MENDELIAN INHERITANCE

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MGL- 6

Homozygous Dominant + Homozygous Dominant

	A	A
A	AA	AA
A	AA	AA

Homozygous Dominant + Heterozygous

	A	A
A	AA	AA
a	Aa	Aa

Hetrozygous dominanat + Hetrozygous Recessive

	a	a
A	Aa	Aa
A	Aa	Aa

Hetrozygous Recessive + Heterozygous Recessive

	A	a
A	AA	Aa
a	Aa	aa

Diploid germ cells in female

Diploid germ cells in male

Meiosis, gamete formation in both female and male:

Eggs

Sperm

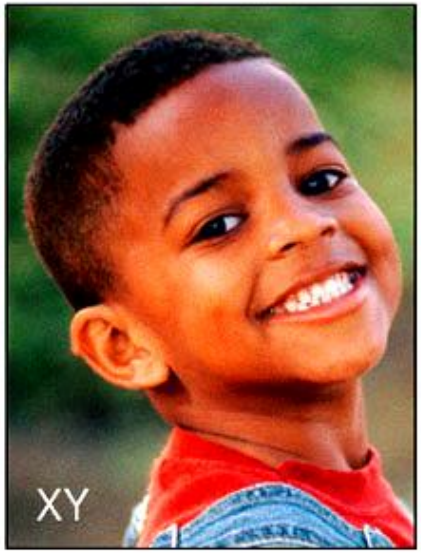
X × Y

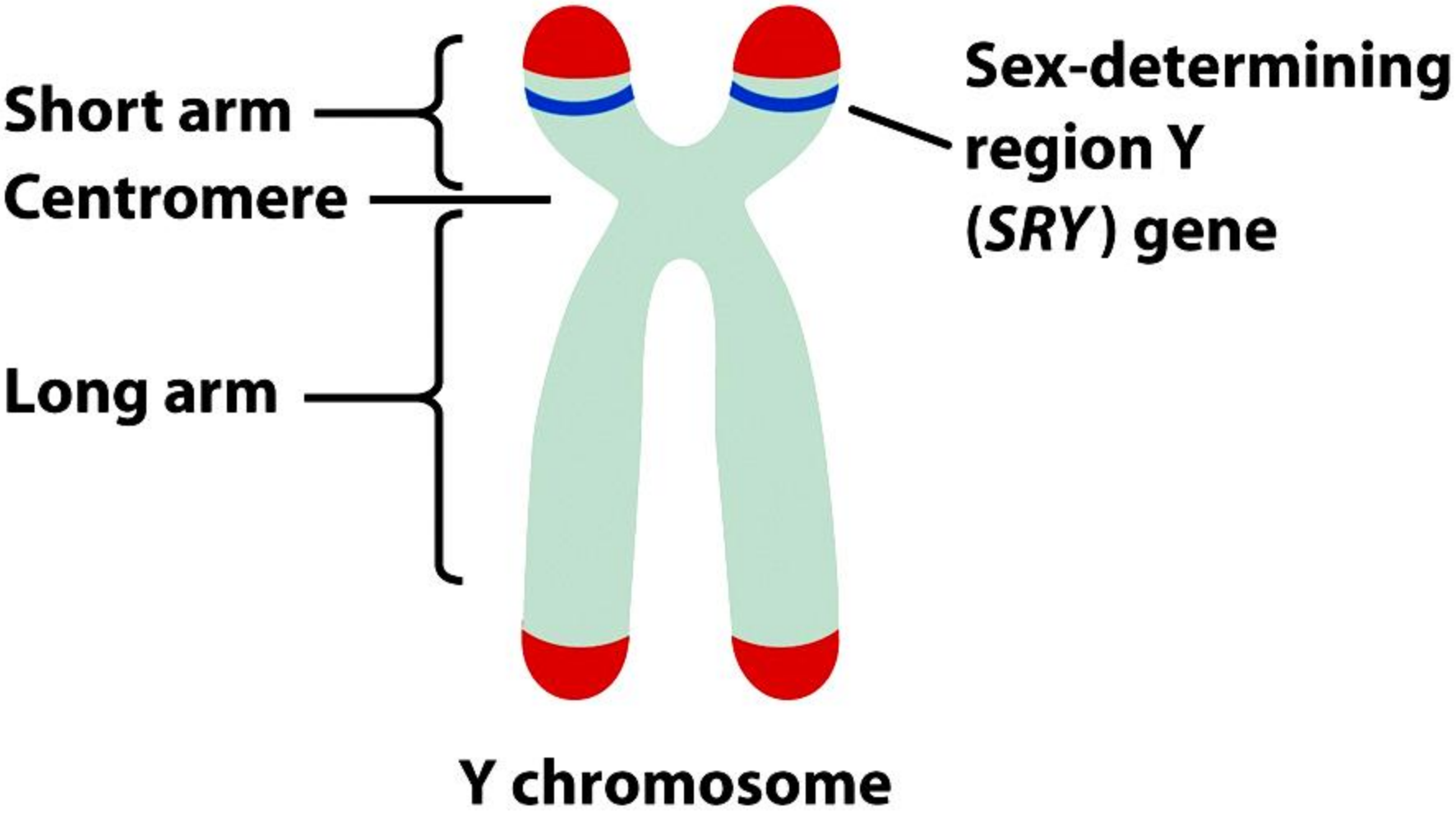
X × X

Fertilization:

	X	X
X	XX	XX
Y	XY	XY

Sex chromosome combinations possible in new individual





4.10 The *SRY* gene is on the Y chromosome and causes the development of male characteristics.

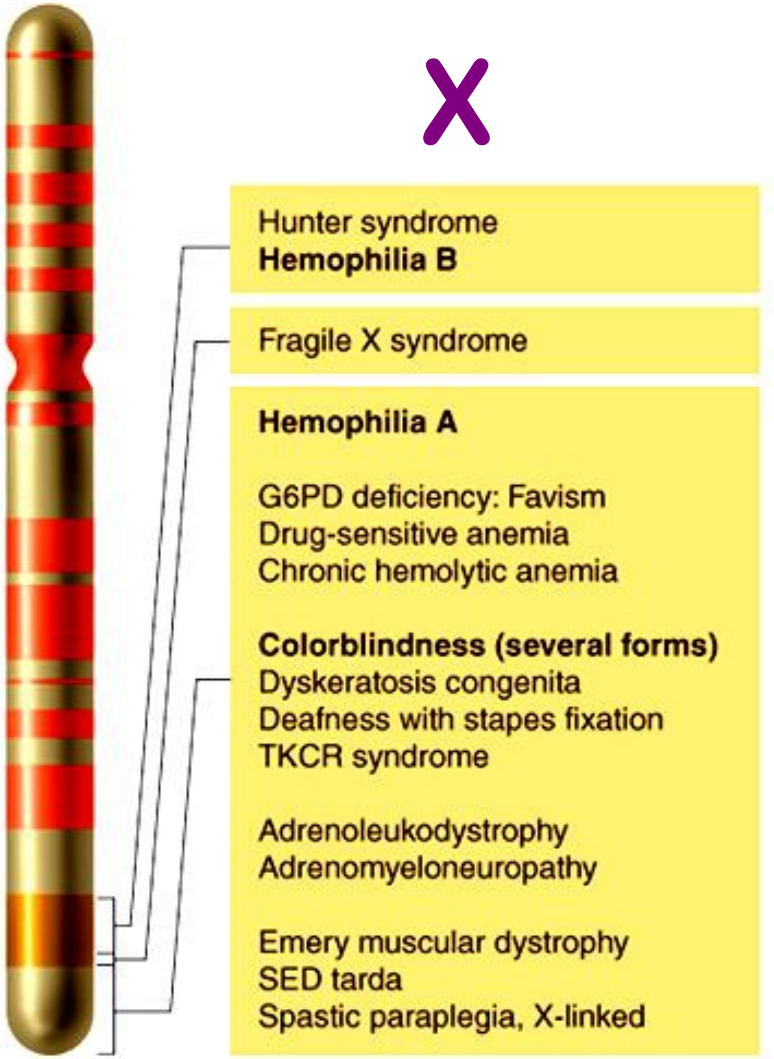
Y-linked Traits

- The Y chromosome is small and therefore does not contain many genes
- Y linked diseases are very rare
- Only passed from father to son.
- Example: Male infertility

Sex-linked inheritance

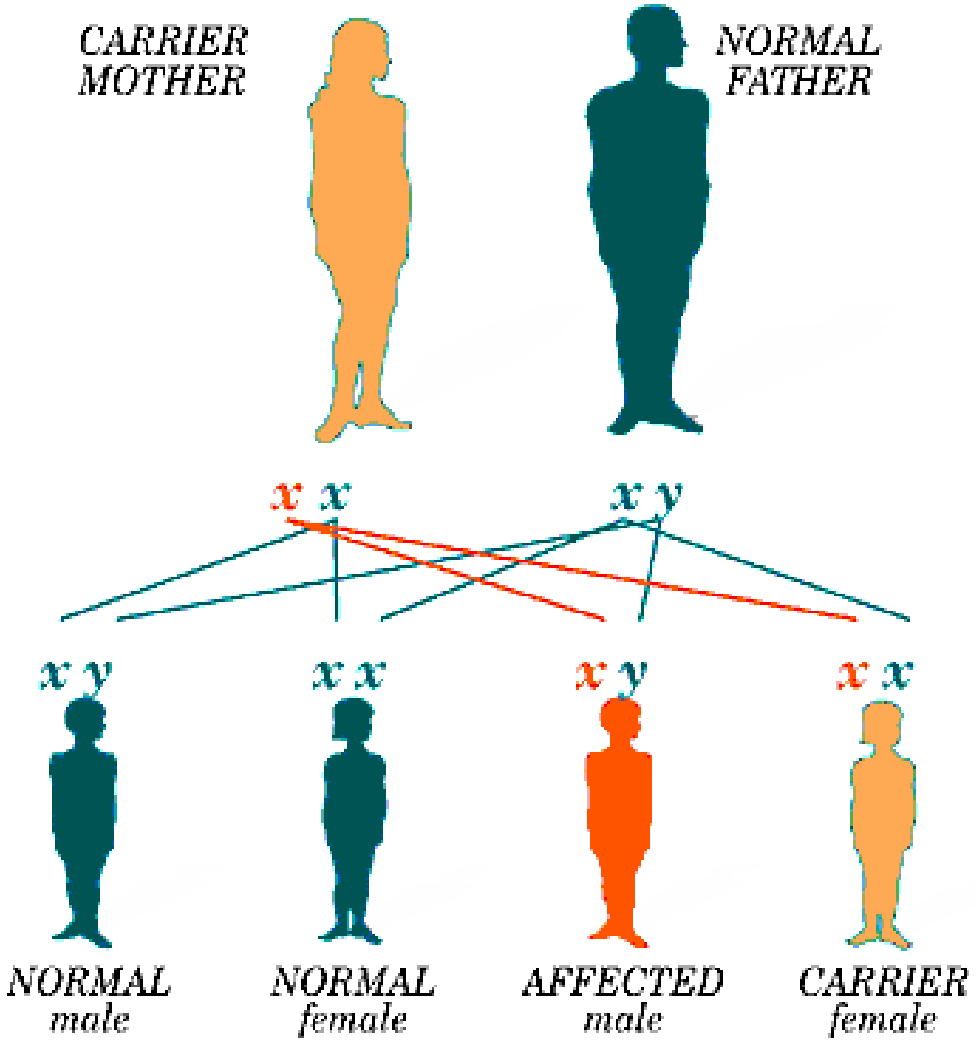
- Males are XY and females are XX
- Two sex chromosomes are very different in size
  Y about ¼ the size of the X
- They are not genetically equivalent
- Traits associated with genes on the X chromosome
  - X-linked
- Traits associated with genes on Y chromosome
  - Y-linked

X Chromosomes Inheritance

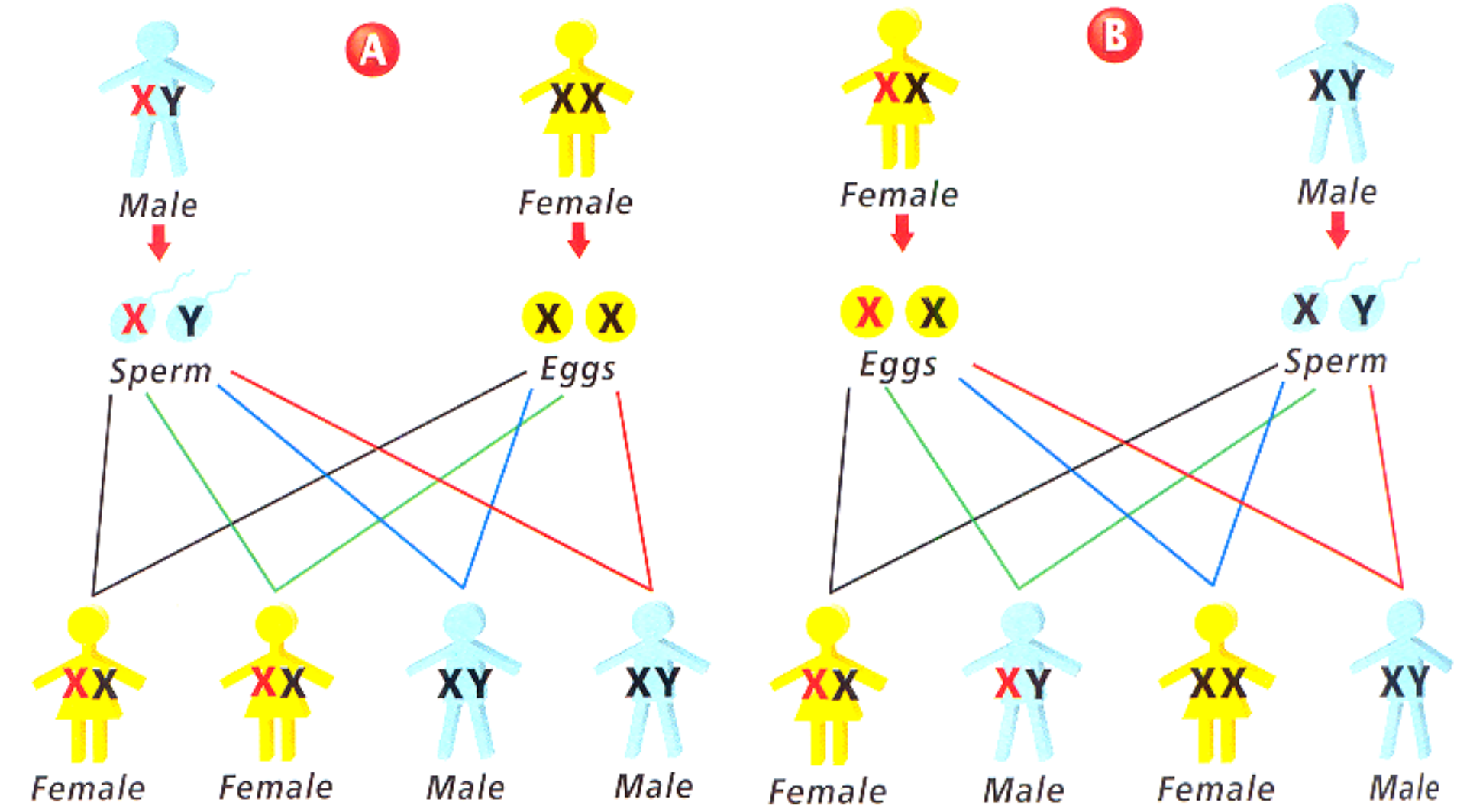


- X-Chromosome = 5% of the human genome Approximately 160 million bp (160Mb).
- > 700 genes identified, most of them are Recessive
- Few of them are Dominant

