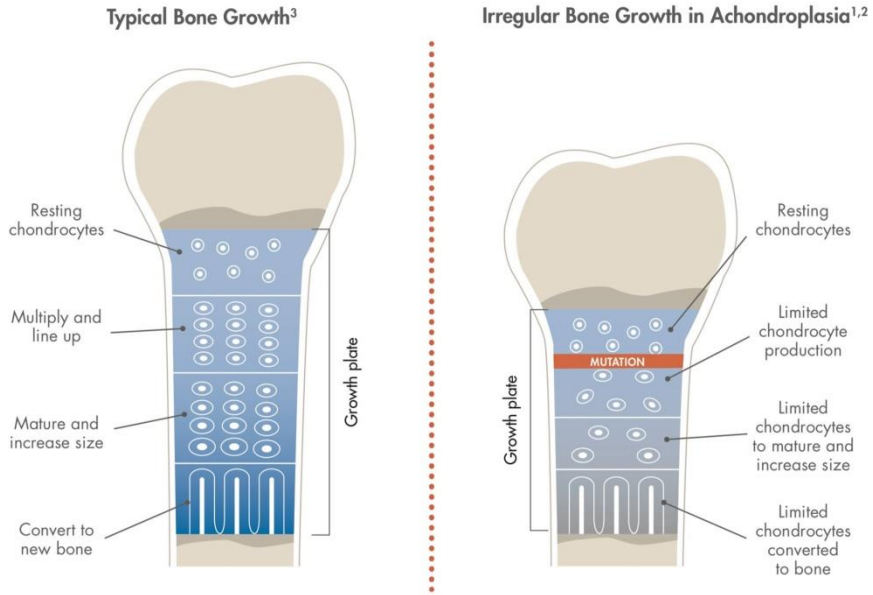
IGF-1: insulin-like growth factor-1, NGF: nerve growth factor,
PDGF: platelet-derived growth factor, FGF: fibroblast growth factor,
VEGF: vascular endothelial growth factor, Eph: ephrin

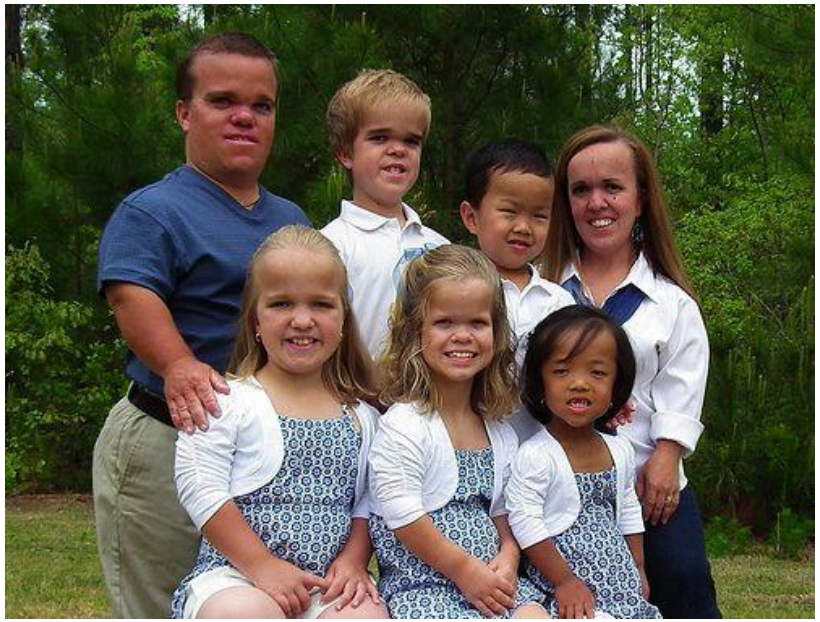


Achondroplasia



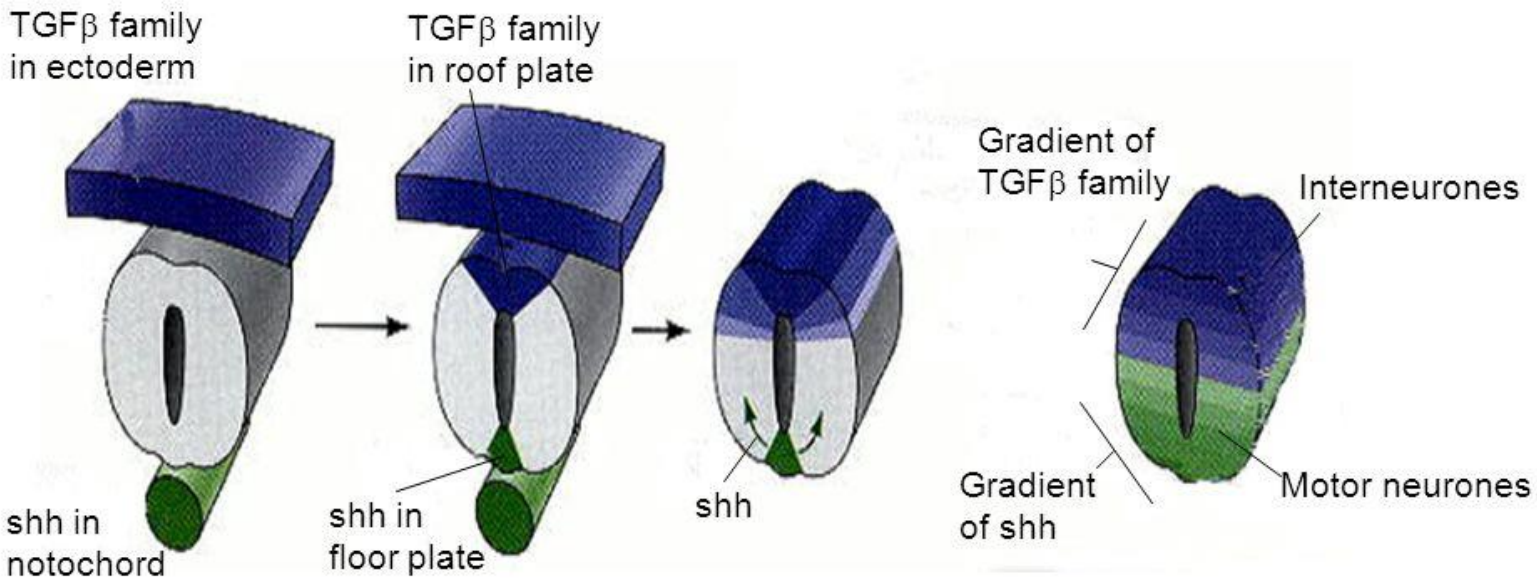






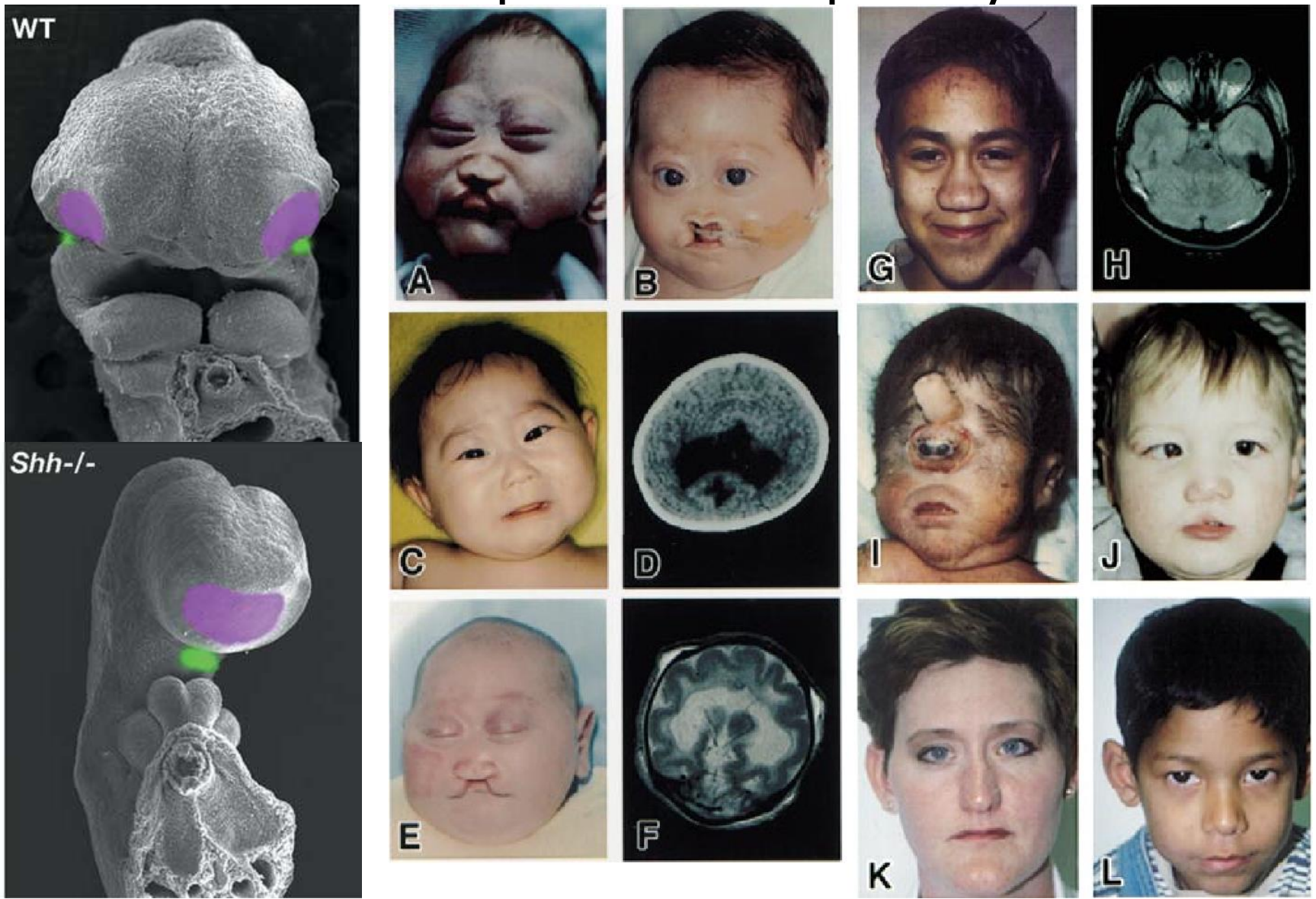
Exam

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-neurones and motor neurones

