Basic Genetics (SQBS 2753)

THE CHROMOSOMAL BASIS OF MENDELISM

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Outline

- Chromosomes
- The Chromosome Theory of Heredity
- Sex-linked Genes in Human Beings
- Sex Chromosomes and Sex Determination
- Dosage Compensation of X-linked Genes

Chromosomes are cellular structures that transmit genetic information

- Breeding experiments and microscopy provided evidence for the chromosome theory of inheritance
- Proper development relies on accurate transmission of genes and accurate maintenance of chromosome number
- The abstract idea of a gene was changed to a physical reality by the chromosome theory

Evidence that genes reside in the nucleus

- 1667 - Anton Van Leeuwenhoek
  - Microscopy revealed that semen contain spermatozoa ("sperm animals")
  - Hypothesized that sperm may enter egg to achieve fertilization
- 1854 – 1874
  - Direct observations of fertilization through union of nuclei of eggs and sperm (frog and sea urchin)
  - Conclusion: something in the nucleus must contain the hereditary material

Evidence that genes reside in chromosomes

- 1880s – improved microscopy and staining techniques
  - Long, threadlike bodies (chromosomes) visualized in the nucleus
  - Movement of these bodies followed through cell division
- Mitosis - nuclear division that generates two daughter cells containing the same number and type of chromosomes as parent cell
- Meiosis - Nuclear division that generates gametes (egg and sperm) containing half the number of chromosomes found in other cells

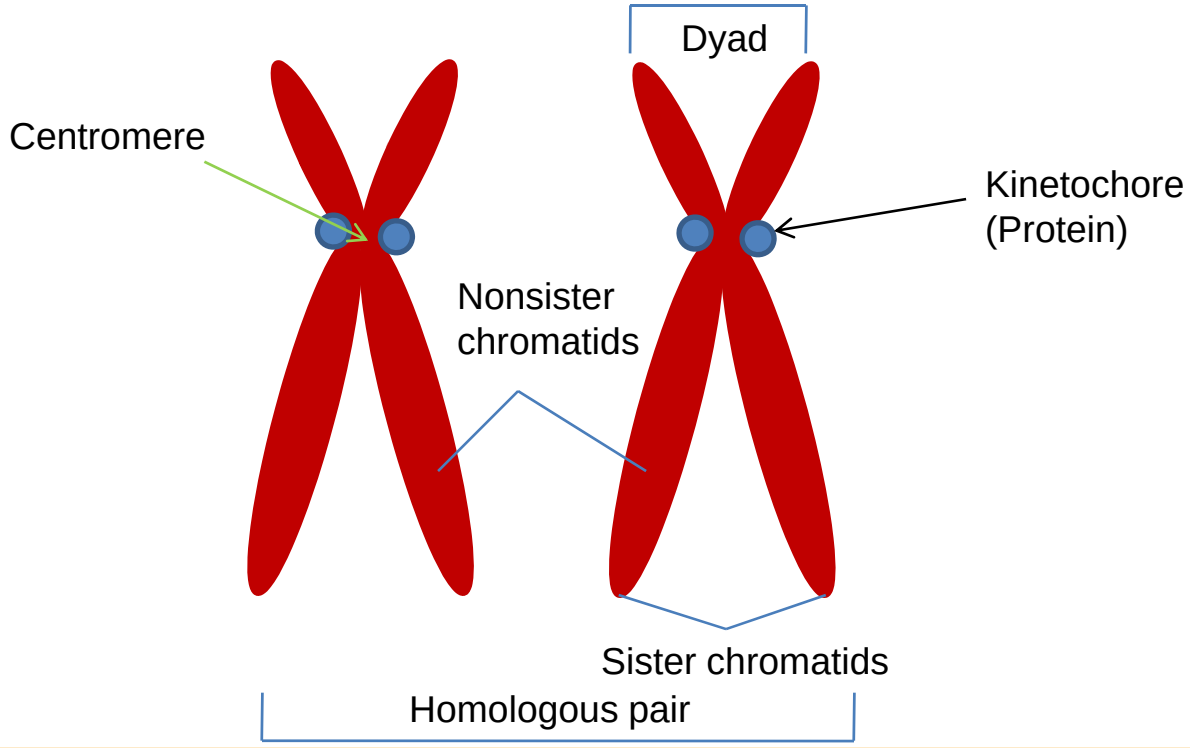
Diploid versus haploid: 2n versus n

- Most body cells are diploid (each chromosome pair has one maternal and one paternal copy)