X-Linked Disorders: Males are at Risk



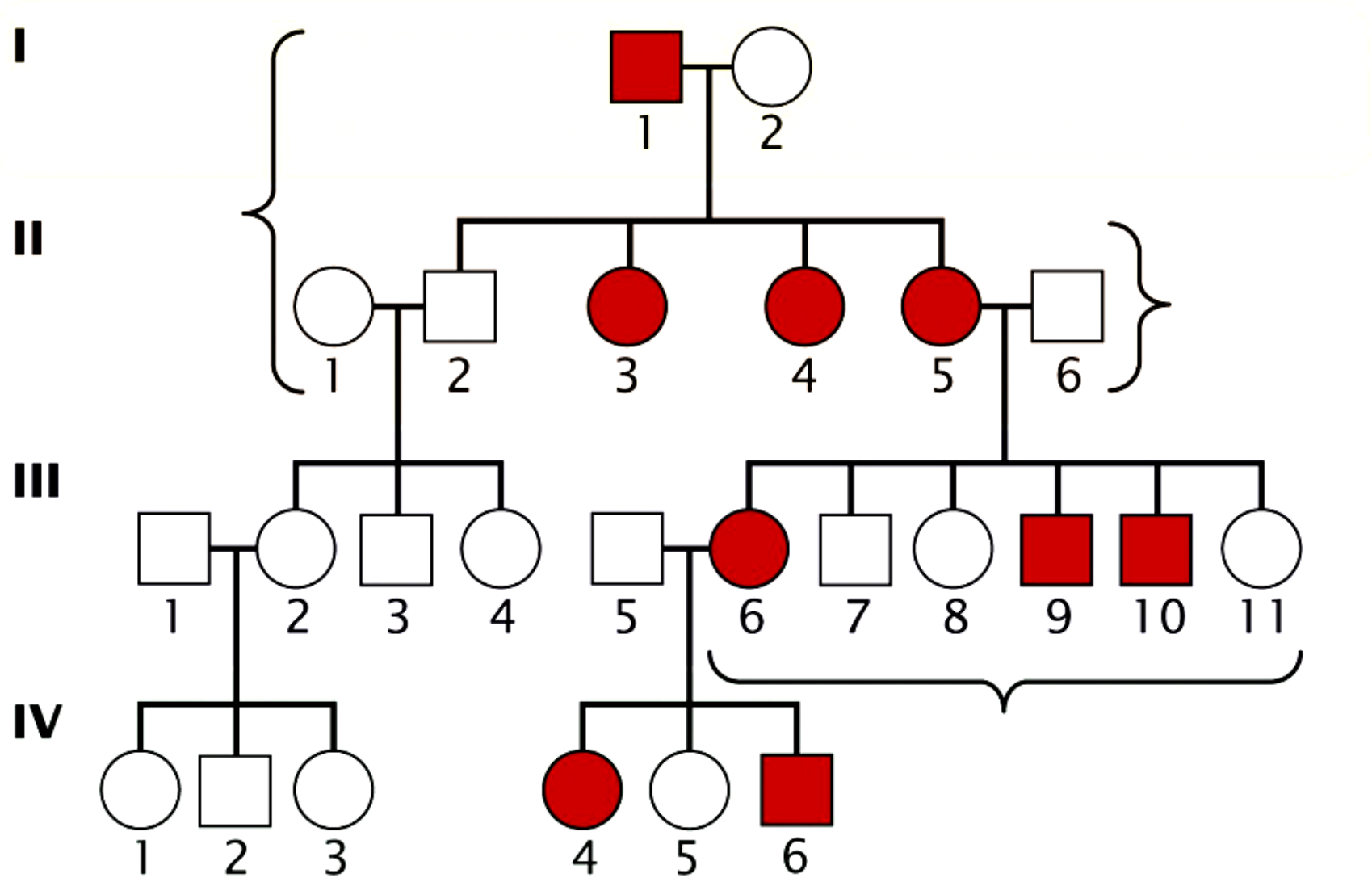
X-linked Inheritance



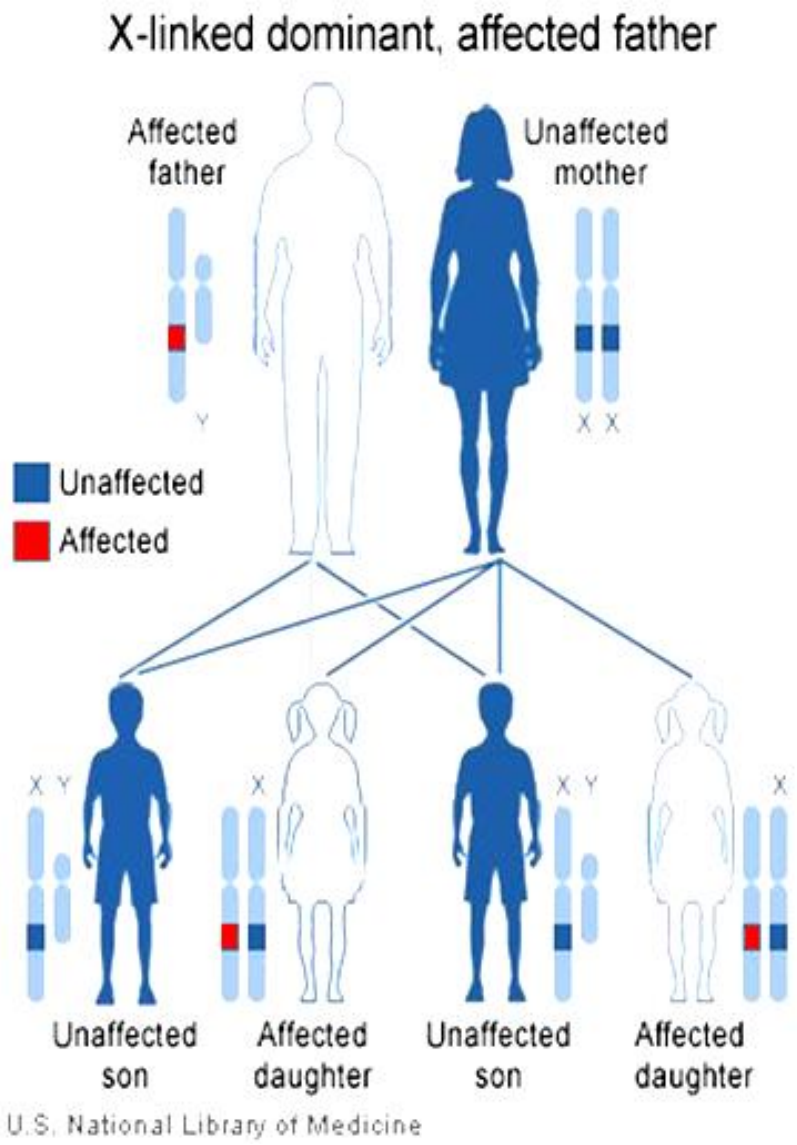
X-linked Dominant Disorders

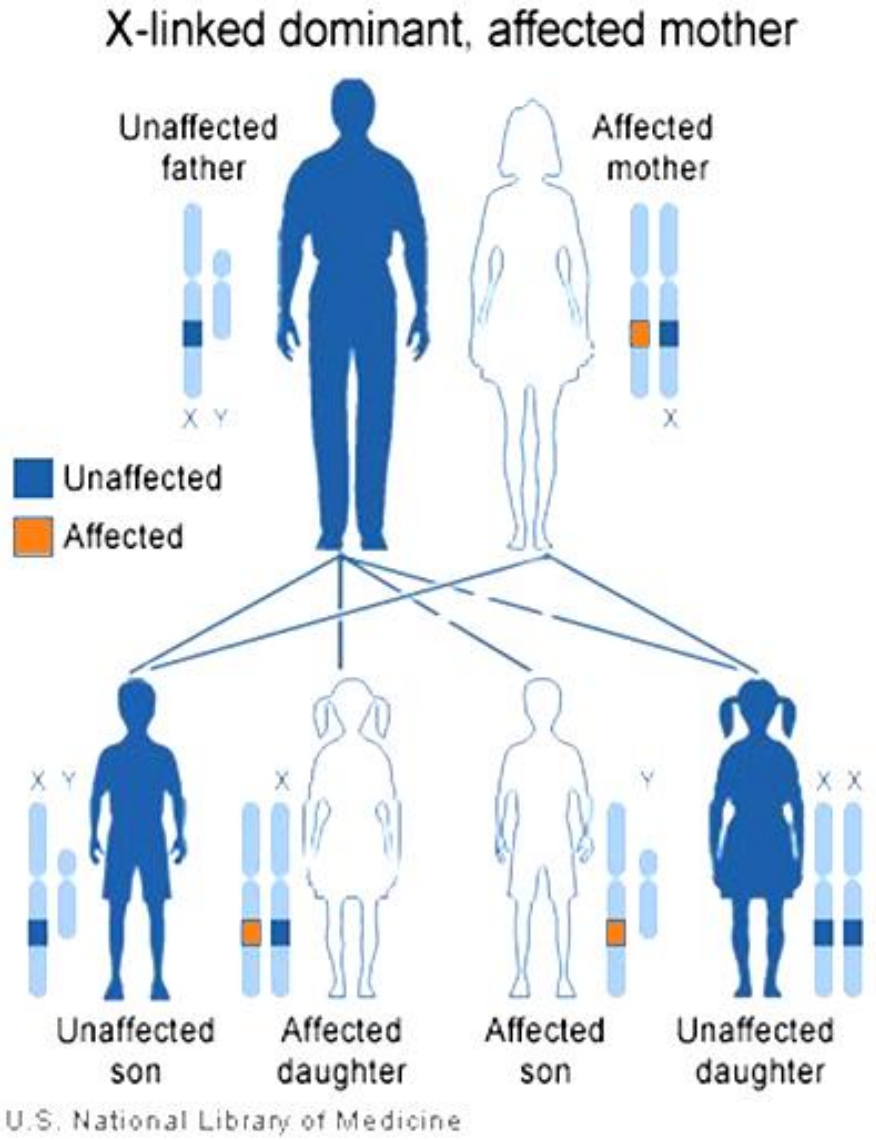
- Affected males will produce all affected daughters, but no affected sons.
- 50% chance that a heterozygous affected female will pass trait to either son or daughter.
- Homozygous females pass on trait to all offspring.
- On average, twice as many females afflicted as males
- Expressed in females with one copy.
- Males are often more severely affected.
- Typically associated with miscarriage or lethality in males.

X-Linked Dominant



X-Linked Dominant Inheritance

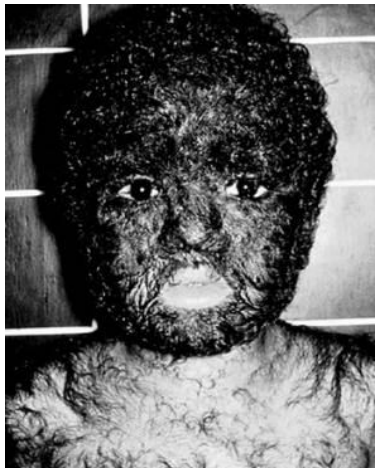


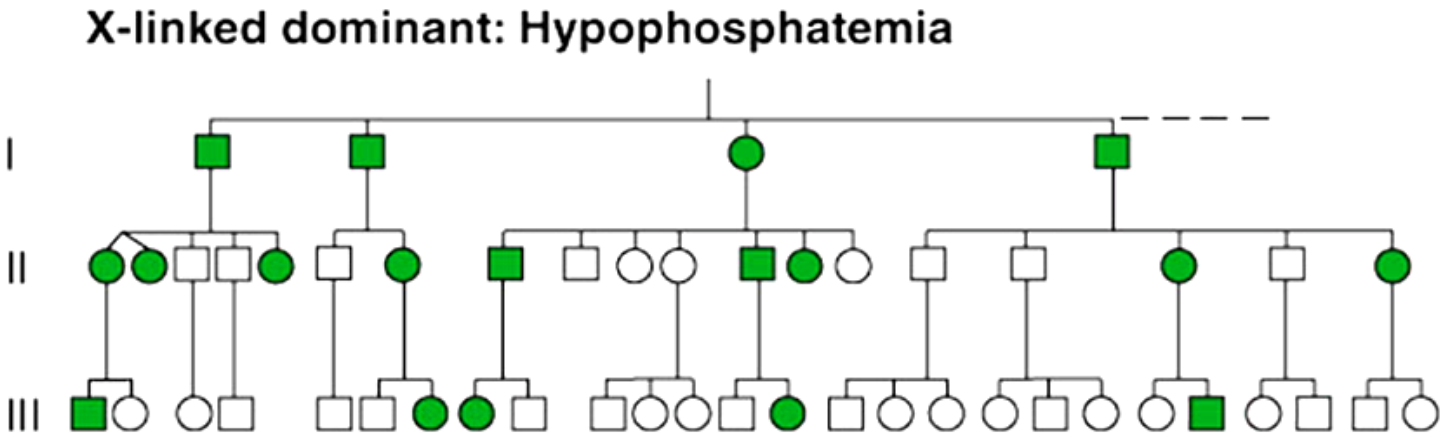


X-Linked Dominant Inheritance

There are very few X-linked dominant traits.

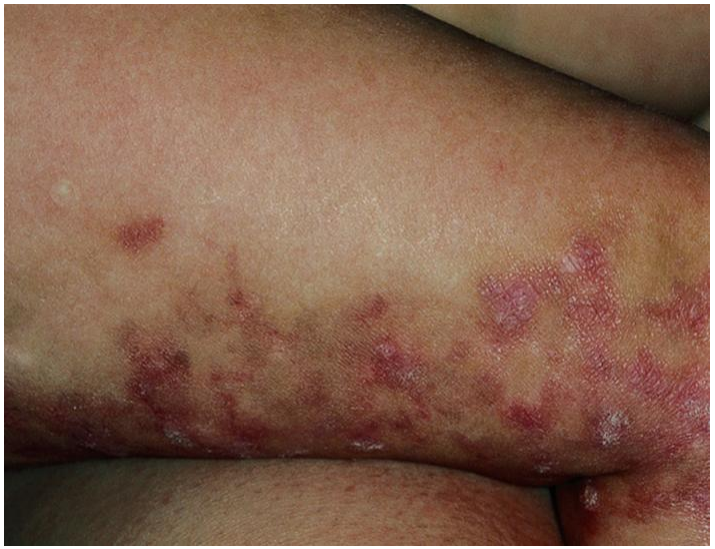
- Dwarfing conditions due to X-linked dominant conditions include another form of chondrodysplasia punctata (X-linked dominant type)
- Incontinentia Pigmenti
- Congenital Generalized Hypertrichosis CGH:
- X-linked hypophoshatemic (Vitamin D-resistant rickets).





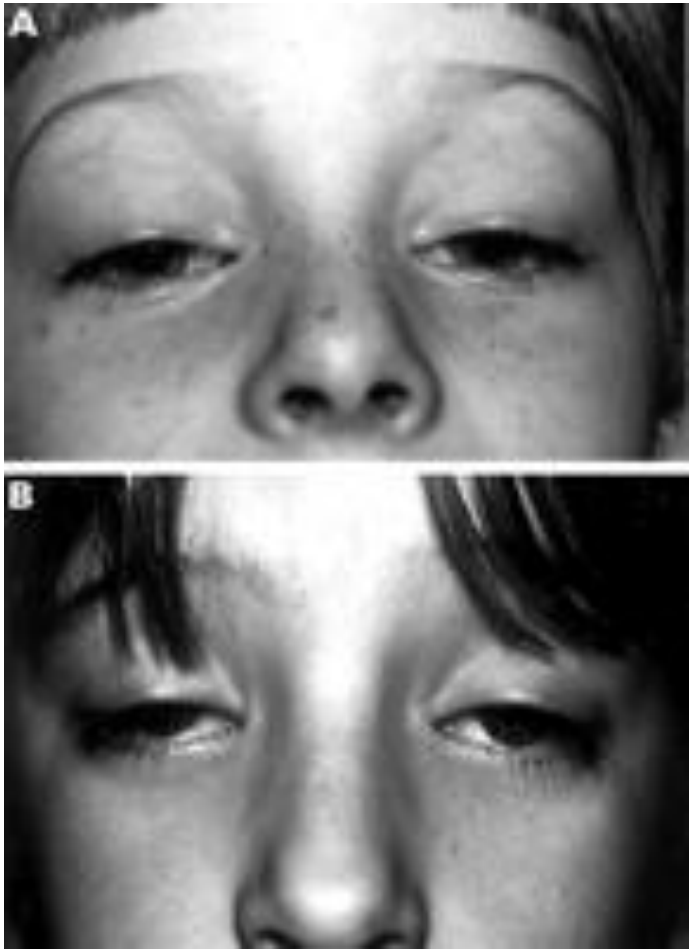
Incontinentia pigmenti

- X-linked dominant trait
- Heterozygous female - pigment swirls on skin, hair and tooth loss, seizures
- Male - death in uterus
- No homozygous females because no males reproduce



X-Linked Dominant Example

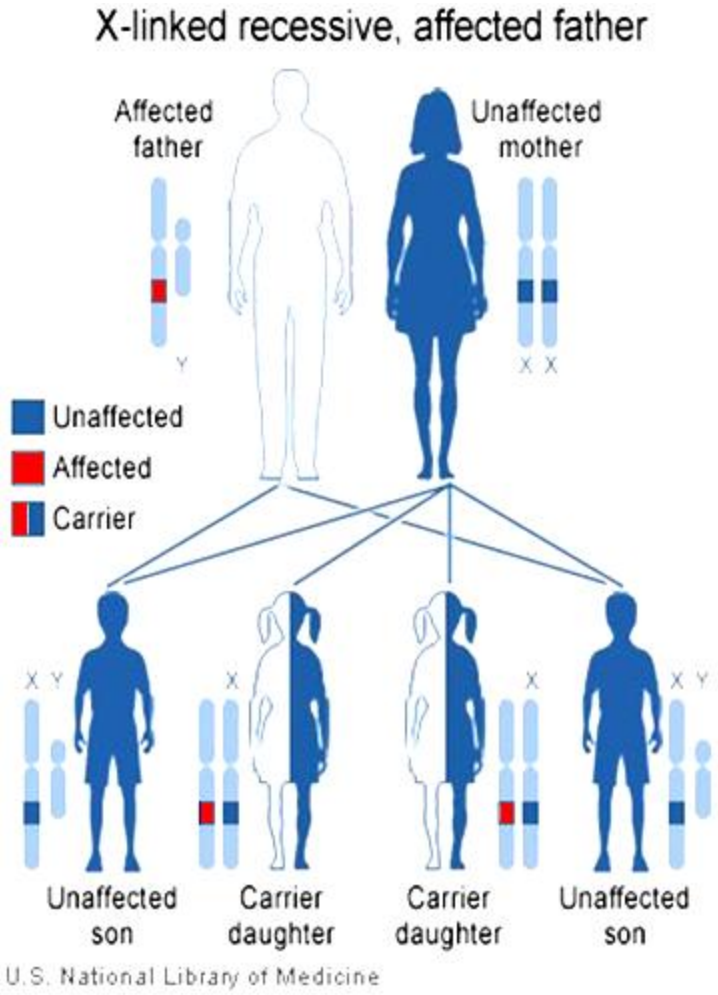
Congenital Bilateral Ptosis: Droopy Eyelids Locus:
Xq24-Xq27.1

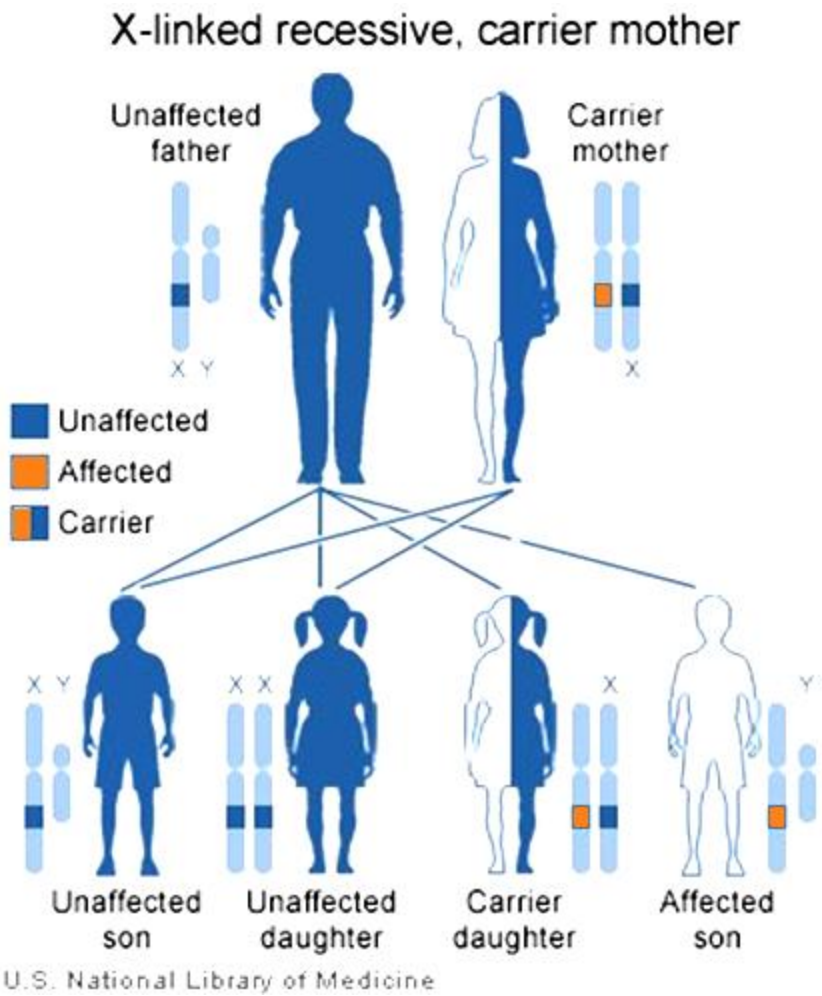


X-linked Recessive Disorders

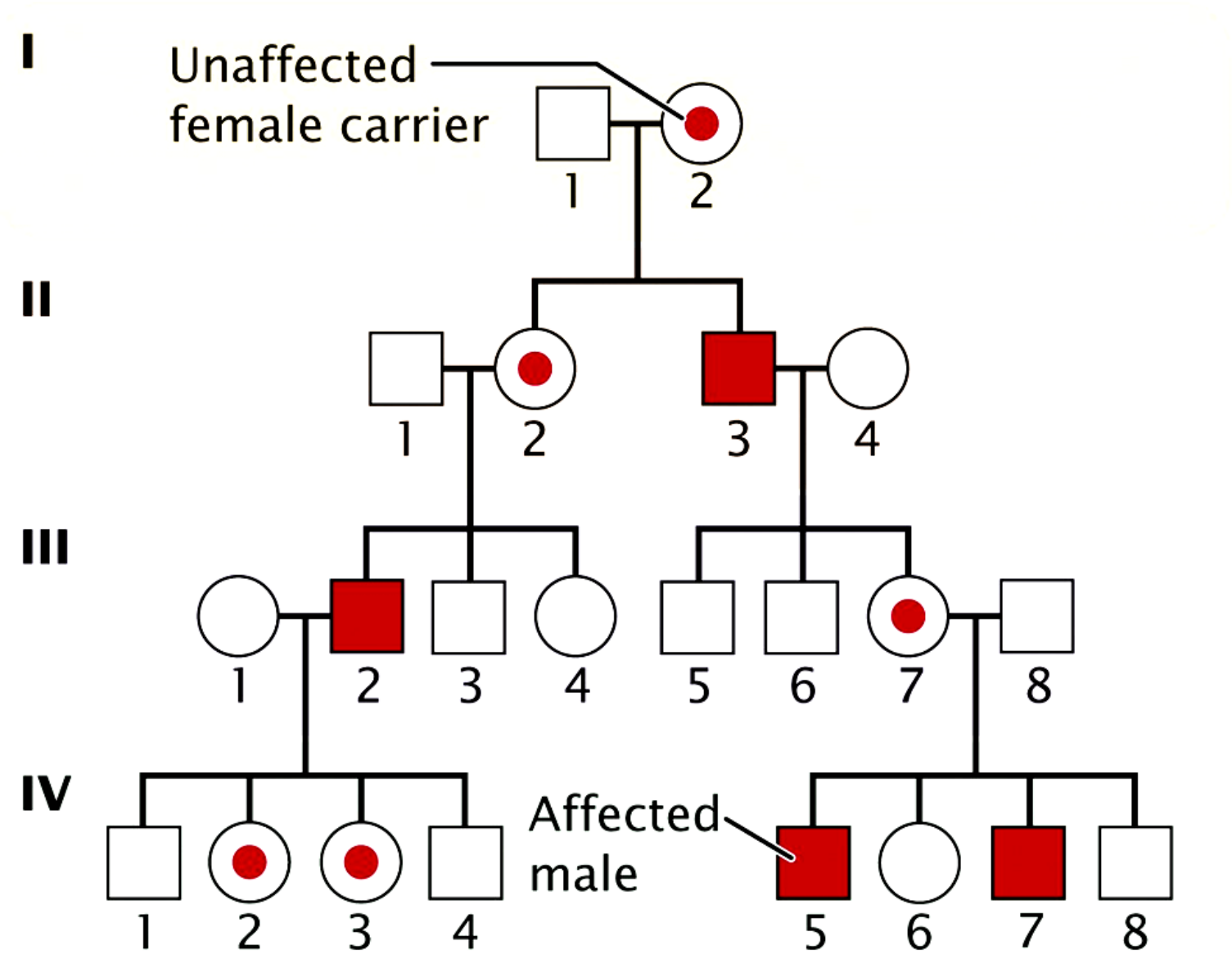
- Abnormal disorder-causing allele is *recessive* and is located on the X-chromosome
- Normal, wild type allele is ***dominant***
- Affects hemizygous males and homozygous females.
- Expressed phenotype much more common in males
- Affected males get the mutant allele from their mothers
- Affected males transmit the mutant allele to all daughters, but not to sons
- Daughters of affected males are usually heterozygous – thus unaffected
- Sons of heterozygous mothers have a 50% chance of being afflicted

