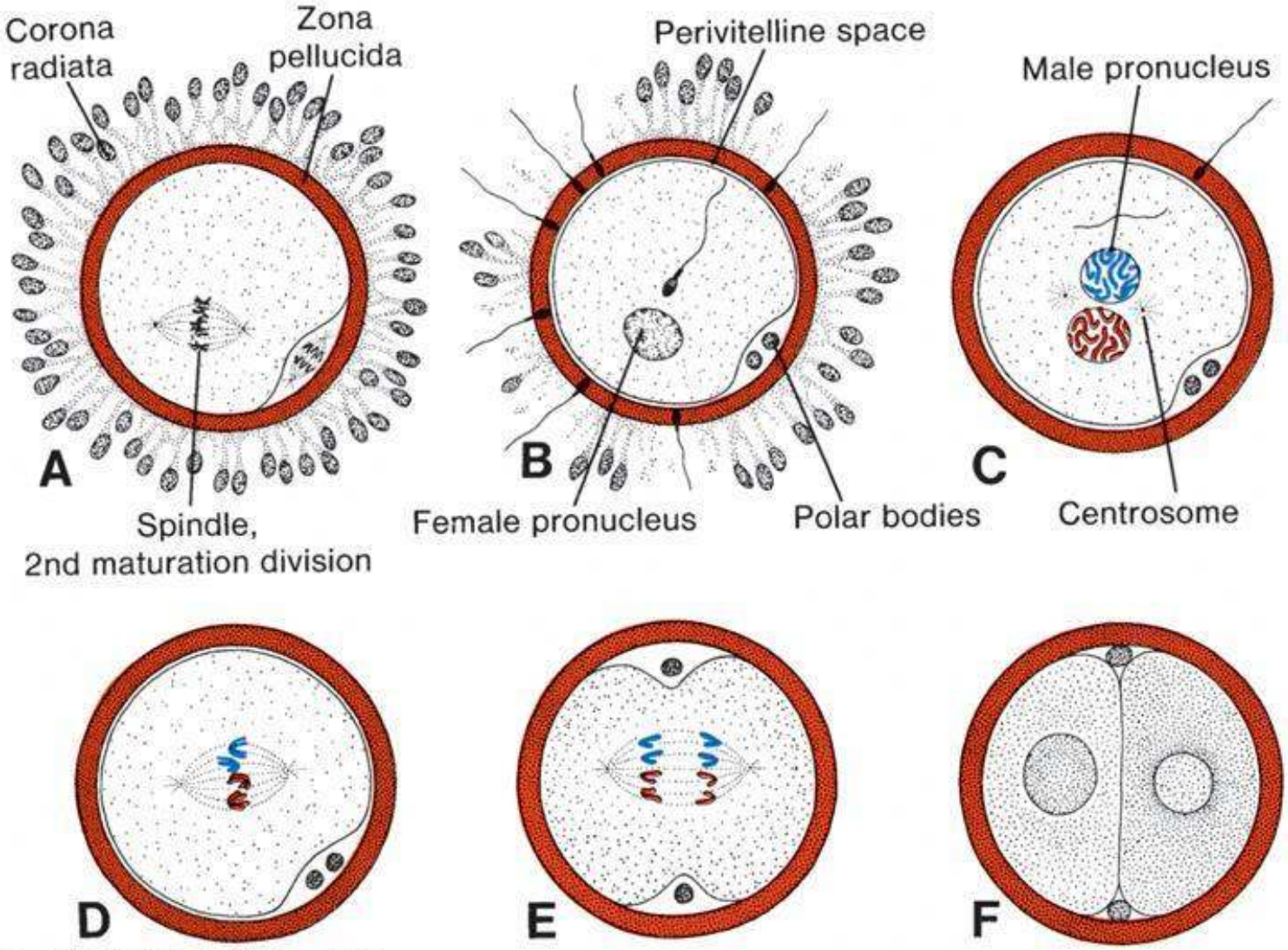
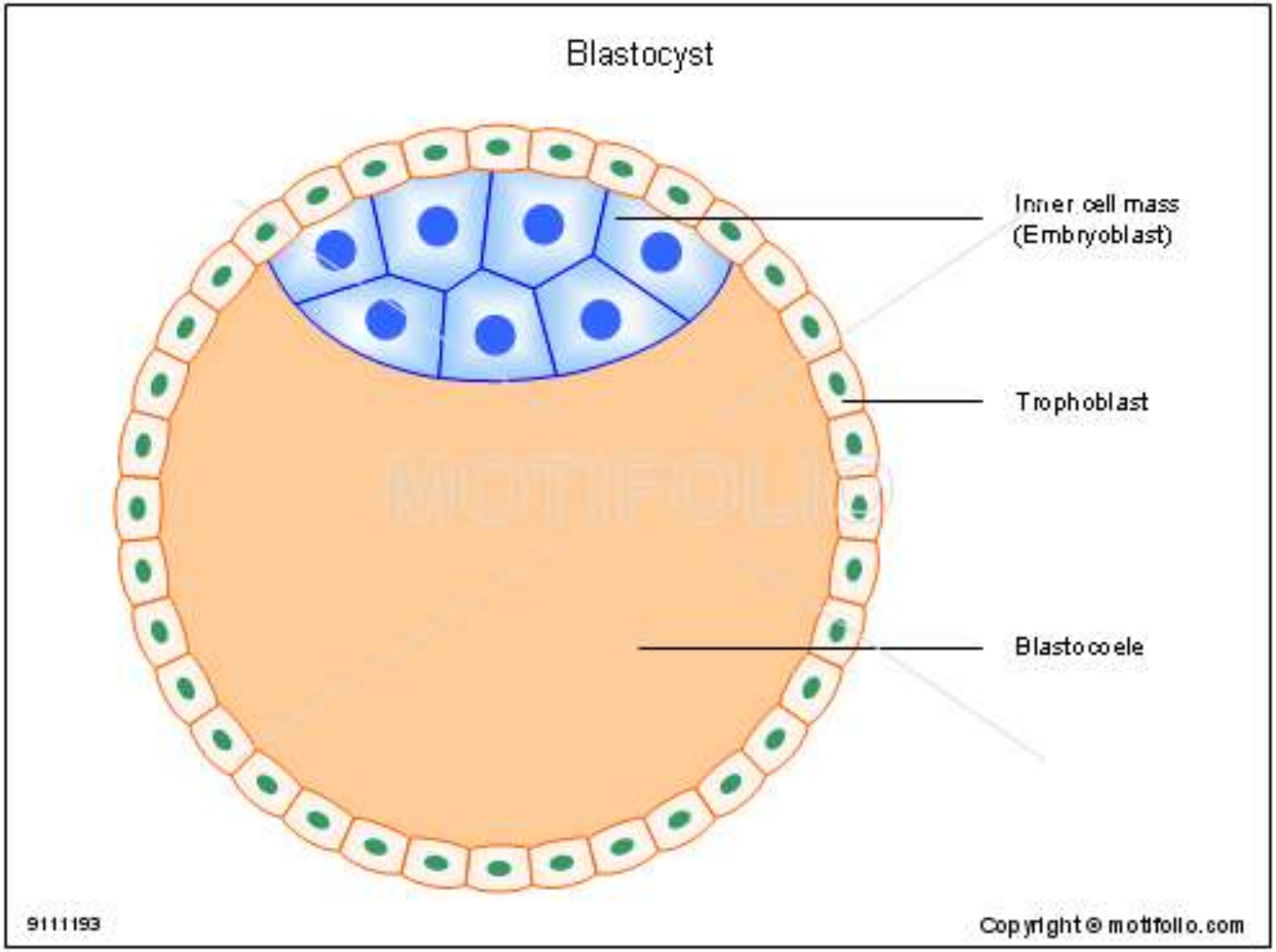
Developmental genetics
chapter 6

2018.

Molecular genetics

(Emery's Elements of medical genetics, 14th ed. Turnpenny P. and Ellard S. Elsevier 2012.)




Blastocyst
Inner cell mass
(Embryoblast)
Trophoblast
Blastocoele
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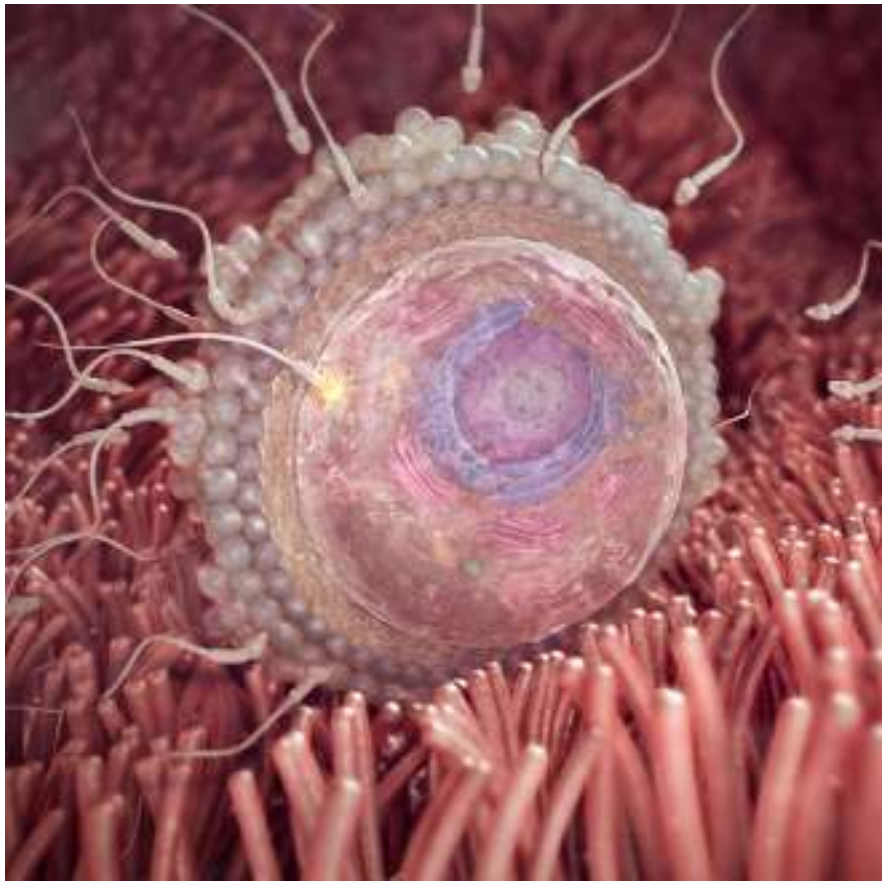
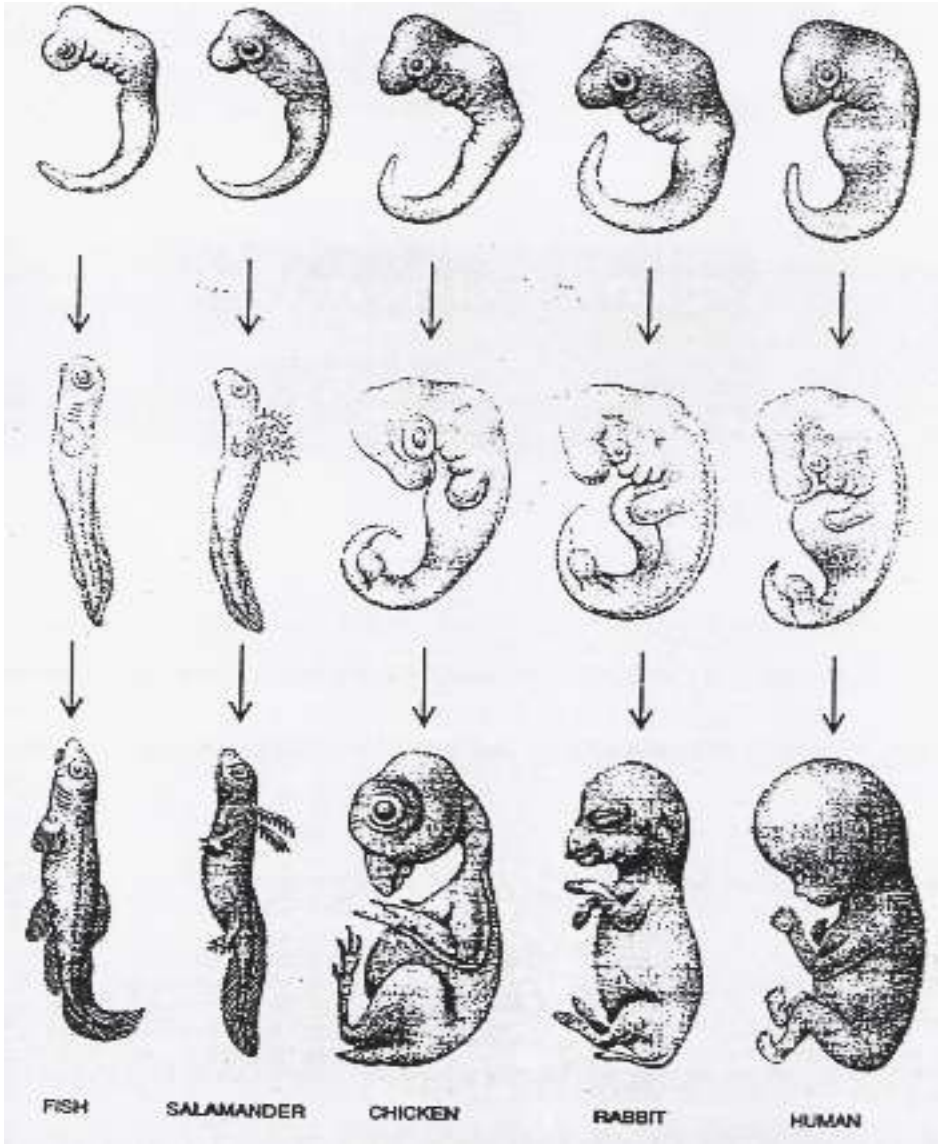
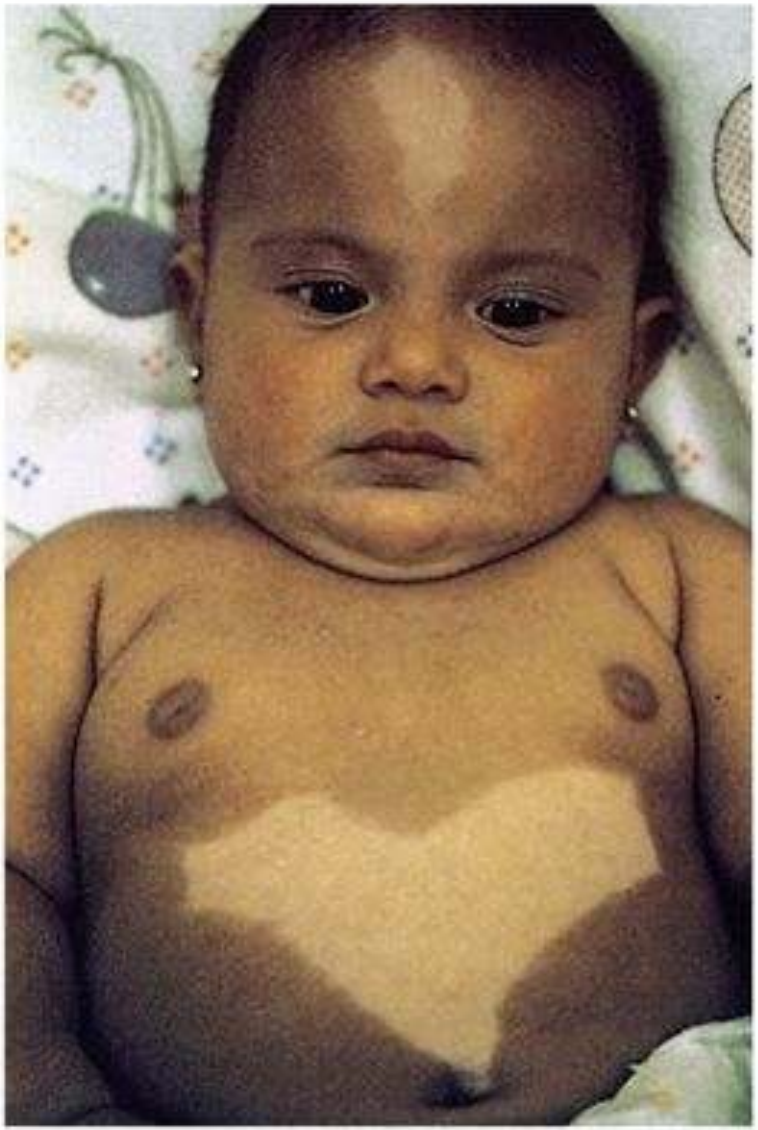
Development of human embrio