- Meiosis → haploid (n) gametes
  - In Drosophila, 2n = 8, n = 4
  - In humans , 2n = 46 and n = 23

Chromosome

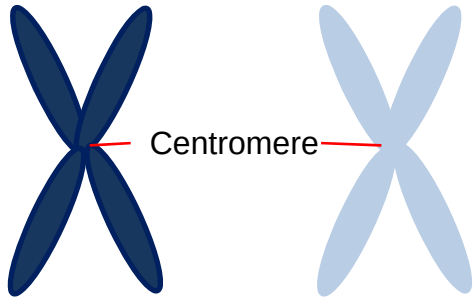
- DNA molecule is packaged into thread-like structures
- Chromatin - DNA & protein



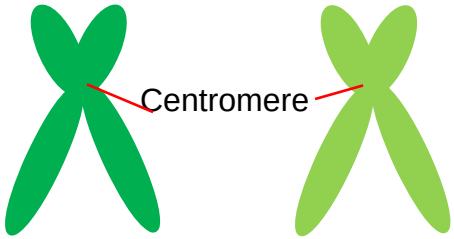
Metaphase chromosomes can be classified by centromere position

- Metacentric chromosome – centromere is in the middle
- Acrocentric chromosome – centromere is near one end

Metacentric Chromosomes



Acrocentric Chromosomes



Chromosome

- each chromosome is duplicated & the duplicated chromosomes are referred to as dyads.
- sister chromatids - each chromosome carrying full genes compliment.
- centromere(constriction point) - 2 parts or “arms”.

  - The short arm -*p* arm; long arm- *q* arm.
- kinetochore -an attachment point - separate the sister chromatids in mitosis.

Chromosome Number

- Haploid (n)
  - Basic, chromosome number, a set of chromosome
- Diploid (2n)
  - Two of each of the chromosome – somatic cell
- Tetraploid (4n), octoploid (8n)

Example of chromosome number in organisms

	Organism	Haploid (n)
Simple eukaryotes	Yeast (*Saccharomyces cerevisiae*)	16
	Mold (*Neurospora crassa*)	7
Plants	Maize (*Zea mays*)	10
	Wheat (*Triticum aestivum*)	21
	Tomato (*Lycopersicon esculentum*)	12
Invertebrate	Fruit fly (*Drosophila melanogaster*)	4
	Mosquito (*Anopheles culicifacies*)	3
	Nematode (Caenorbabditis elegans)	6
Vertebrate	Human being (*Homo sapiens*)	23
	Mouse (*Mus musculus*)	20
	Cat (*Felis domesticus*)	36
	Chicken (*Gallus domesticus*)	39
	Fish (*Esox lucius*)	25

Homologous chromosomes are matched in size, shape , and banding patterns

- Homologs contain the same set of genes, but can have different alleles for some genes
- Nonhomologs carry completely unrelated sets of genes
- Karyotype – micrograph of stained chromosomes arranged in homologous pairs
  - Sex chromosomes – unpaired X and Y chromosome
  - Autosomes – all chromosomes except X and Y
- Cells of each species have a characteristic diploid number of chromosomes
    - e.g. *D. melanogaster*, 2n = 8; sweet peas, 2n = 14; goldfish, 2n = 94; dogs, 2n = 78

Karyotype of a human male

- Photos of metaphase human chromosomes (2n = 46, n = 23)
- Each homologous pair arranged in order of decreasing size
- http://www.visualsunlimited.com/image/I00

Sex determination in fruit flies and humans

In *Drosophila*, ratio of X chromosomes to autosomes determines gender

In humans, presence or absence of Y chromosome determines gender

Abnormal numbers of X or Y chromosomes have different effects in humans and flies

	SEX CHROMOSOMES					
	XXX	**XX**	**XO**	**XY**	**XXY**	**XYY**
Human	Nearly normal female	Normal female	Turner female (sterile)	Normal male	Klinefelter male (sterile)	Normal or nearly normal male
Drosophila	Dies	Normal female	Sterile male	Normal male	Normal female	Normal male