X-Linked Recessive Inheritance





X-linked Recessive



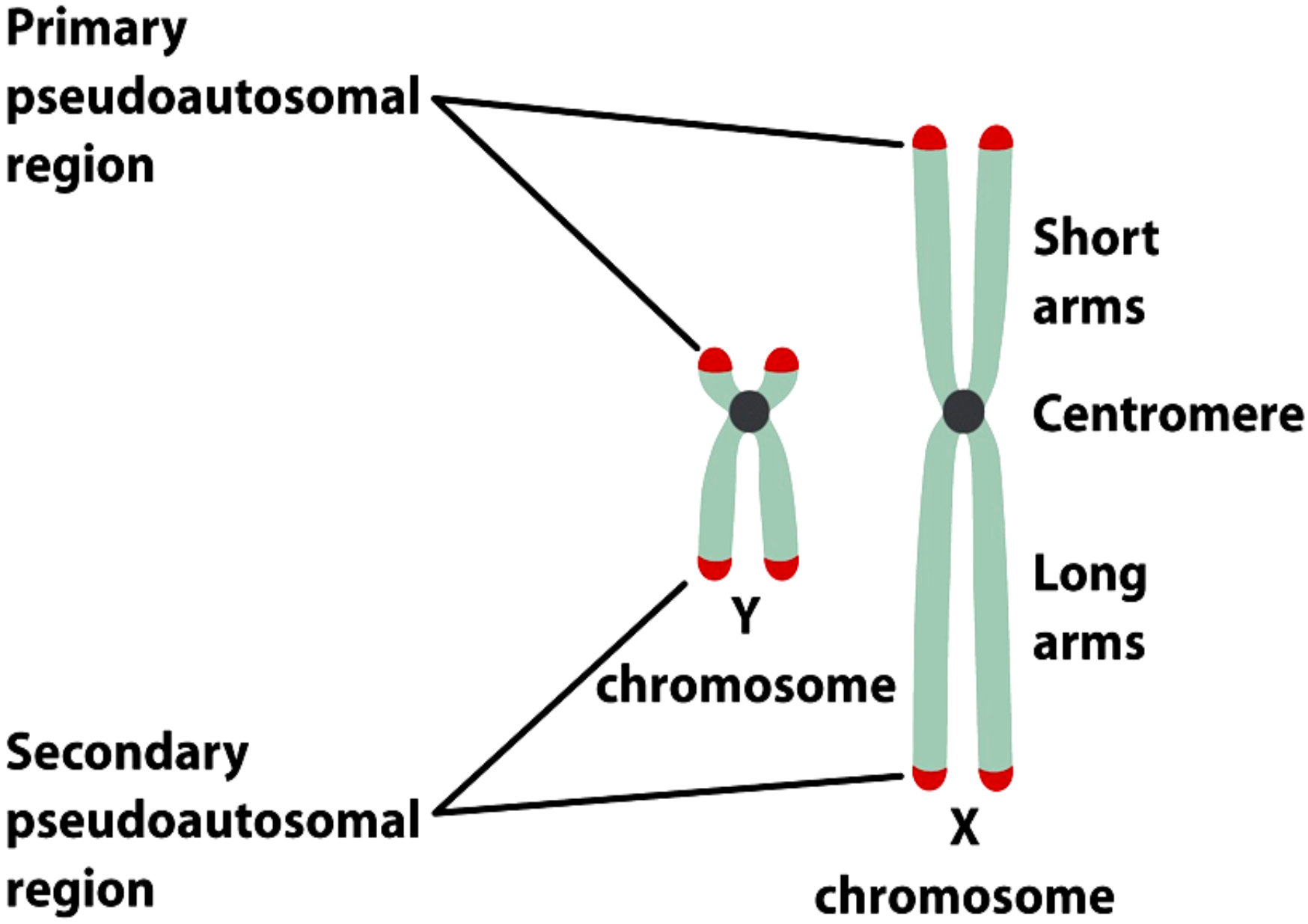
X-Linked Recessive Inheritance

Pitfalls in Recognizing X-Linked Recessive Inheritance and Providing Genetic Counseling

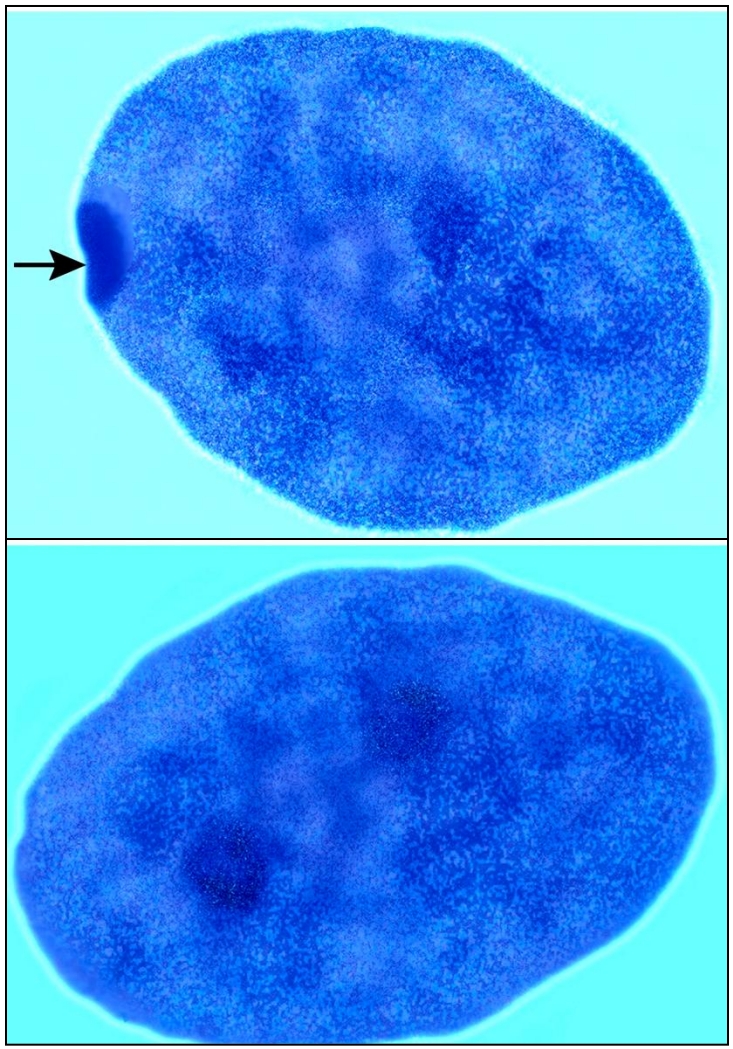
- **Small Families.** Small family size and few male children may make the pattern of an X-linked recessive disorder difficult to diagnose.
- **New Mutation.** An affected male may be the first person in the family with the condition, due to a mutation arising for the first time . sperm, egg or embryo
- **Germline Mosaicism.** A new mutation may arise in testis or ovary, resulting in a parent who can pass on the condition or the carrier state to children, without being either affected (in the case of a male parent) or a carrier (in the case of a female parent).

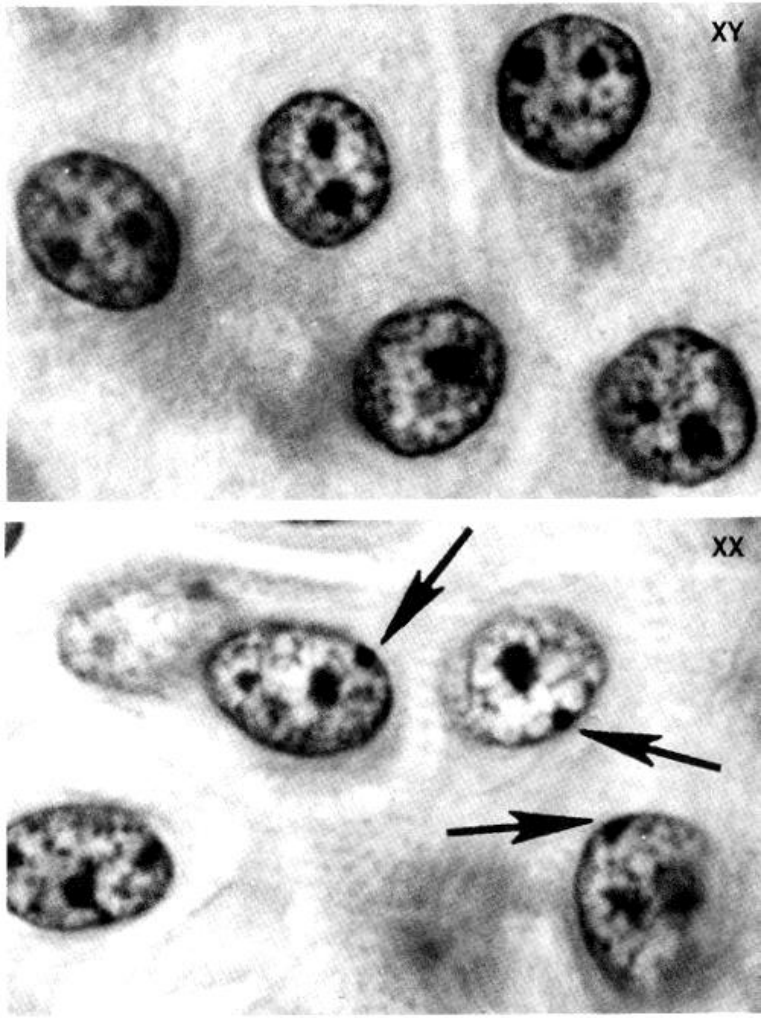
X-linked Recessive Disorders

TRAIT	Phenotype
• Adrenoleukodystrophy	Atrophy of the adrenal gland; maternal Deterioration; death 1-5 Y after onset
• Color Blindness	Green (60-75%); Red (25 – 40%)
• Fabry disease	MD α-Galactozidase A deficiency Cardiac and Renal , Death
• G-6-P-D	Benign, can cause sever fetal anemia Due to certain food and drugs
• Hemophilia A	Lack of factor VIII
• Hemophilia B	"Christmas Disease" lack of factor IX
• Ichethiosis	Skin disorder causing large, dark scales on extremities
• Lynch-Nyhan S	MD Hypoxanthine guanine Phosphoribisyl transferase (HGPRT) Deficiency: MR, Self-mutilation Early death
• Muscular dystrophy	Many types


Primary pseudoautosomal region
Short arms
Centromere
Long arms
Y chromosome
Secondary pseudoautosomal region
X chromosome

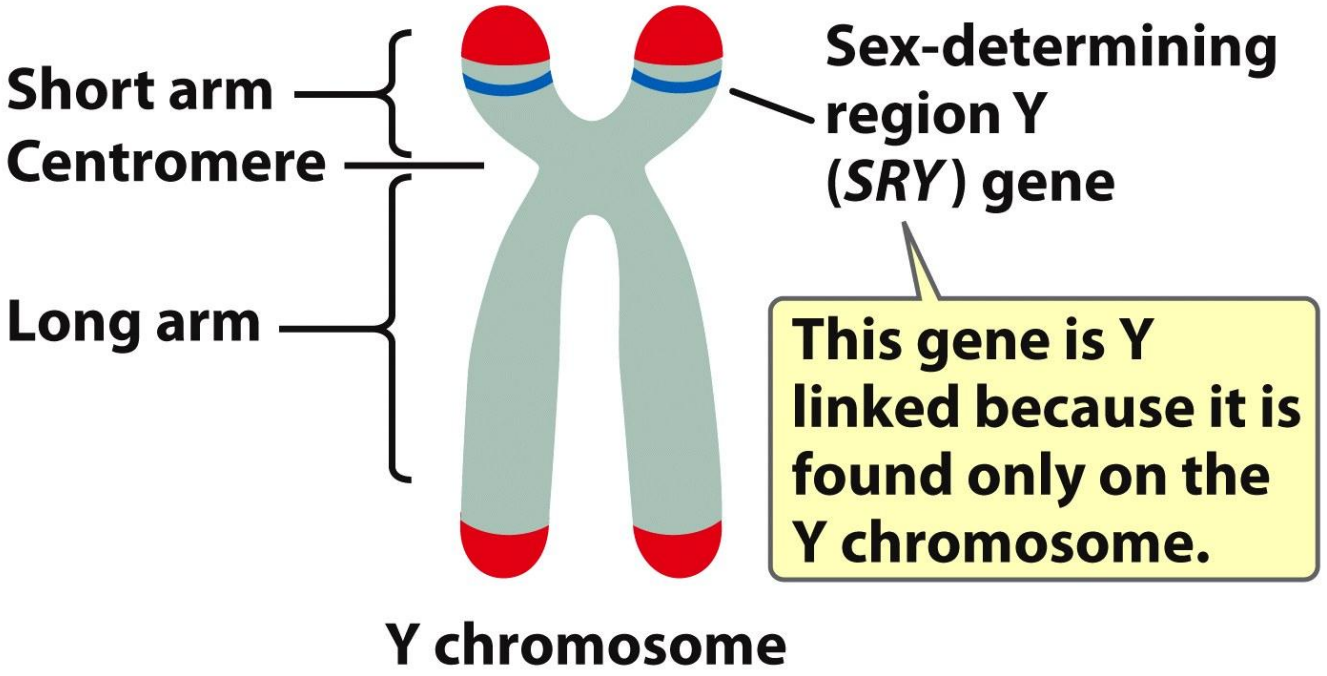
Dosage Compensation





The male-determining gene in humans

- Sex-determining region Y (SRY) gene
- Androgen-insensitivity syndrome
  - Caused by the defective androgen receptor

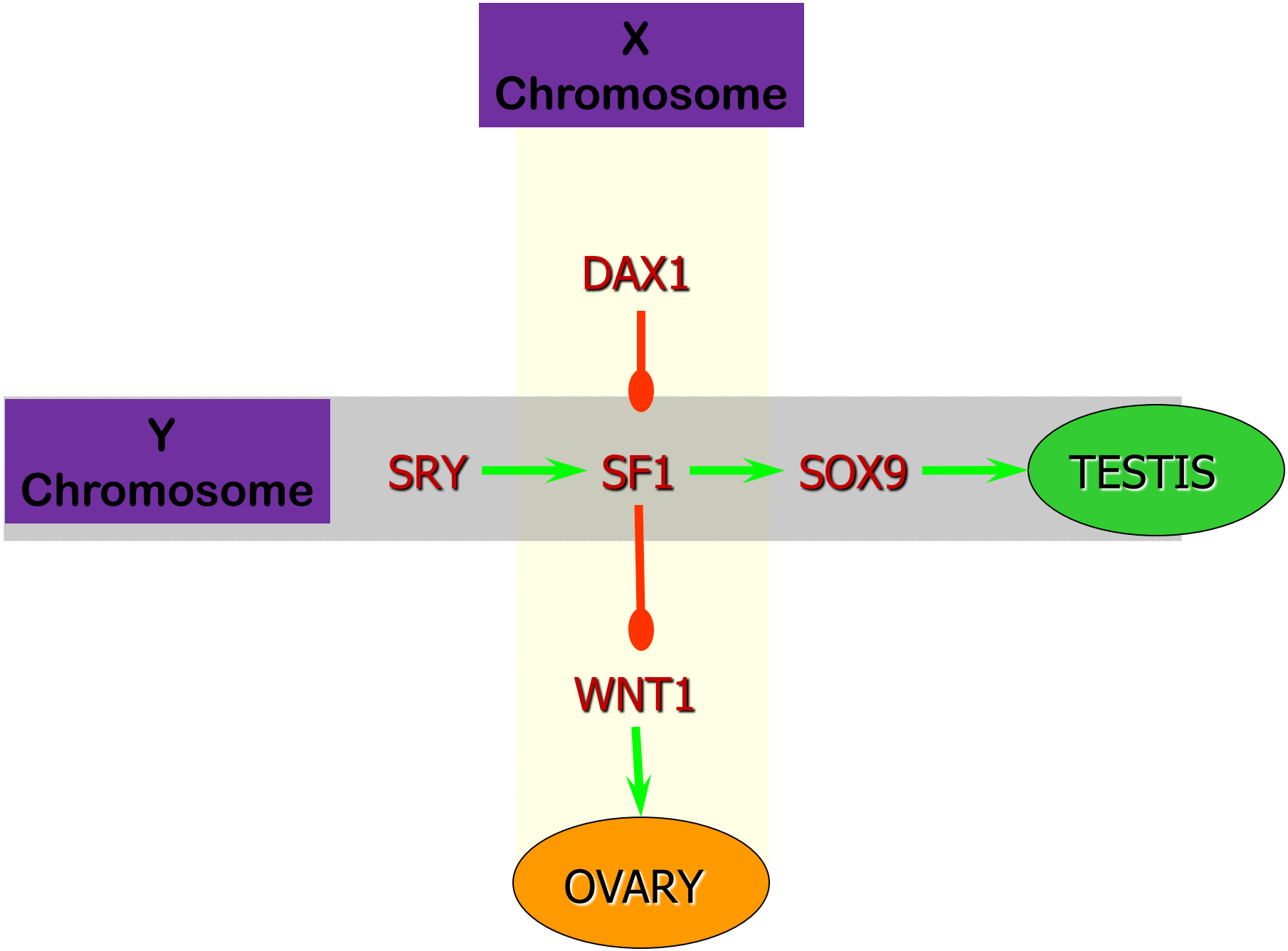


Defining Sex

- **Chromosomal sex**
- **Gonadal sex**
- **Phenotypic sex**
- Formation of male or female reproductive structures depends on
  - Gene action
  - Interactions within the embryo
  - Interactions with other embryos in the uterus
  - Interactions with the maternal environment

Sex Differentiation

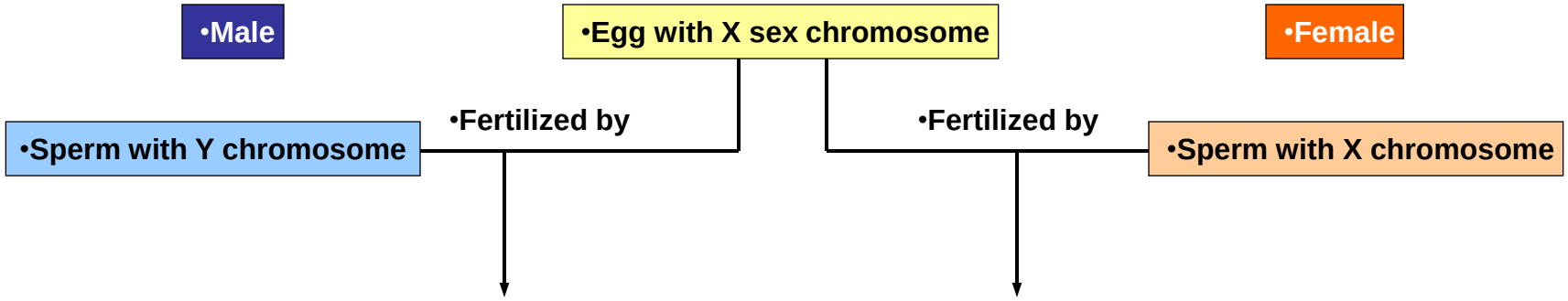
- In early embryo there are two internal duct systems
  - Wolffian (male)
  - Müllerian (female)
- At 7 weeks, developmental pathways activate different sets of genes
- Cause undifferentiated gonads to develop as testes or ovaries
- Determine the gonadal sex of embryo

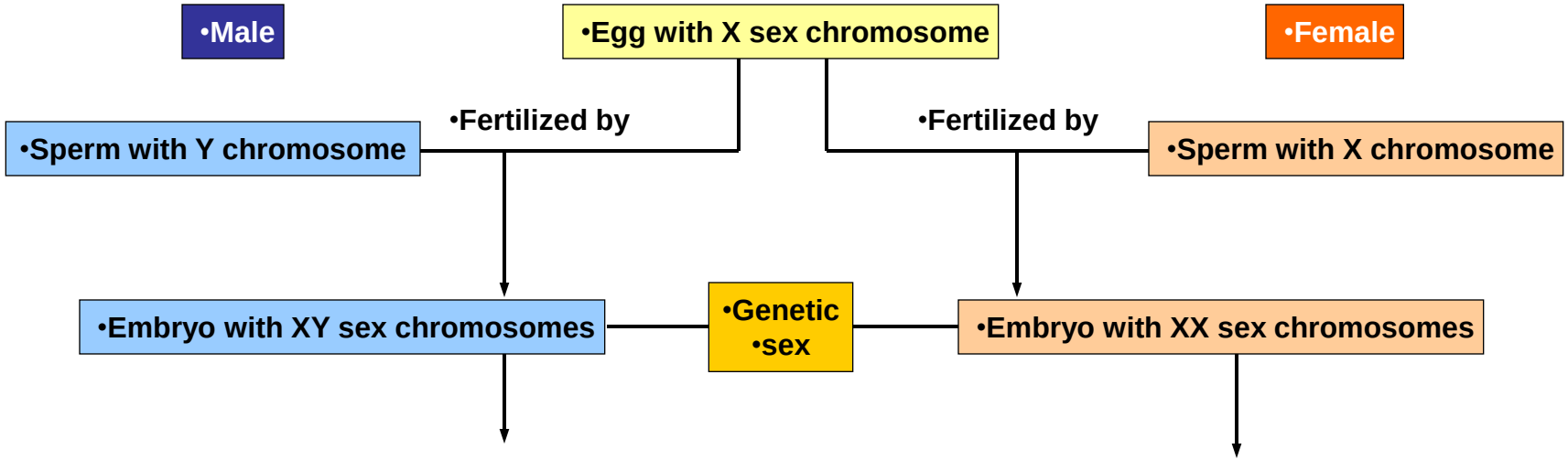

X
Chromosome
DAX1
Y
Chromosome
SRY
SF1
SOX9
TESTIS
WNT1
OVARY

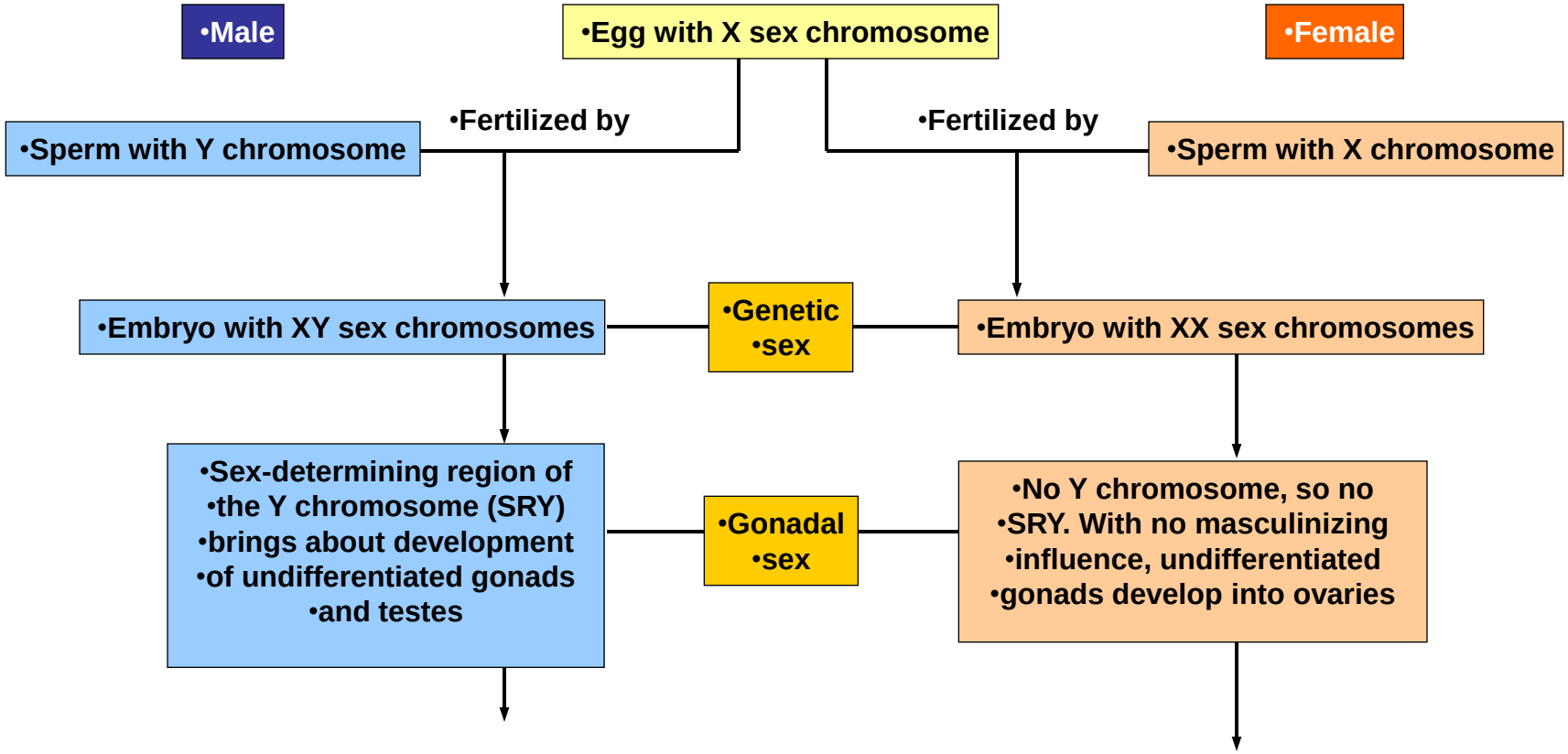
•Male

•Egg with X sex chromosome

•Female


•Male
•Egg with X sex chromosome
•Female
•Fertilized by
•Fertilized by
•Sperm with Y chromosome
•Sperm with X chromosome