Stage	Time from Conception	Length of Embryo/Fetus
Pre-embryonic		
First cell division	30 h	
Zygote reaches uterine cavity	4 d	
Implantation	5–6 d	
Formation of bilaminar disc	12 d	0.2 mm
Lyonization in female	16 d	
Formation of trilaminar disc and primitive streak	19 d	1 mm
Embryonic stage		
Organogenesis	4–8 w	
Brain and spinal cord are forming, and first signs of heart and limb buds	4 w	4 mm
Brain, eyes, heart and limbs developing rapidly, and bowel and lungs beginning to develop	6 w	17 mm
Digits have appeared. Ears, kidneys, liver and muscle are developing	8 w	4 cm
Palate closes and joints form	10 w	6 cm
Sexual differentiation almost complete	12 w	9 cm
Fetal stage		
Fetal movements felt	16–18 w	20 cm
Eyelids open. Fetus is now viable with specialized care	24–26 w	35 cm
Rapid weight gain due to growth and accumulation of fat as lungs mature	28–38 w	40–50 cm


FISH
SALAMANDER
CHICKEN
RABBIT
HUMAN



Trilaminar disc

Organ and Tissue Origins

Ectodermal

- Central nervous system
- Peripheral nervous system
- Epidermis, including hair and nails
- Subcutaneous glands
- Dental enamel

Mesodermal

- Connective tissue
- Cartilage and bone
- Smooth and striated muscle
- Cardiovascular system
- Urogenital system

Endodermal

- Thymus and thyroid
- Gastrointestinal system
- Liver and pancreas

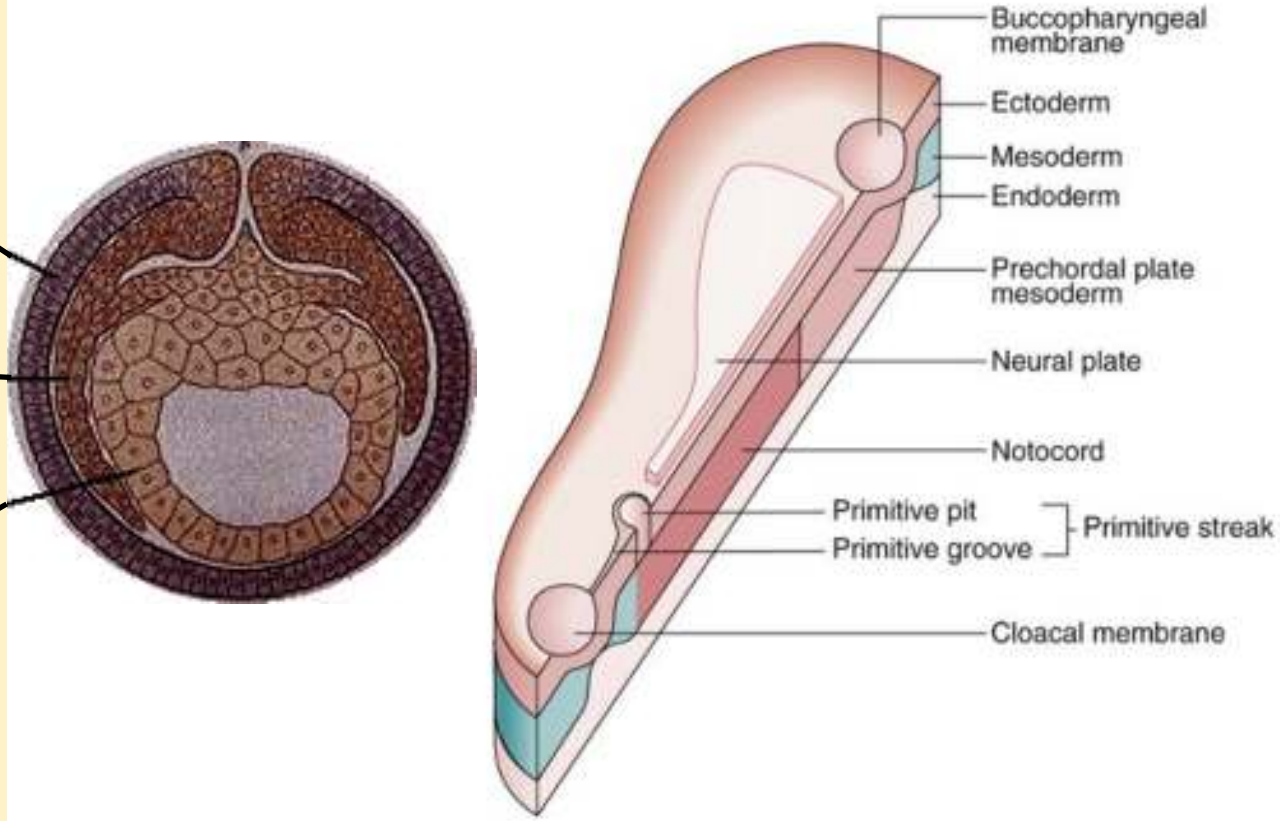
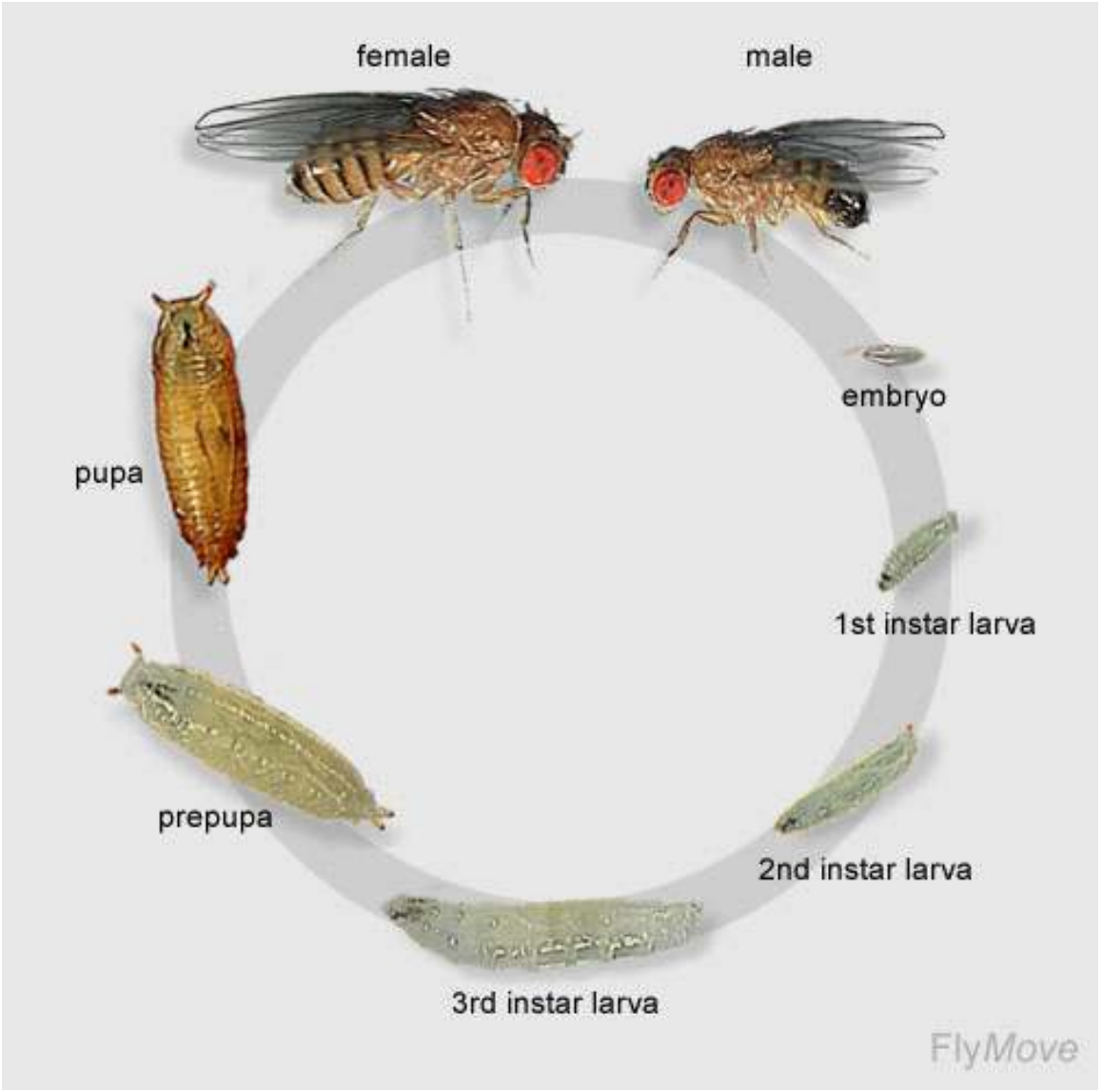


FIGURE 6.1 A schematic trilaminar disc, sectioned along the rostrocaudal axis.

Fruit fly life cycle

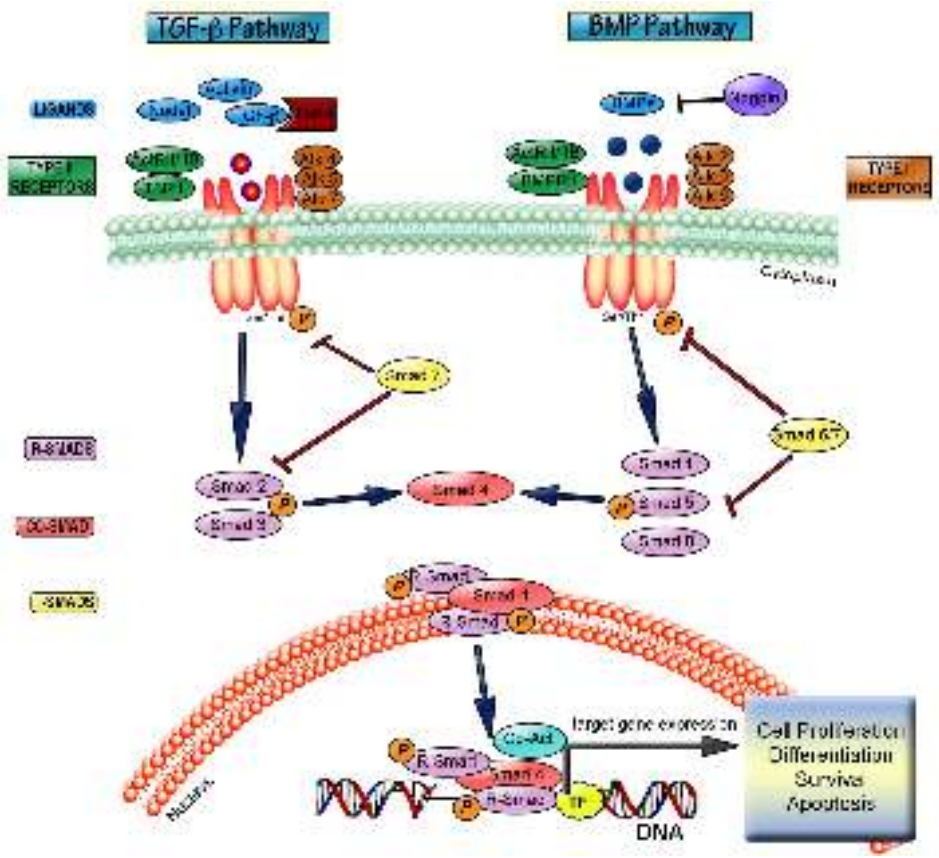


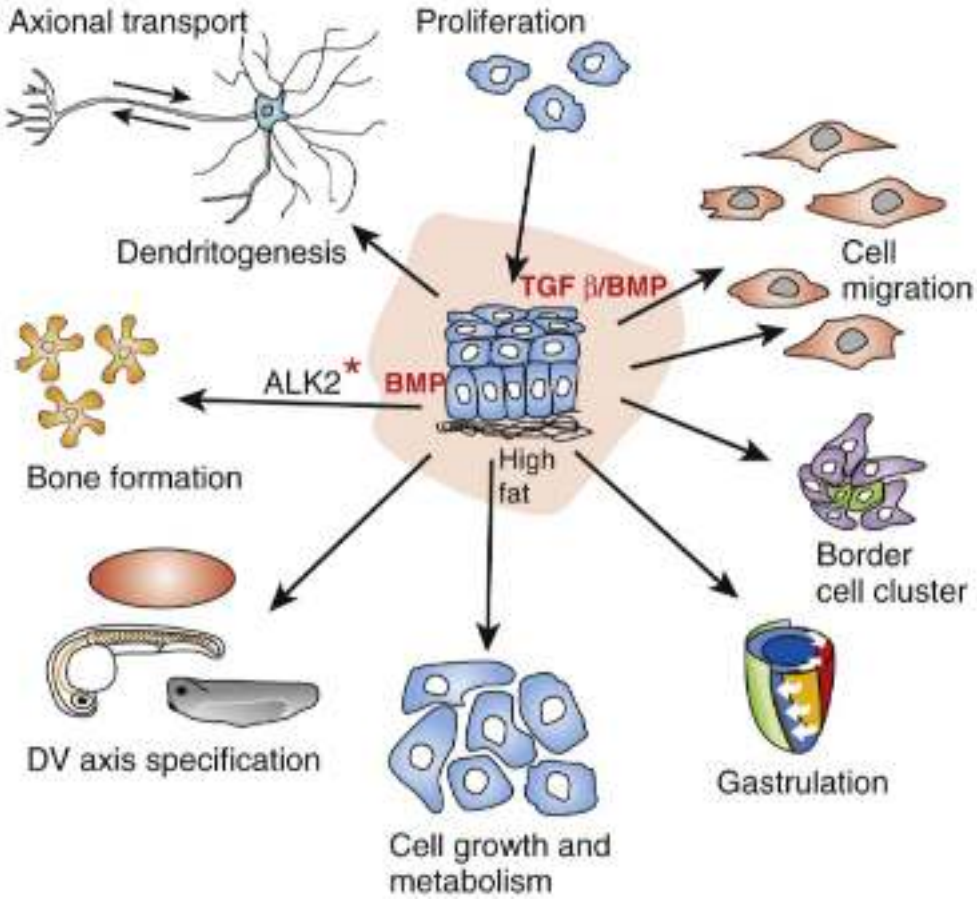
Developental gene families in humans

Transcription factors, transcription regulators, growth factors, cell receptors,morphogenes, cytokines…