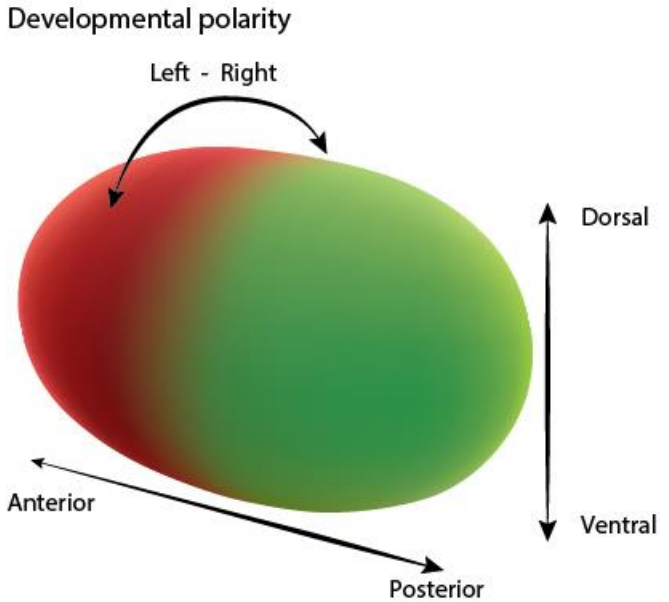
SHH mutations: holoprosencephaly

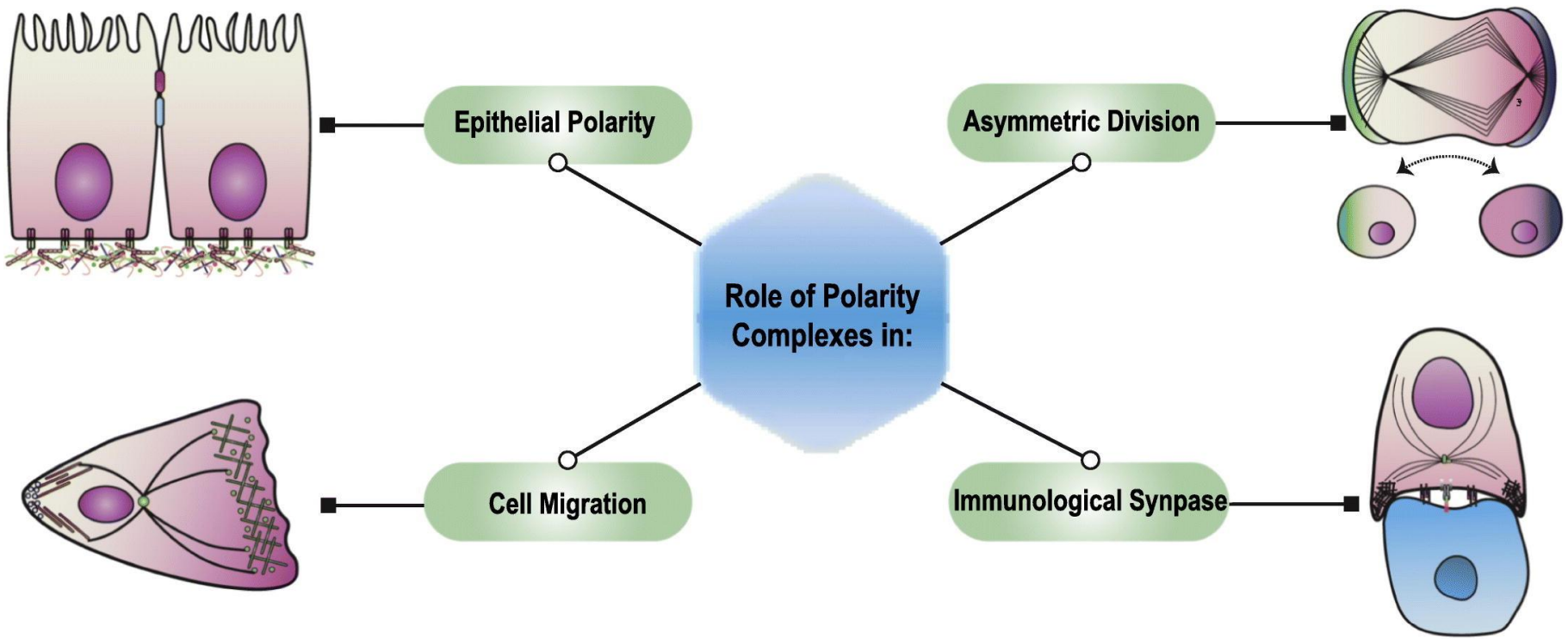


Chapters

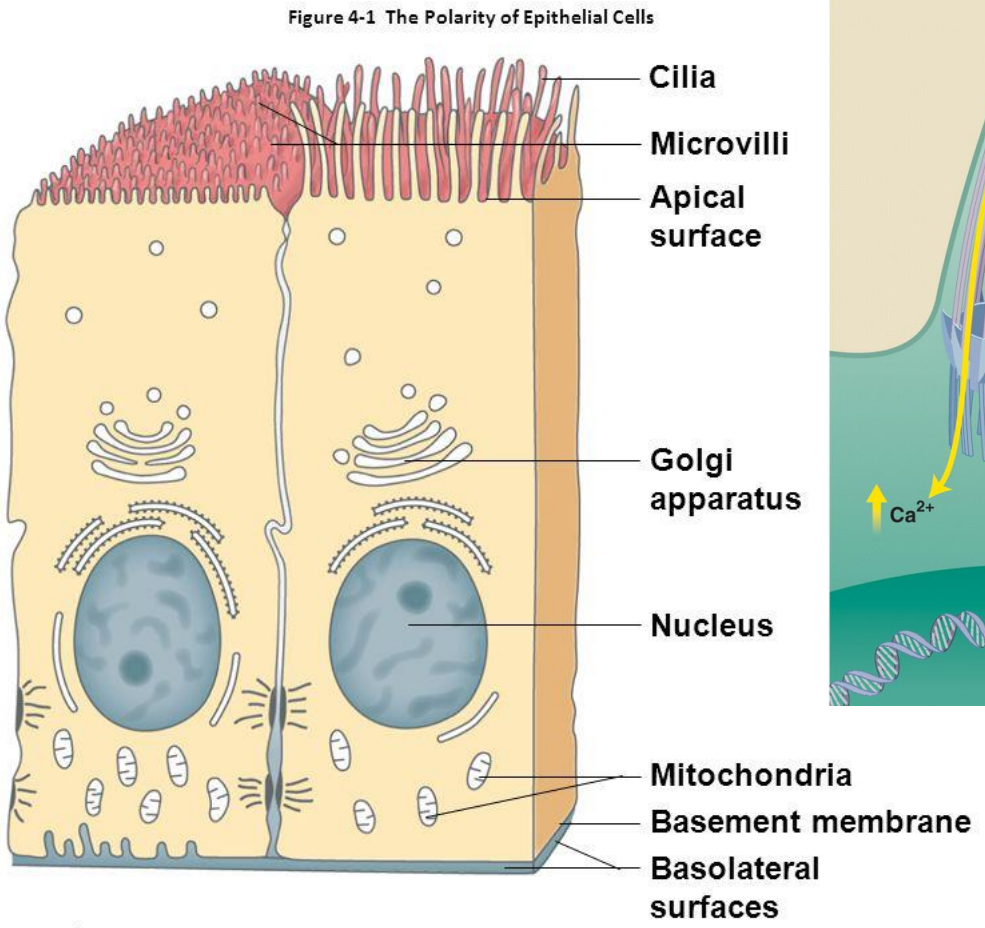
- **Basic Concepts of Developmental Biology**
  - Overview of Embryological Development
  - Fate, Specification, and Determination
  - Axis Specification and Pattern Formation
- **Cellular and Molecular Mechanisms in Development**
  - Gene Regulation by Transcription Factors
  - Morphogens and Cell to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

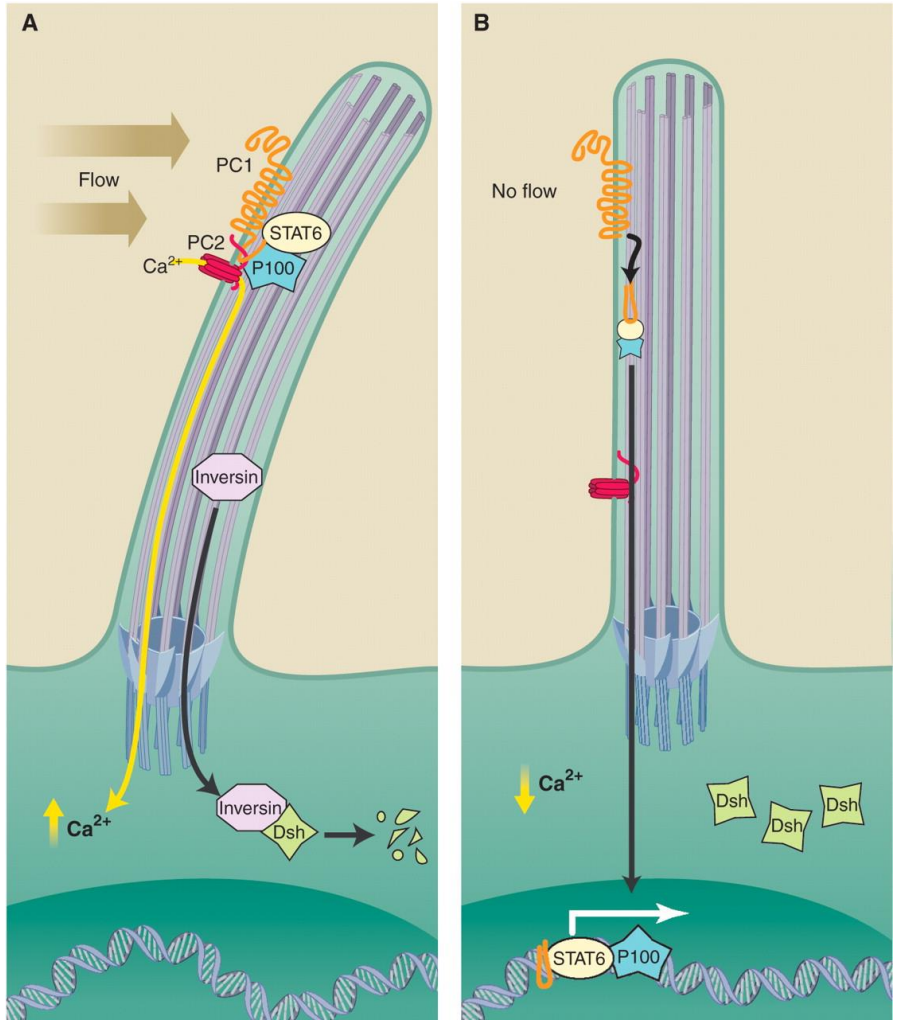
- Cells must organize themselves with respect to their position and polarity in their microenvironment
- The acquisition of polarity by a cell can be viewed as the cellular version of axis determination with respect to the development of the overall embryo