•Male
•Egg with X sex chromosome
•Female
•Fertilized by
•Fertilized by
•Sperm with Y chromosome
•Sperm with X chromosome
•Embryo with XY sex chromosomes
•Genetic
•sex
•Embryo with XX sex chromosomes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•the Y chromosome (SRY)
•brings about development
•of undifferentiated gonads
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•Gonadal
•sex
•No Y chromosome, so no
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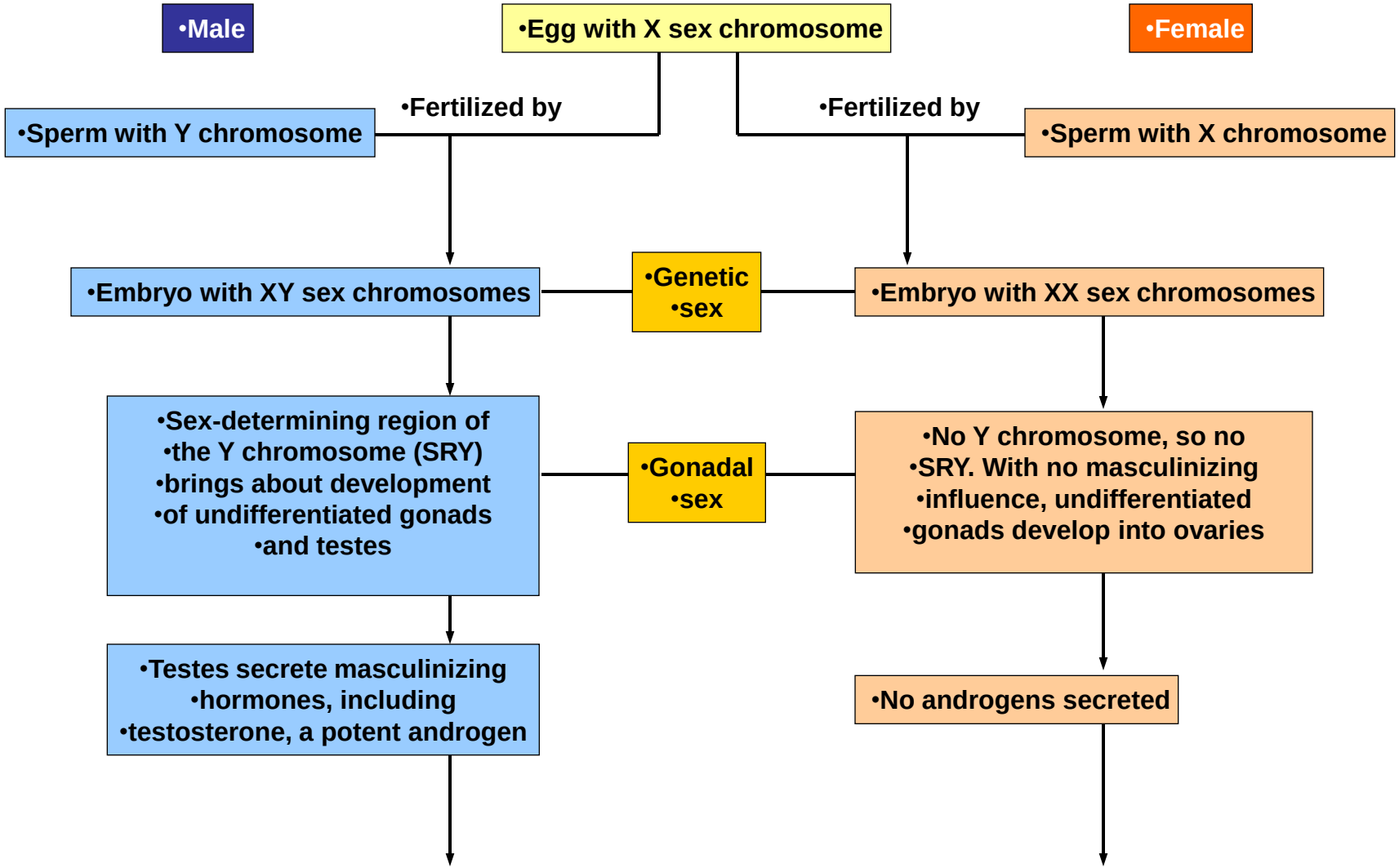
•gonads develop into ovaries


•Male
•Egg with X sex chromosome
•Female
•Fertilized by
•Fertilized by
•Sperm with Y chromosome
•Sperm with X chromosome
•Embryo with XY sex chromosomes
•Genetic
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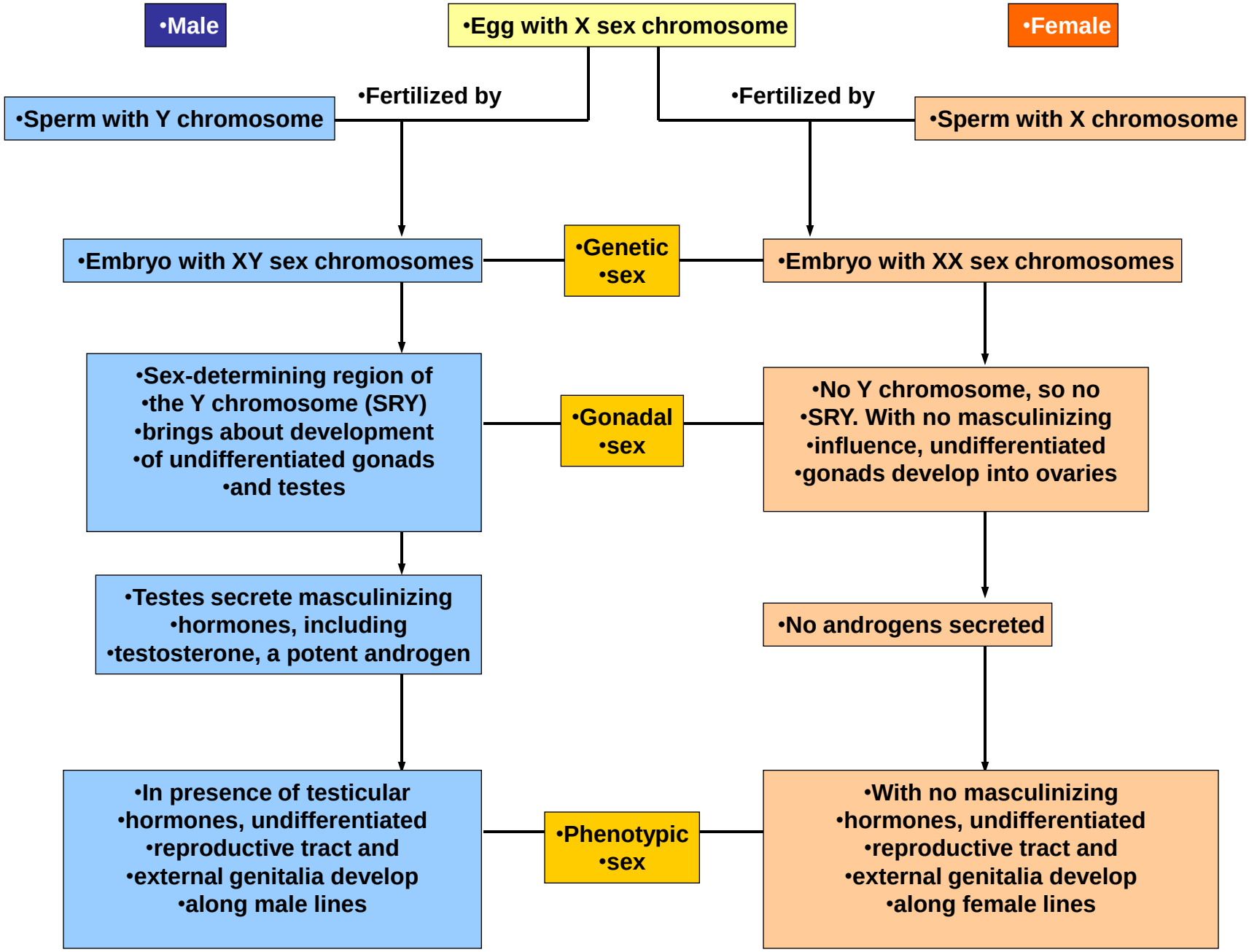
•influence, undifferentiated
•gonads develop into ovaries
•Testes secrete masculinizing
•hormones, including
•testosterone, a potent androgen
•No androgens secreted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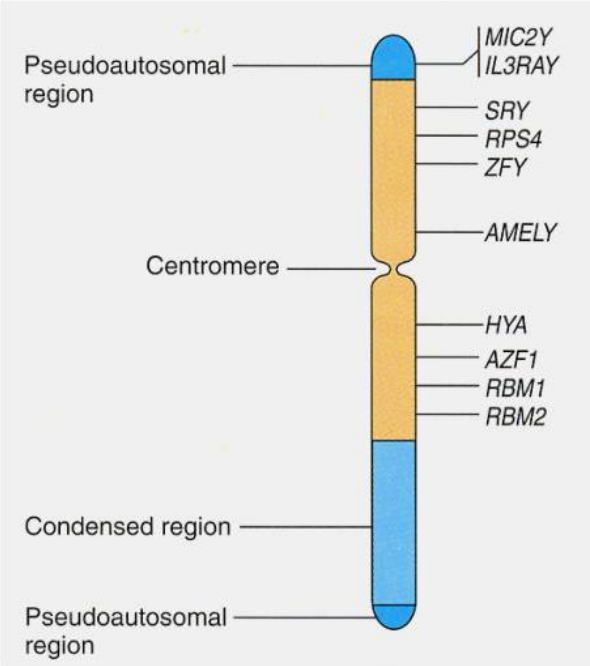
•influence, undifferentiated
•gonads develop into ovaries
•Testes secrete masculinizing
•hormones, including
•testosterone, a potent androgen
•No androgens secreted
•In presence of testicular
•hormones, undifferentiated
•reproductive tract and
•external genitalia develop
•along male lines
•Phenotypic
•sex
•With no masculinizing
•hormones, undifferentiated
•reproductive tract and
•external genitalia develop
•along female lines

Mutations that Alter Phenotypic Sex

- **Hemaphrodites**
  - Have both male and female gonads
- **Androgen insensitivity**
  - XY males become phenotypic females
- **Pseudohermaphroditism**
  - XY males at birth are phenotypically female; at puberty develop a male phenotype

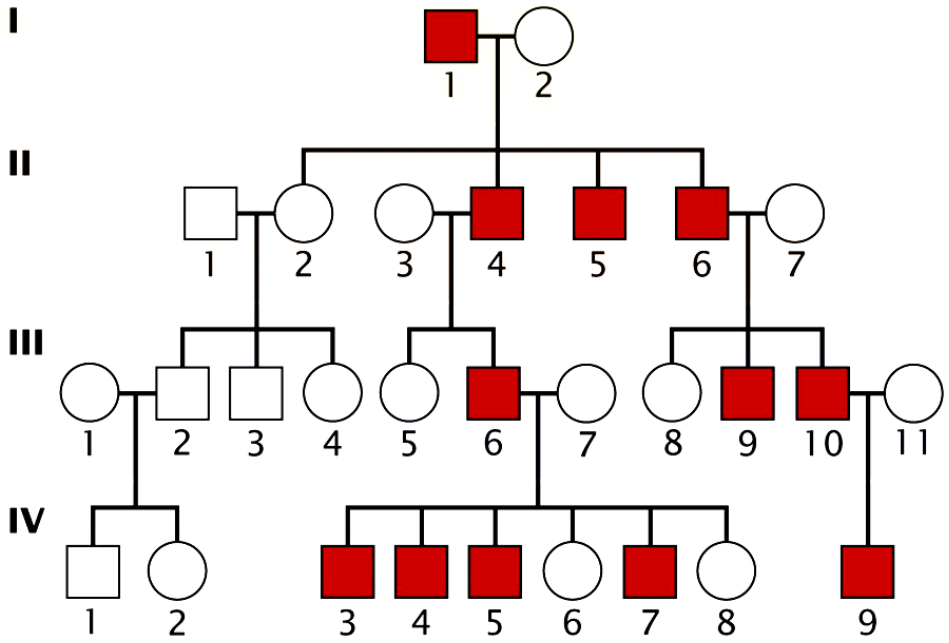
Y Chromosome Inheritance

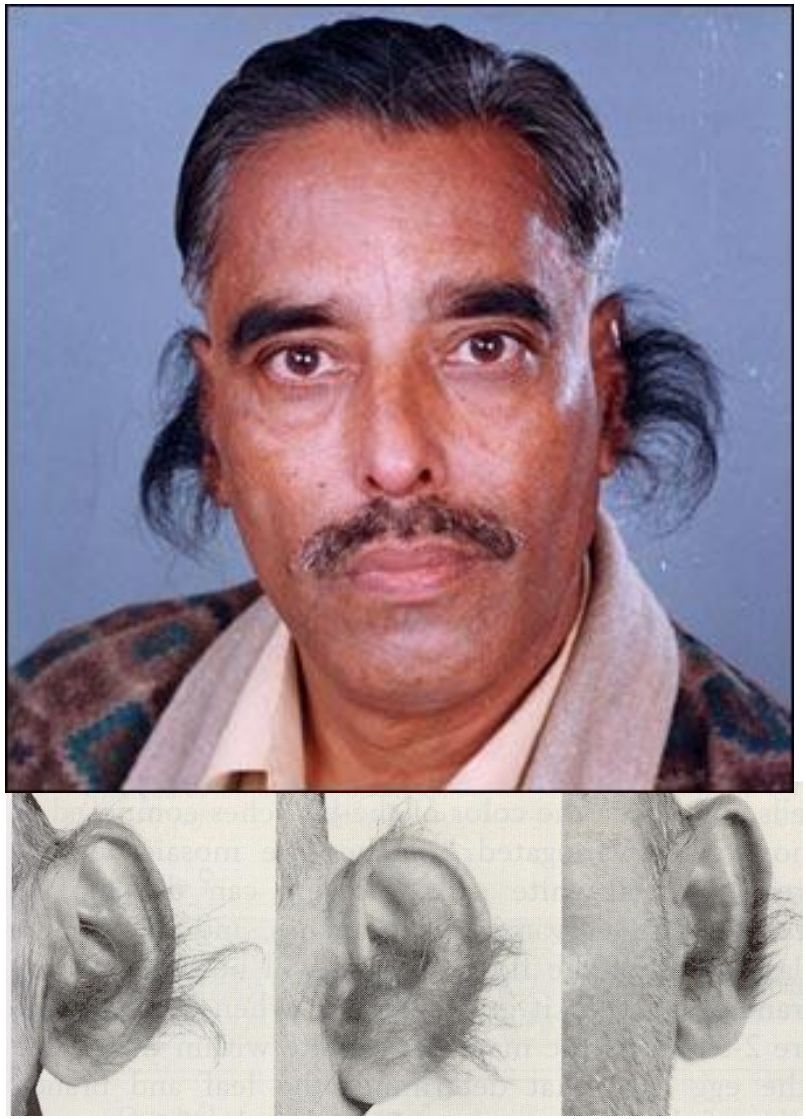
- Y-Chromrosome = 70Mb
- Few dozen genes **(Holandric)** are found on Y
- Male differentiation genes
- Testis-specific spermatogenesis factor
- Minor Histocompatibility genes (HY)
- Several housekeeping genes
- Transmission strictly from father to son



Y-Linked Traits

HYPERTRICHOSIS PINNAE AURIS (Hairy ears),

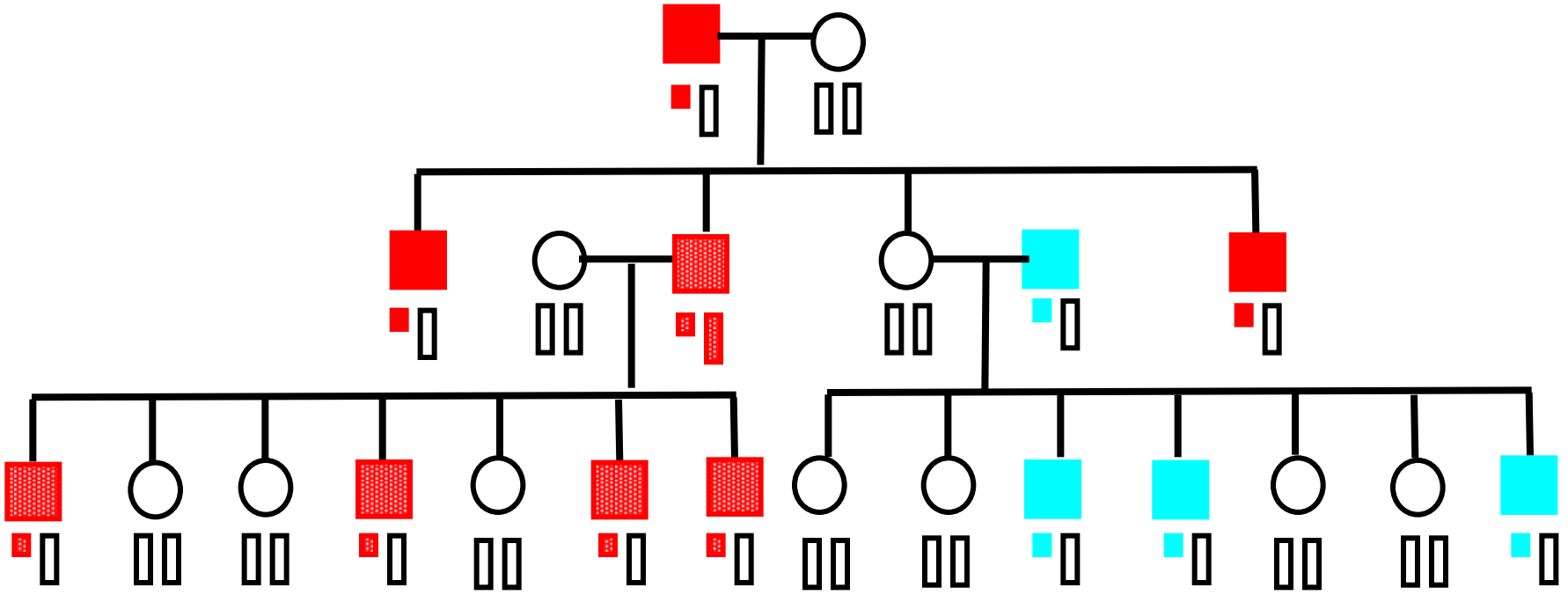




Can happen later in life.