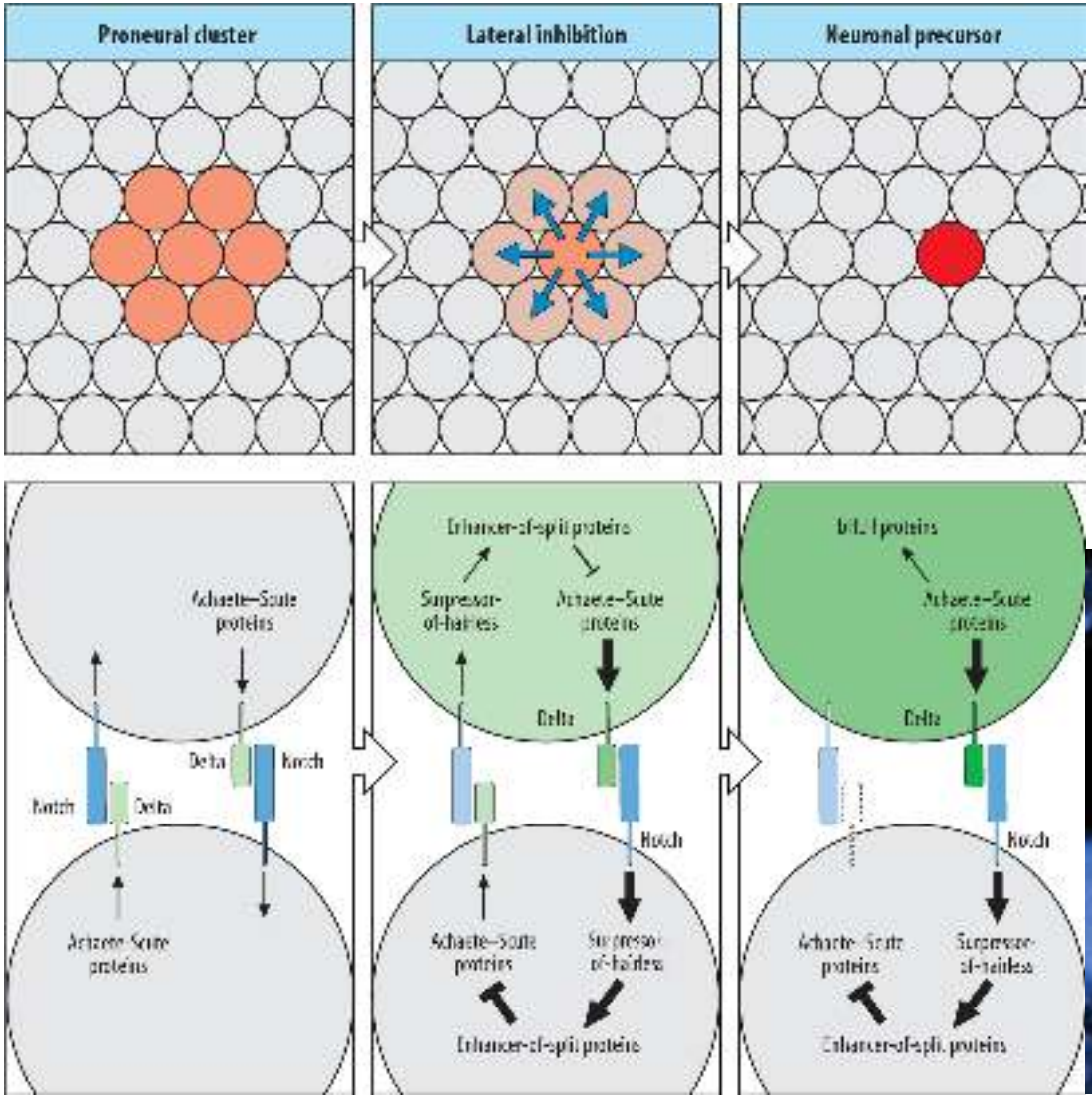
- TGF-β superfamily of cytokines (TGFβ; BMP - SMAD)
- Wingless (Wnt)
- Hedgehog (HH), Patched, GLI - (brain)
- Nodal, FGFs, BMPs
- Notch-delta (somits)
- Homeobox
- PAX
- SOX (High mobility group) T-box genes
- Zinc finger genes,
- RET protooncogene,
- FGF receptors,…..

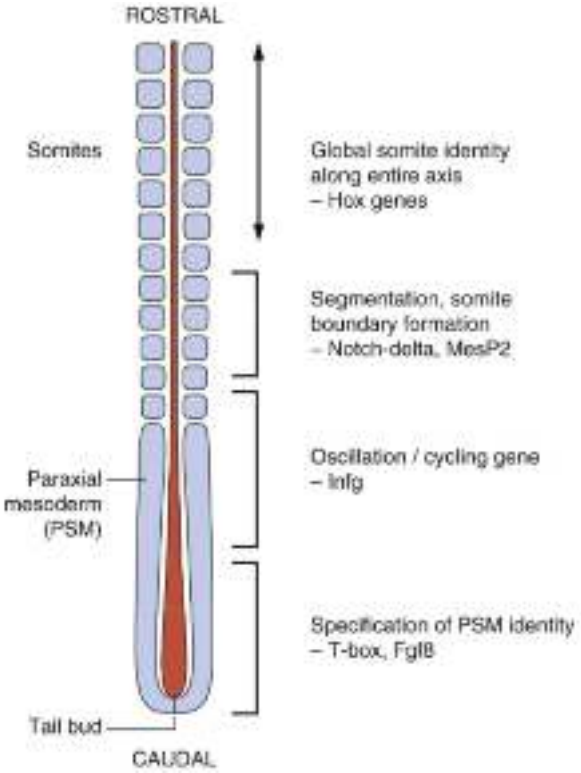
TGF-β genes (33 members fromcytokine family) **/ BMP**





Delta-Notch signaling

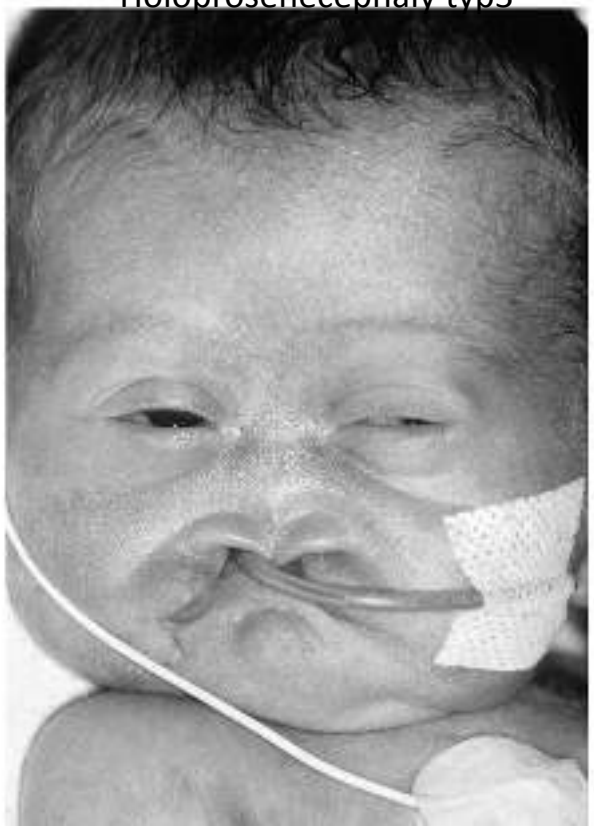


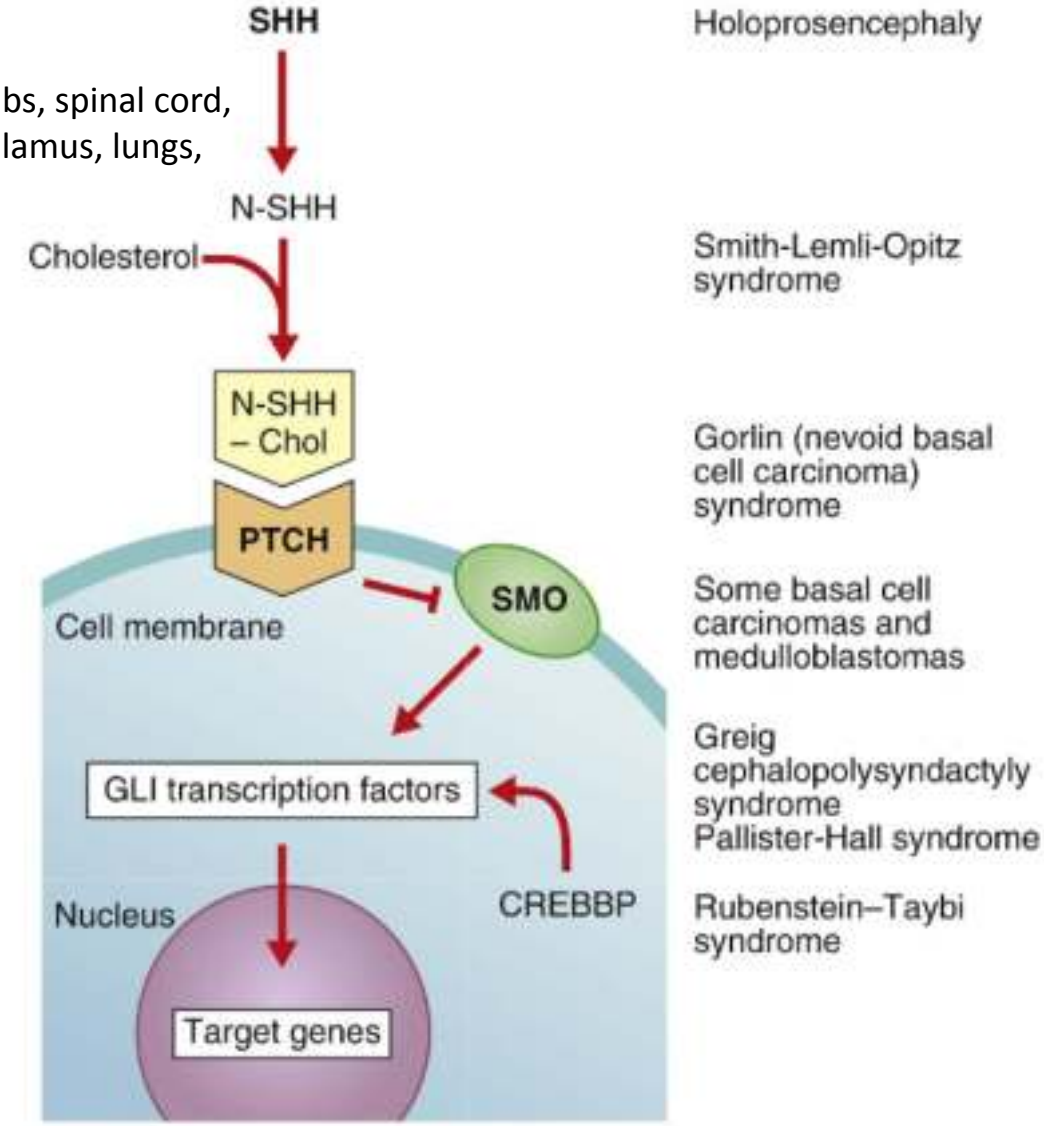


Sonic hedgehog / Patched GLI

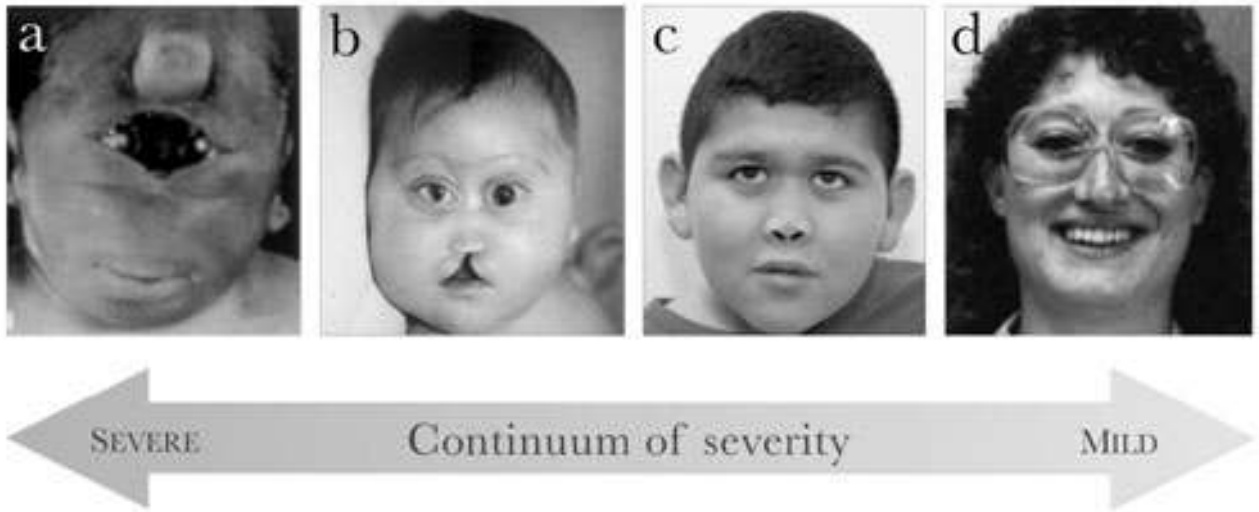
(Brain, limbs, spinal cord, axons, thalamus, lungs, teeth)