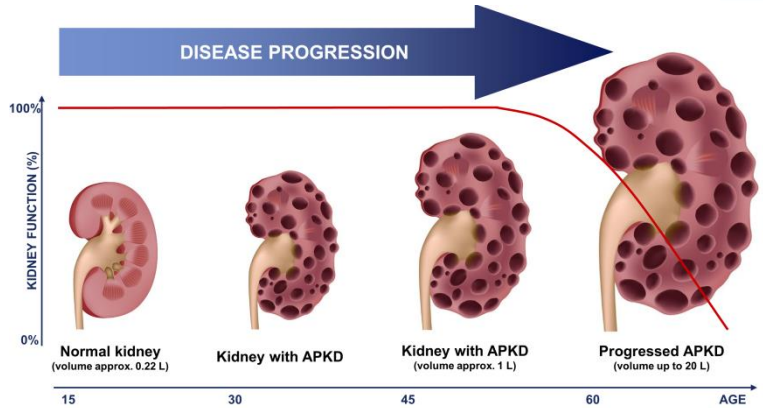


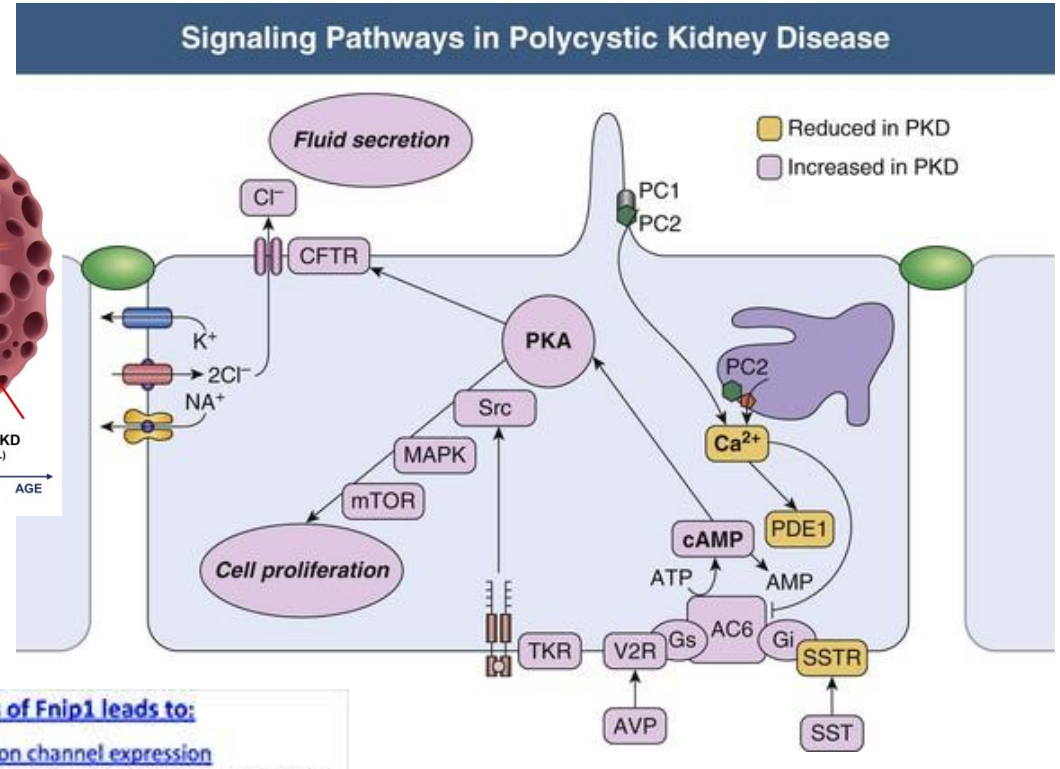


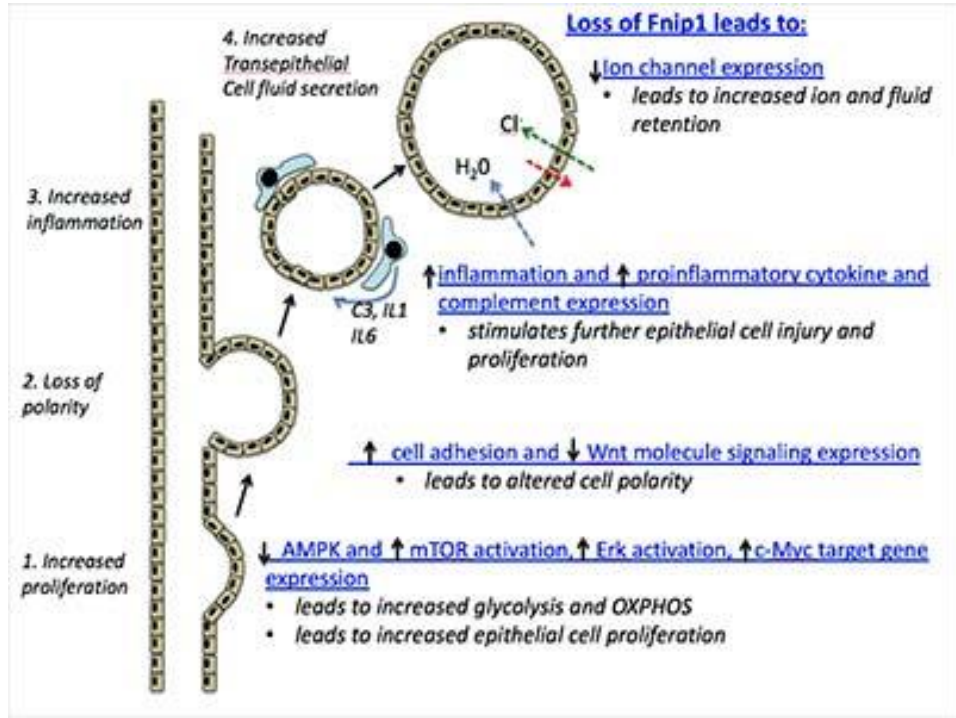
Primary cilium






DISEASE PROGRESSION
100%
KIDNEY FUNCTION (%)
0%
Normal kidney
(volume approx. 0.22 L)
Kidney with APKD
Kidney with APKD
(volume approx. 1 L)
Progressed APKD
(volume up to 20 L)
15
30
45
60
AGE

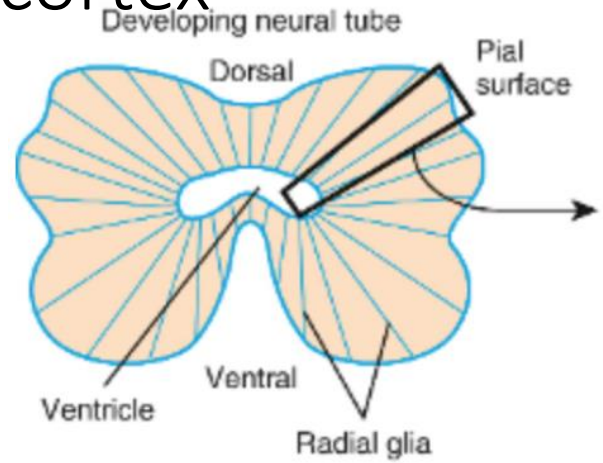

Signaling Pathways in Polycystic Kidney Disease
Fluid secretion
Reduced in PKD
Increased in PKD
Cl⁻
CFTR
PC1
PC2
K⁺
2Cl⁻
NA⁺
PKA
Src
MAPK
mTOR
Cell proliferation
PC2
Ca2+
cAMP
PDE1
ATP
AMP
AC6
Gs
Gi
TKR
V2R
SSTR
AVP
SST

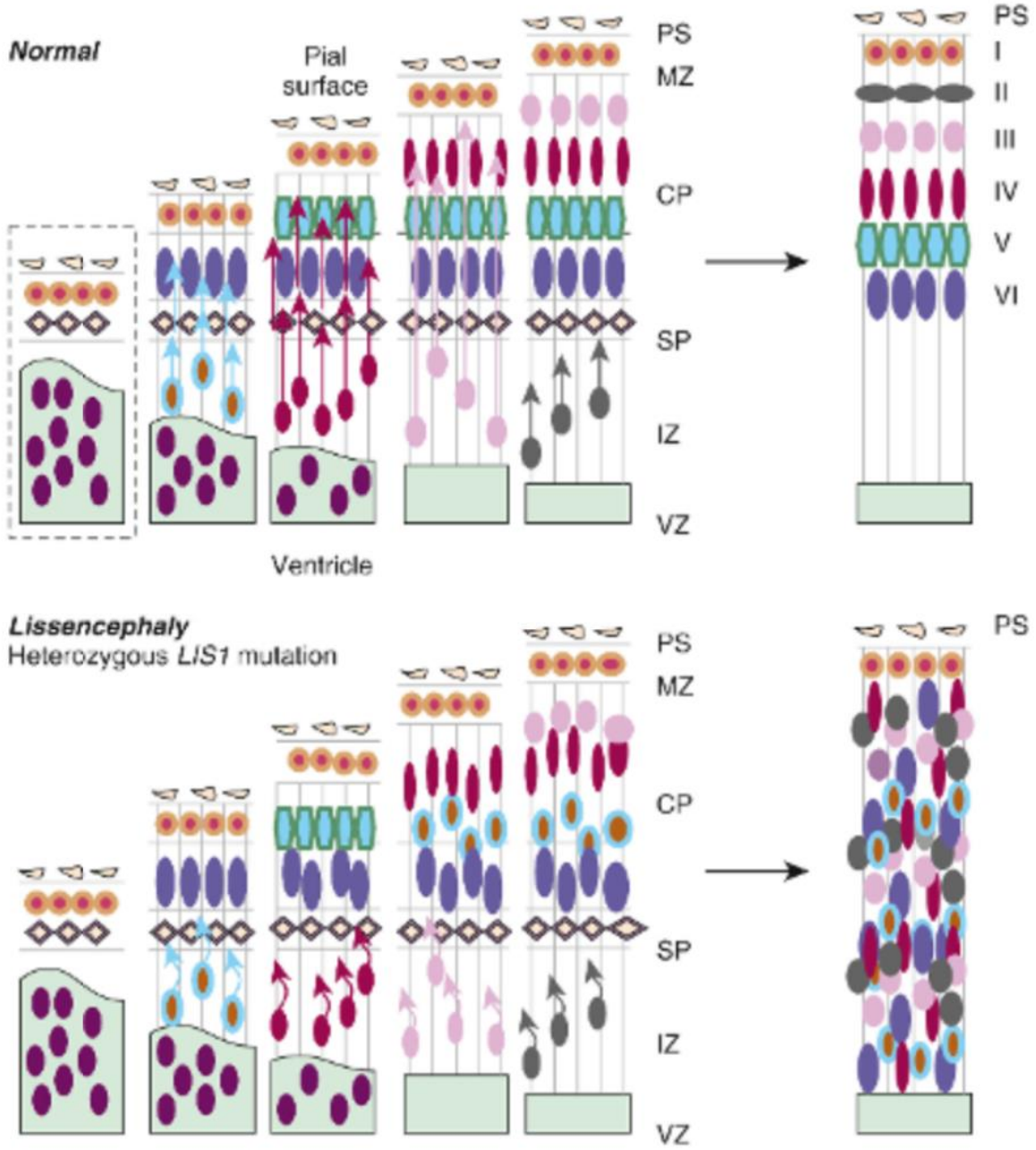

4. Increased Transepithelial Cell fluid secretion
Cl⁻
H2O
3. Increased inflammation
C3, IL1
IL6
2. Loss of polarity
1. Increased proliferation
Loss of Fnip1 leads to:
↓Ion channel expression
• leads to increased ion and fluid retention
↑inflammation and ↑ proinflammatory cytokine and complement expression
• stimulates further epithelial cell injury and proliferation
↑ cell adhesion and ↓ Wnt molecule signaling expression
• leads to altered cell polarity
↓ AMPK and ↑ mTOR activation, ↑ Erk activation, ↑c-Myc target gene expression
• leads to increased glycolysis and OXPHOS
• leads to increased epithelial cell proliferation

Chapters

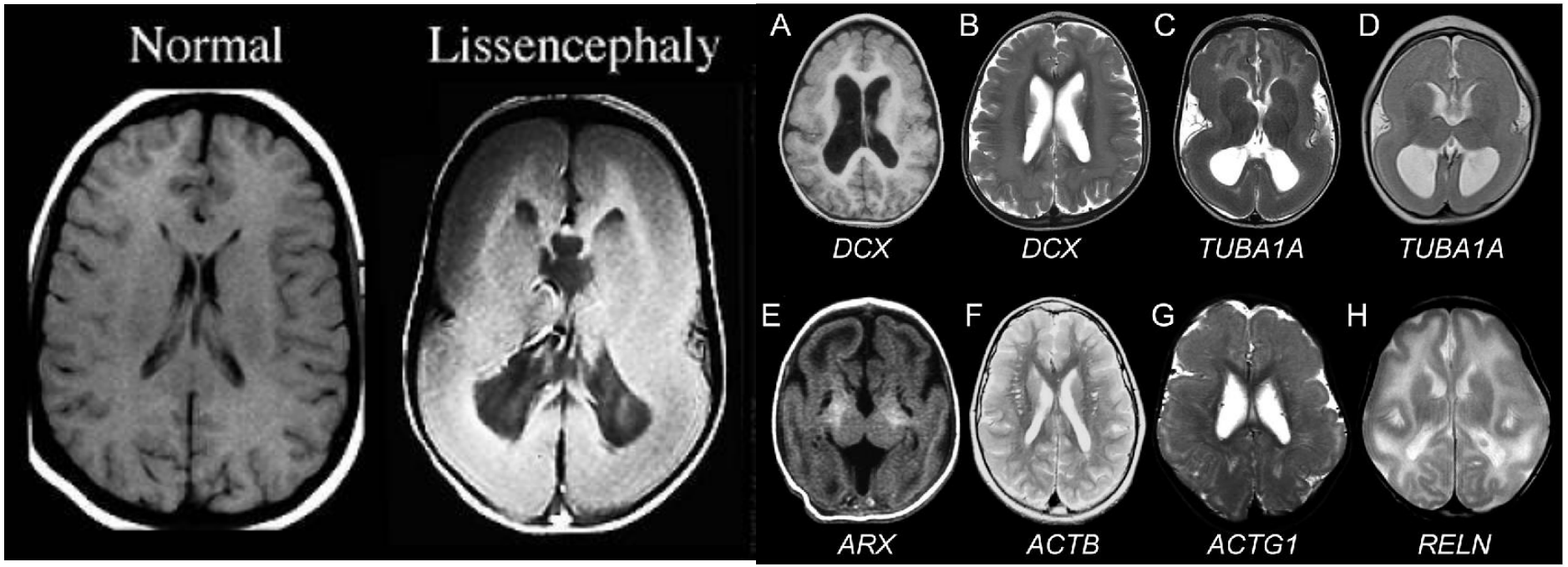
- **Basic Concepts of Developmental Biology**
  - Overview of Embryological Development
  - Fate, Specification, and Determination
  - Axis Specification and Pattern Formation
- **Cellular and Molecular Mechanisms in Development**
  - Gene Regulation by Transcription Factors
  - Morphogens and Cell to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