Y-linked

The Y chromosome serves as a paternal marker through history



- DNA mutations on the Y can serve as markers for the male lineage

Y-linked traits

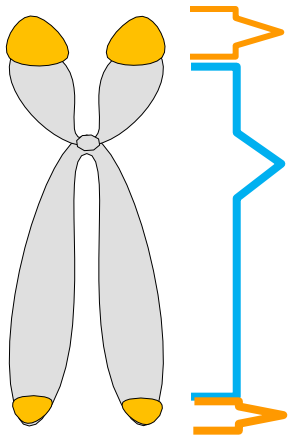
- Related to genes unique to the Y chromosome
  - are present only in males (no afflicted females)
  - passed directly from fathers to sons
    hemizygous – always expressed

- Very rare - only about 3 dozen Y-linked traits known
  - Often associated with infertility

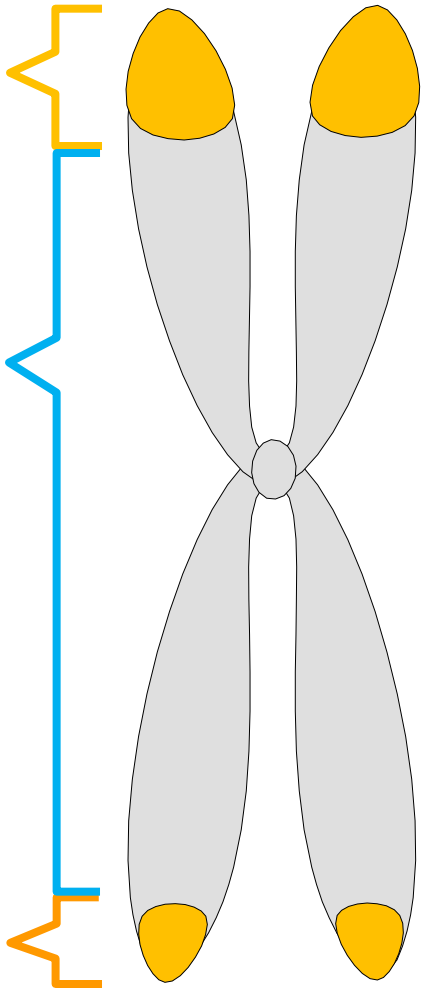
- One important gene

  - TDF – testis determining factor
  - Also known as SRY
  - Sex determining region of the Y chromosome

Organization of Human Sex Chromosomes



Length: 50,286,555 bp
Gene Count: 160



Many genes escape inactivation

Xce – X chromosome inactivation center

Length: 153,692,391 bp
Gene Count: 1228

Sequence Homologies of the X and Y Chromosomes

- 15% ox X Chr. Escape Inactivation
- Tips of P and q arms escape inactivation
- Steroid sulfatase
- Xg blood group
- Kallman Syndrome
  (hypogonadism inability to perceive odor)
- Housekeeping genes

PAR regions

PAR = pseudo autoszomal region

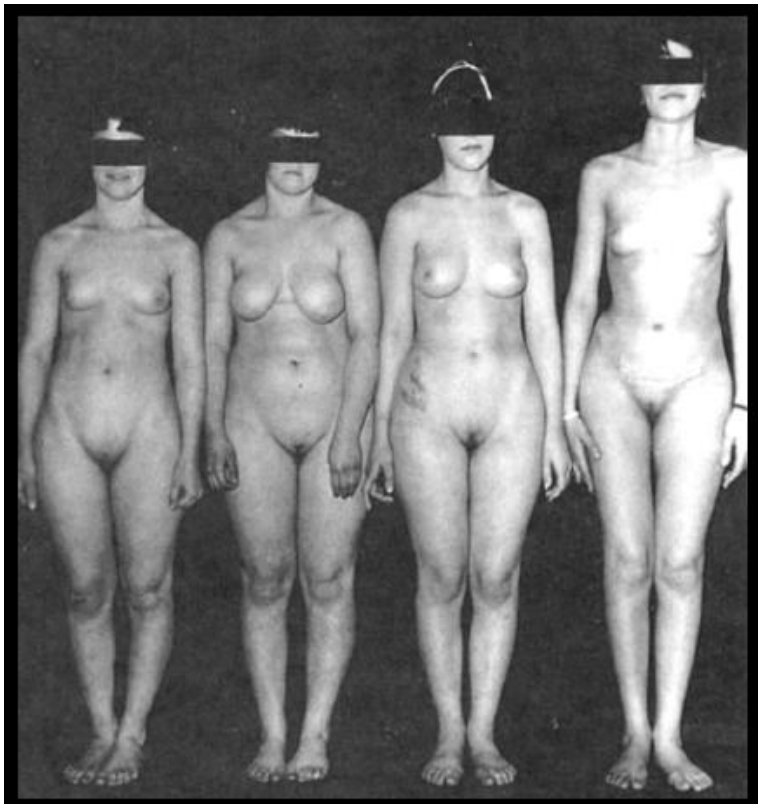
- **Never gets inactive**
- **Telomeric position on the two sex chro.**
- **PAR1 – 2.6 Mb; PAR2 – 320 kb**
- **Provide choice for partial meiotic pairing of X-Y chrs**
- **„Obligatory crossing over" in PAR1 (e.g. Xg blood group, IL-3 receptor)**

Frequent problems resulting disfunctions in sexual differentiation

- mutations of SRY
- disturbed biosynthesis of androgens
- mutations of androgen receptor
- errors of AMH
- XY/XO mosaicism
- Wnt and WT-1 mutations (differentiation of gononephrotom)

Testicular feminisation

Genotype: XY
Testosteron in sera is normal
Testis in the abdominal cavity
Feminine statue

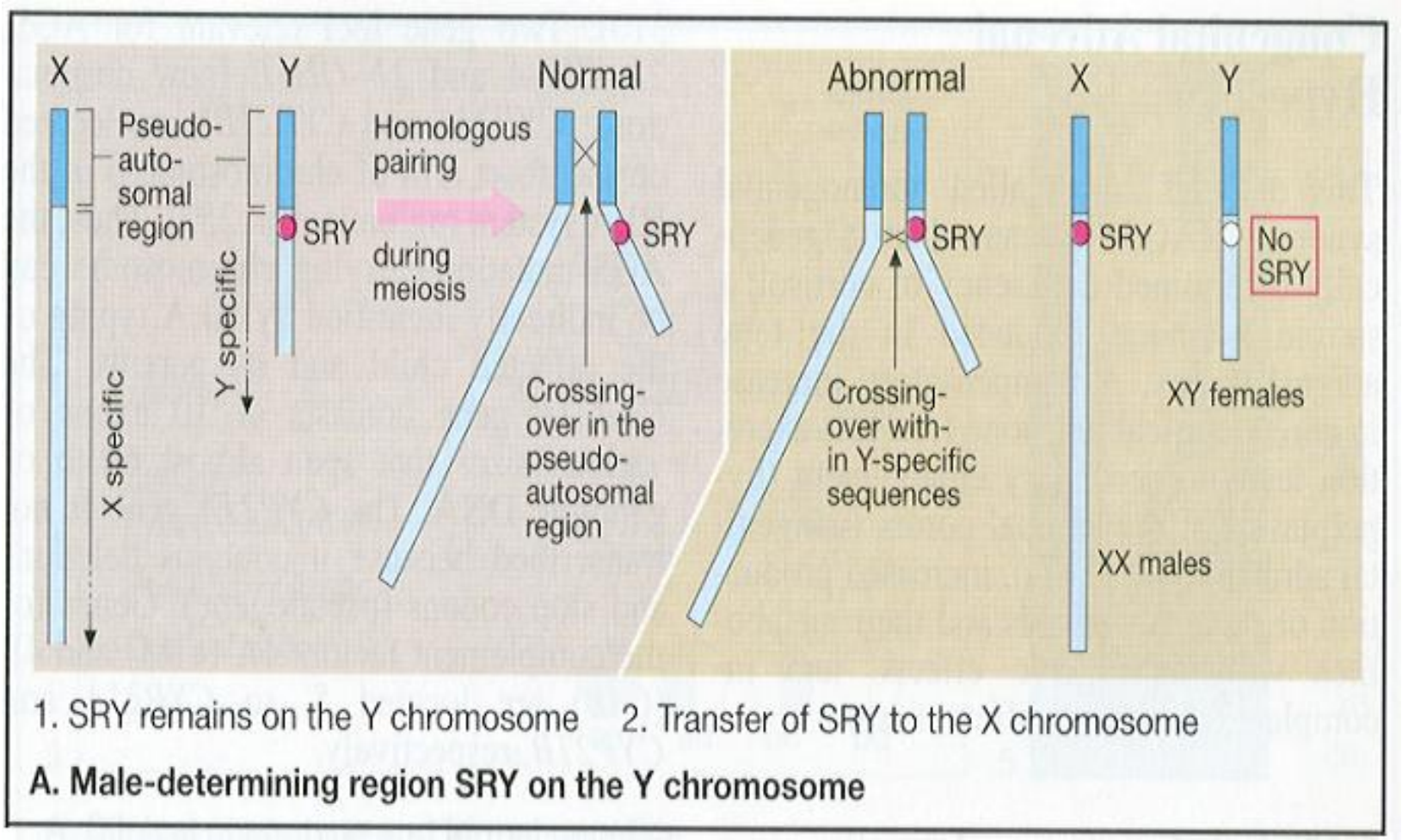


Reasons:

- Error of differentiation after testosteron action?
- Testosteron can influence development of Wolff-tubule at differentiation?

Reason: MUTATION OF TESTOSTERON RECEPTOR

Male-Determining Region SRY on the Y Chromosome



Sex-Limited, Sex-Influenced

- **Sex-Limited:** Autosomal genes
  - Affects a structure/process/behavior found only in one sex due to anatomical differences, Inherited Uterine or Testicular defects

- **Sex-Influenced:** Autosomal genes

  Baldness, Dominant in males and recessive in females, carrier females have thinner hair

X-Chromosome Inactivation

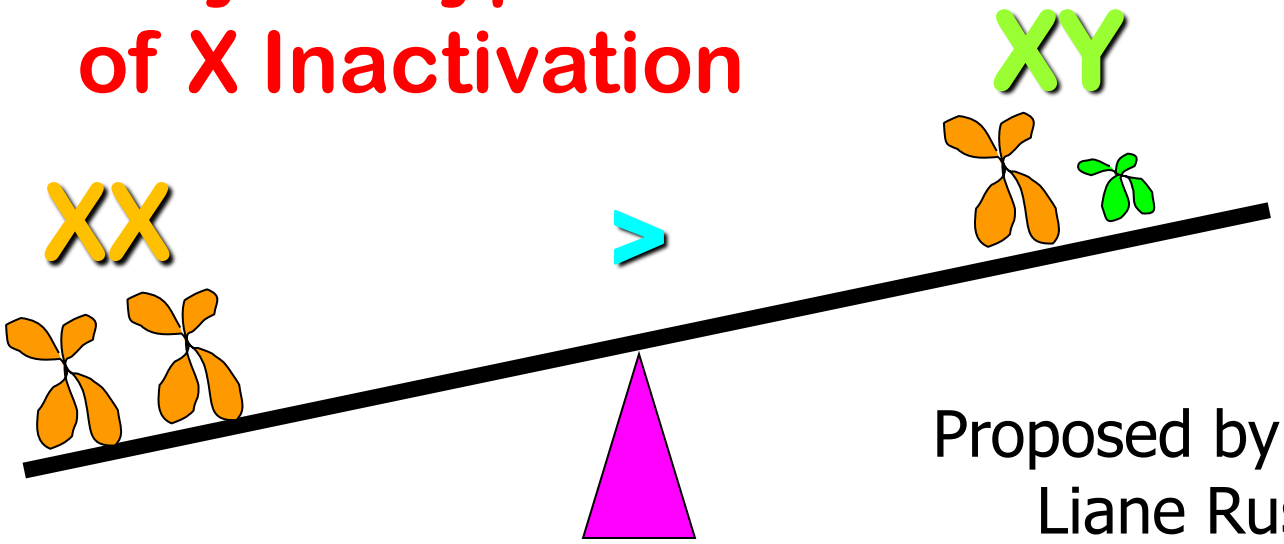
The Lyon Hypothesis of X Inactivation

- Proposed by Mary Lyon and Liane Russell (1961)

- Which X is inactivated? Inactivation of X chromosome occurs randomly in somatic cells during embryogenesis

- Progeny of cells all have same inactivated X chromosome as original, creating mosaic individual

The Lyon Hypothesis of X Inactivation



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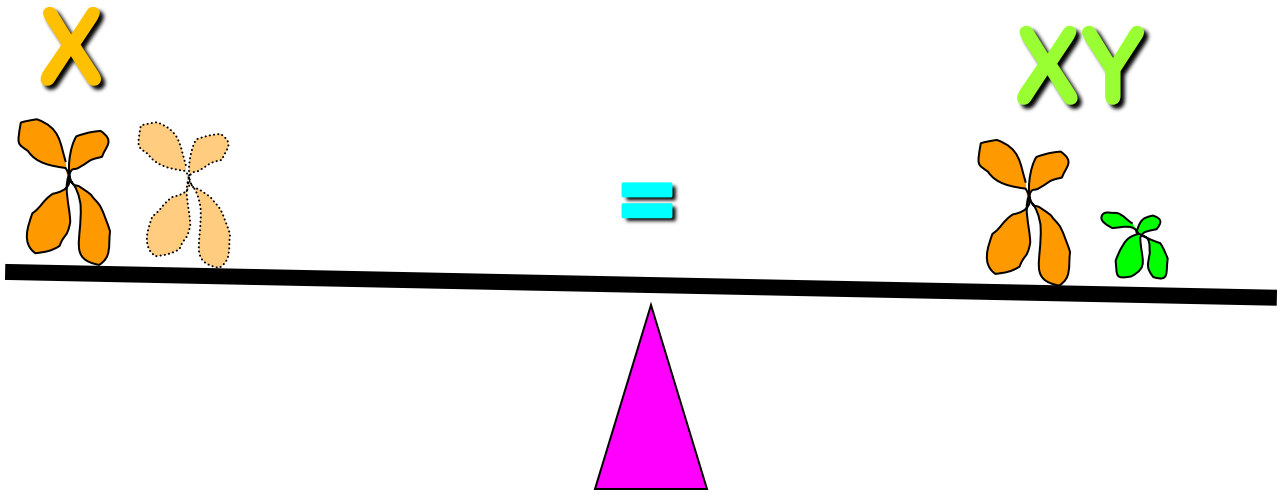


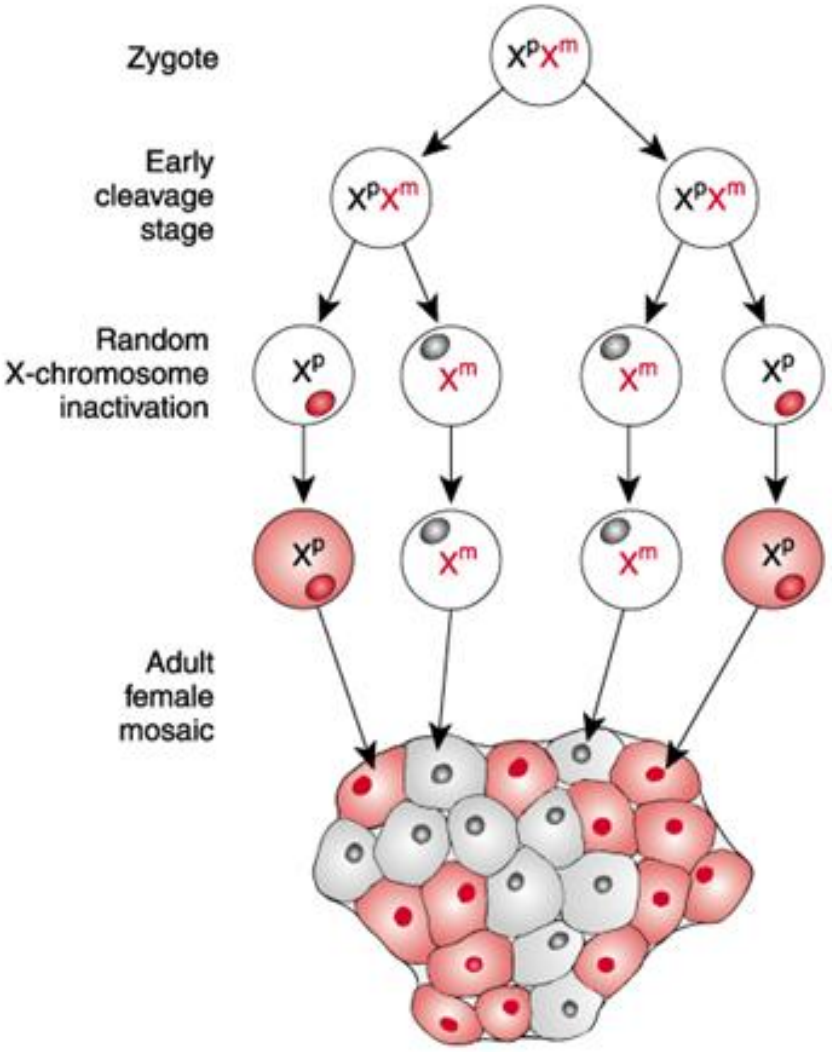
Inactivation of X chromosome

- Takes place randomly in the early phase of development in healthy female
- The same X chrs gets inactive in the offspring generations of cells
- A product of Xq13 (Xist) is significant in the process
- Virtually all genes of X chr turn into inactive phase (except genes responsible for inactivation)
- Female are mosaic for inactive X chrs as maternal and paternal X chrs get inactive, too

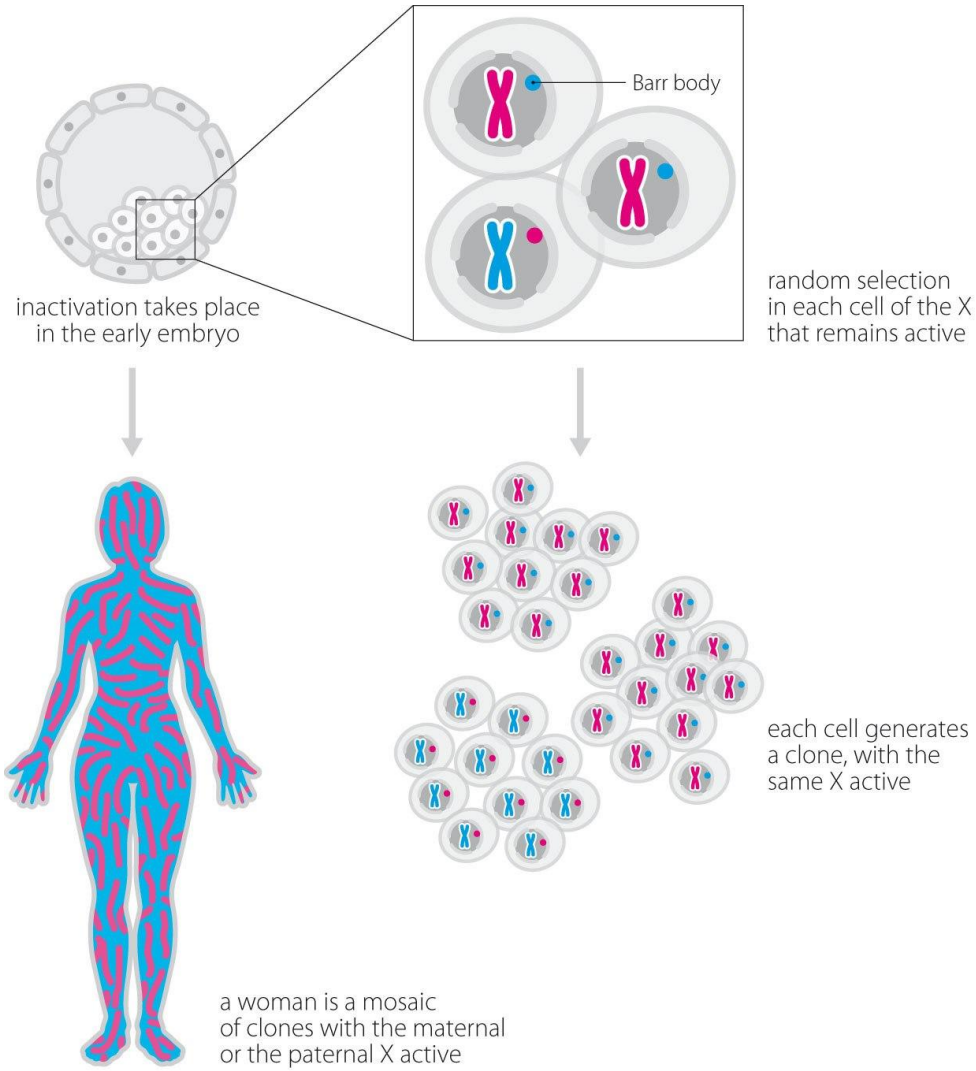
Male: constitutional hemizygotes
Female: functional hemizygotes

X - Inactivation

- The Lyon hypothesis states that one X chromosome in the cell is randomly inactivated early in the embryonic development of females
- Inactivation results in 'dosage compensation',
- The X inactivation center is located on Xq 13 (1 Mb). The **XIST** : **X** **I**nactive **S**pecific **T**ranscript. gene is transcribed only from the inactive X - chromosome.



X-inactivation is an epigenetic process.