Mechanisms of sex determination differ between species

- Heterogametic sex – gender with two different kinds of gametes
- Homogametic sex – gender with one type of gamete

	Male	Female
Human	XY	XX
Drosophila	XY	XX
Birds and butterflies	ZZ	ZW
Bees and wasps	haploid	diploid
Lizards, alligators	warm temperature	cool temperature
Tortoises, turtles	cool temperature	warm temperature
Anemone fish	young adults	older adults

THE CHROMOSOME THEORY OF HEREDITY

The chromosome theory of inheritance

- Walter Sutton – 1903, chromosomes carry Mendel's units of heredity
- Two copies of each kind of chromosome
- Chromosome complement is unchanged during transmission to progeny
- Homologous chromosomes separate to different gametes
- Maternal and paternal chromosomes move to opposite poles
- Fertilization of eggs by random encounter with sperm
- In all cells derived from fertilized egg, half of chromosomes are maternal and half are paternal

Validation of the chromosome theory

Prior to 1910, the chromosome theory of inheritance was supported by two circumstantial lines of evidence

- Sex determination associates with inheritance of particular chromosomes
- Events in mitosis, meiosis, and gametogenesis ensure constant numbers of chromosomes in somatic cells

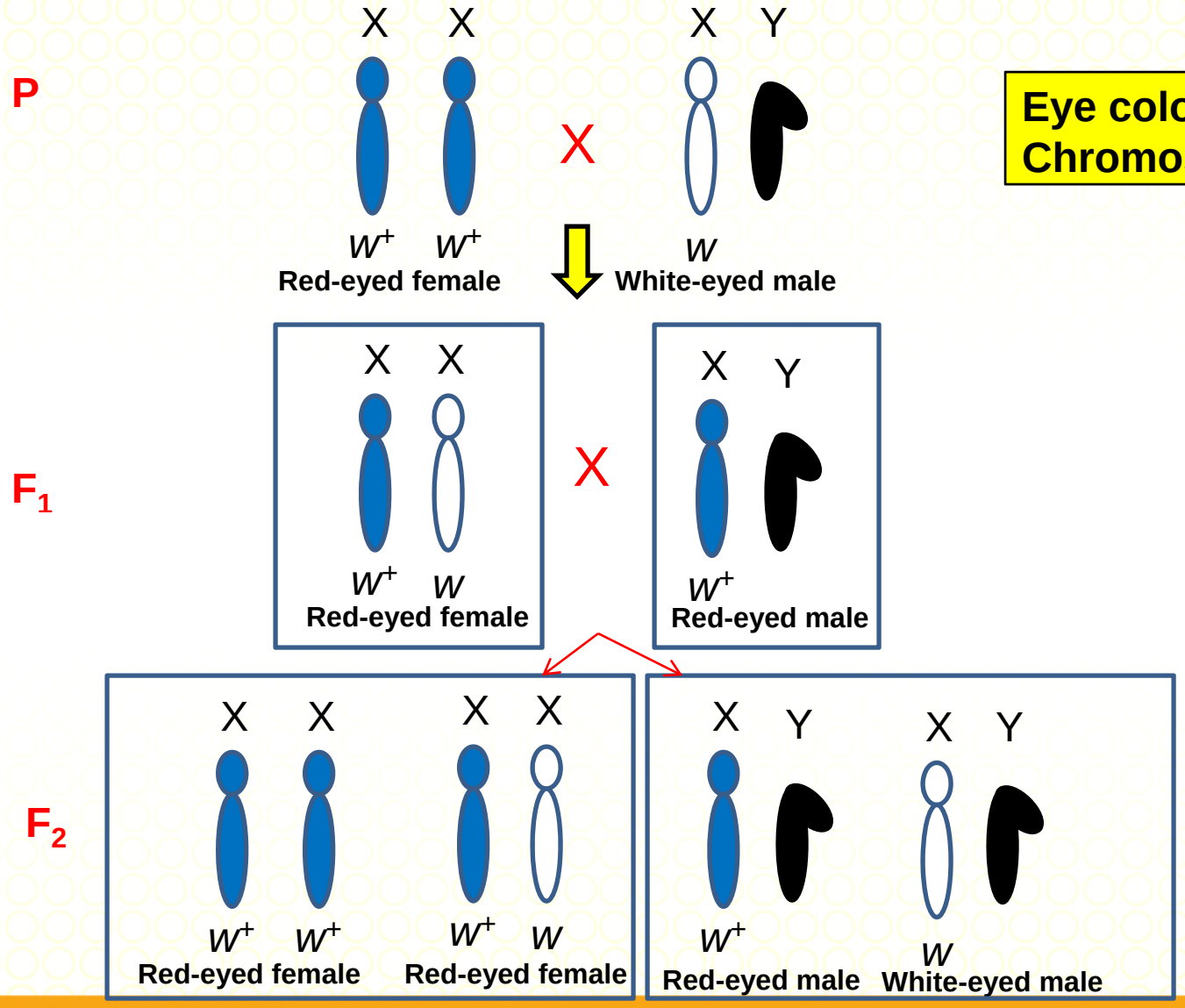
This theory confirmed and validated by:

- Inheritance of genes and chromosomes correspond in every detail
- Transmission of particular chromosome coincides with transmission of traits other than for sex determination

Chromosome Theory of Heredity

- Studies on the inheritance of a sex-linked trait in *Drosophila*
  - The meiotic behavior of chromosome
  - Basis for Mendel's Principles of Segregation and Independent Assortment
- Thomas H. Morgan (1990) – fruit fly, *Drosophila melanogaster*
  - Genes are located on chromosomes

Inheritance of white eye in *Drosophila*



SEX-LINKED GENES IN HUMAN BEINGS

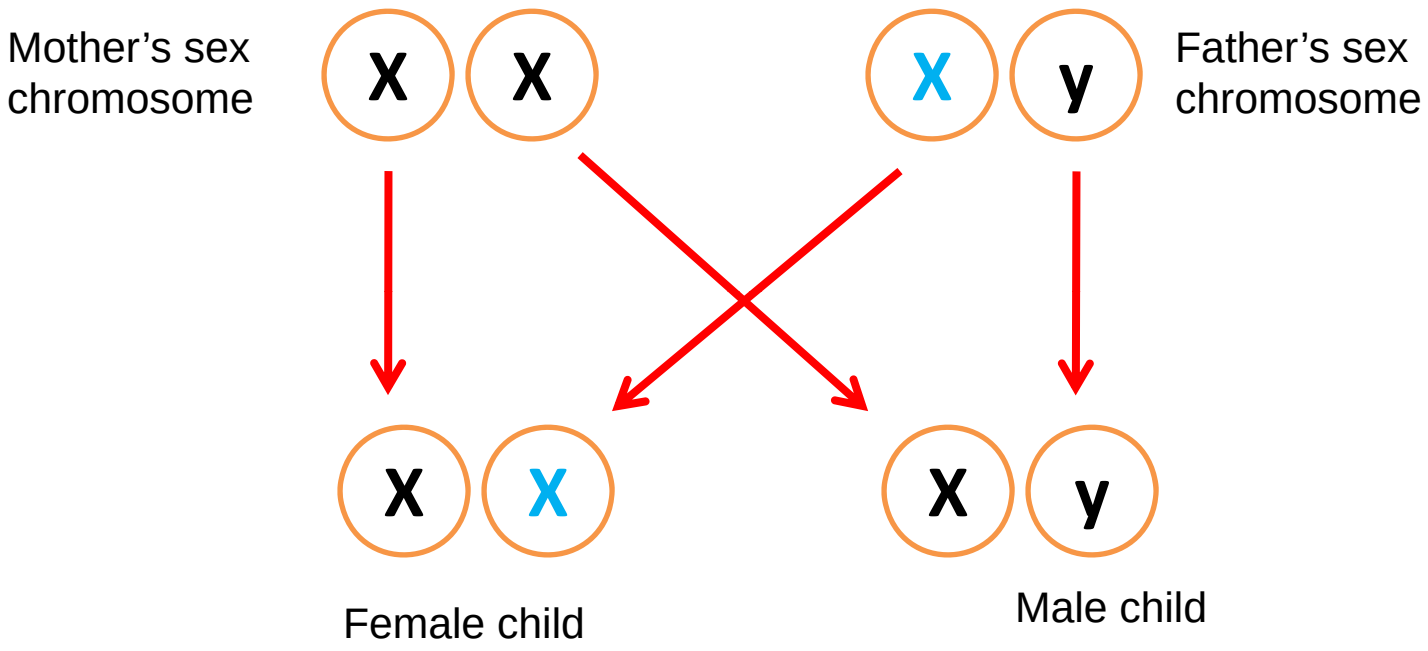
Sex-linked

- Sex chromosomes (X & Y) not only carry genes that determine male / female traits but some other characteristics too.