Neuronal migration in cortex

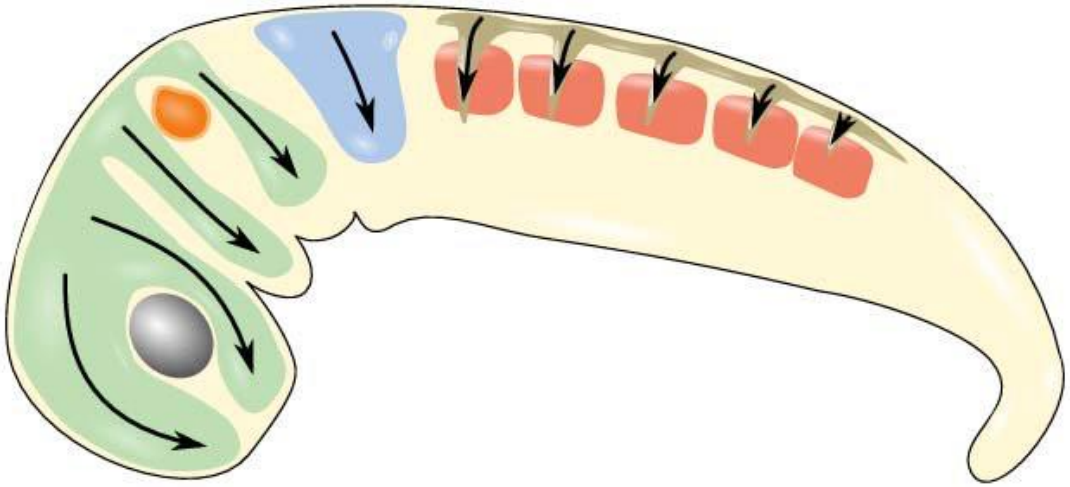


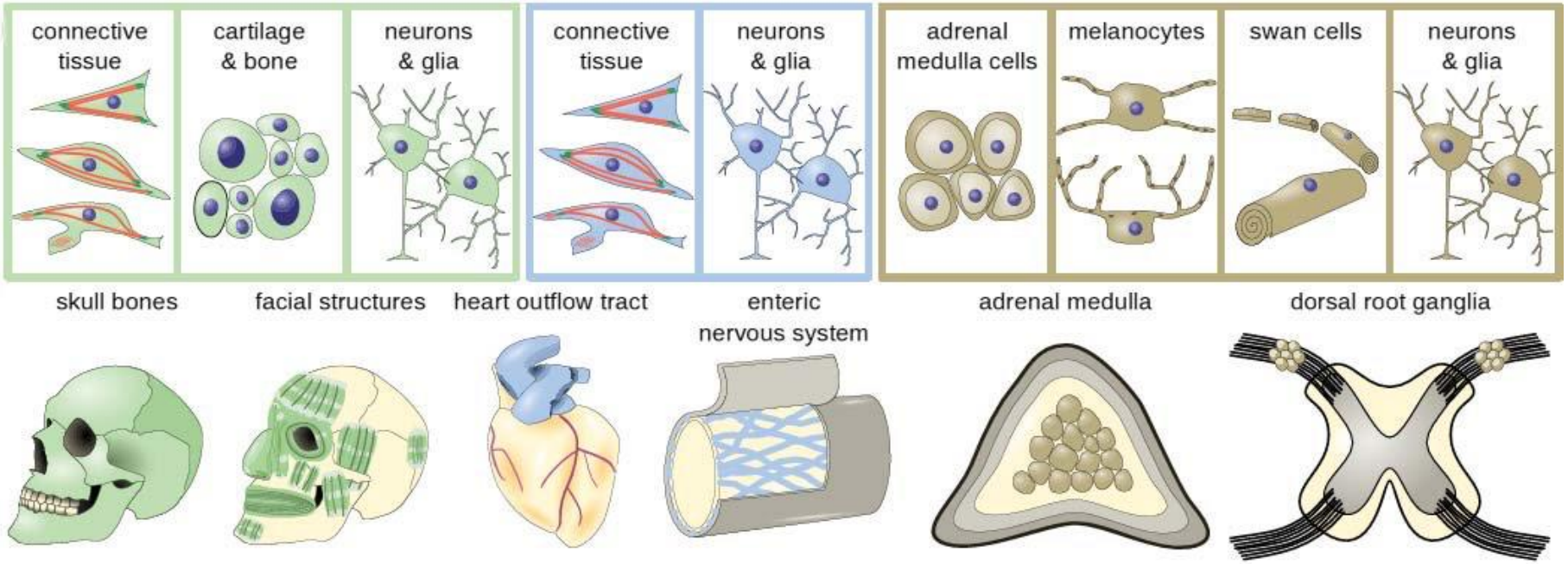


Neuronal migration defects in cortex

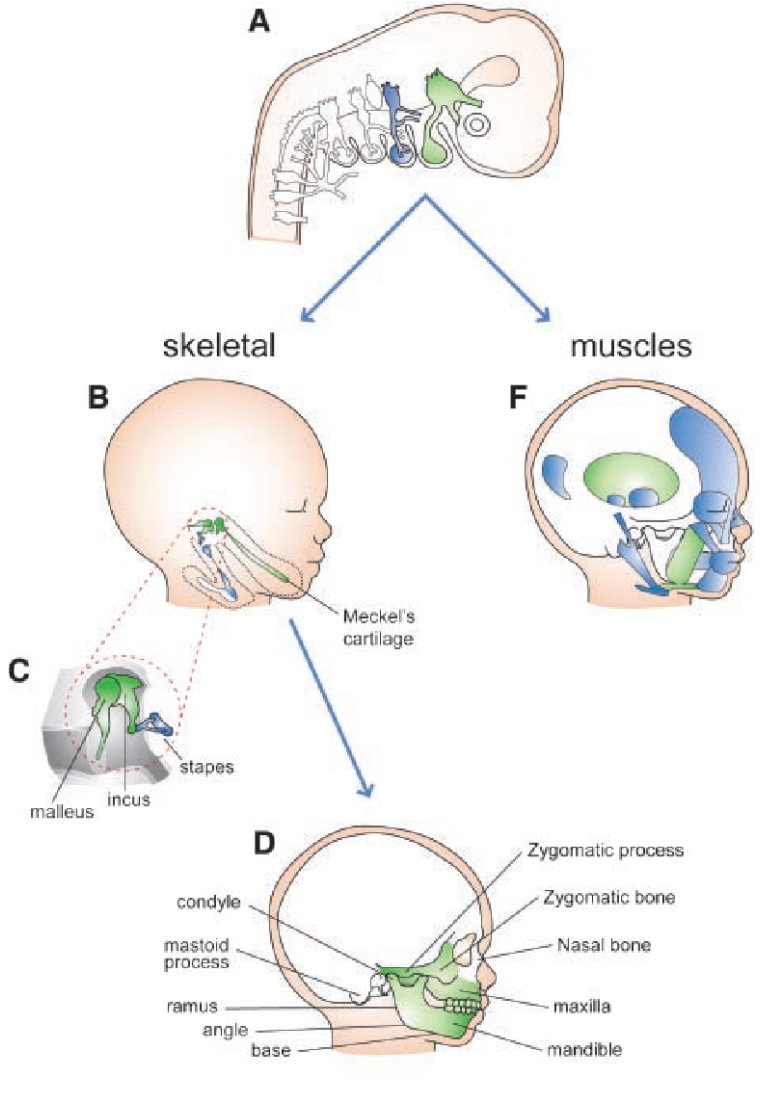


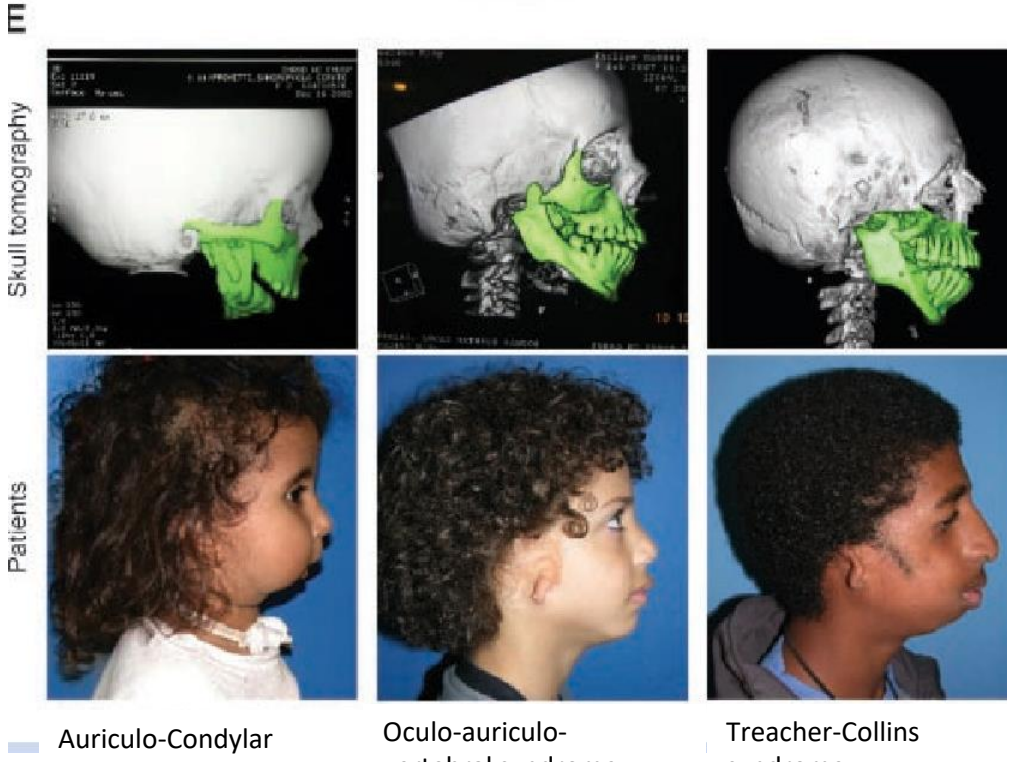
Neural crests cells





Neurocristopathies

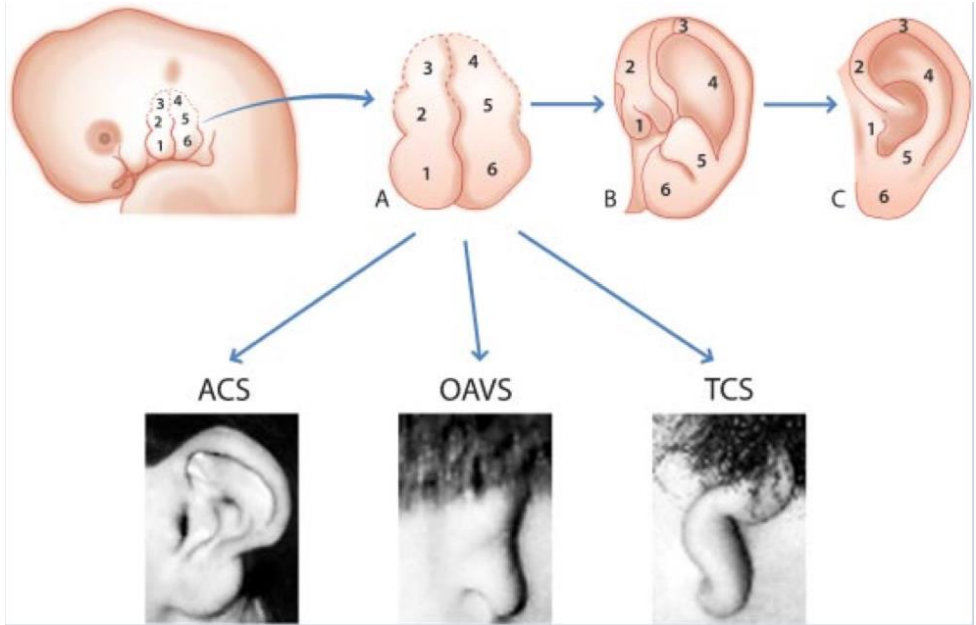




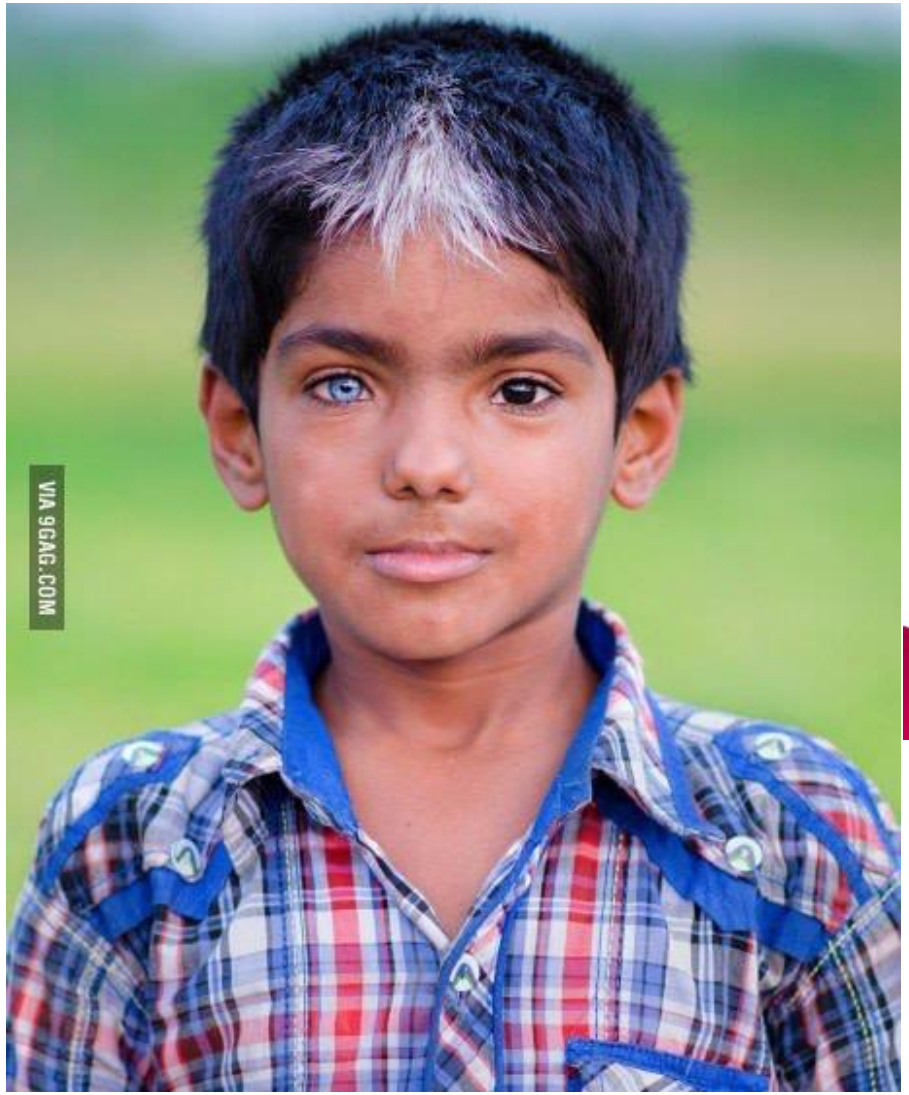
Auriculo-Condylar syndrome

Oculo-auriculo-vertebral syndrome

Treacher-Collins syndrome



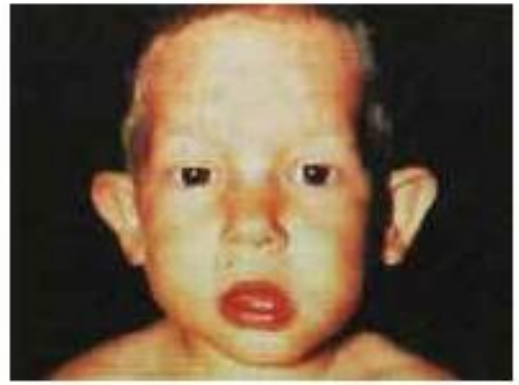
Waardenburg syndrome

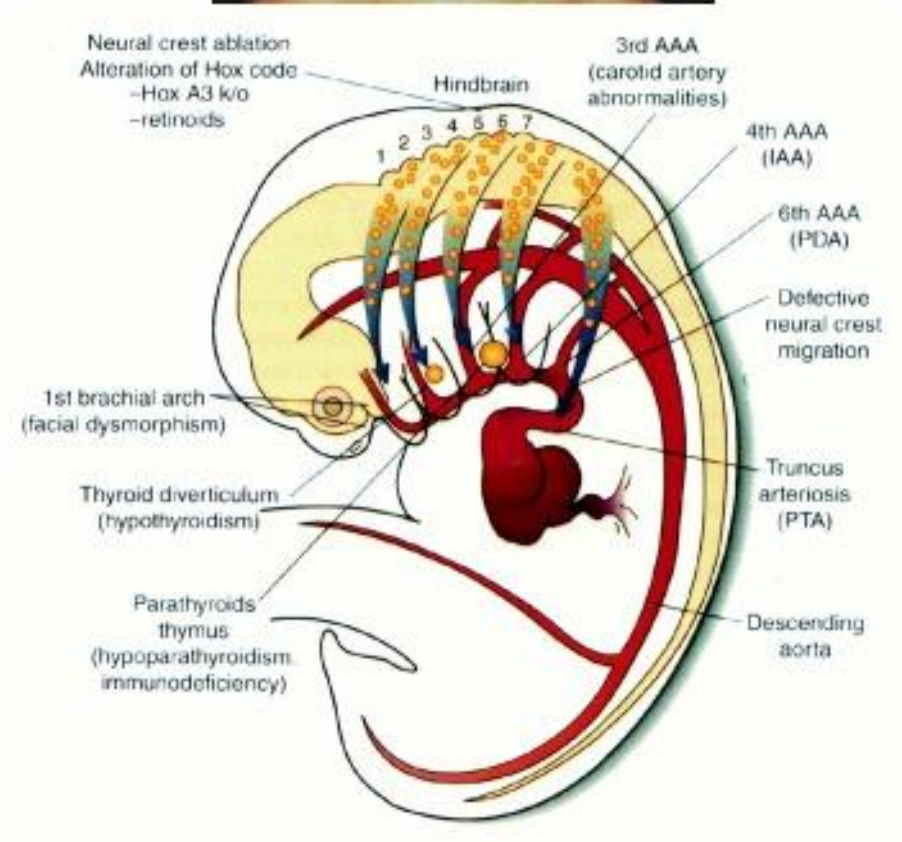


Symptoms:

- 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

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