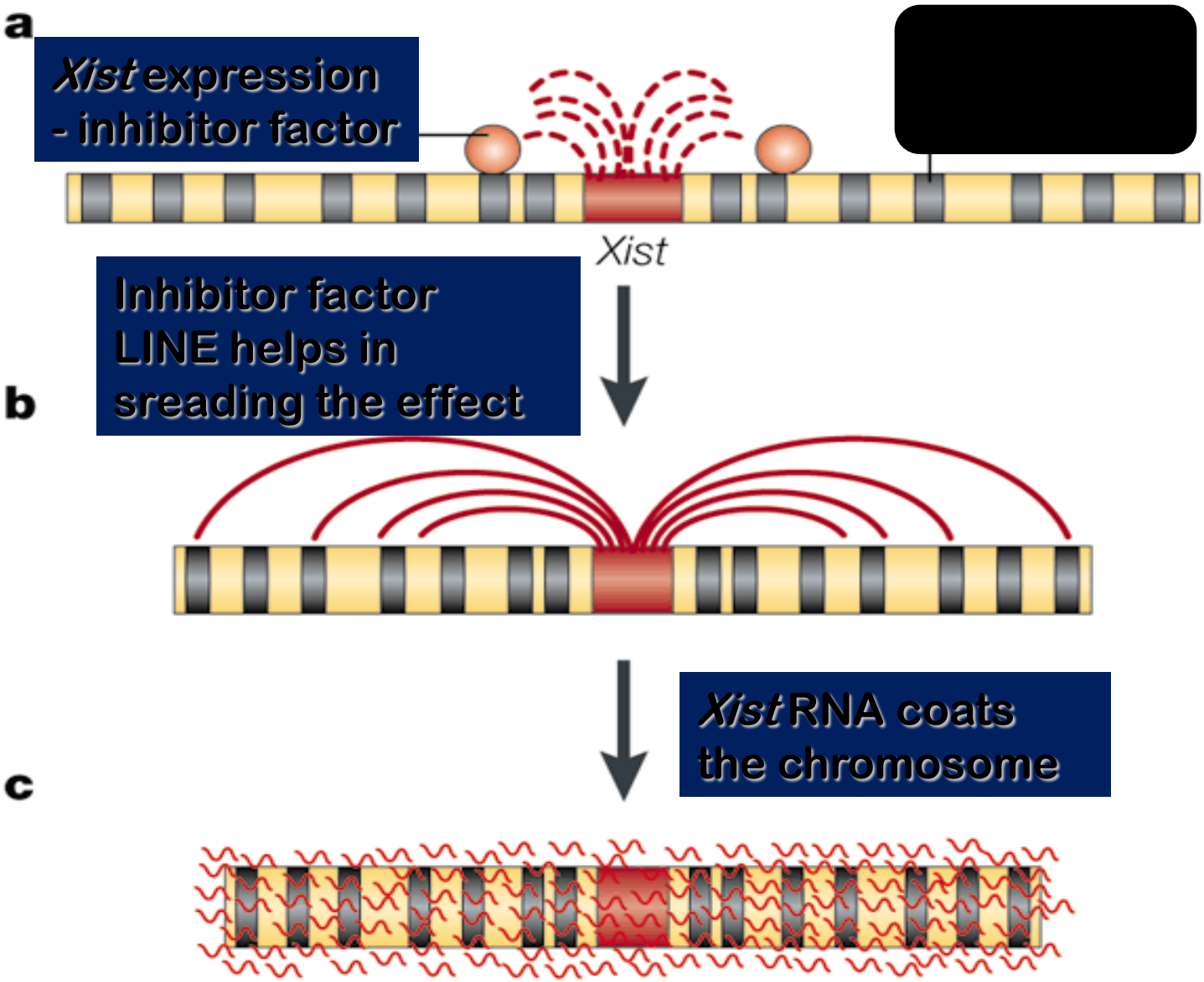
- Because of X-inactivation every female is a mosaic of cell lines with different active X chromosomes
- Early in the development of female, one **X**-chromosome is inactivated at random **(7-10 days after fertilization)**
- Zygout around 24 cell

X Chromosome Inactivation

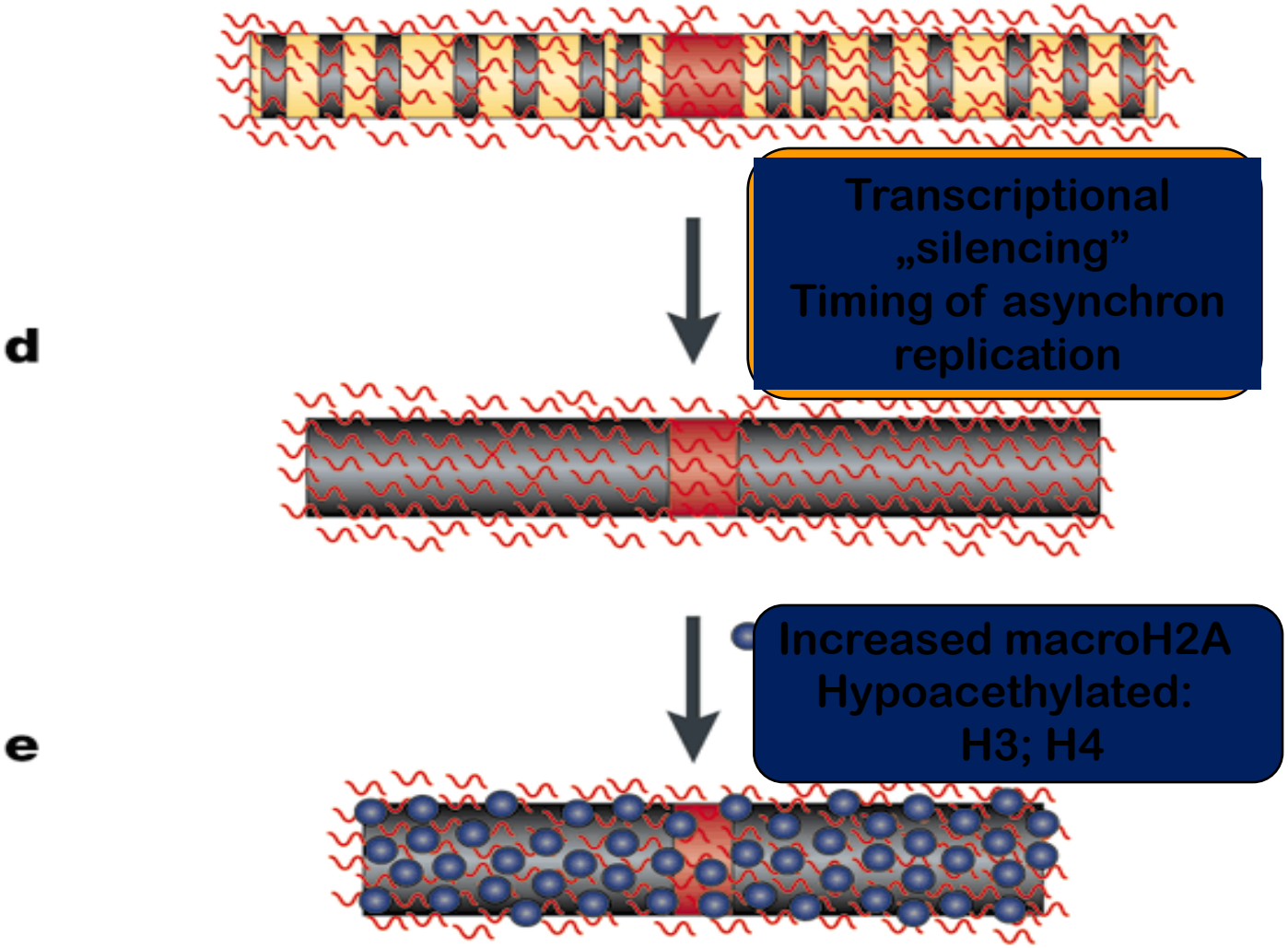
- Mechanism of X Chromosome inactivation

- XIC – X chromosome Inactivation Center
  - XIC controls expression of the *XIST* gene
  - *XIST*: X-inactive-specific transcript
  - *XIST* produces a non-coding 17 kb RNA molecule
  - "Coats" the entire *local* X-chromosome – *cis*-acting

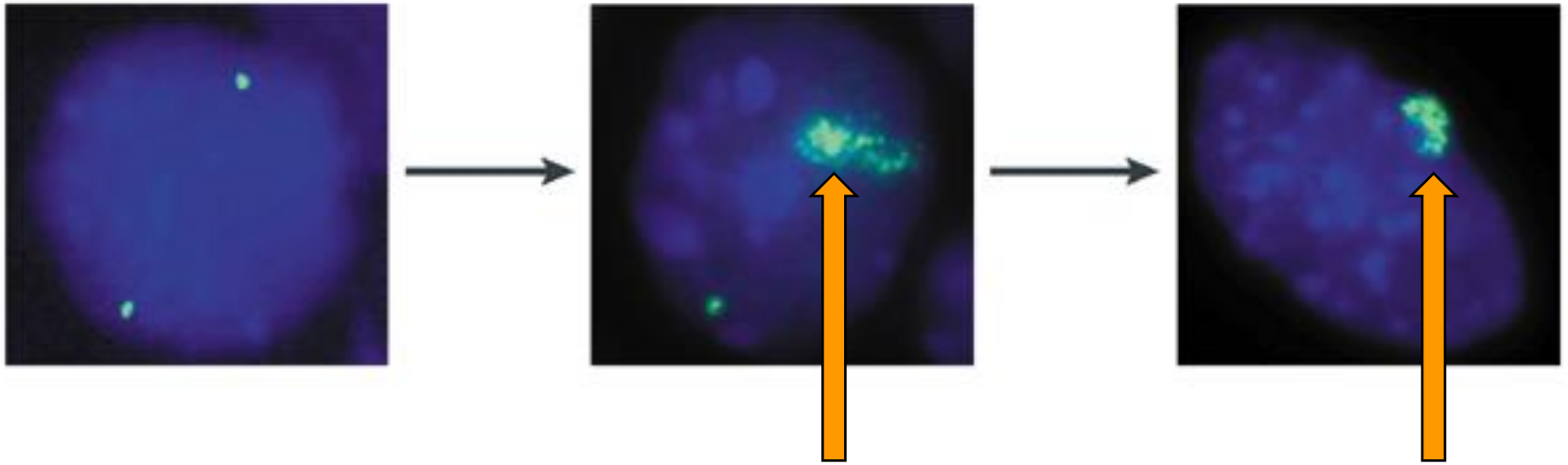
Inactivation of X chromosome (1)



X kromoszóma inaktiválódása (2)



Xist transcription in embryonic stem cells

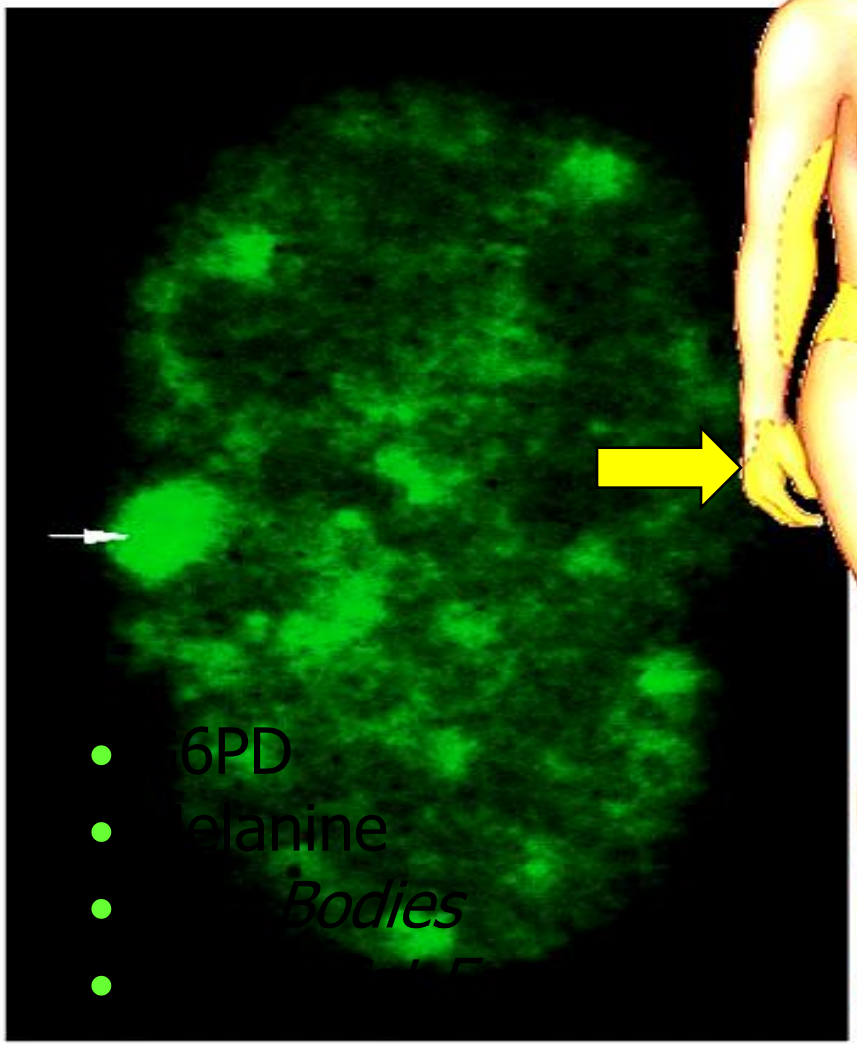


Xist is active on both X chrs'

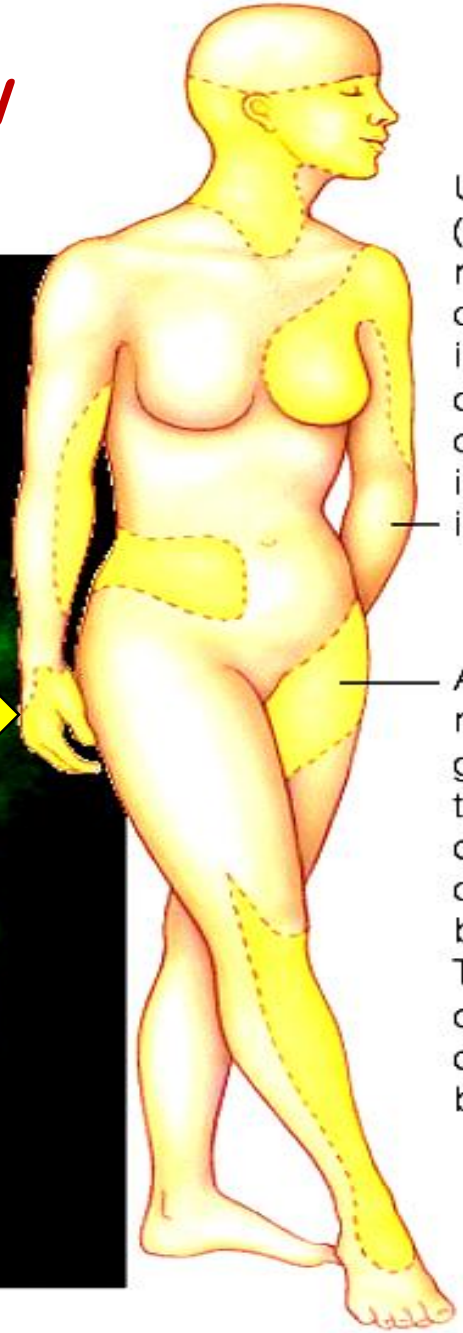
Inactive X chrs is covered by RNA

Only the inactive, „RNA-coated" Xchrs is detectable

Anhidrotic Ectodermal Dysplasia



- 6PD
- elanine
- *Bodies*
-

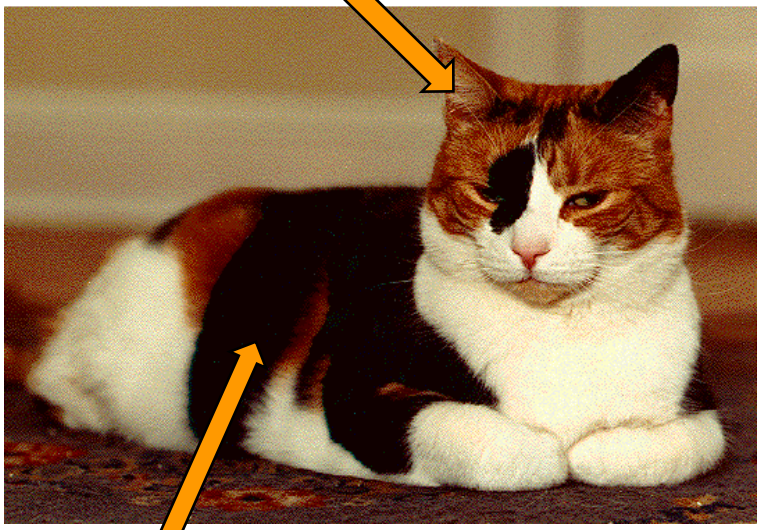


Unaffected skin (X chromosome with recessive allele was condensed; its allele is inactivated. The dominant allele on other X chromosome is being expressed in this tissue.)

Affected skin with no normal sweat glands (In this tissue, the X chromosome with dominant allele has been condensed. The recessive allele on the other X chromosome is being transcribed.)

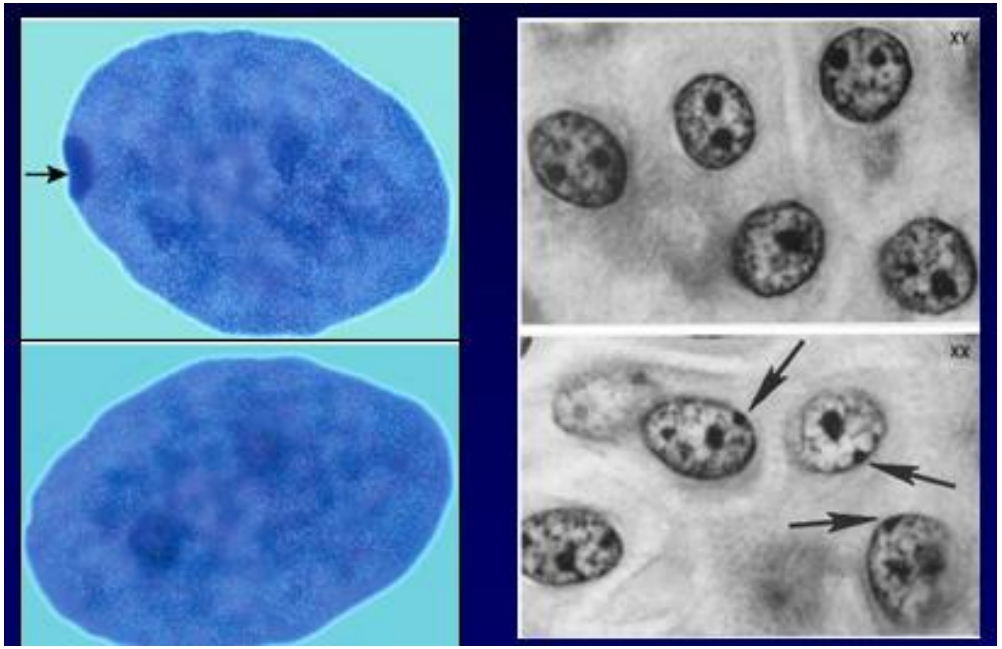
Mosaicism Reveals the Random Inactivation of one X chromosome

X^b active



X^B active

Bar Bodies



Non-Traditional Types of Gene Disorders (NTGD)

Classification of genetic disorders

- Chromosomal
- Single gene
  - Autosomal recessive
  - Autosomal dominant
  - X-linked recessive
  - X-linked dominant
- Nontraditional GD
- Multifactorial
- Somatic mutations (cancer)

Non-Traditional Types of Gene Disorders (NTGD)

- Mosaciasm
- Imprinting
- Trinucleotide expansion

- Uniparental Disomy
- Mitochondrial
- Fragile X Syndrome

Uniparental Disomy

- **Uniparental disomy** (UPD) is defined as the presence of two homologous chromosomes inherited in part or in total from only one parent.
- This means that one parent has contributed two copies of a chromosome and the other parent has contributed no copies.
- The incidence of UPD is estimated to be as high as 2.8 to 16.5 per 10,000 conceptions.

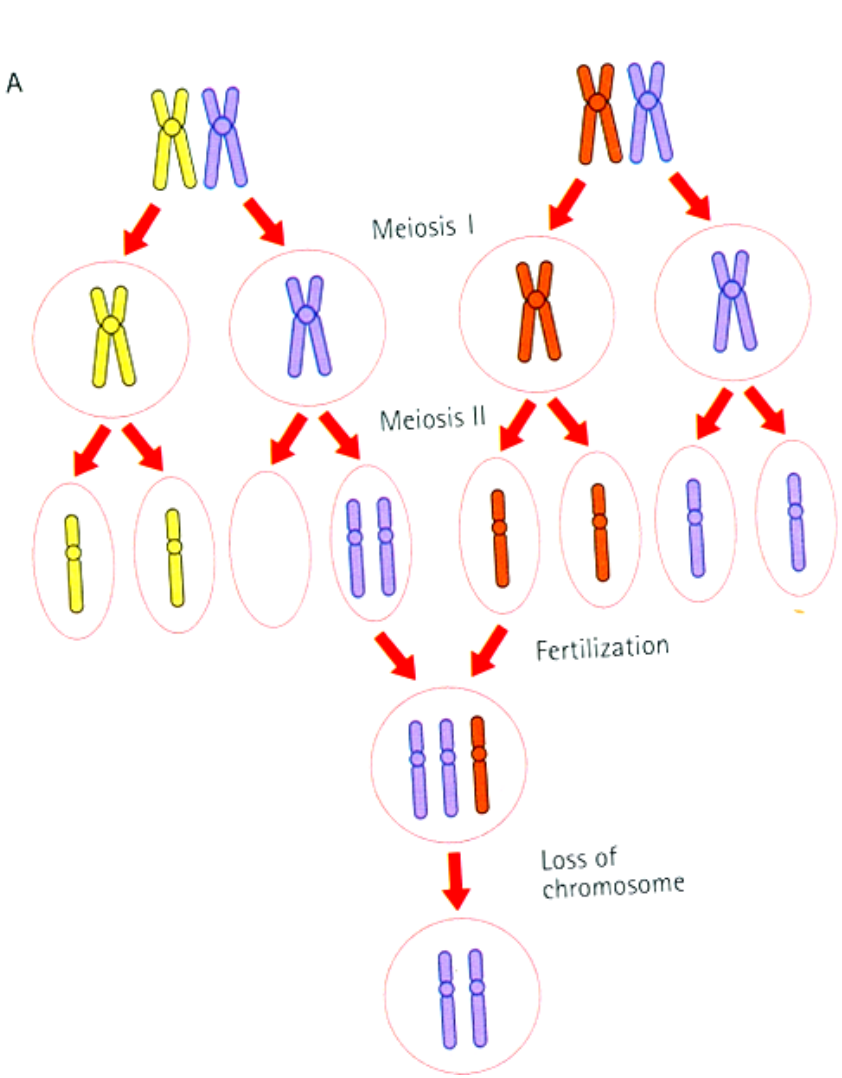
- **Isodisomy:** If the parent passed on two copies of the same chromosome (as results from non-disjunction in meiosis II).