- Genes of sex chromosome = sex-linked
  - Y-linked – men only; both for X-linked

- Men - X and Y; women - two X's.

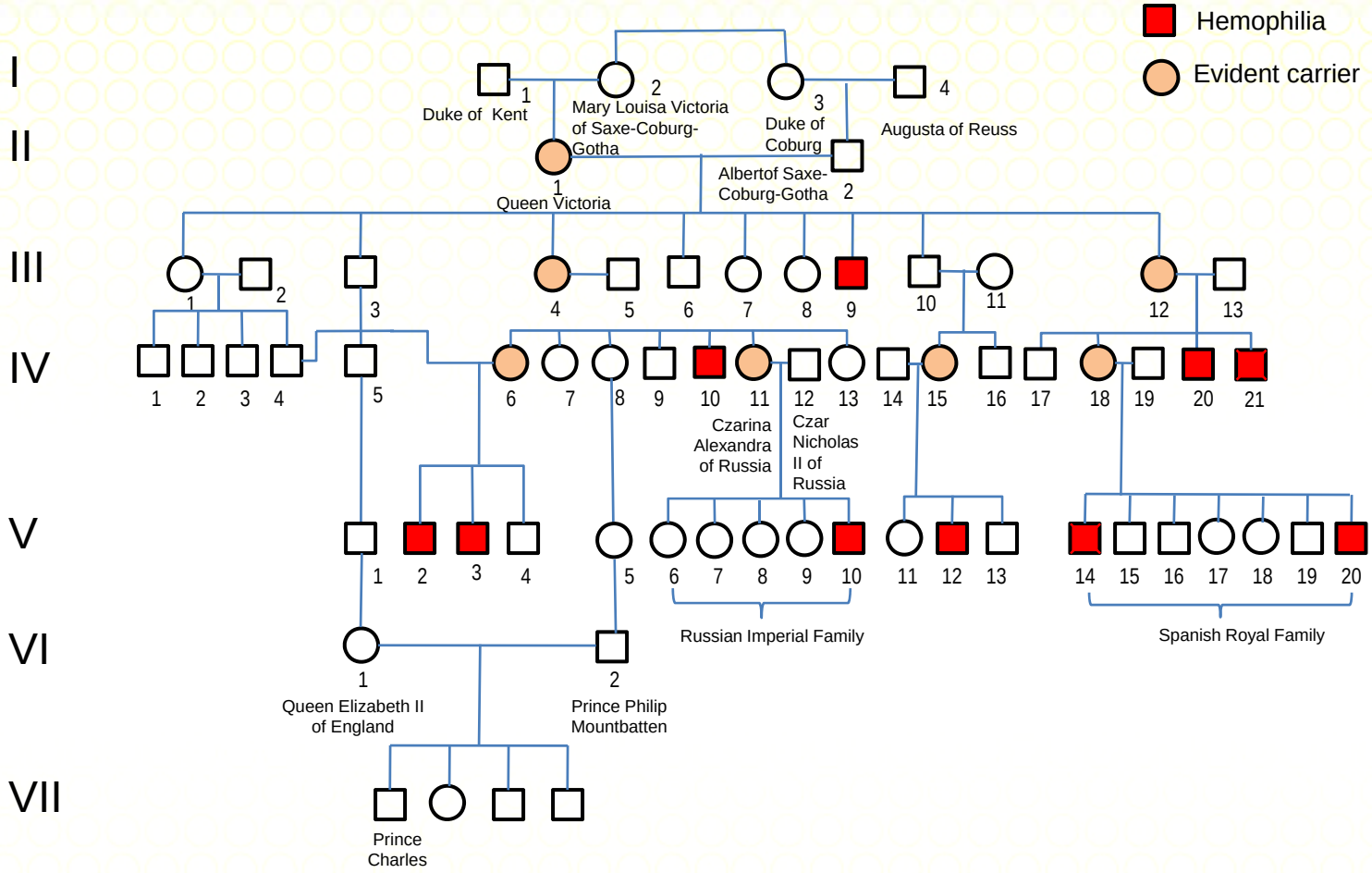
Sex linkage in human



Human X-linked Traits

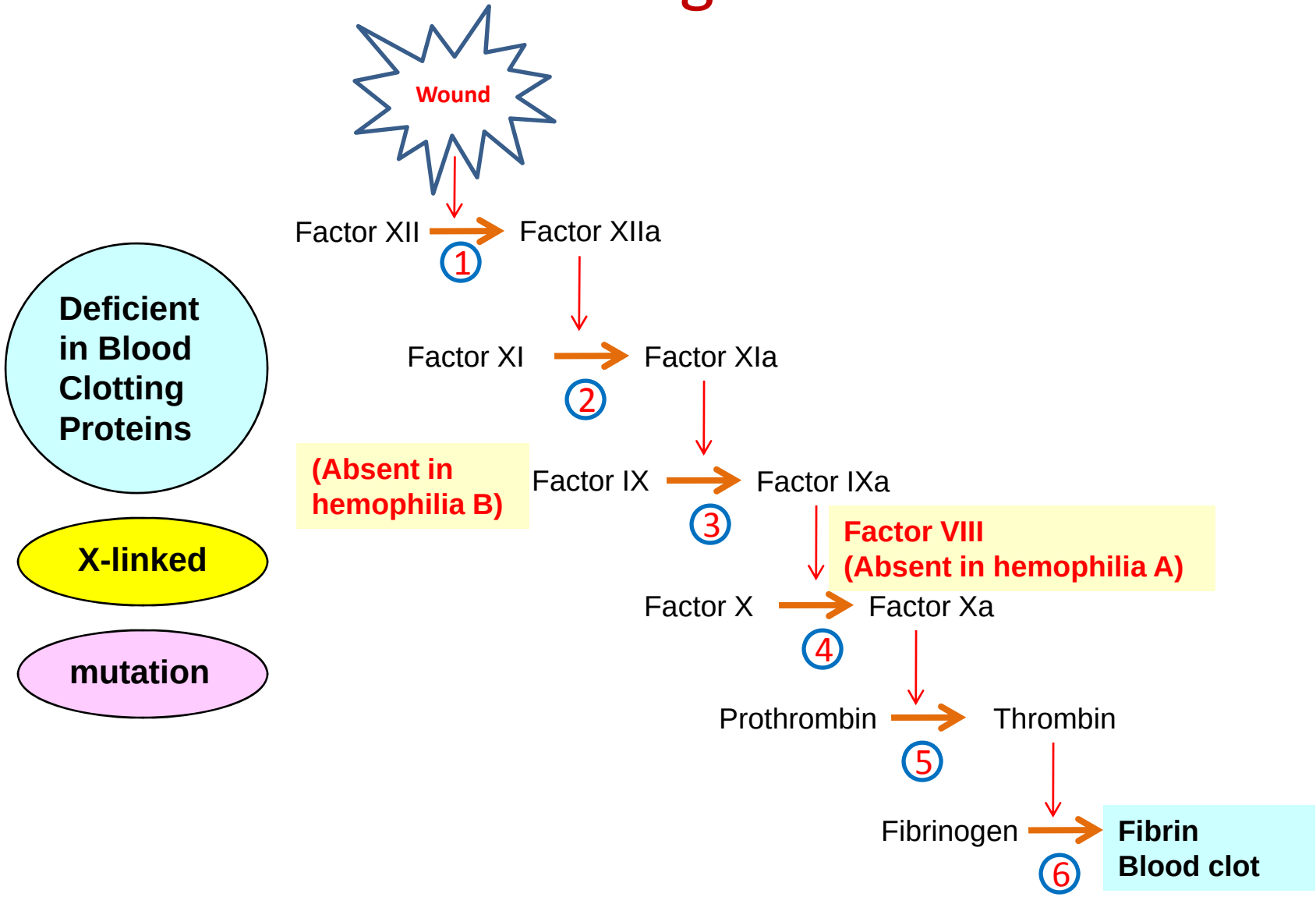
Condition	Characteristics
Hemophilia A	Clotting deficiency; deficiency of clotting factor VIII
Hemophilia B	Deficiency of clotting factor IX
G-6-PD	Deficiency of glucose-6-phosphate
Color blindness, deutan type	Insensitivity to green light
Color blindness, protan type	Insensitivity to red light
Fabry's disease	Deficiency of galactosidase A; heart and kidney defects, early death
Lesch-Nyhan syndrome	Deficiency of hypoxanthine-guanine phosphoribosyltransferase enzyme (HPRT) leading to motor and mental retardation, self-mutilation and early death