Programmed cell death (apoptosis)

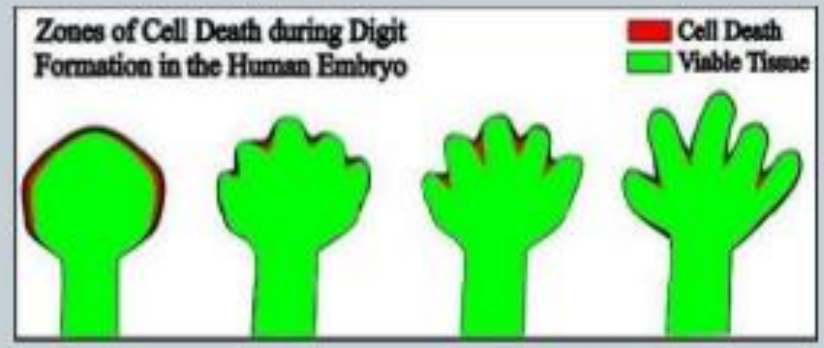
- Critical function in development, necessary for the morphological development of many structures
- It occurs wherever tissues need to be remodeled during morphogenesis
  - separation of the individual digits
  - perforation of the anal and choanal membranes
  - establishment of communication between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

Importance Of Apoptosis

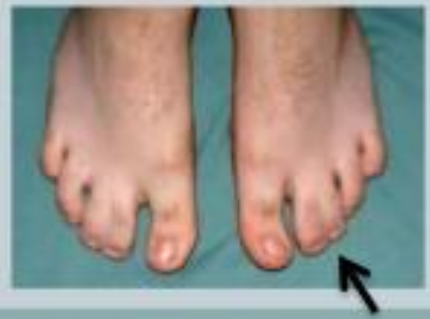
❖Apoptosis is a beneficial and important phenomenon:

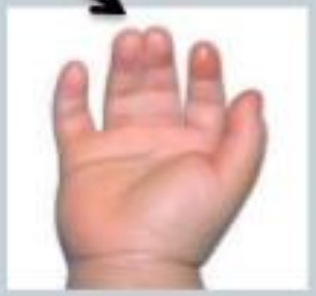
➢ In embryo

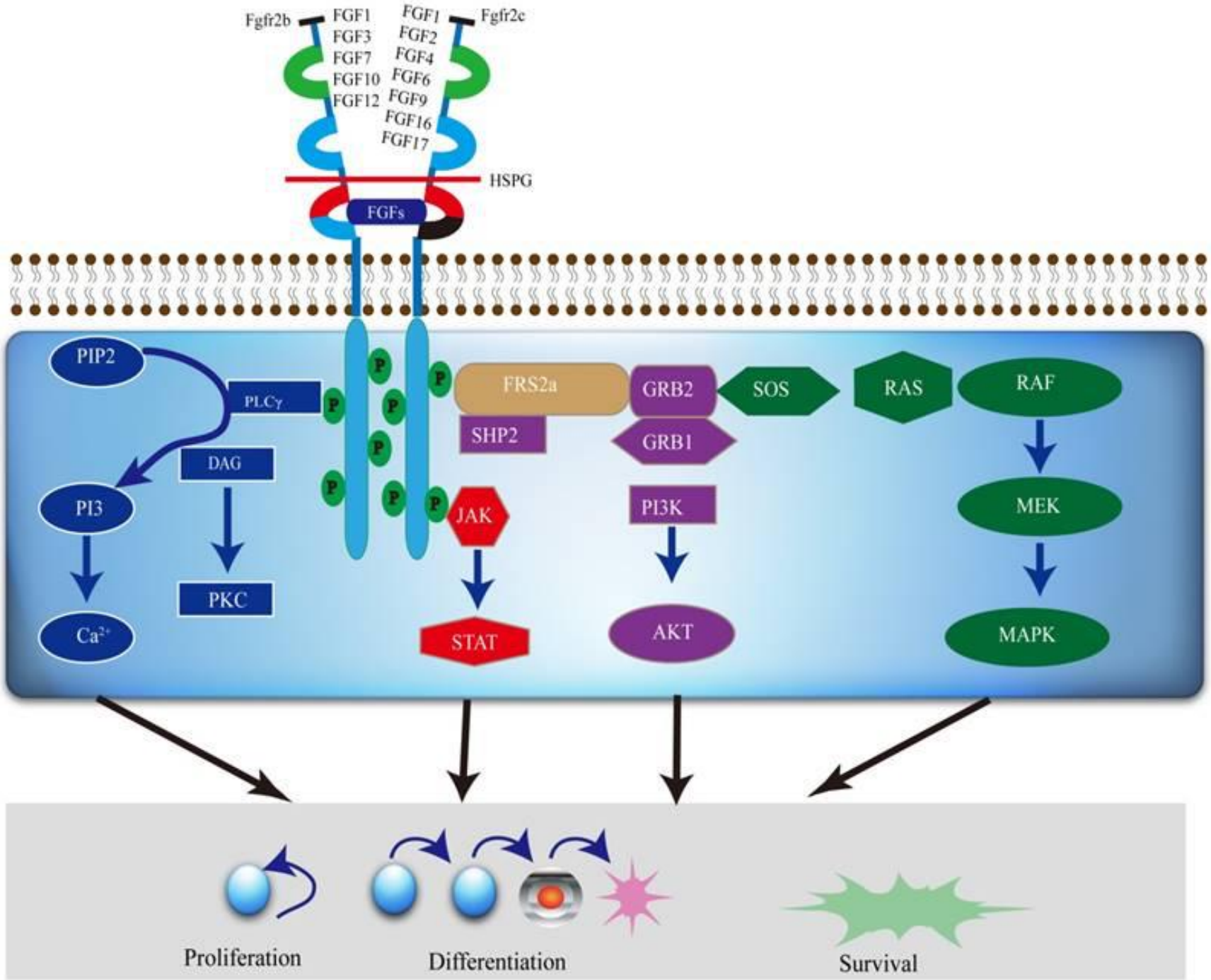
1. During embryonic development, help to digit formation.