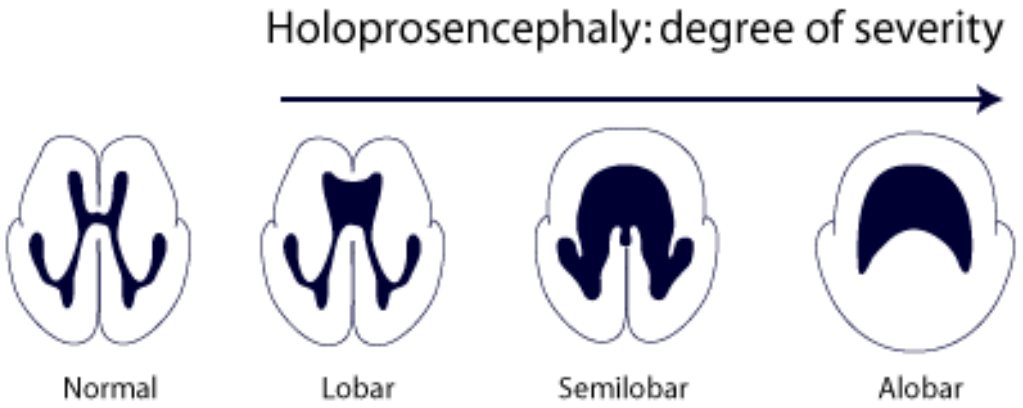
Holoprosenecephaly typ3



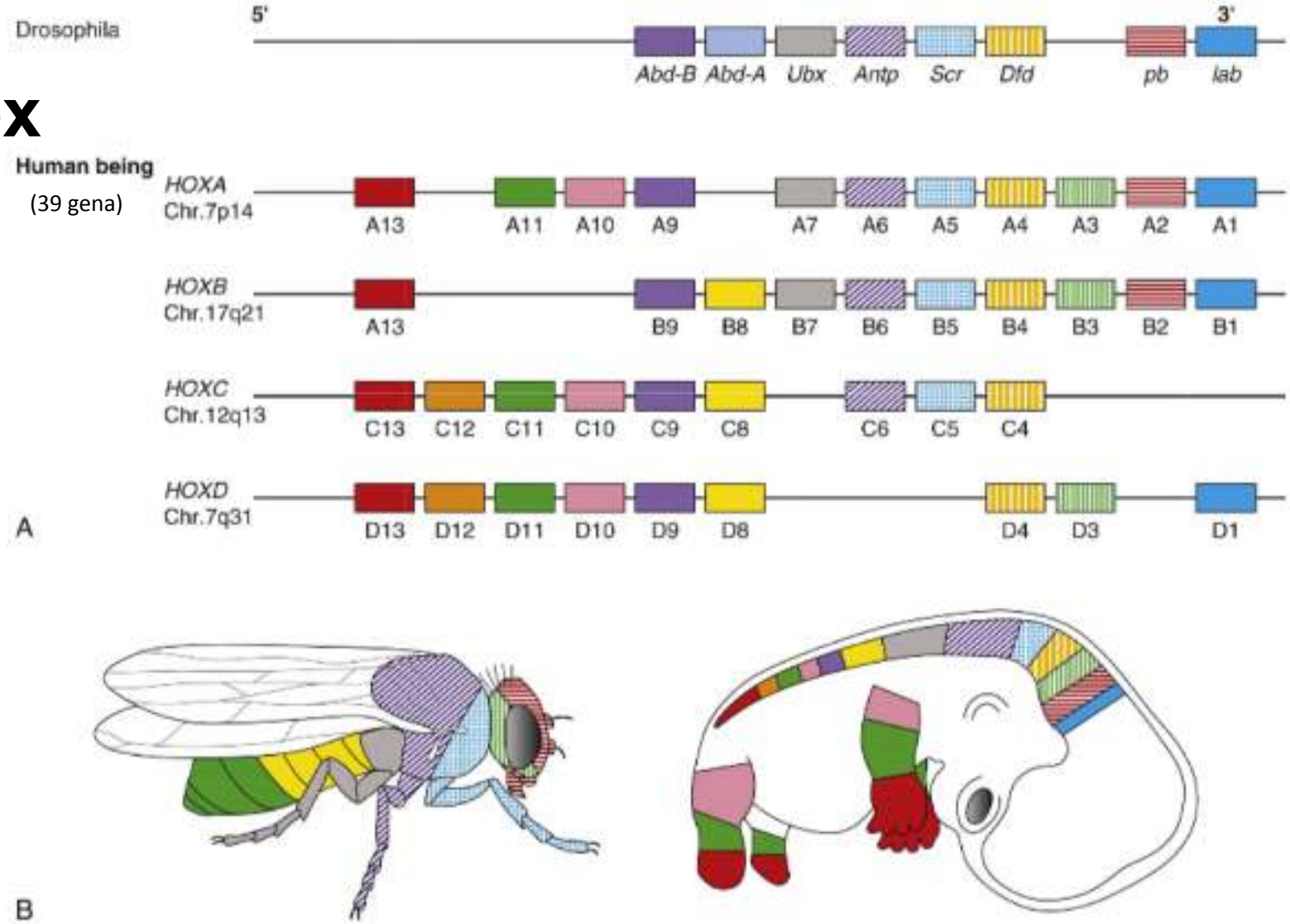


Holoprosencephaly Hedgehog (HH), Patched, GLI)

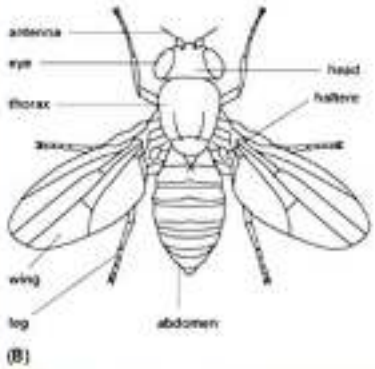




Homeobox genes



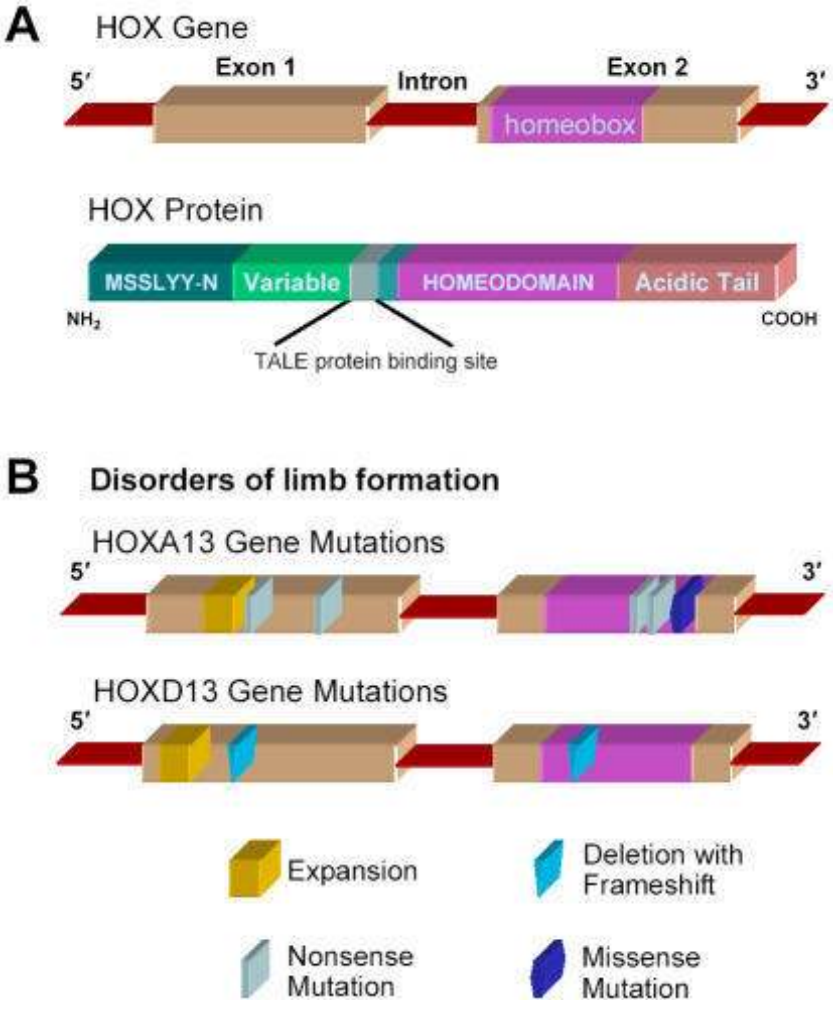
Homeotic mutations (egz.)