Hemophilia inheritance

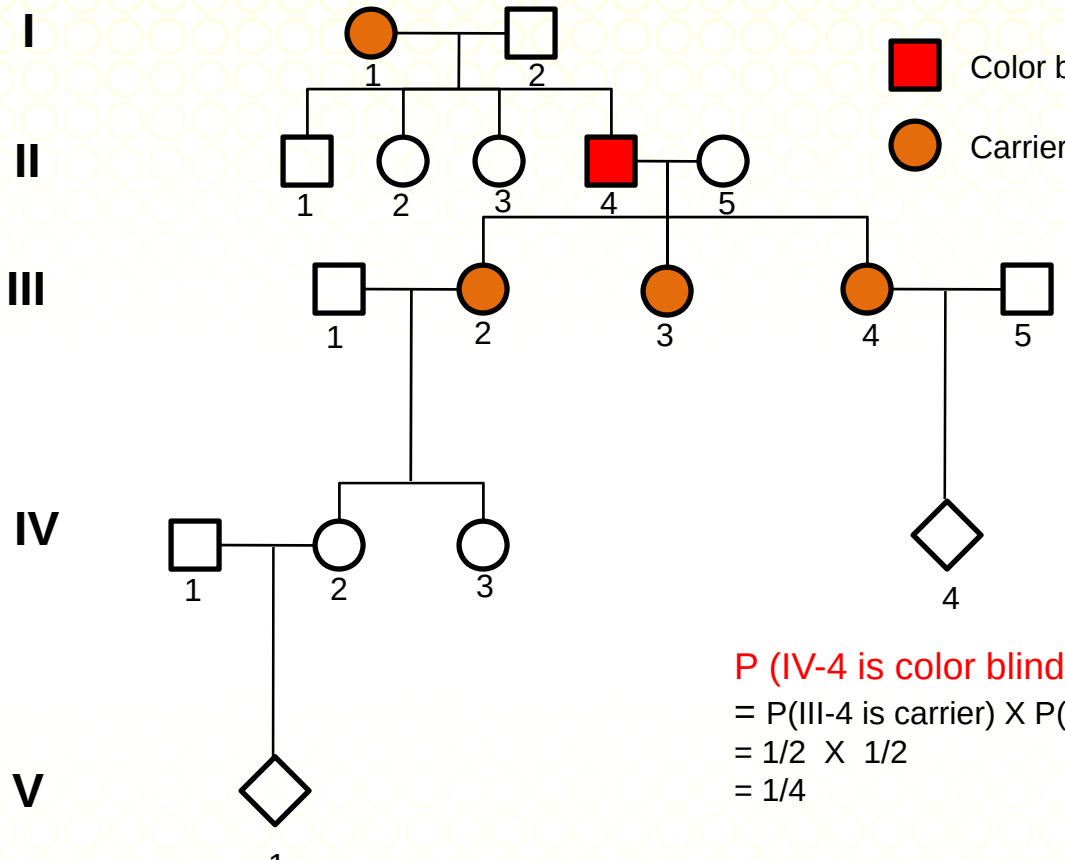


An X-linked Blood-Clotting Disorder

Blood coagulation



Color Blindness

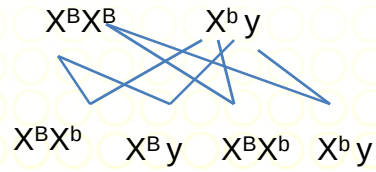


P (IV-4 is color blind) ?

= P(III-4 is carrier) X P(III-5 is affected)

= 1/2 X 1/2

= 1/4



P (V-1 is color blind) ?