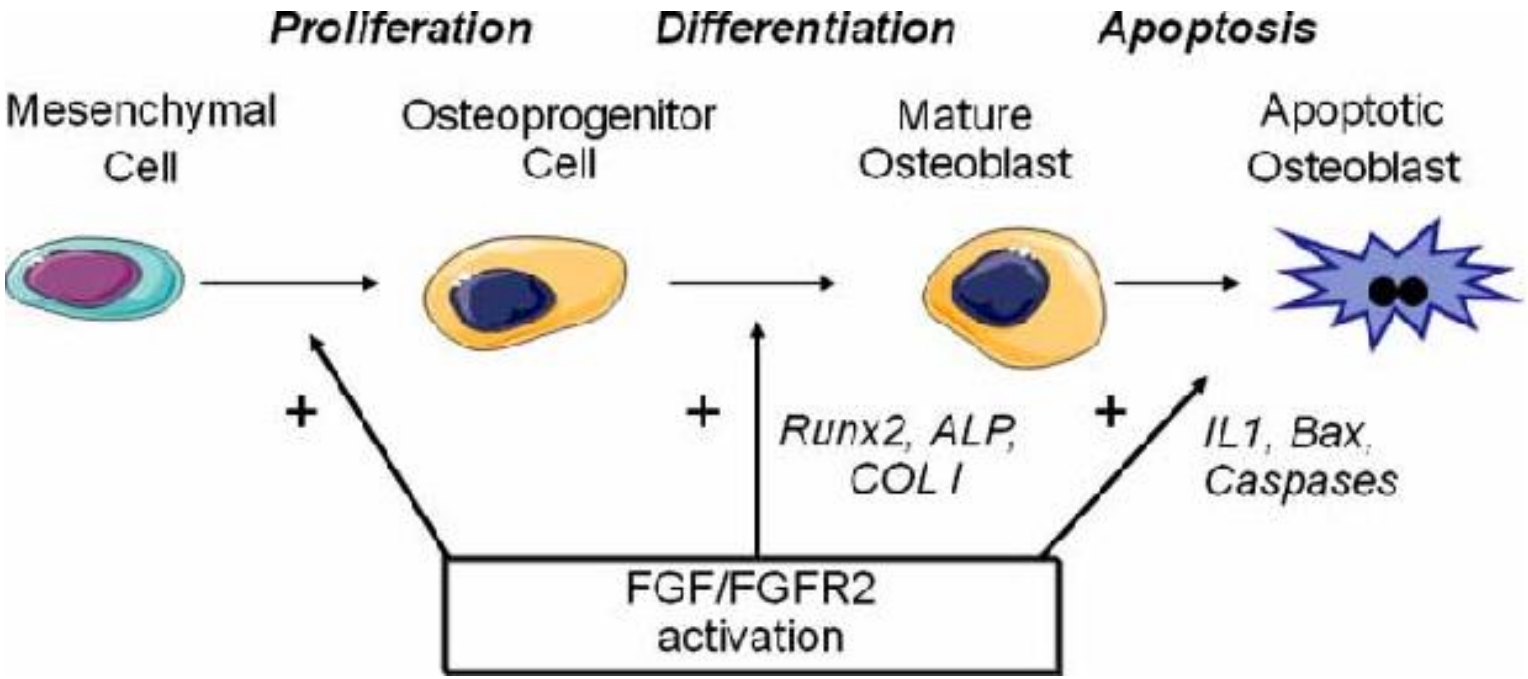
- Lack of apoptosis in humans can lead to webbed fingers called "syndactyly ".

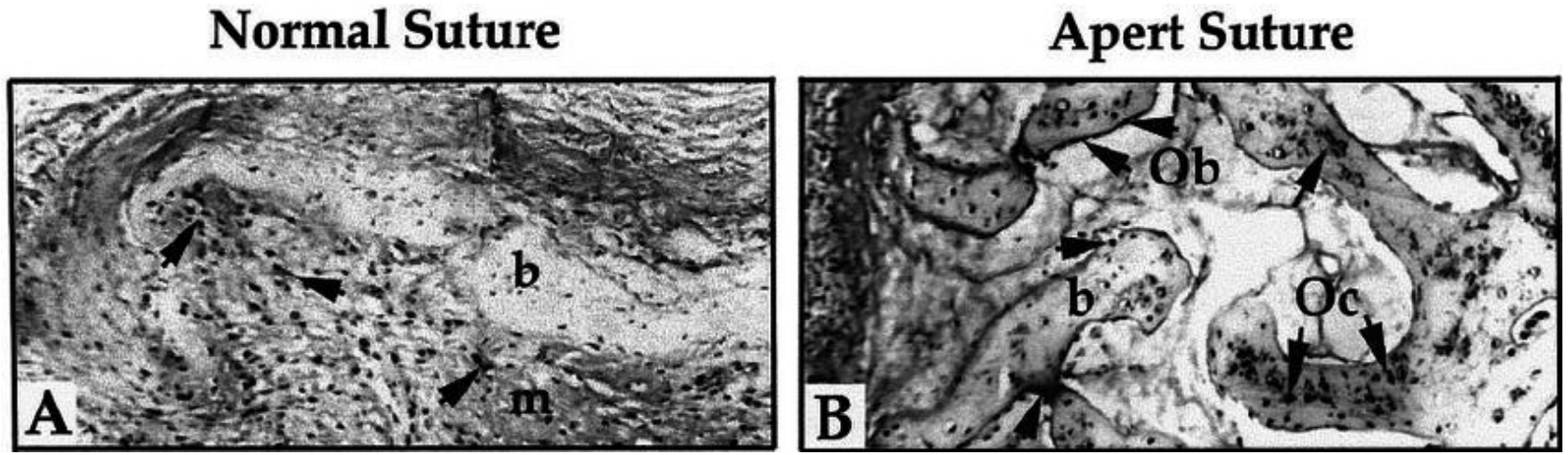





Fgfr2b
FGF1
FGF3
FGF7
FGF10
FGF12
FGF1
FGF2
FGF4
FGF6
FGF9
FGF16
FGF17
Fgfr2c
HSPG
FGFs
PIP2
PLCγ
DAG
PI3
PKC
Ca2+
FRS2a
SHP2
JAK
STAT
GRB2
GRB1
SOS
PI3K
AKT
RAS
RAF
MEK
MAPK
P
Proliferation
Differentiation
Survival

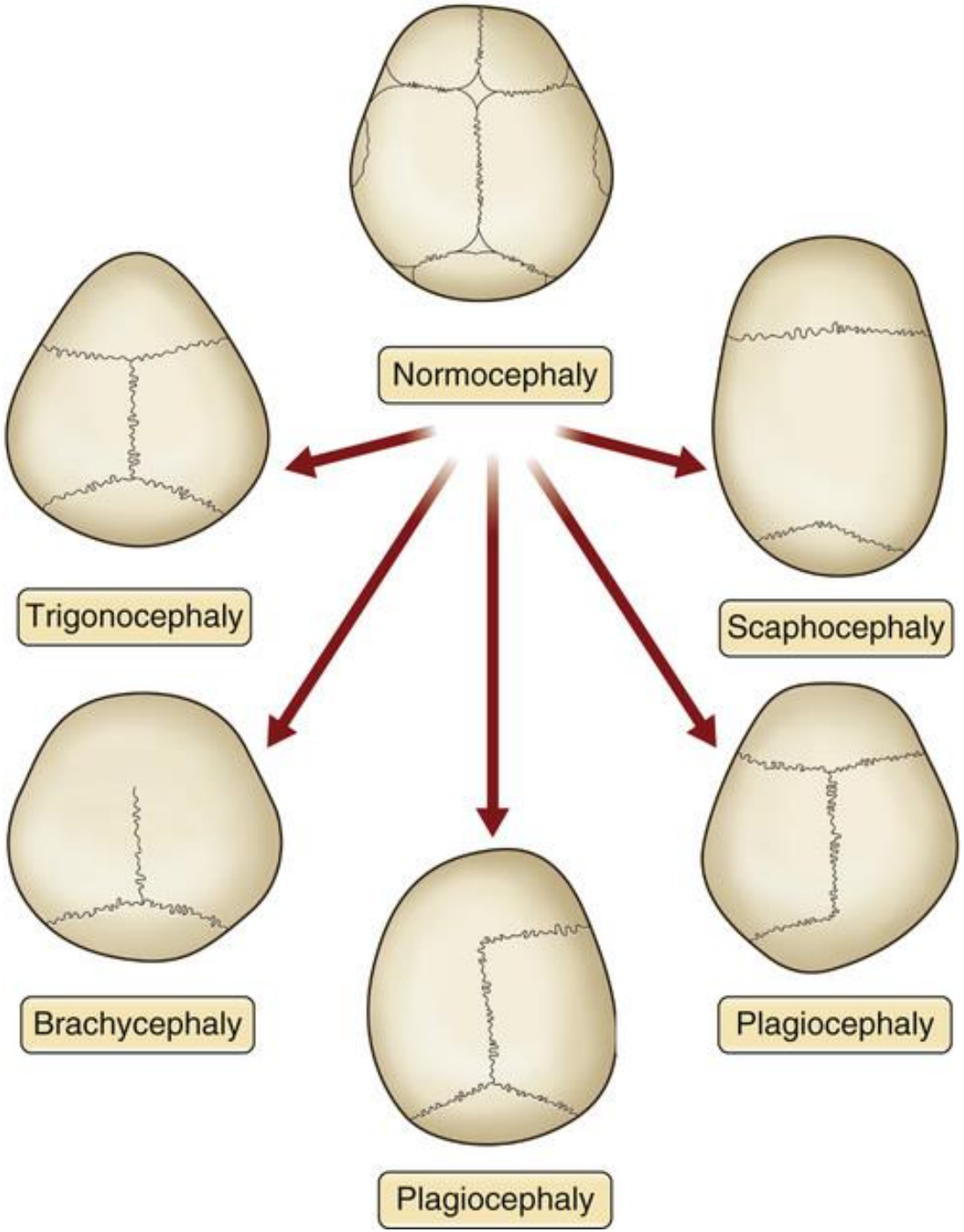
FGFR2 mutation



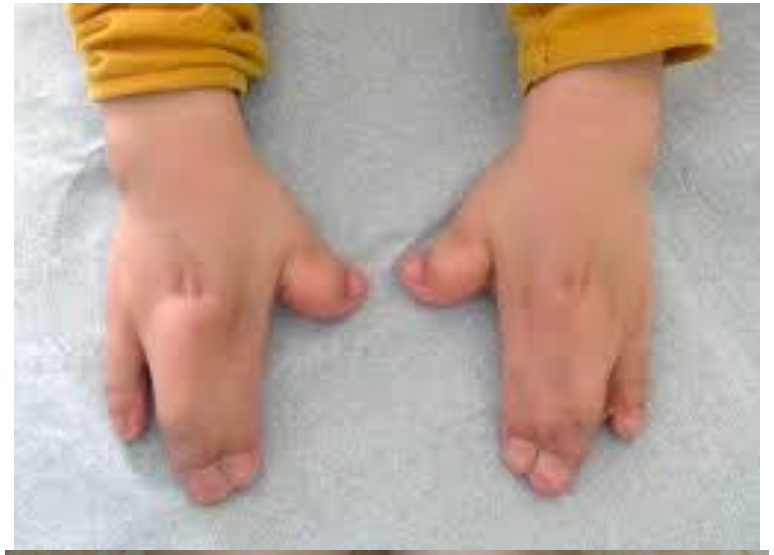


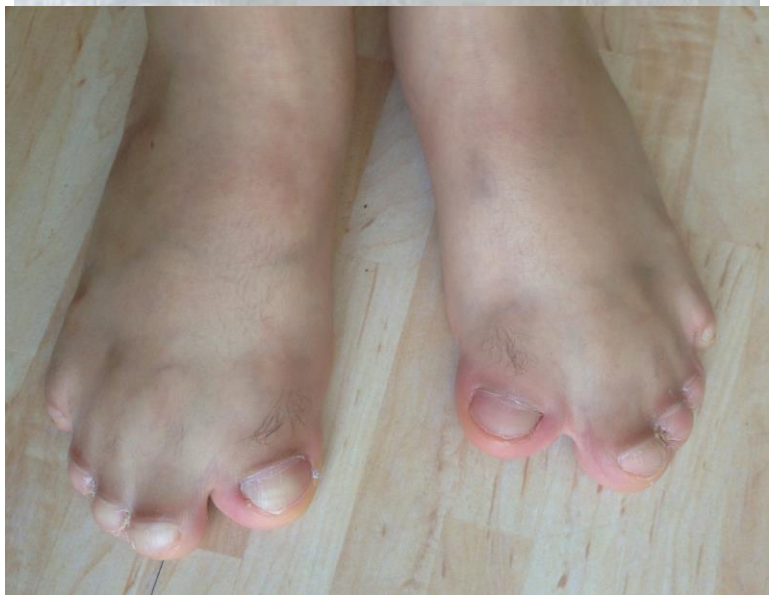
The Apert S252W FGFR-2 mutation induces premature osteoblast apoptosis in the human suture. Normal (A) and Apert (B) coronal sutures were prepared for TUNEL analysis. The Apert suture shows numerous TUNEL-positive mature osteoblasts (Ob) along the bone trabeculae and TUNEL-positive osteocytes (Oc) in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