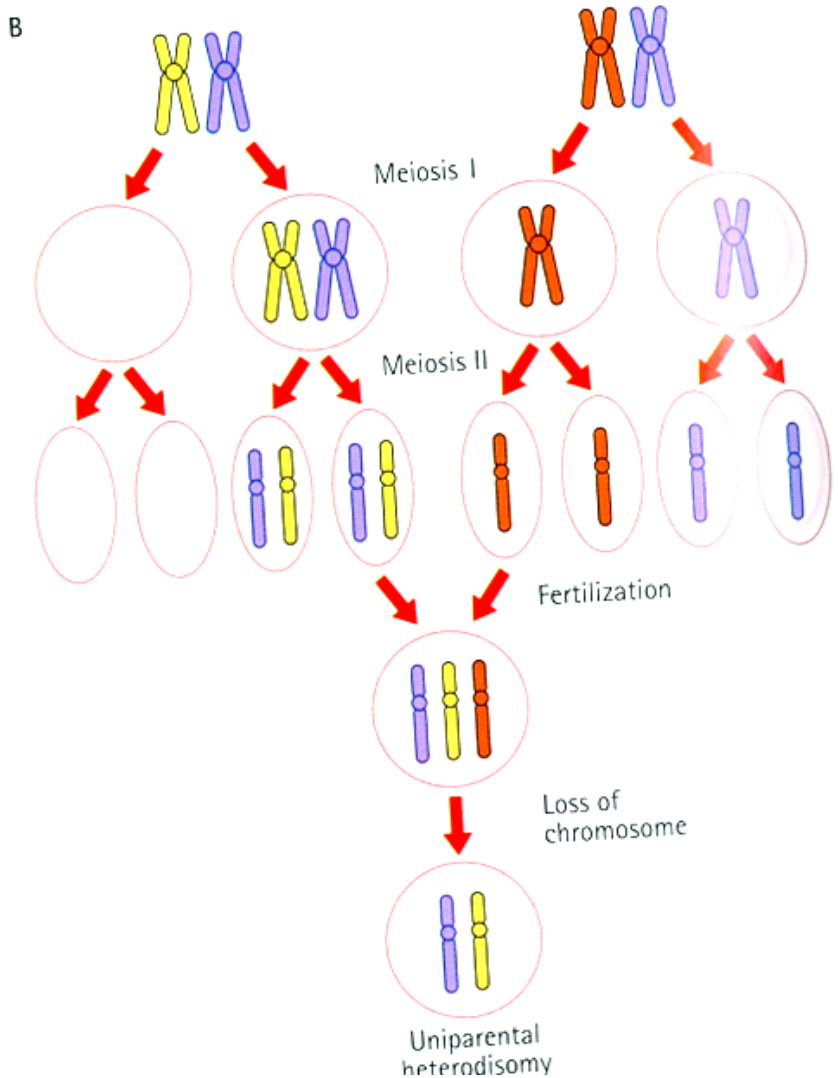
- **Heterodisomy.** If the parent provides one copy of each homolog (as results from non-disjunction in meiosis I),

Examples

- Cases of PWS & AS
- Two CF patients with short stature, inherited two identical copies of most or all of their maternal chr. 7. In both cases, the mother happened to be a carrier for CF
- Father-to-son transmission of hemophilia, affected boy inherited both X & Y from father
- Expression of X-linked in homozygous form in a female offspring of a carrier mother and a normal father

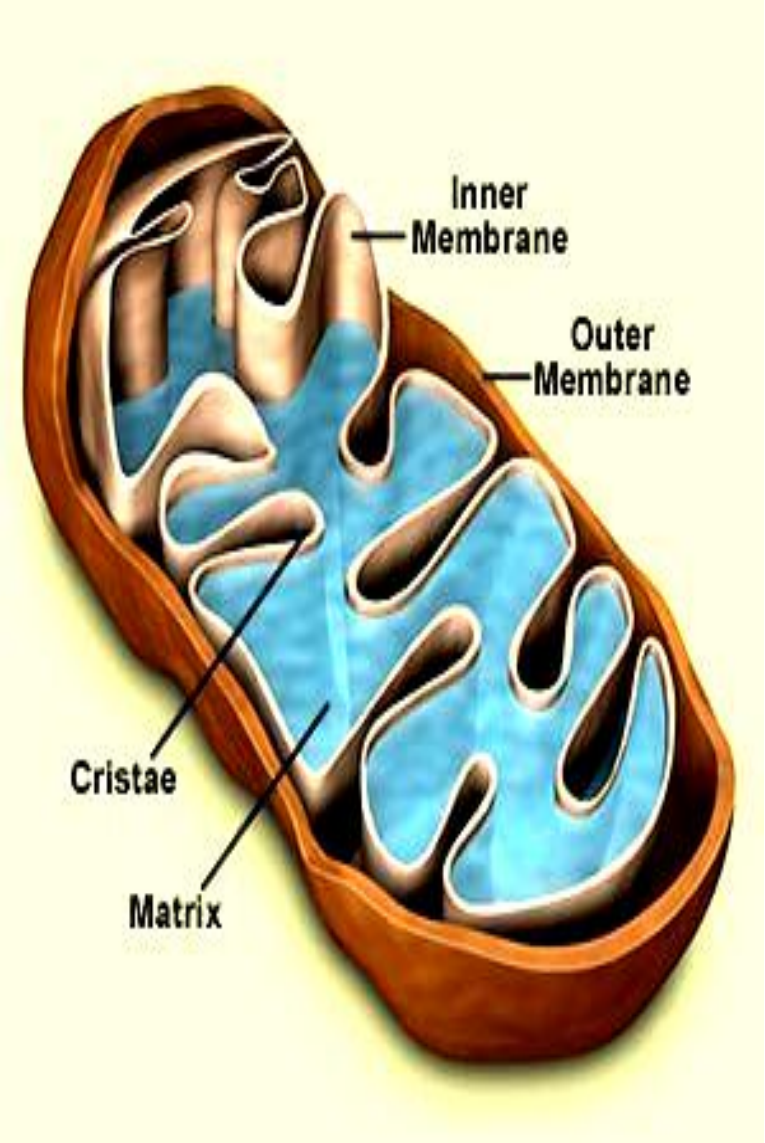
Uniparental Disomy





MITOCHONDRIAL GENETICS

Mitochondrion



- A cellular organelle probably of endosymbiotic origin that resides in the cytosol of most nucleated (eurkaryotic) cells.
- This organelle produces energy by oxidising organic acids and fats with oxygen by the process of **oxidative phosphorylation** and generates oxygen radicals (reactive oxygen species ROS)as a toxic by-product
- Contains small circular DNA.
- No crossing over or DNA repair.
- Many copies of the mitochondrial genome per cell.
- 37 genes, no histones, no introns.
- Maternal inheritance

Mitochondrial Inheritance

- Each cell contains hundreds of mitochondria, each of which contains multiple copies of a 16.5 Kb circular DNA molecule.
- The entire human mitochondrial chromosome has been cloned and sequenced.
- Oxidative Phosphorolation to produce ATP
- Although most proteins functioning in the mitochondria are encoded by nuclear genes some are encoded by mitochondrial genes, and mutations can lead to energy failure.

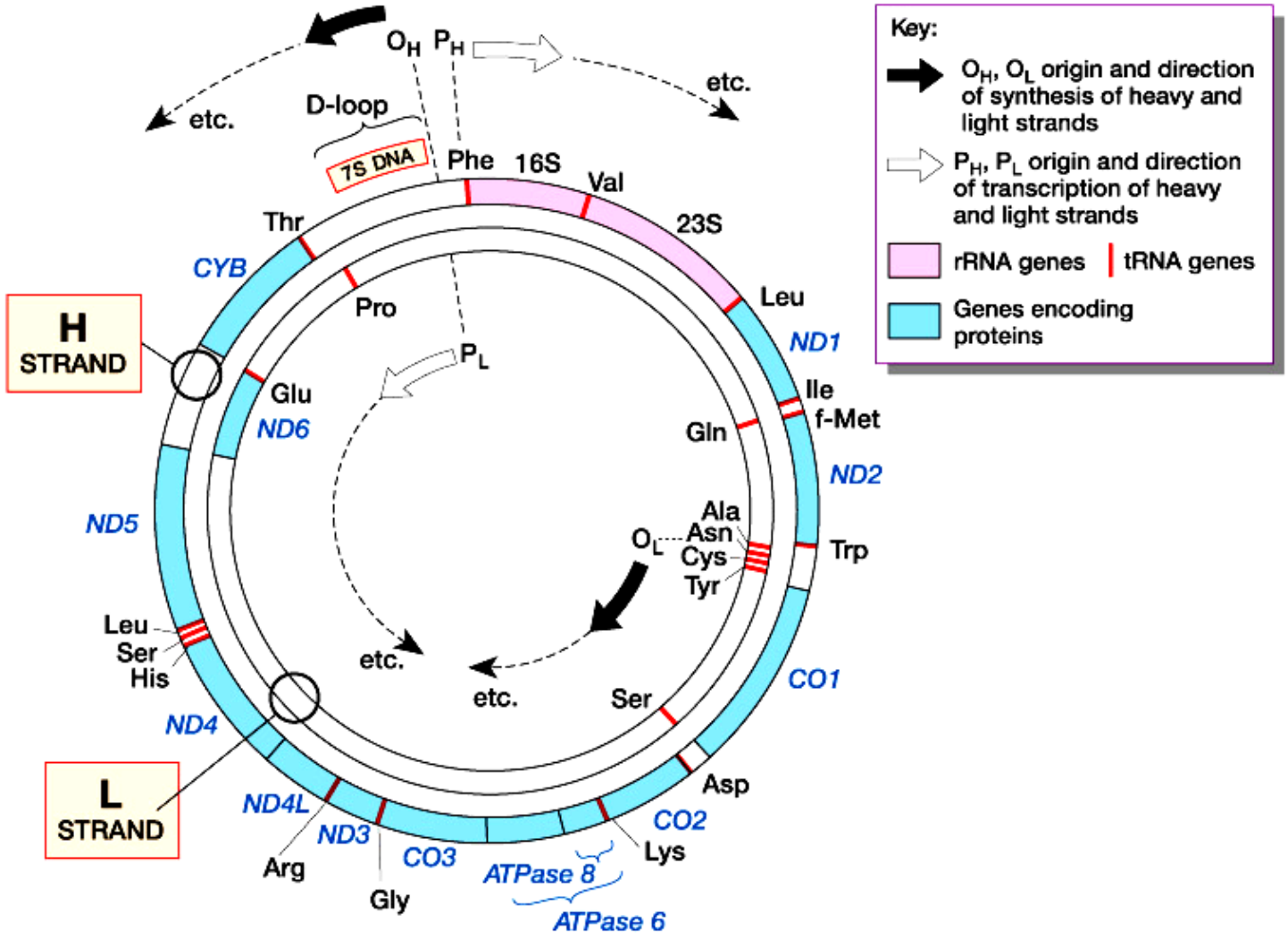


Figure 9-2 Human Molecular Genetics, 3/e. (© Garland Science 2004)

Mt Enzymes

- Mitochondria perform cellular respiration after the cytosolic glycolysis step.
- The enzymes needed, include:

a. Pyruvate dehydrogenase.
b. Electron transport and OP enzymes.
c. Citric acid cycle enzymes.
d. Fatty acid oxidation enzymes

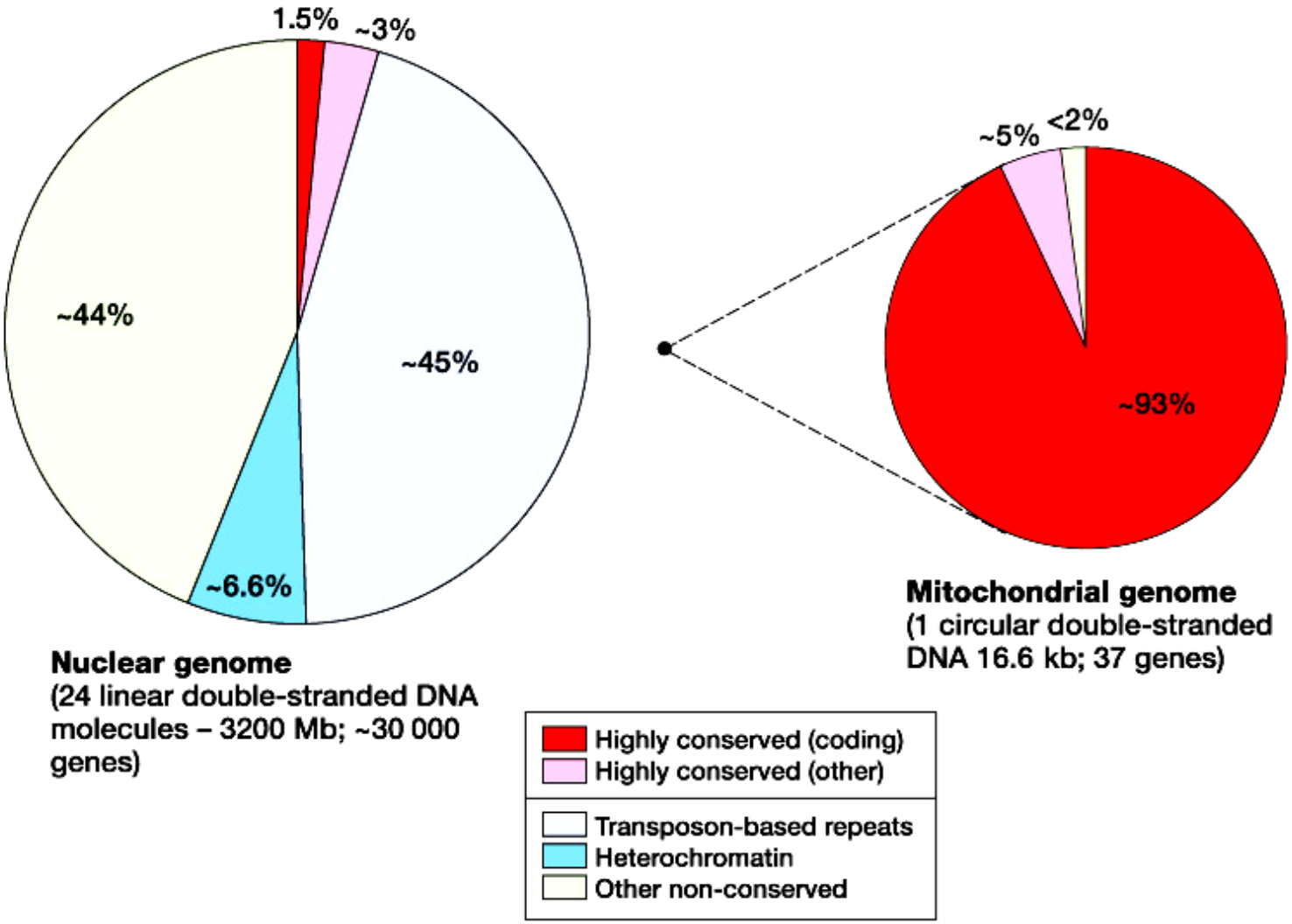


Figure 9-1 Human Molecular Genetics, 3/e. (© Garland Science 2004)

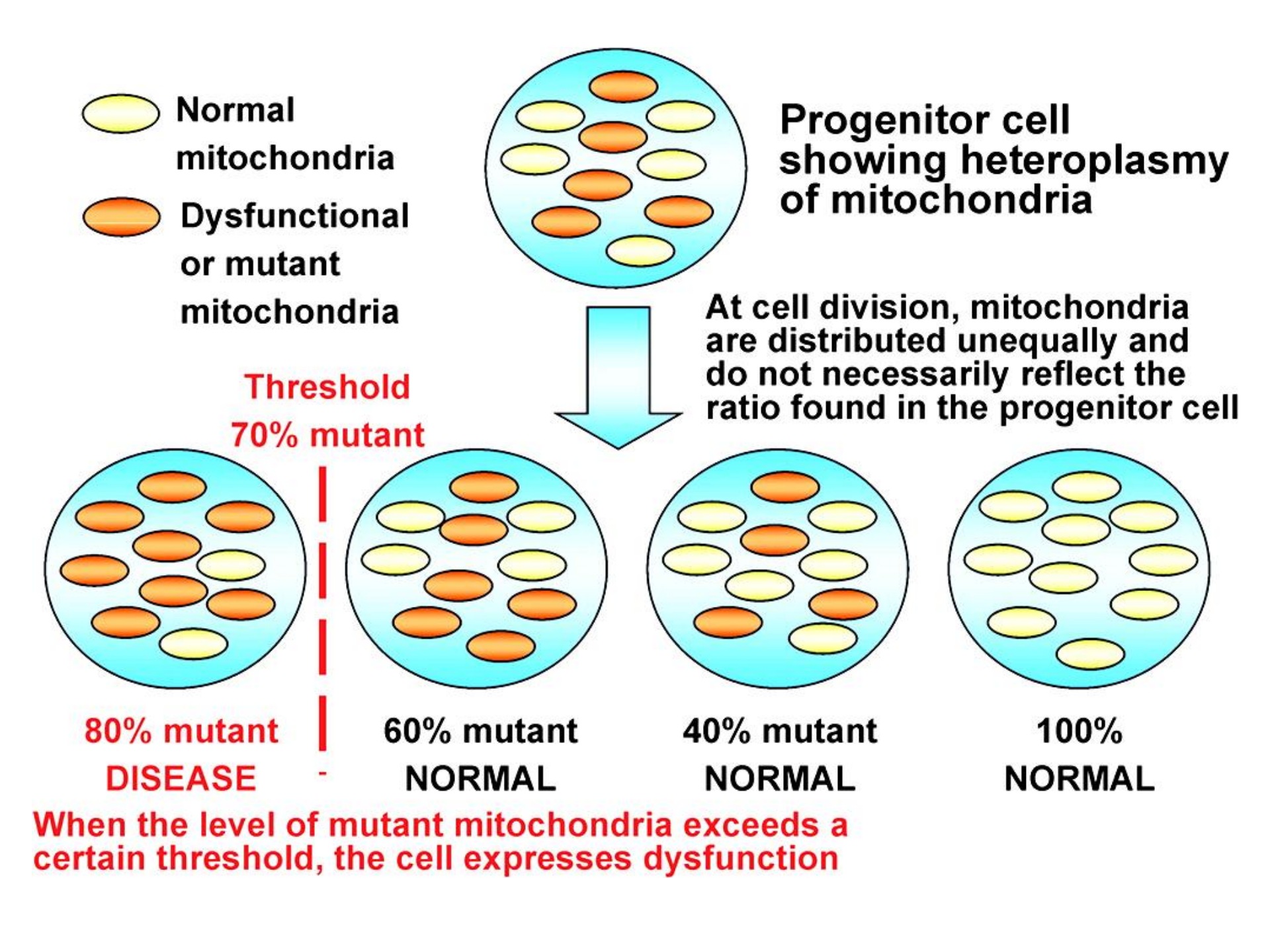
Mitochondrial Inheritance

- In humans, at fertilization, the ovum contributes significantly more cytoplasm to the zygote than does the sperm.
- The sperm mitochondria degenerate upon penetration of the ovum.
- Mitochondria in offspring are exclusively maternal in origin.
- Phenotype results from maternal transmission

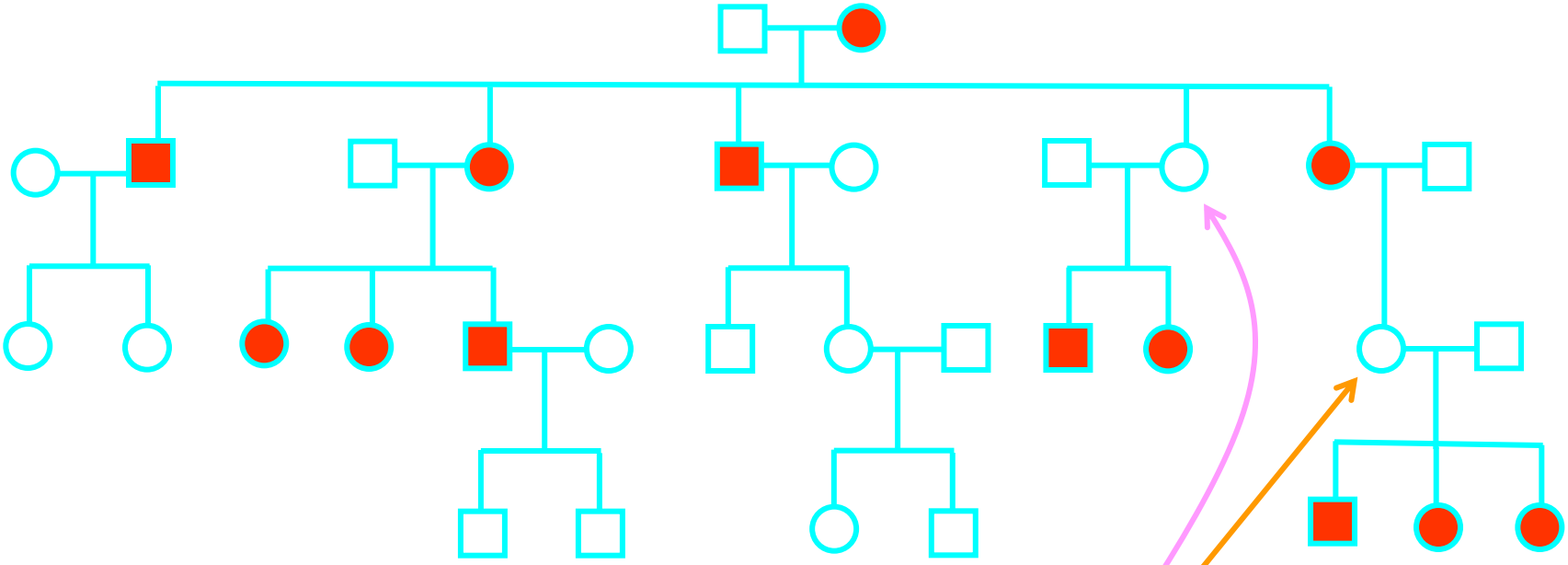
Mitochondrial Inheritance

- Mutations in mitochondrial genes are also the cause of several single gene disorders.