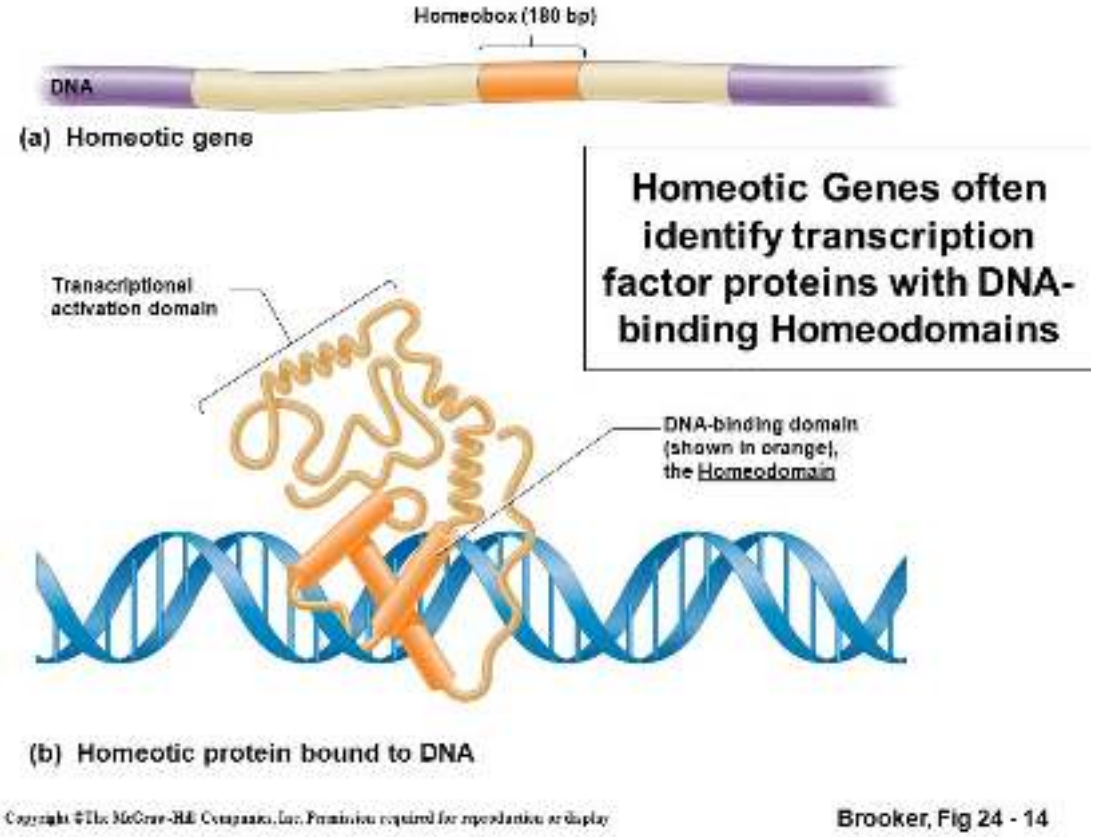


Normal adult fly

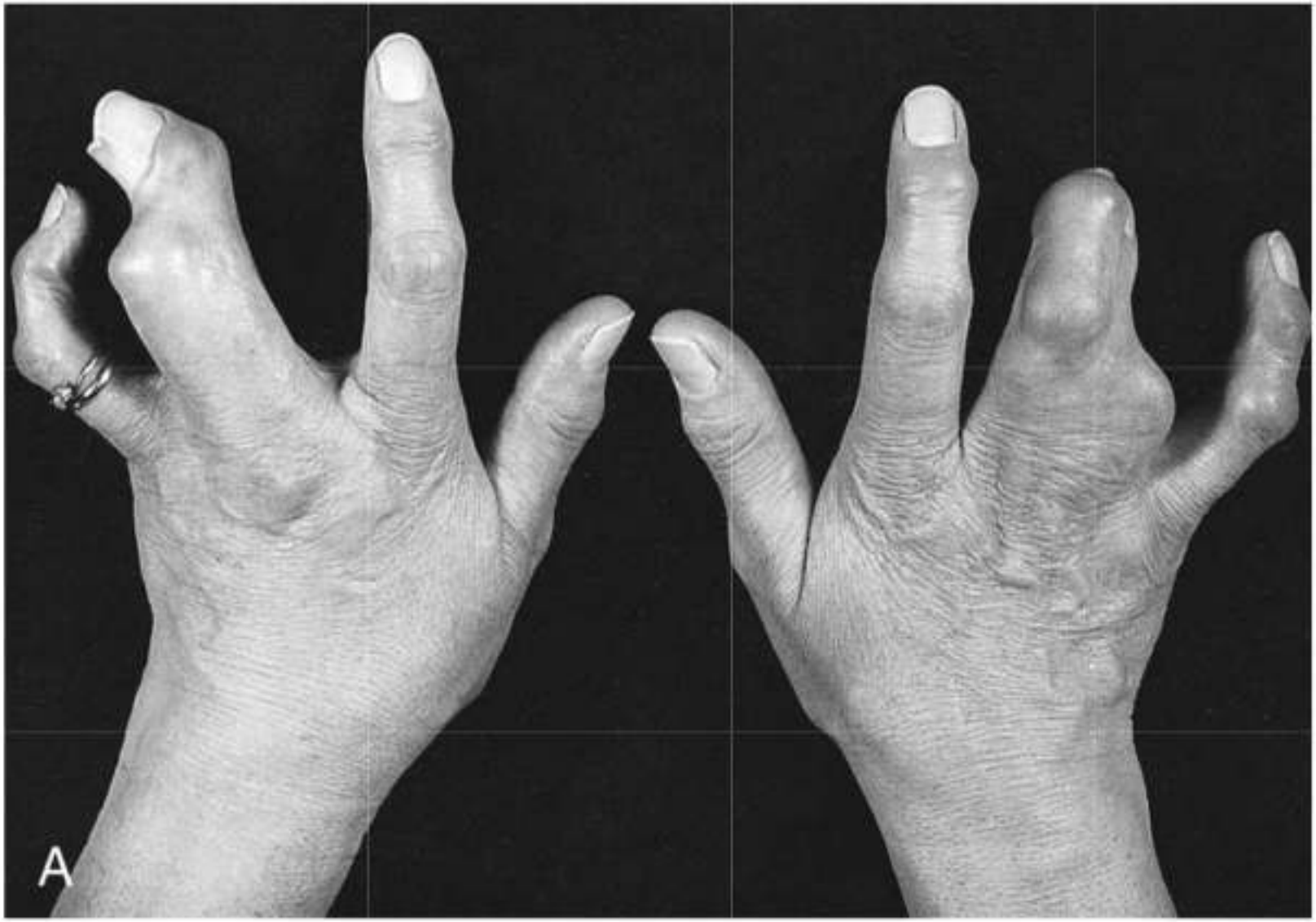
Antennapedia mutant

Bithorax mutant

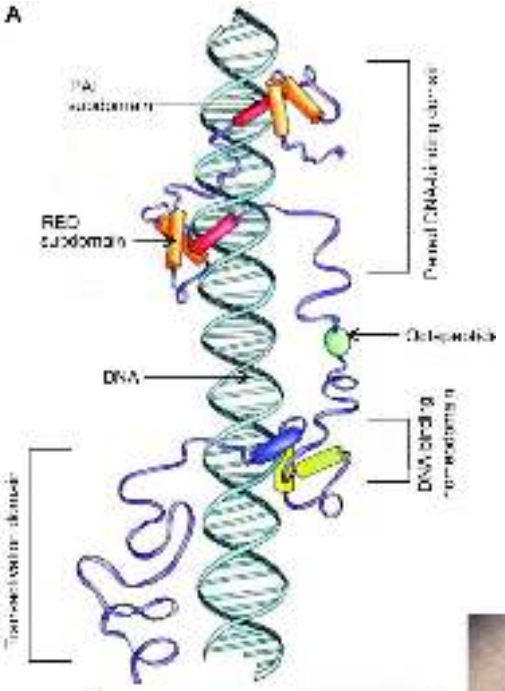




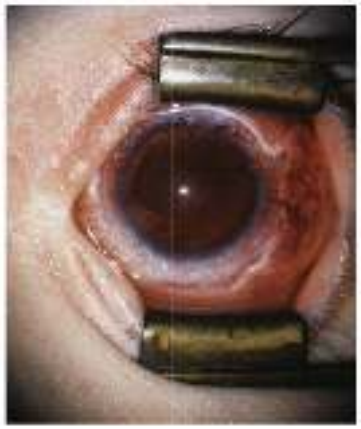
Brooker, Fig 24 - 14

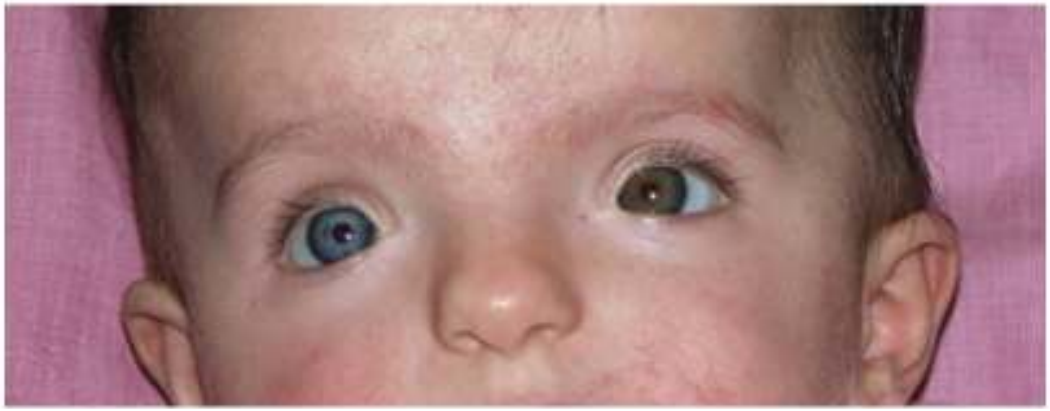

A

PAX genes



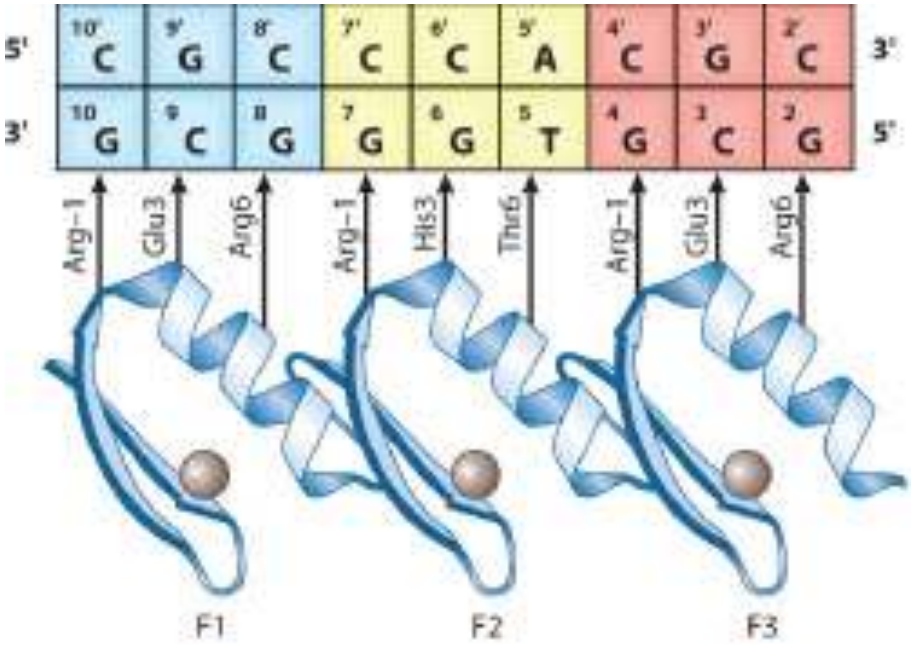
Gene	Chromosome Location	Developmental Abnormality
PAX2	10q24	Renal-coloboma syndrome
PAX3	2q35	Waardenburg syndrome type 1
PAX6	11p13	Aniridia
PAX8	2q12	Absent or ectopic thyroid gland
PAX9	14q12	Oligodontia





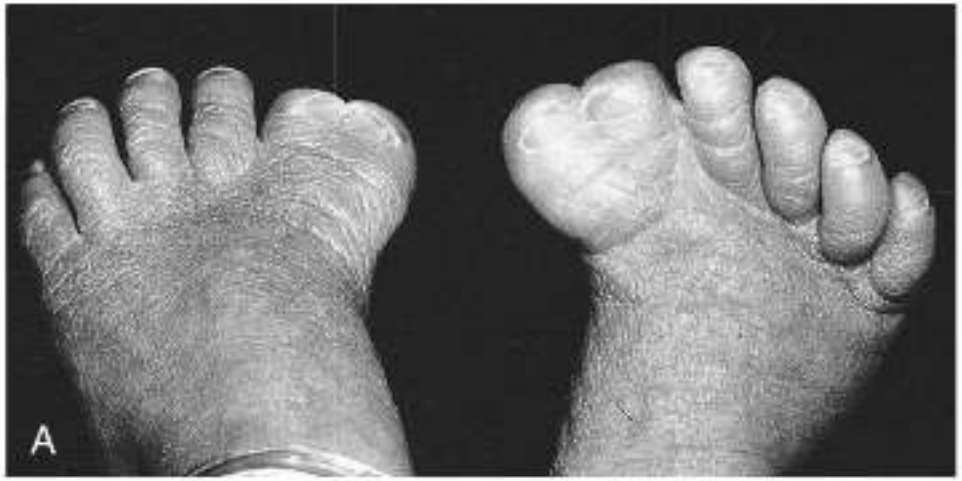
Zinc finger genes

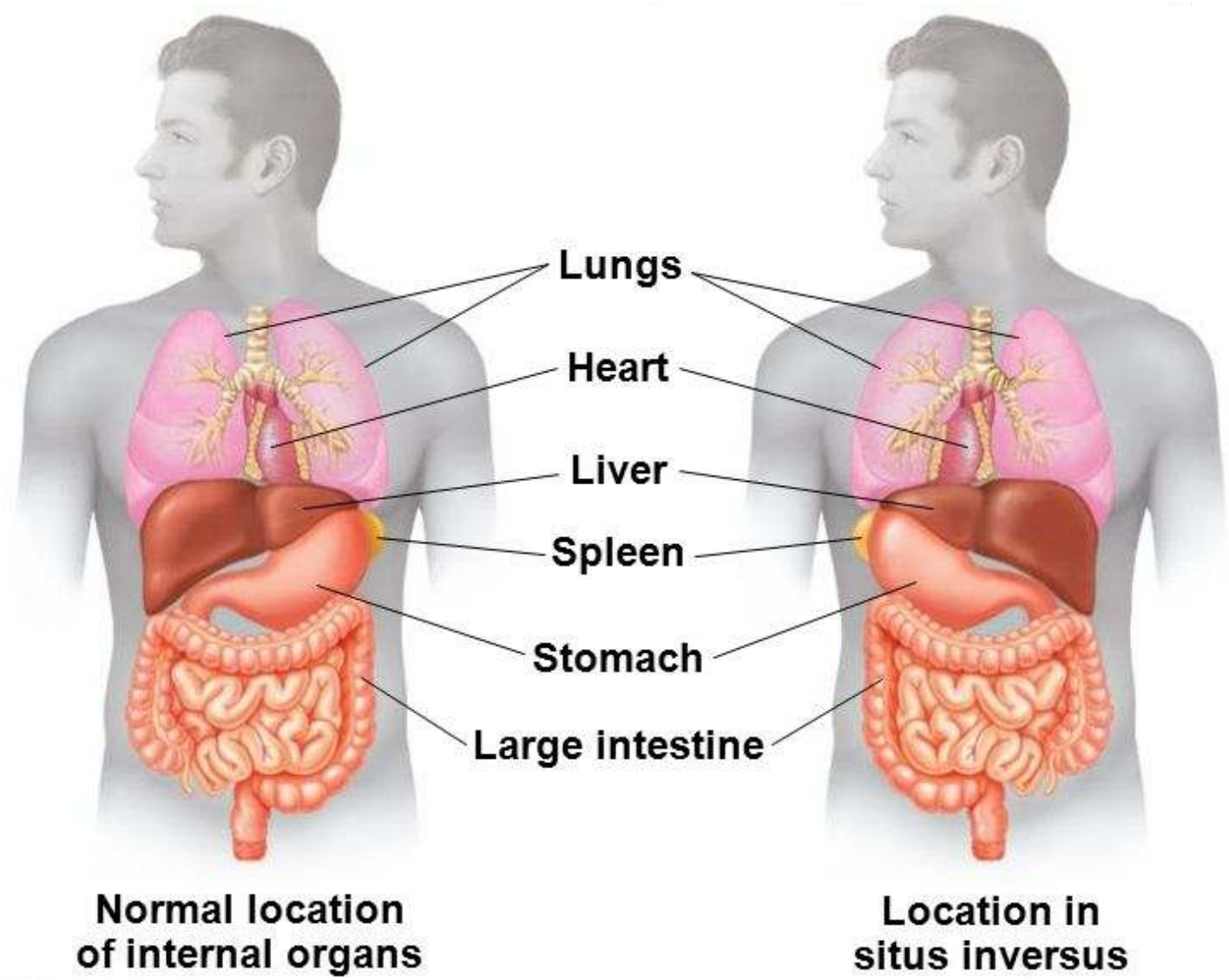
Gene	Chromosome Location	Developmental Abnormality
GLI3	7p13	Greig syndrome and Pallister-Hall syndrome
WT1	11p13	Denys-Drash syndrome
ZIC2	13q32	Holoprosencephaly
ZIC3	Xq26	Laterality defects



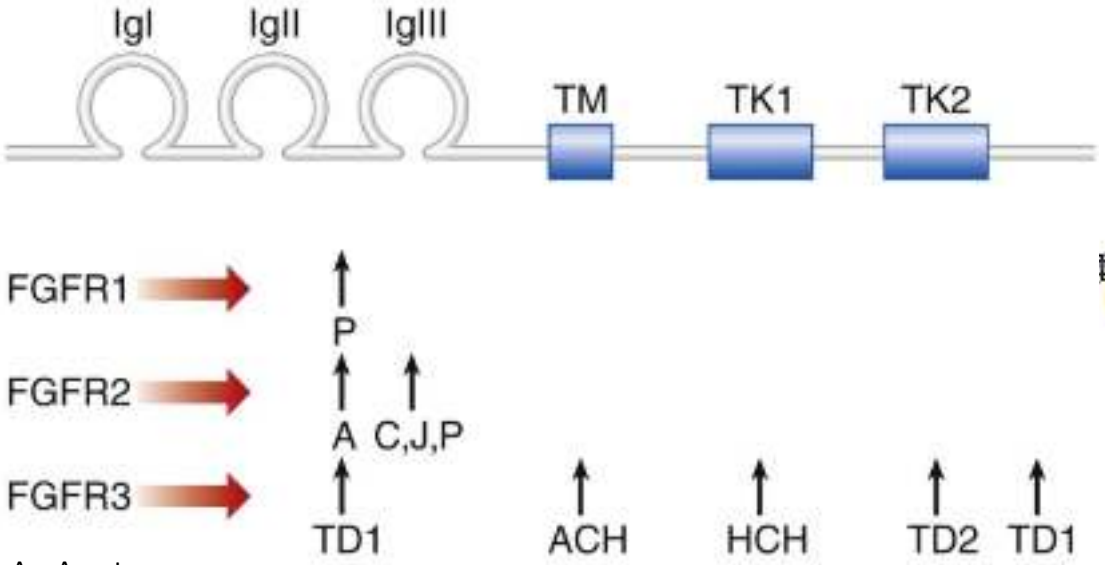
Abnormalities of head, hands, feet.
Laterality defects (situs inversus).

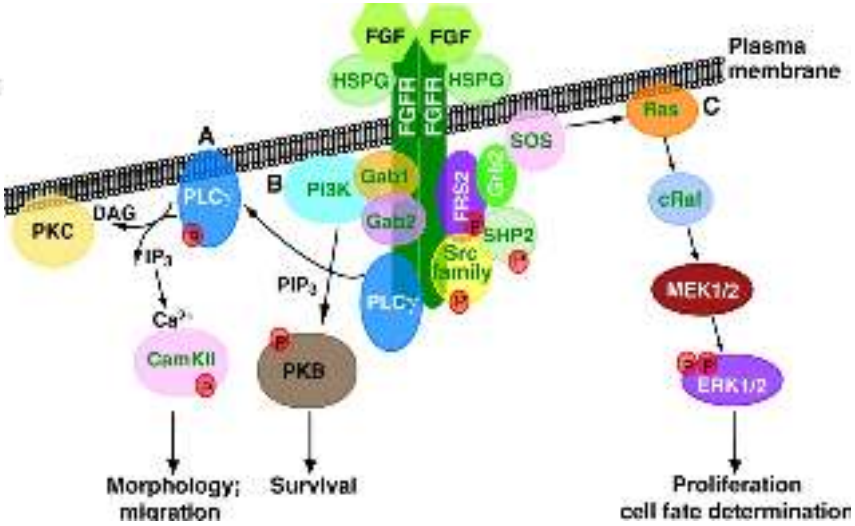
Greig syndrom (polysyndactyly)




Lungs
Heart
Liver
Spleen
Stomach
Large intestine
Normal location
of internal organs
Location in
situs inversus

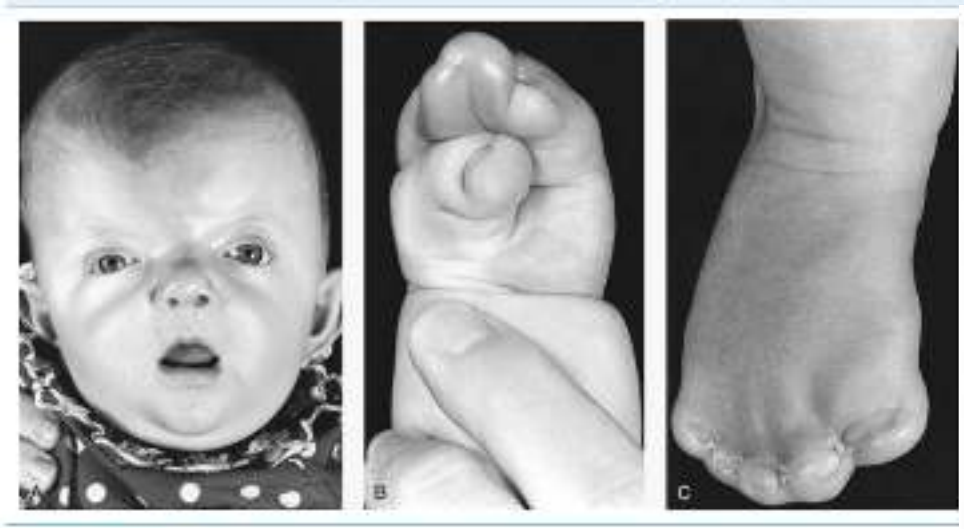
FGF receptor signaling





A – Apert
C - Crouizon
TK – tyrosin kinase
Ig – immunoglobulin domene
TM – transmembrane domene
P – Pfeiffer
J – Jackson Weiss
TD – Thanatophoric dysplasia
ACH – Achondroplasia
HCH - Hypochondroplasia