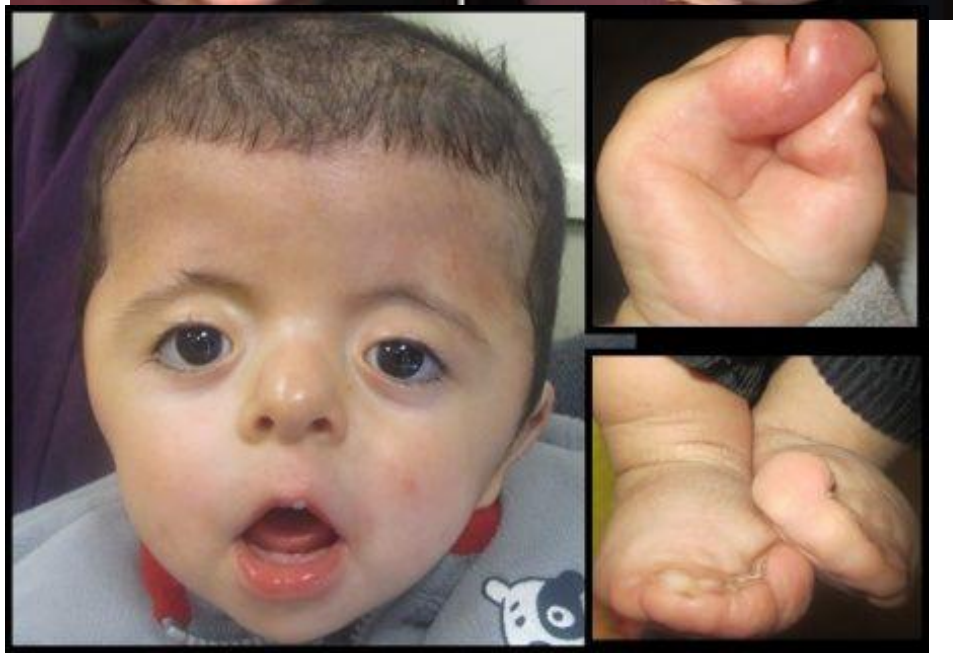
Craniostenosis



Apert syndrome (FGFR2 mutation)



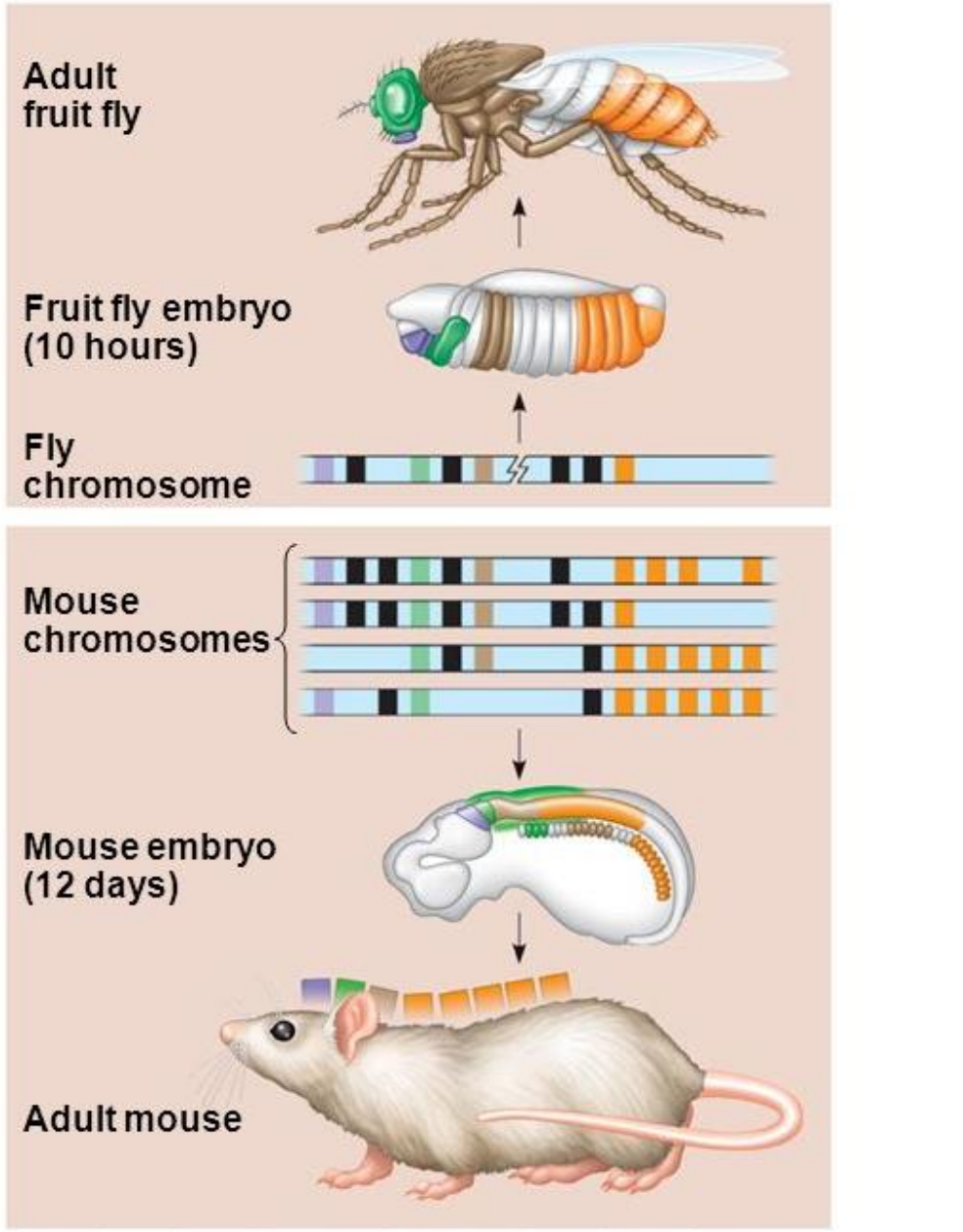


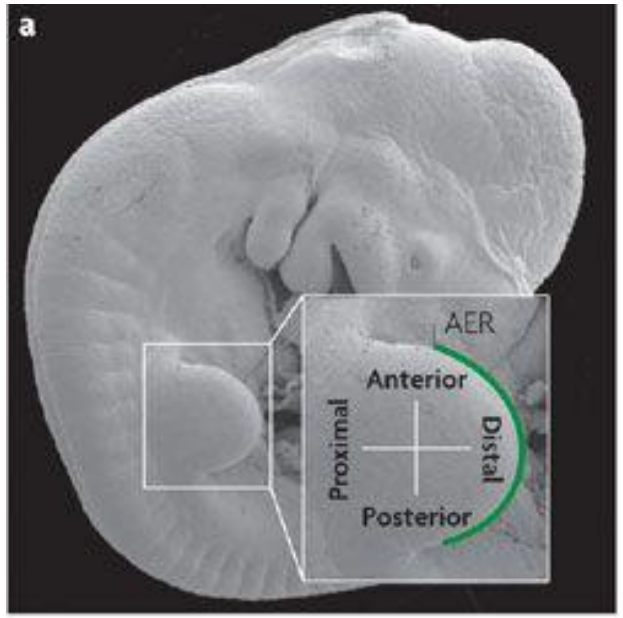


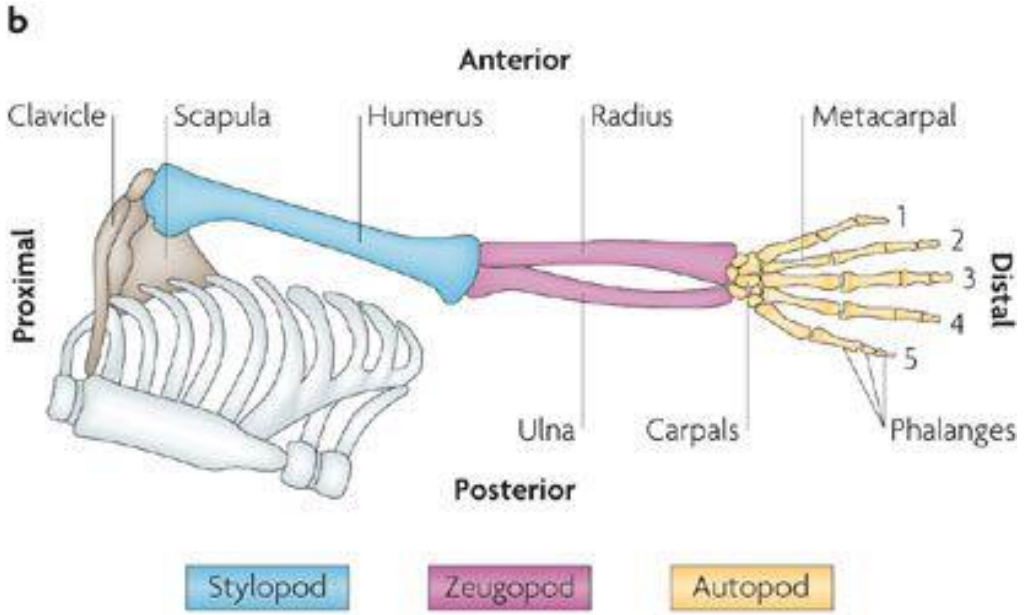
Chapters

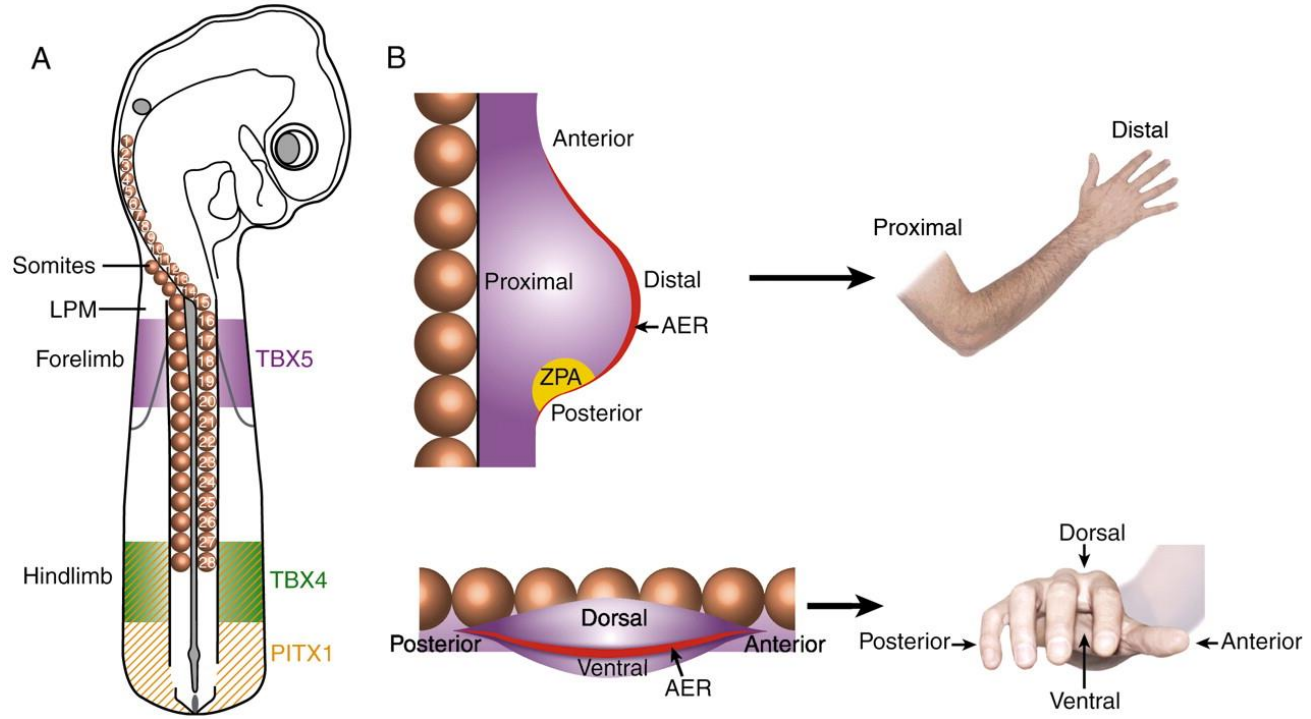
- **Basic Concepts of Developmental Biology**
  - Overview of Embryological Development
  - Fate, Specification, and Determination
  - Axis Specification and Pattern Formation
- **Cellular and Molecular Mechanisms in Development**
  - Gene Regulation by Transcription Factors
  - Morphogens and Cell to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