- Mutation rate in mt is 10 times more than in nuclear DNA due to the lack of DNA repair mechanism and free oxygen radicals?


Normal mitochondria
Dysfunctional or mutant mitochondria
Progenitor cell showing heteroplasmy of mitochondria
At cell division, mitochondria are distributed unequally and do not necessarily reflect the ratio found in the progenitor cell
Threshold
70% mutant
80% mutant
DISEASE
60% mutant
NORMAL
40% mutant
NORMAL
100%
NORMAL
When the level of mutant mitochondria exceeds a certain threshold, the cell expresses dysfunction

Mitochondrial inheritance



Complications

- Incomplete penetrance
- Variable expression

Examples of Diseases Due to Mutations and Deletions in Mitochondrial DNA

Abbreviation	MIM No.	Designation
LHON	535000	Leber's hereditary optical neuropathy (Missence M)
MELAS	540000	Mitochondrial encephalomyopathy
	540050	Lactic acidosis with stroke-like signs (Single base M)
MERRF	545030	Myoclonic epilepsy and ragged red fibers (Single base M)
MMC*	590050	Maternally inherited myopathy and cardiomyopathy
NARP*	551500	Neurogenic muscular weakness with ataxia and retinitis pigmentosa
CEOP*	258470	Progressive external ophthalmoplegia
KSS*	530000	Kearns-Sayre syndrome (ophthalmoplegia, pigmental degeneration of the retina, and cardiomyopathy)
PEAR*	557000	Pearson syndrome (bone marrow and pancreatic failure)
ADMIMY*	157640	Autosomal dominant inherited mitochondrial myopathy with mitochondrial deletion in the D loop (type Zeviani)

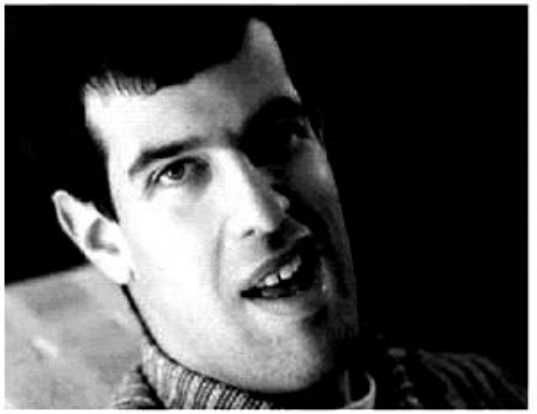
FRAGILE S SYNDROME

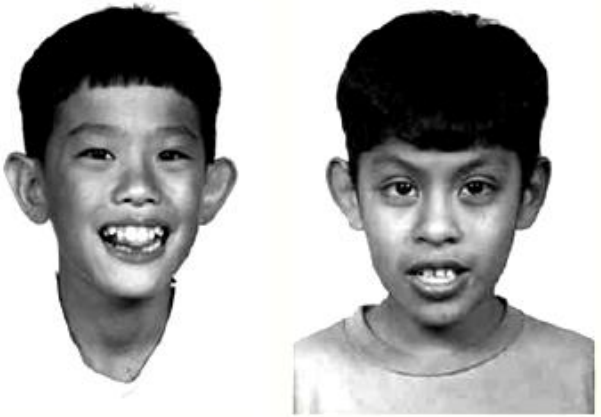
Fragile X Syndrome

- The most common cause of inherited mental retardation (MR).
- Second only to Down syndrome as an etiology for MR.
- Incidence of approximately 1 in 4000 males and 1 in 8000 females
- Found among all ethnic groups and occurs in families with no history of mental retardation
- 1 in 259 women are carriers of the fragile X premutation
  - Only the mother has to be a carrier for the fetus to be at risk for fragile X syndrome

Fragile X Syndrome

- Males:
  - Moderate to severe mental retardation, learning disabilities
  - Long face, prominent ears, macro-orchidism
  - Physical phenotype can be subtle, especially in young boys
  - Hyperactivity, autism (approx. 1/3), hand flapping, hand biting, disordered speech and language
  - males are generally unable to live independently

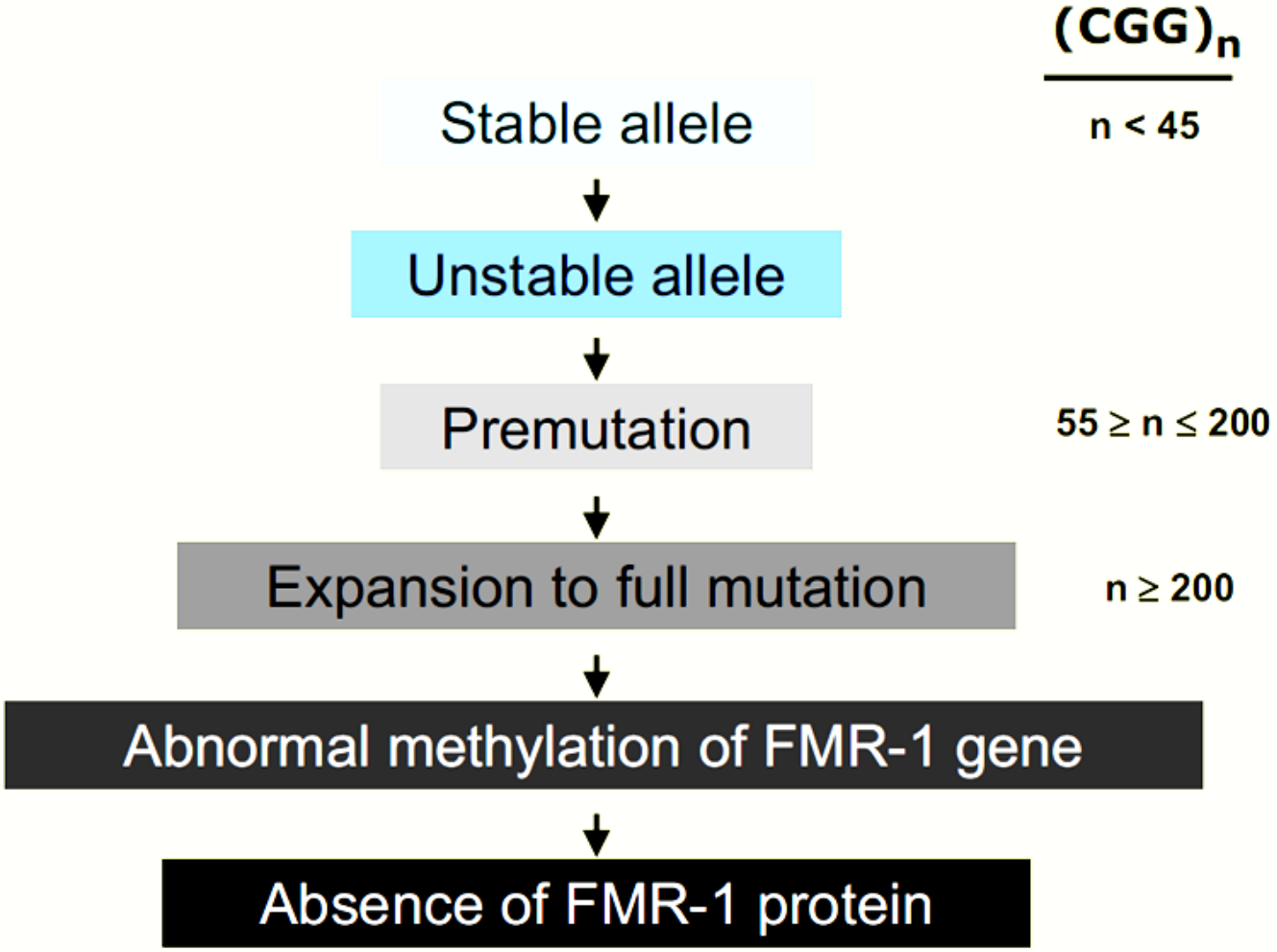




Fragile X Syndrome

- **Females:**
  - Less frequent and less severe in females
  - Mild to moderate mental retardation, learning disabilities
    - About 1/3 of females have significant intellectual disability.
  - Long face, prominent ears (more subtle in females than in males)
  - Poor eye contact, attention problems, shyness and social anxiety

FMR-1 gene: a triplet repeat disease



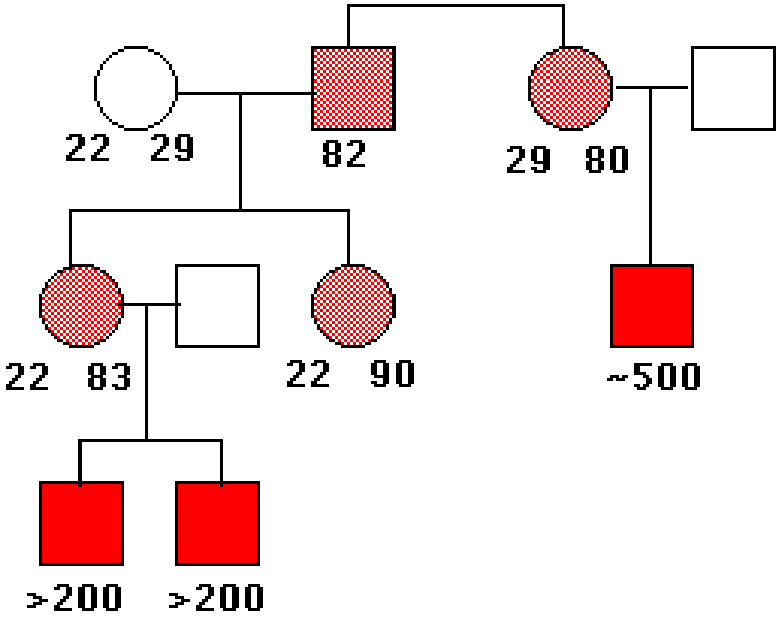
Risk of Premutation Expansion: size of repeat and gender

Maternal Repeat Size	% Of Offspring With a Full Mutation
55-59	3.7%
60-69	5.3%
70-79	31.1%
80-89	57.8%
90-99	80.1%
>100	94-100%

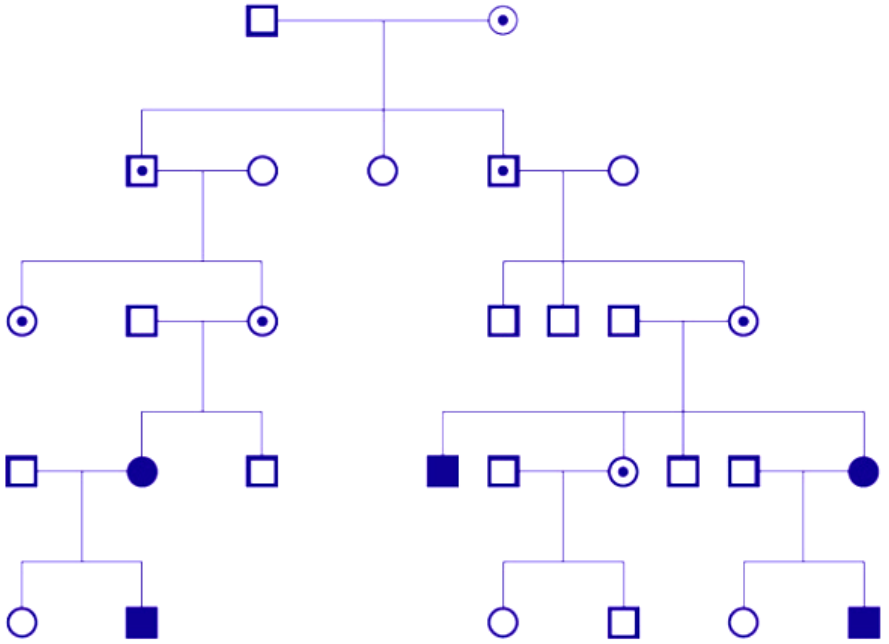
Source: Nolin et al., 2003

Genetic Anticipation Explained

A Fragile X family

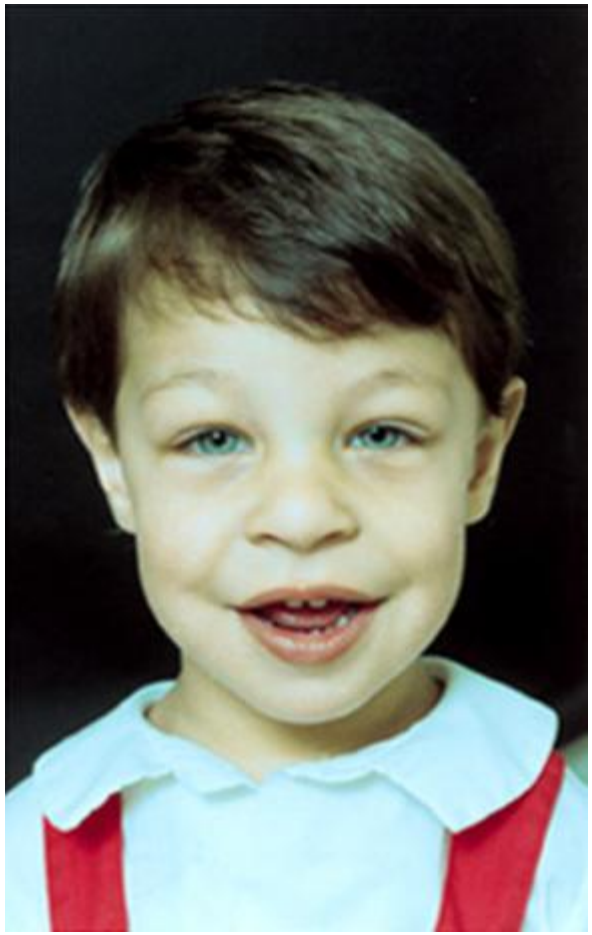


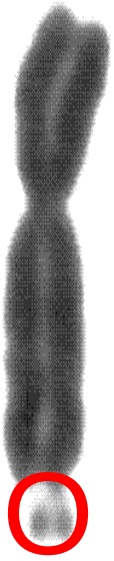
Fragile X syndrome has a complicated inheritance

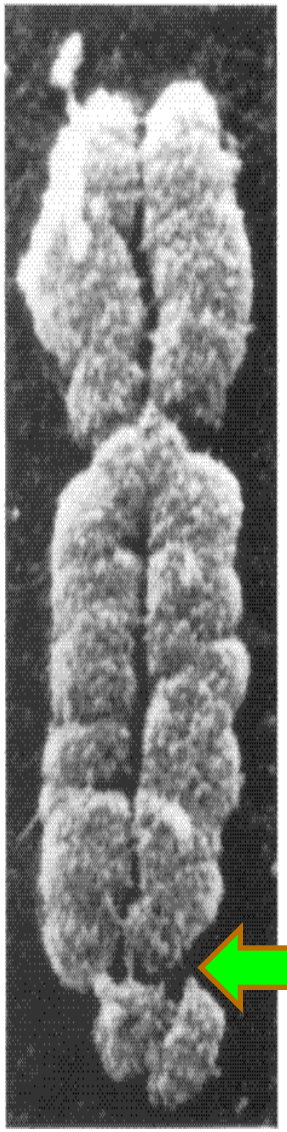


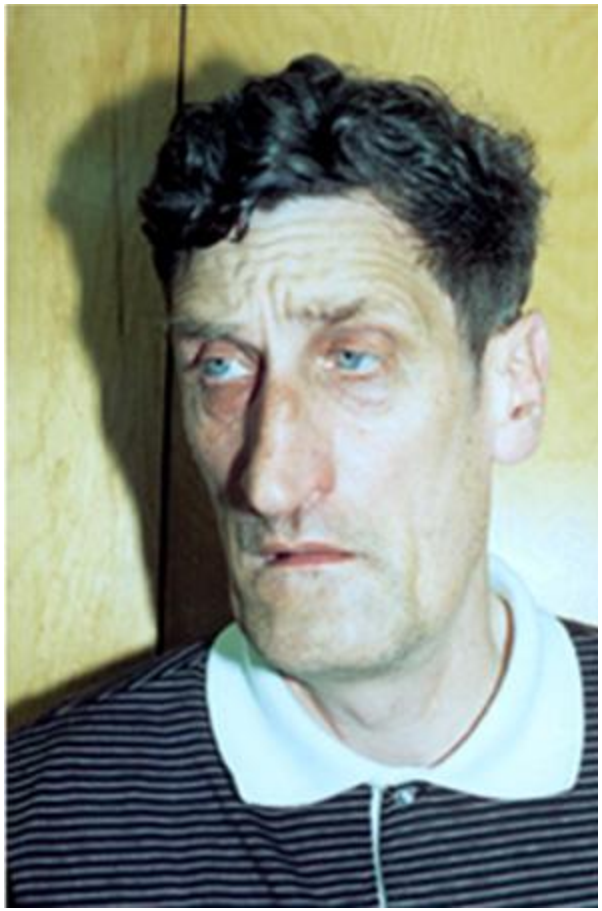
- Progressive increase in size of CGG repeat
- Requires a female transmission to go to full mutation

FRAGILE X SYNDROME









Fragile Site

Rules of Inheritance

Autosomal Recessive

- Appears in both sexes with equal frequency
- Trait tend to skip generations
- Affected offspring are usually born to unaffected parents
- When both parents are hetzyg. ~1/4 of the progeny will be affected
- Appears more frequently among the children of consanguine marriages

Autosomal Dominant

- Appears in both sexes with equal frequency
- Both sexes transmit the trait to their offspring
- Does not skip generations
- Affected offspring must have an affected parent unless they posses a new mutation
- When one parent is affected (het.) and the other parent is unaffected, ~ 1/2 of the offspring will be affected
- Unaffected parents do not transmit the trait

Mitochondrial

- Trait is inherited from mother only
- All children of a mother are at risk to be affected or carriers
- An individual will be affected with a mitochondrial disorder if the percentage of mitochondria possessing mutated mtDNA reaches a threshold value beyond which the normal mtDNA does not compensate for the mutated mtDNA.

X-Linked Dominant

- Both males and females are affected; often more females than males are affected
- Does not skip generations. Affectd sons must have an affected mother; affected daughters must have either an affected mother or an affected father
- Affected fathers will pass the trait on to all their daughters
- Affected mothers if heterozygous will pass the trait on to 1/2 of their sons and 1/2 of their daughters

X-Linked Recessive

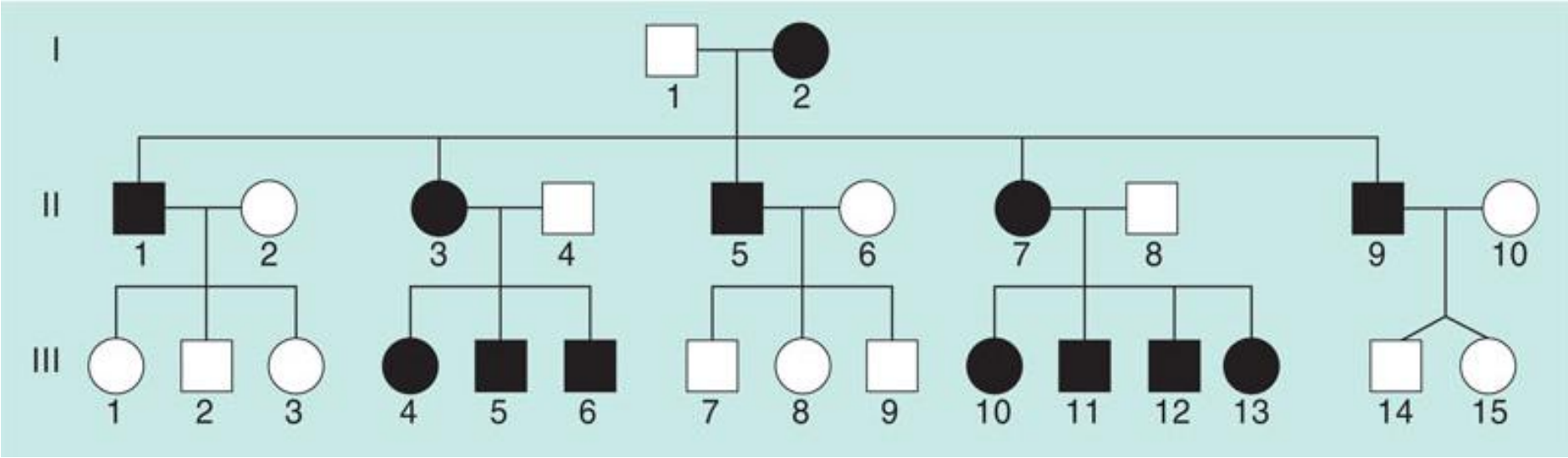
- More males than females are affected
- Affected sons are usually born to unaffected mothers, thus the trait skips generations
- Approximately 1/2 of carrier mothers' sons are affected
- It is never passed from father to son
- All daughters of affected fathers are carriers

Y-Linked Dominant

- Only males are affected
- It is passed from father to all sons
- It does not skip generations

Another pattern of inheritance!

- What features characterize this pattern of inheritance?



- Mother's children all inherit the trait.
- Father's children never inherit the trait!