Gene	Chromosome	Syndrome
Craniosynostosis syndromes		
FGFR1	8p11	Pfeiffer
FGFR2	10q25	Apert Crouzon Jackson-Weiss Pfeiffer
FGFR3	4p16	Crouzon (with acanthosis nigricans)
Skeletal dysplasias		
FGFR3	4p16	Achondroplasia Hypochondroplasia Thanatophoric dysplasia



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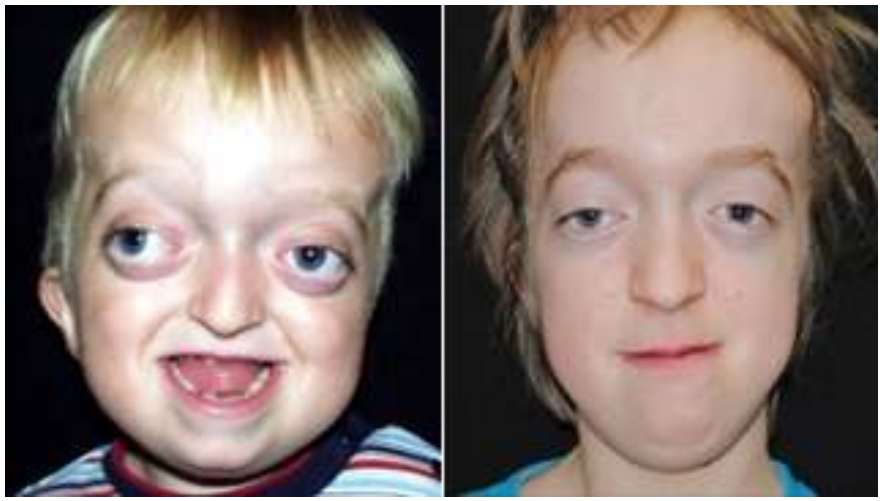


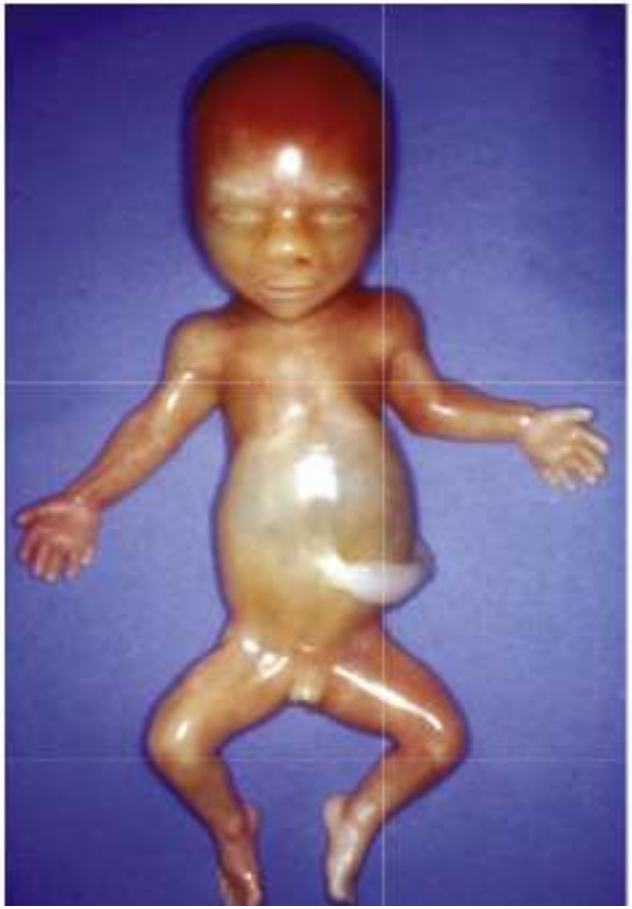
4

Different FGF signaling disorders:

- 1. Apert
- 2. Achondroplasia
- 3. Thanatophoric dysplasia
- 4. Crouzon

Ciliopathies

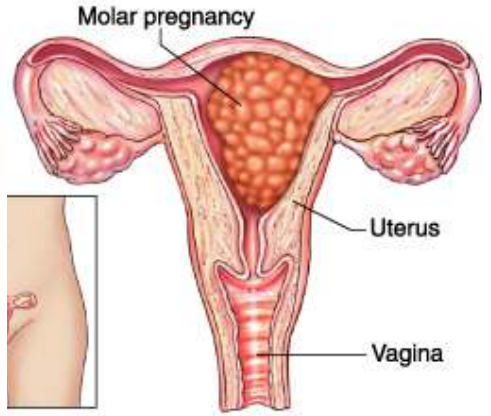
Disease/Syndrome	Gene	Chromosome Locus	Body System(s) Affected
Alstrom syndrome	*ALMS1*	2p13	Retina, adipose, endocrine, heart
Jeune asphyxiating thoracic dystrophy	*IFT80*	15q13	Skeleton
Bardet-Biedl syndrome	*BBS1-BBS14*	Multiple	Multisystem, including retina, kidney, skeleton
Craniectodermal dysplasia (Sensenbrenner syndrome)			Kidney, liver
Ellis van Creveld syndrome	*EVC1, EVC2*	4p16	Skeleton, heart
Joubert syndrome	*JBTS1* (+ others)	9q34.3	Brain
Leber congenital amaurosis	*GUCY2D, RPE65* (+ others)	17p13, 1p31 (+ others)	Retina
McKusick Kaufman syndrome	*BBS6*	20p12	Limb, heart, urogenital tract
Meckel Gruber syndrome	*MKS1* (+ others)	17q23 (+ others)	Brain, kidney, liver
Nephronophthisis (types 1–4)	Nephrocystin (+ others)	Multiple	Kidney
Oro-facio-digital syndrome type 1	*OFD1* (+ others)	Xp.22 (+ others)	Skeleton (limb, face)
Polycystic kidney disease	Multiple	Multiple	Kidney
Primary ciliary dyskinesia (Kartagener syndrome)	Multiple	Multiple	Multi-system
Senior-Loken syndrome	Multiple	Multiple	Retina, kidney
Short rib polydactyly syndrome	*DYNC2H1*	11q13	Skeleton, kidney, urogenital tract

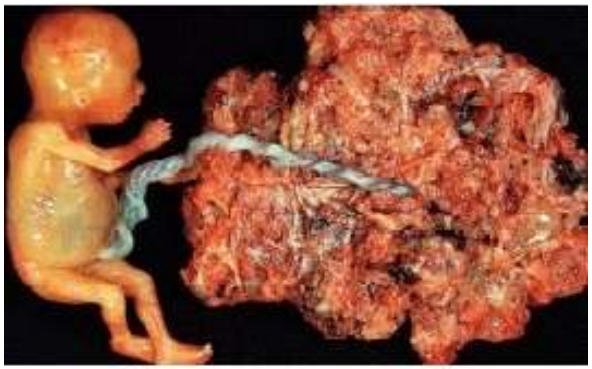


Hydatiform moles

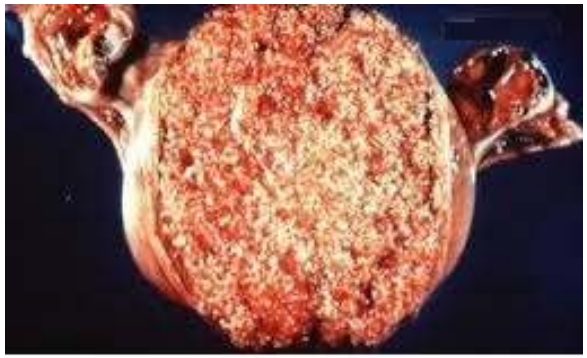
TABLE 6.9 Characteristics of Partial and Complete Hydatidiform Moles

	Partial Mole	Complete Mole
No. of chromosomes	69	46
Parental origin of chromosomes	23 maternal 46 paternal	All 46 paternal
Fetus present	Yes, but not viable	No
Malignant potential	Very low	High