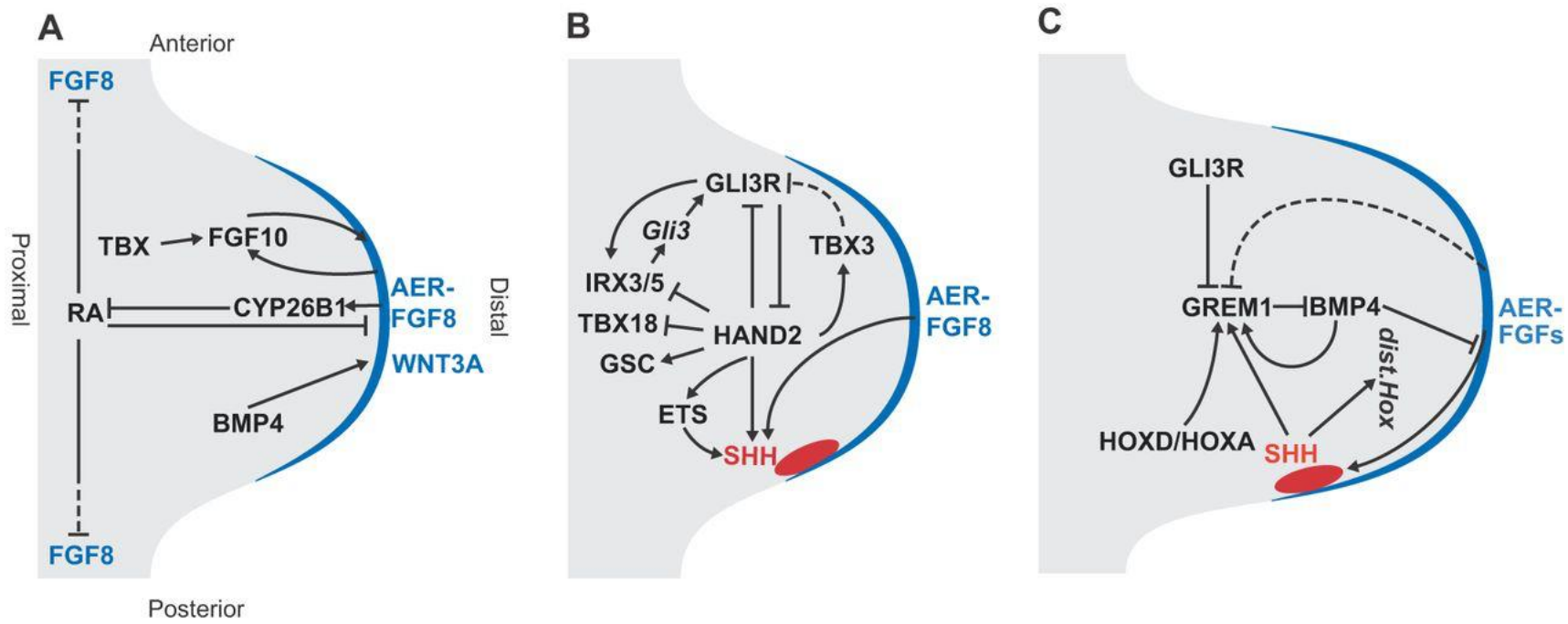
- Organogenesis requires the coordination of multiple developmental processes
  - **Proliferation**
  - **Differentiation**
  - **Migration**
  - **Apoptosis**
- To understand how these processes interact and work together, developmental biologists typically study embryogenesis in a model organism, such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

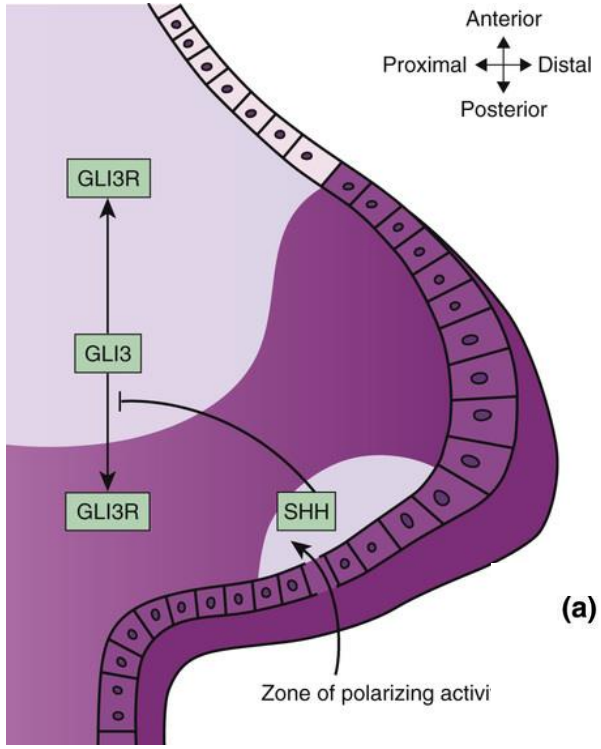



a
AER
Anterior
Proximal
Distal
Posterior

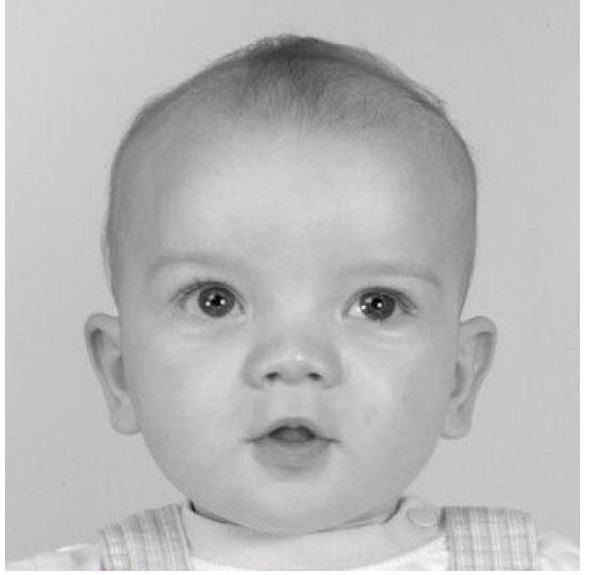

b
Anterior
Clavicle
Scapula
Humerus
Radius
Metacarpal
Proximal
Distal
1
2
3
4
5
Ulna
Carpals
Phalanges
Posterior
Stylopod
Zeugopod
Autopod

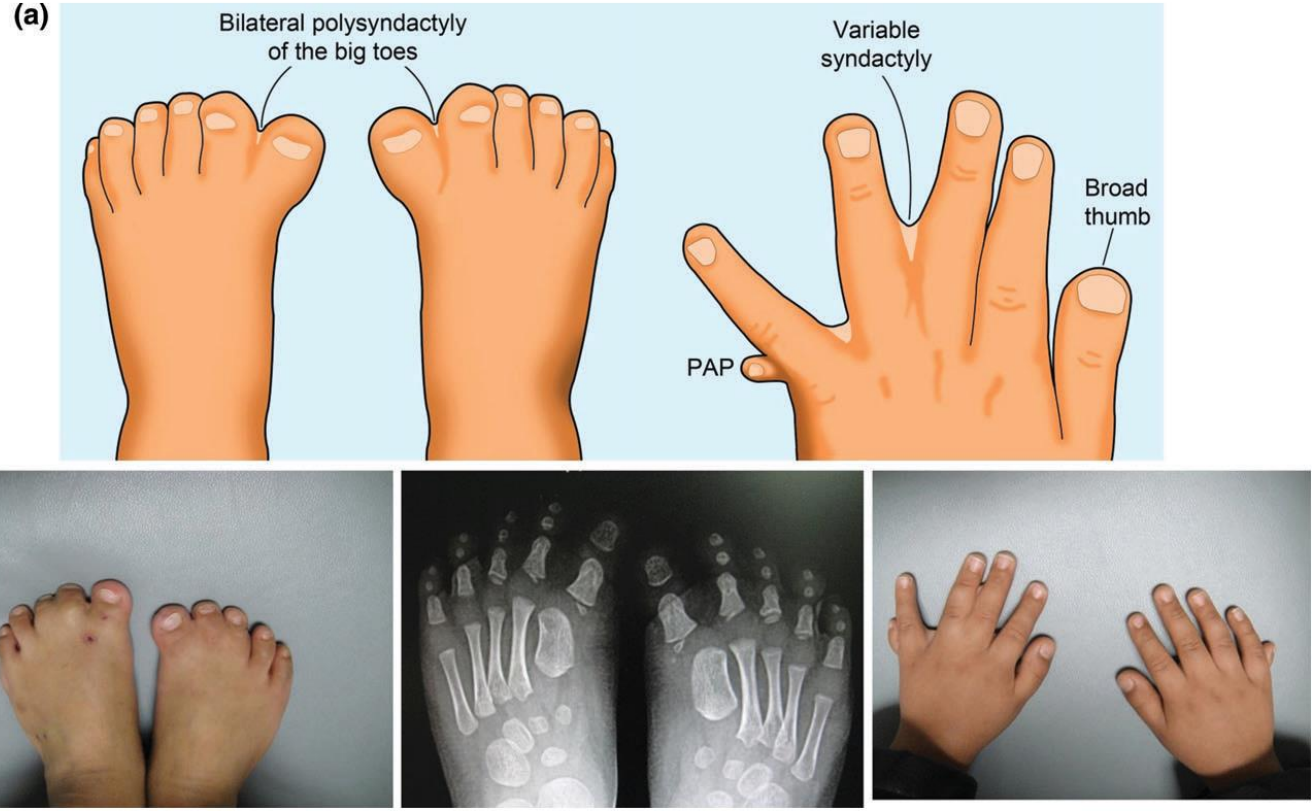

A
Somites
LPM
Forelimb
TBX5
Hindlimb
TBX4
PITX1
B
Anterior
Proximal
Distal
AER
ZPA
Posterior
Distal
Proximal
Dorsal
Posterior
Anterior
Ventral
AER
Dorsal
Posterior
Anterior
Ventral


A
Anterior
FGF8
Proximal
TBX
FGF10
AER-
FGF8
RA
CYP26B1
Distal
WNT3A
BMP4
FGF8
Posterior
B
GLI3R
Gli3
TBX3
IRX3/5
TBX18
HAND2
AER-
FGF8
GSC
ETS
SHH
C
GLI3R
GREM1
BMP4
AER-
FGFs
dist.Hox
HOXD/HOXA
SHH



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?