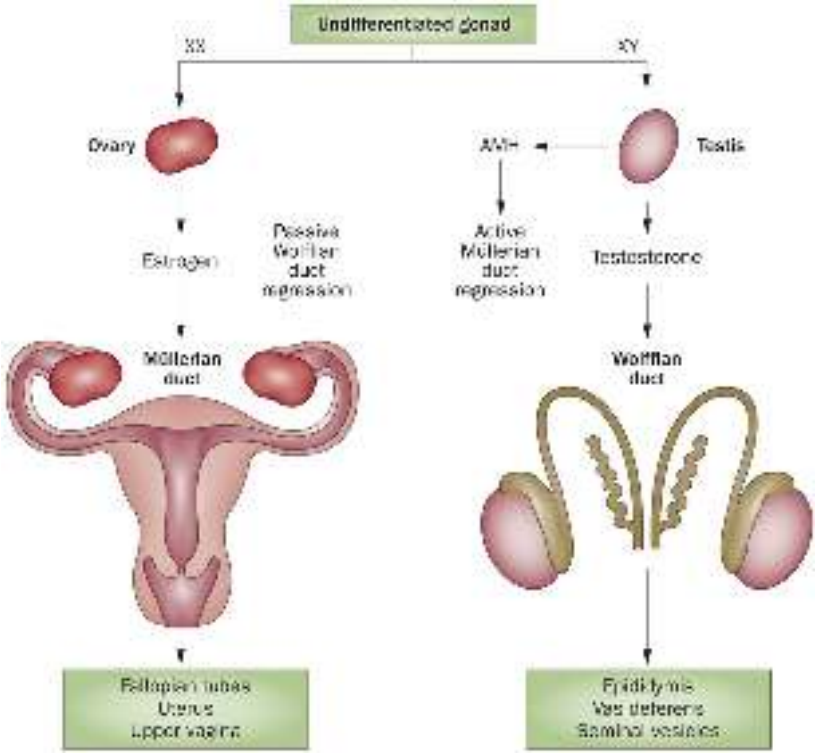


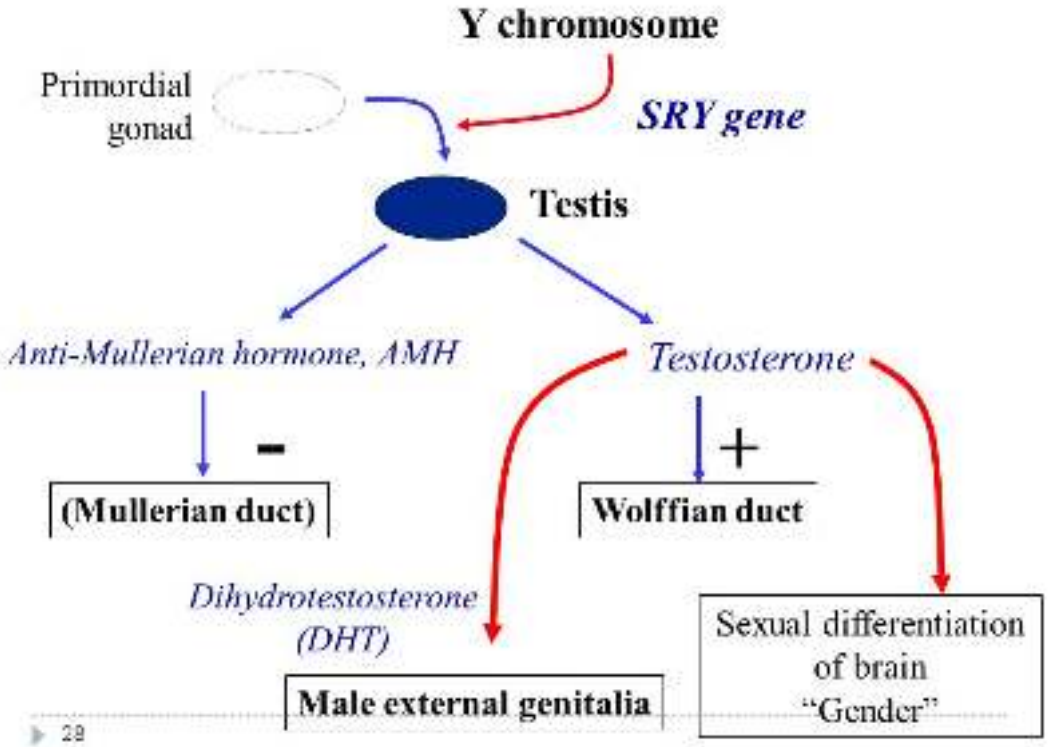
Partial Molar Pregnancy



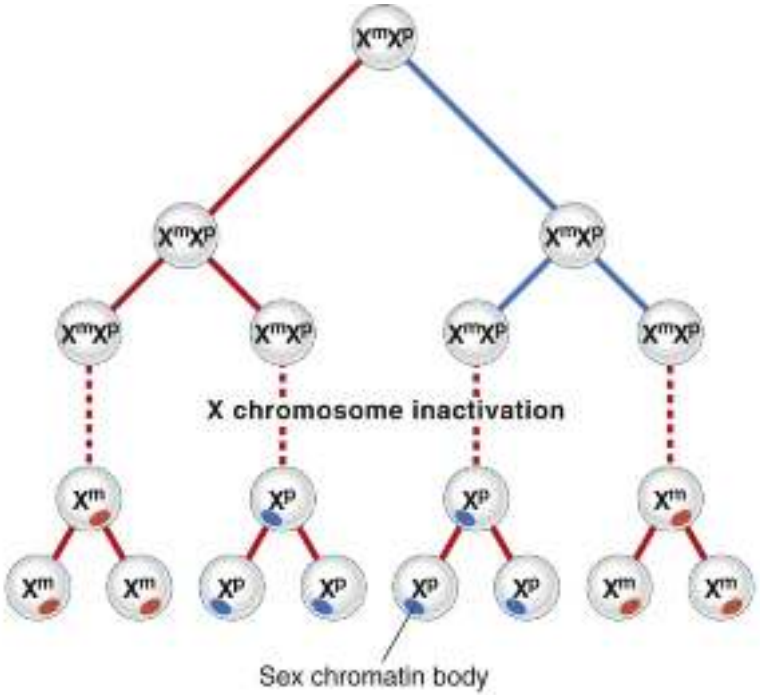
Complete Molar Pregnancy

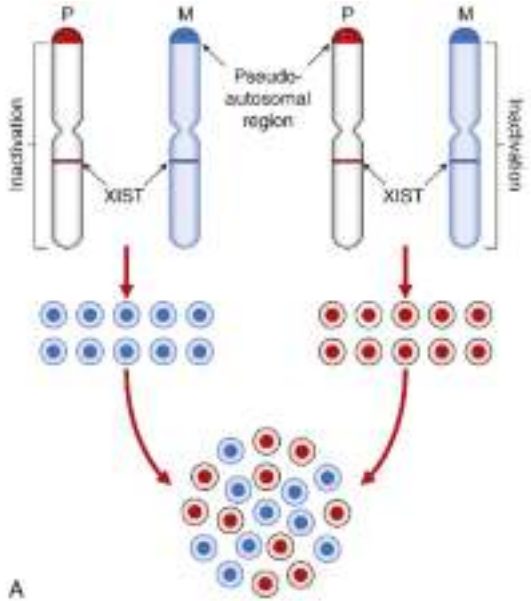
Sex differentiation - SRY

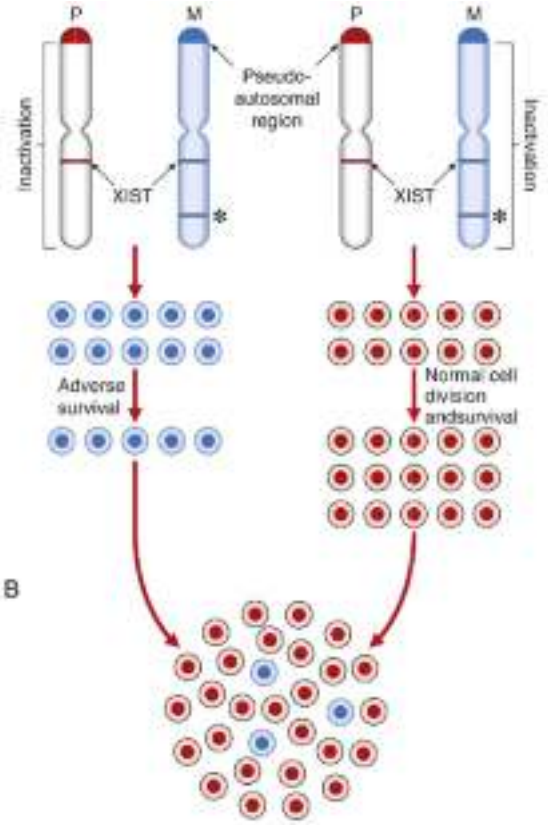




X-chromosome inactivation

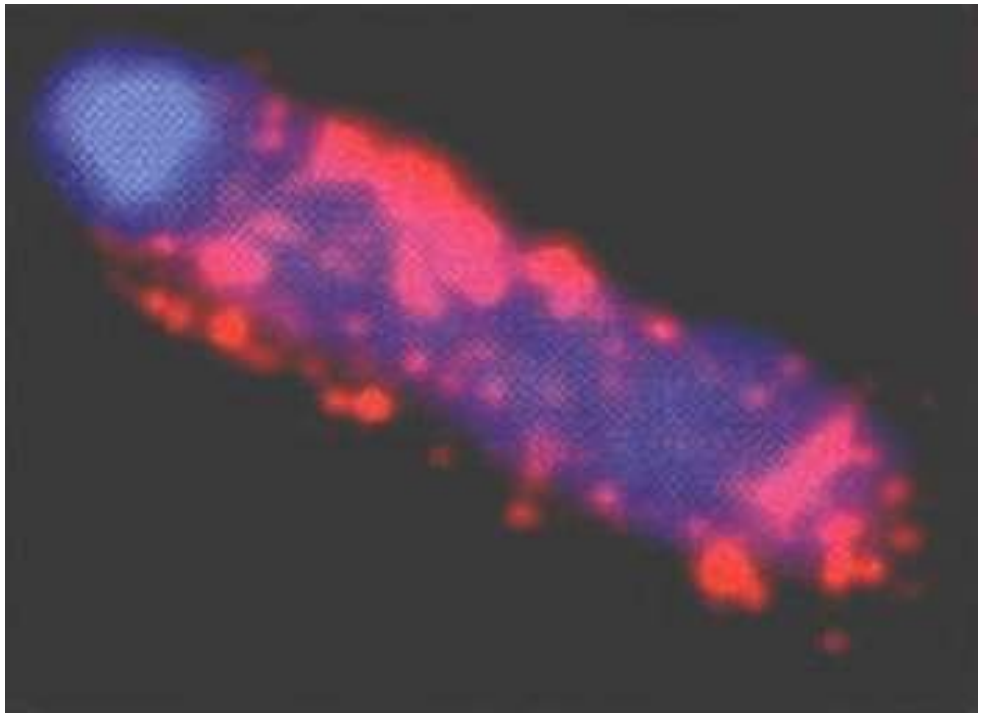






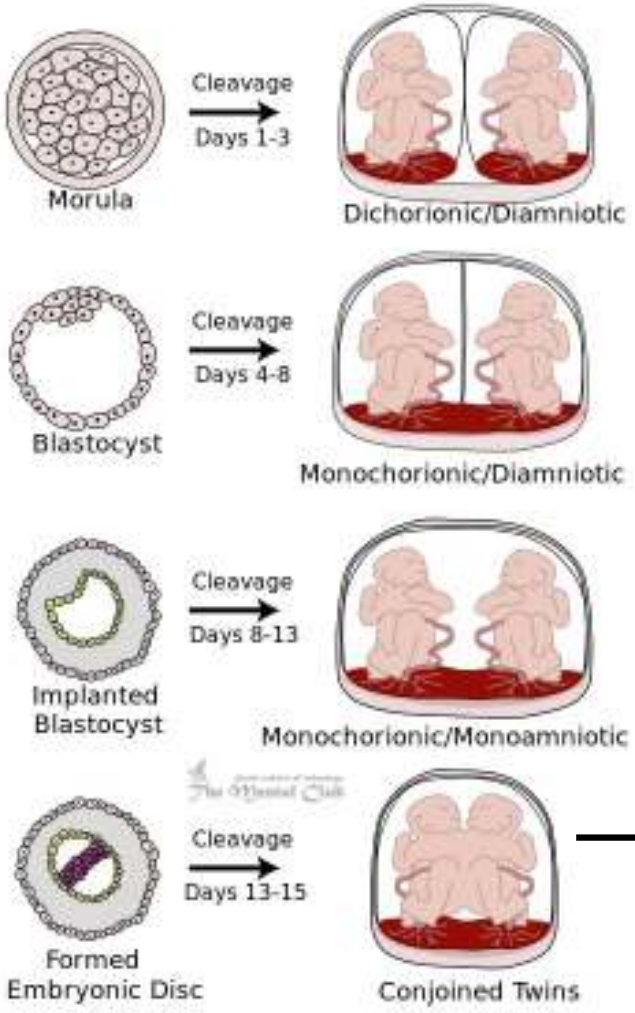
Lyonisation – X chromosome inactivation

- XIST RNA promotes metilation (epigenetic silencing) of inactivated X-chromosome
- Pseudoautosomal region remains active
- Both X chromosomes are active in sex organs

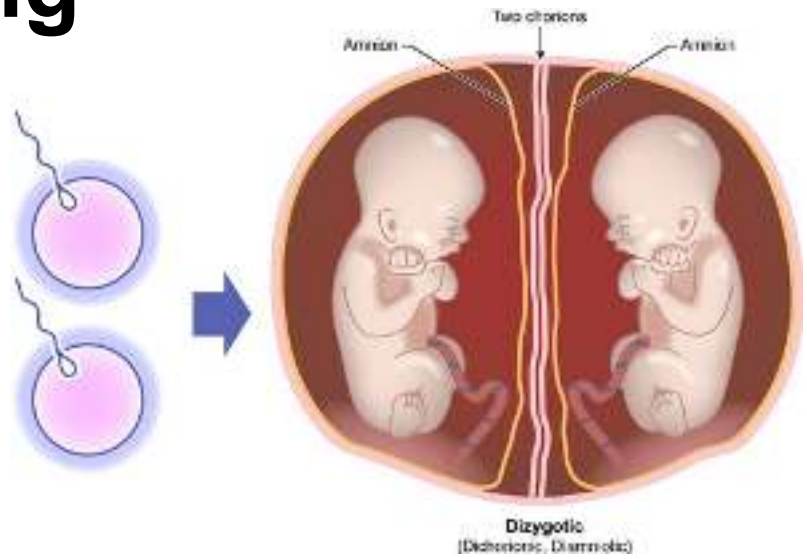


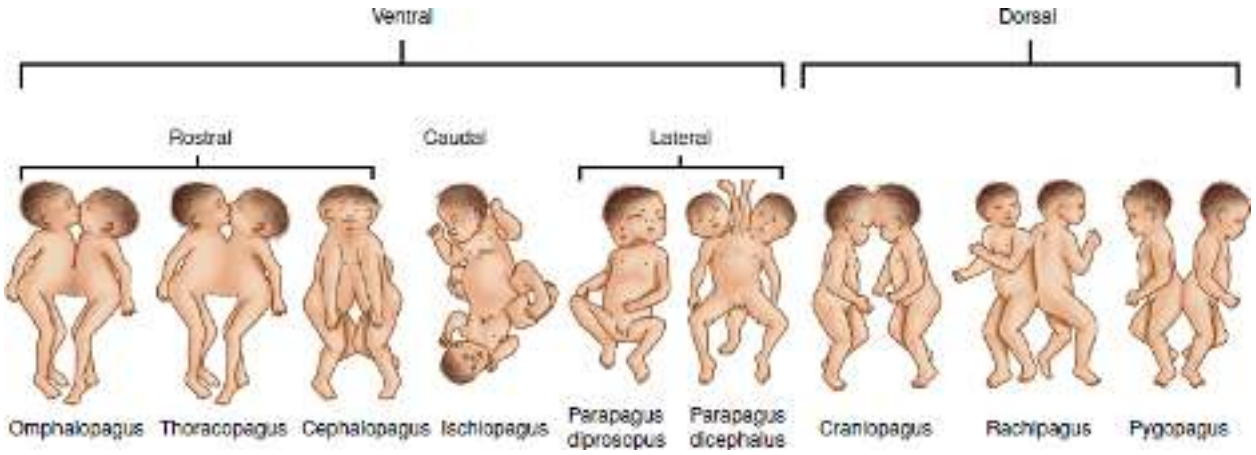
Twinning

Monozygotic:



Dizygotic:





Patterns of inheritance

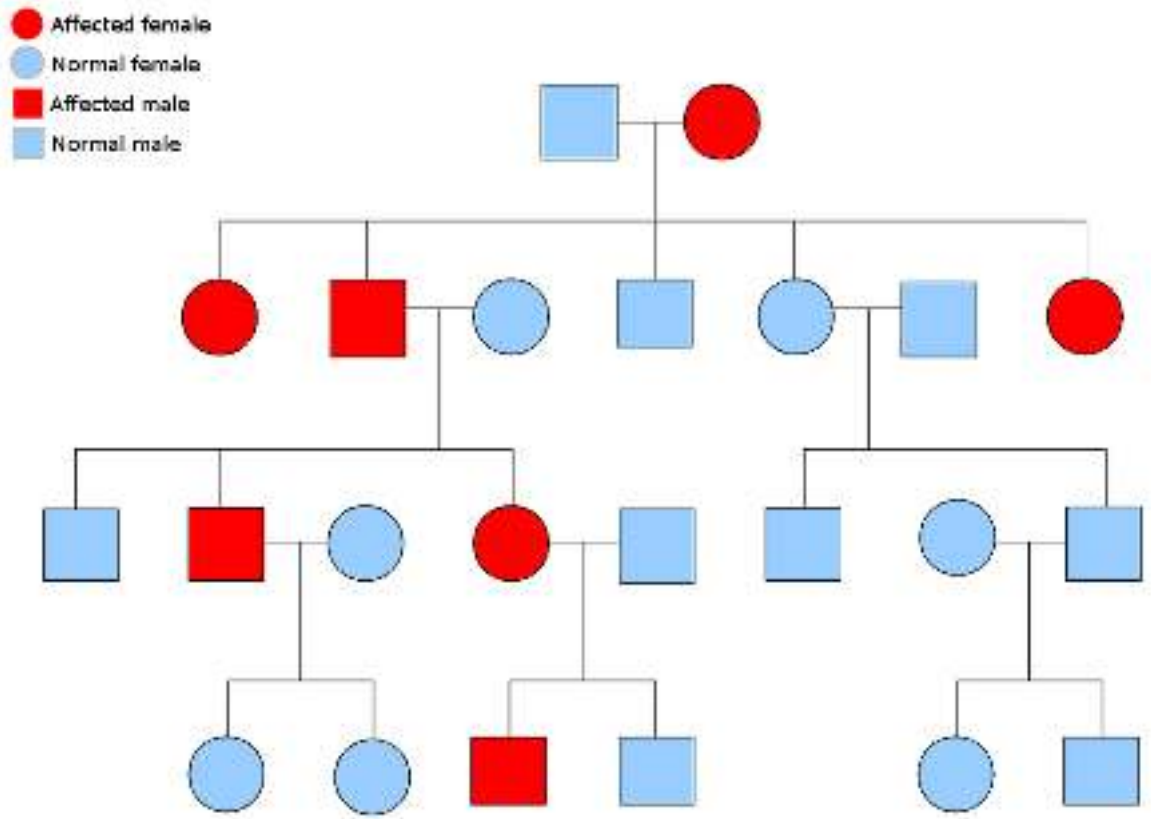
Chapter 7

Inheritance pattern

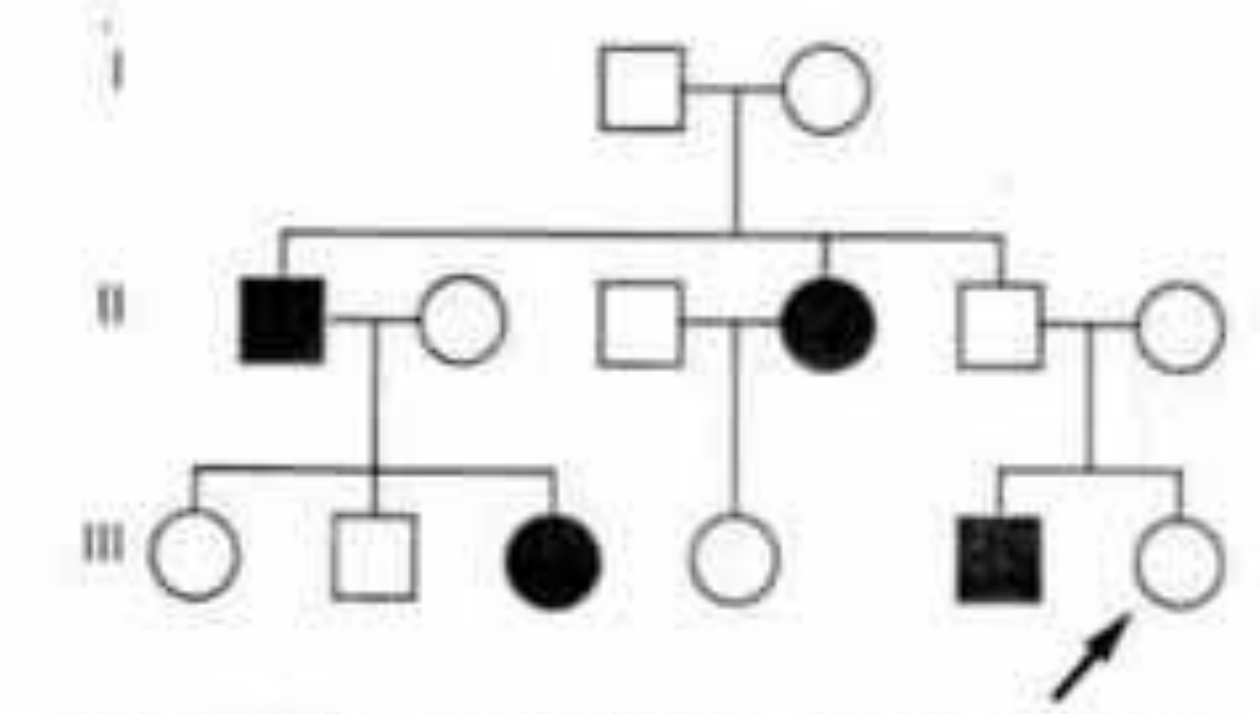
Mendelian inheritance:

- Autosomal: -dominante
  - recessive
- Sex-linked: -X linked recessive
  - X linked dominante
  - Y linked (holandric)

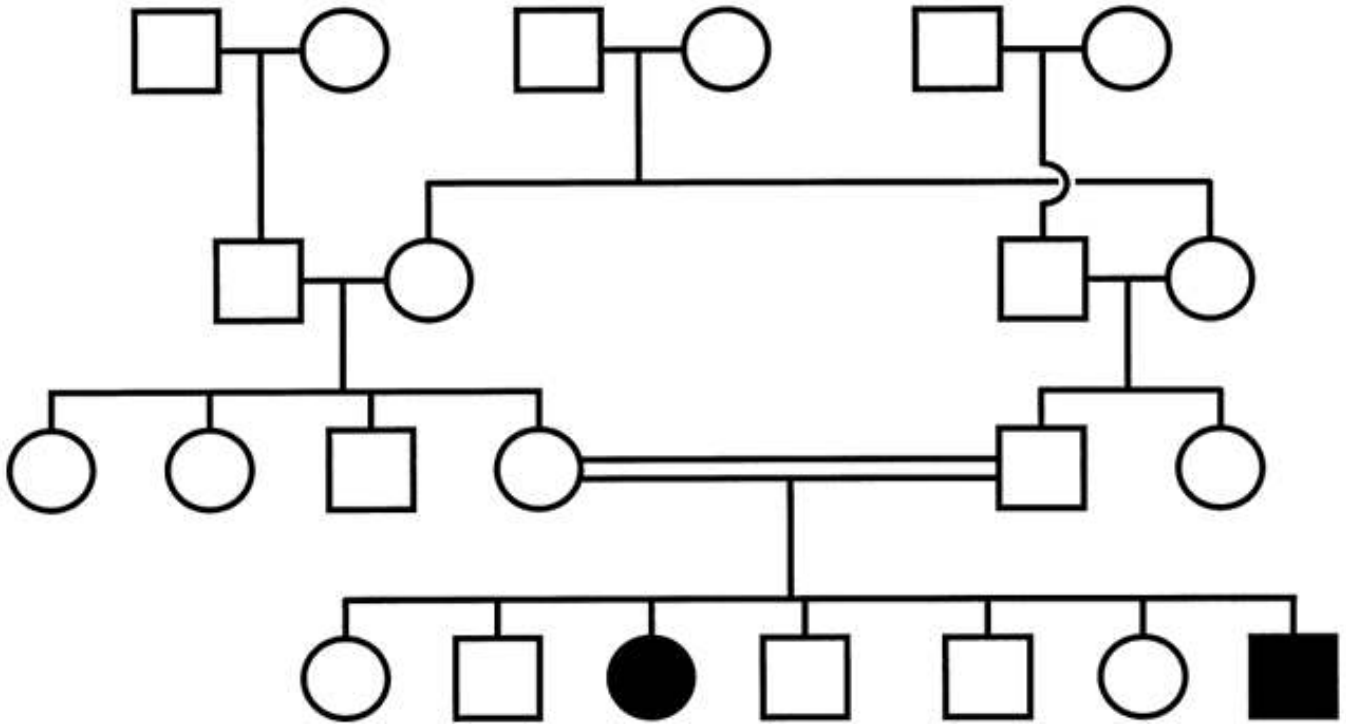
Autosomal dominant (50% risk)



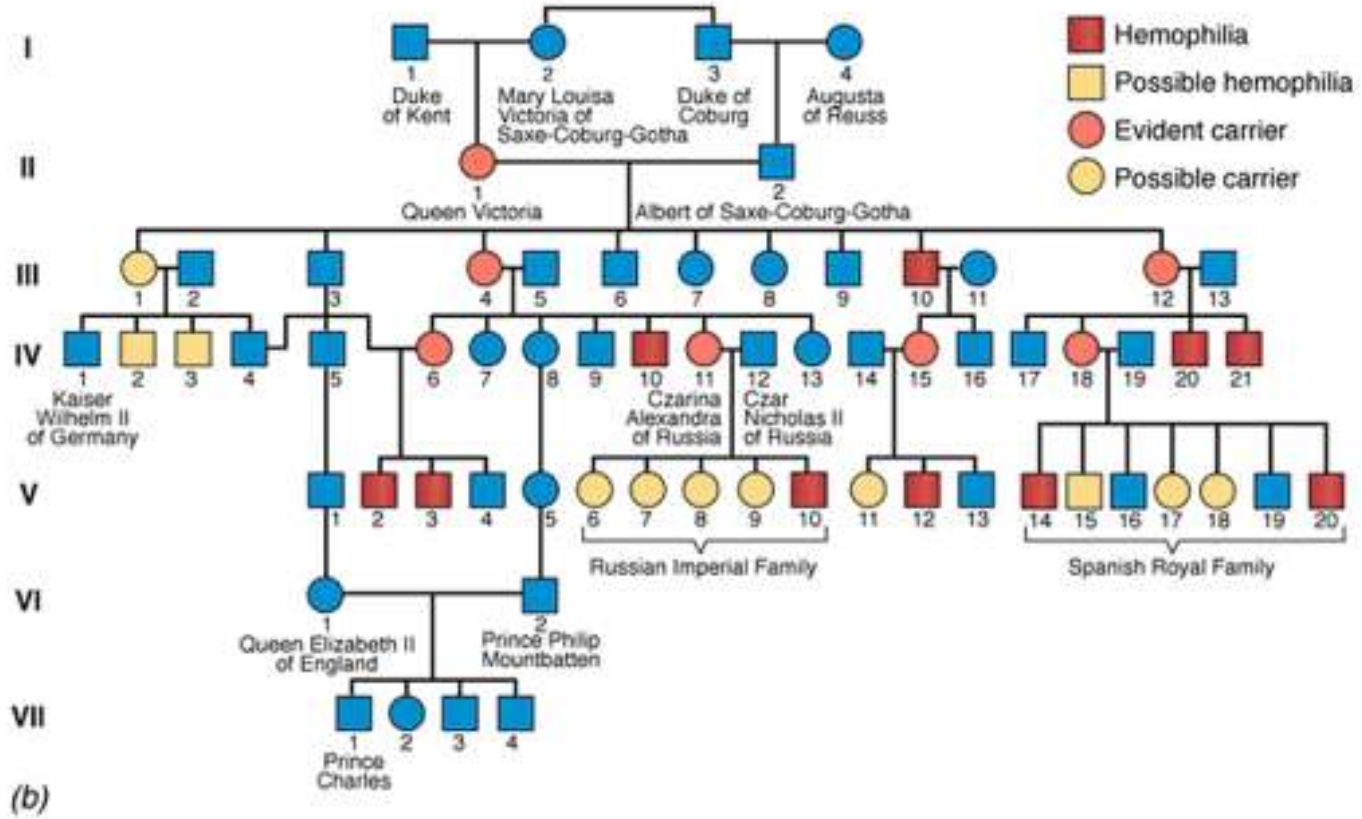
Autosomal dominante with reduced penetrance (non penetrance)



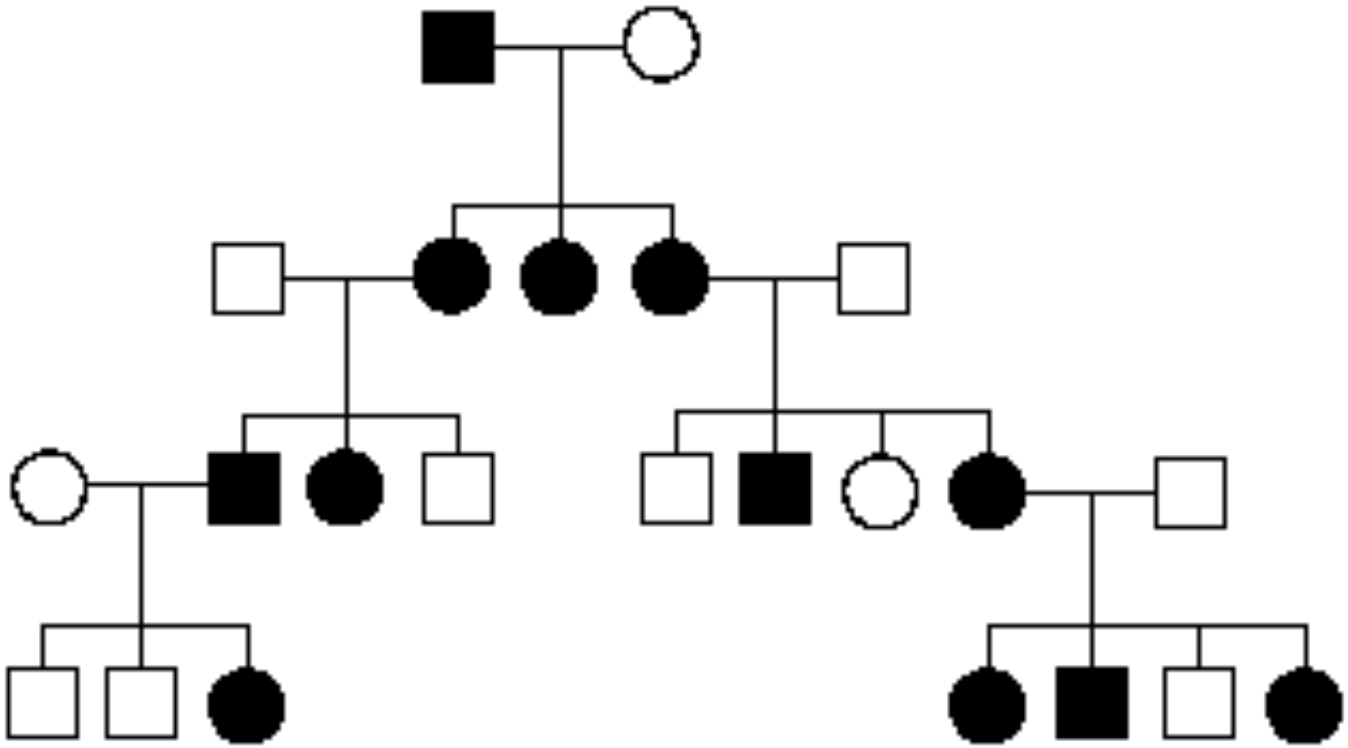
Autosomal recessive inheritance
- Cosanguinity (25% risk)



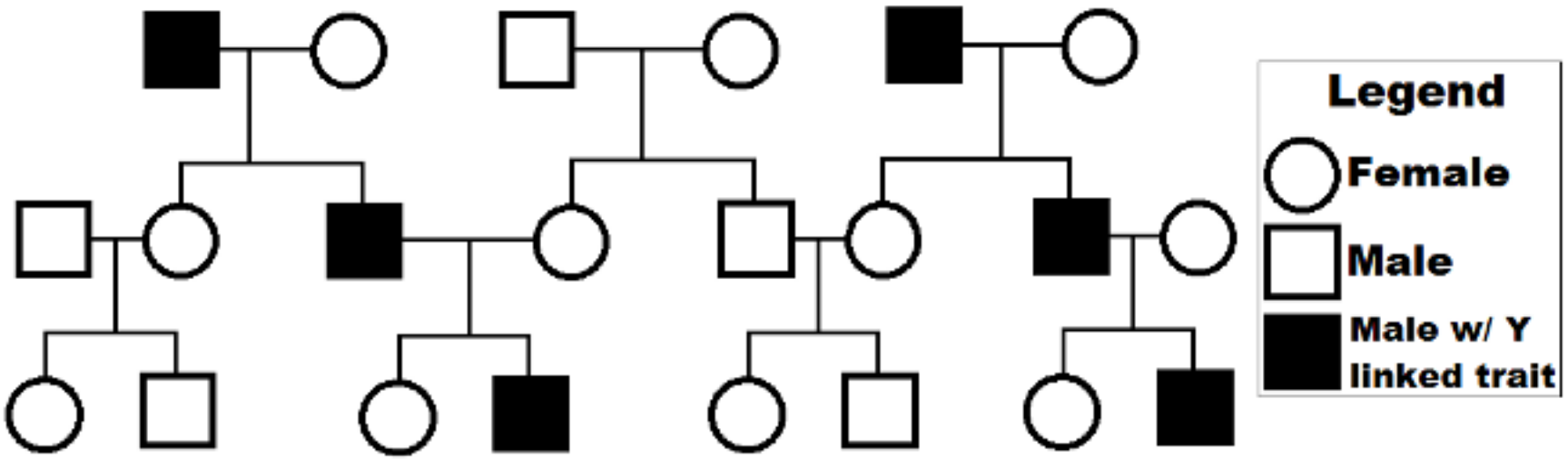
X linked recessive



X linked dominante



Y-linked inheritance



BOX 7.1

Features that Support the Single-Gene or Mendelian Patterns of Inheritance

Autosomal Dominant

Males and females affected in equal proportions
Affected individuals in multiple generations
Transmission by individuals of both sexes (i.e., male to male, female to female, male to female, and female to male)

Autosomal Recessives

Males and females affected in equal proportions
Affected individuals usually in only a single generation
Parents can be related (i.e., consanguineous)

X-Linked Recessive

Only males usually affected
Transmitted through unaffected females
Males cannot transmit the disorder to their sons (i.e., no male-to-male transmission)

X-Linked Dominant

Males and females affected but often an excess of females
Females less severely affected than males
Affected males can transmit the disorder to their daughters but not to sons

Y-Linked Inheritance

Affected males only
Affected males must transmit it to their sons

Nonmendelian inheritance

- **Anticipation:** the symptoms of the genetic disorder become apparent at an earlier age with each generation
- **Mosaicism** = consists of more than one cell type (occurs during early development): - somatic

  - germ cells
- **Uniparental disomy**: heterodysomy or isodisomy

  - Genomic imprinting
- **Mitochondrial inheritance**
- Multifactorial diseases

Genomic imprinting
- alternative methylation patern

Angelman (15q11-q13)

- paternal uniparental disomy
- UBE3A (ubiquitin 3 ligase), expresed from a mother is missing

Prader willy (15q11-q13)

- maternal uniparental disomy
- SNRPN (small nuclear ribonucleoprotein polypeptide N) and adjacent genes, expressed from a father, are missing

11p15 region:

- **Beckwith-Wiedemann** syndrom (paternal uniparental disomy)
  - IGF2 overexpression → overgrowth)
- **Russel-Silver** syndrom (maternal uniparental disomy) – growth retardation

Mitochondrial inheritance

- Heteroplasmy: a wide range of clinical severity
- Effects energy metabolism of a cell