= P(III-2 is carrier) X P(IV-1 is affected) X P (IV-2 is carrier)

= 1/2 X 1/2 X 1/2 = 1/8

Key Points

- Disorders such as hemophilia and color blindness, which are caused by recessive X-linked mutations, are more common in males than in females.
- In humans the Y chromosome carries fewer genes than the X chromosome.
- In humans pseudoautosomal genes are located on both the X and Y chromosomes.

SEX CHROMOSOMES AND SEX DETERMINATION

Sex Determination in *Drosophila*

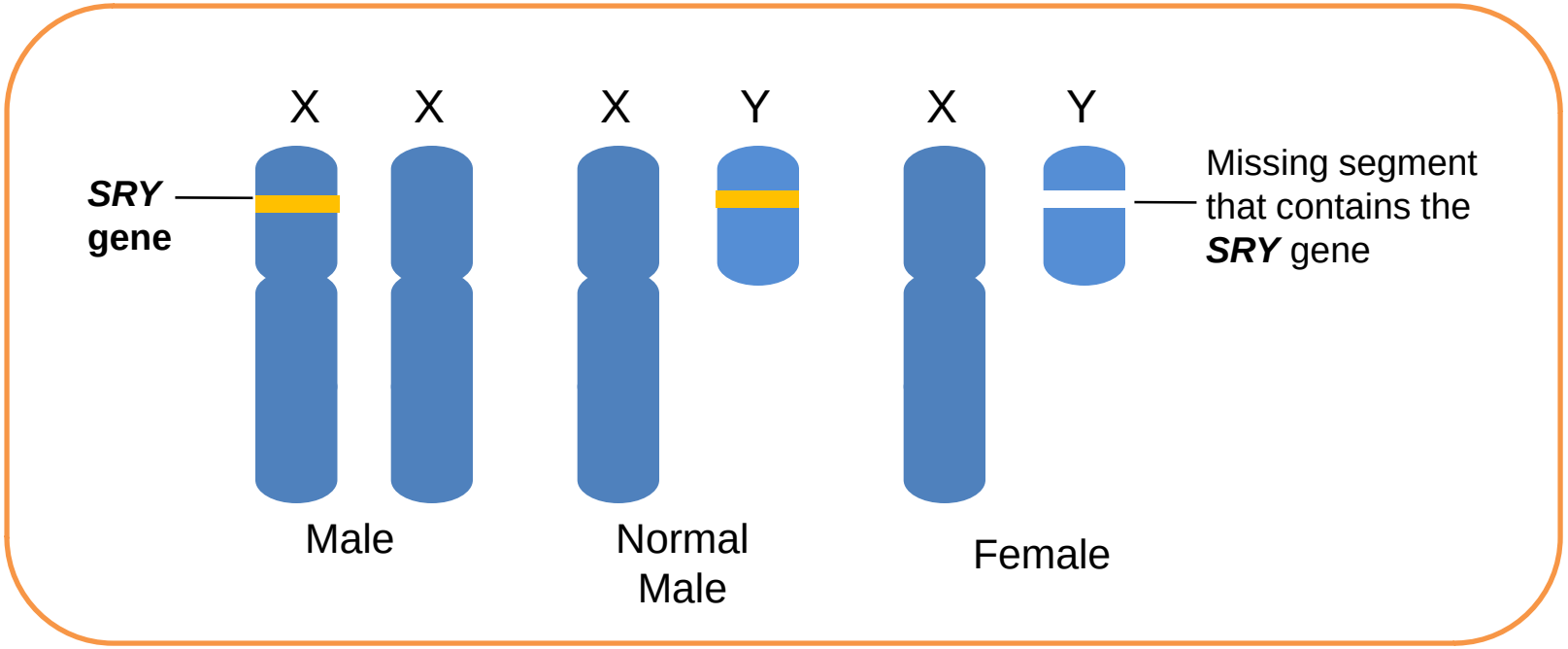
- Y Chromosome – plays no role in sexual phenotype but requires for male sterility – Bridges, 1921.
- X-linked gene, Sxl (sex lethal) – key in sex determination.
- If X:A $\geq$ 1.0, sxl activates, zygote develops a female.
- If X:A $\leq$ 0.5 , sxl inactivates, develops as a male.

Ratio of X Chromosomes to Autosomes and the Corresponding Phenotype in *Drosophila*

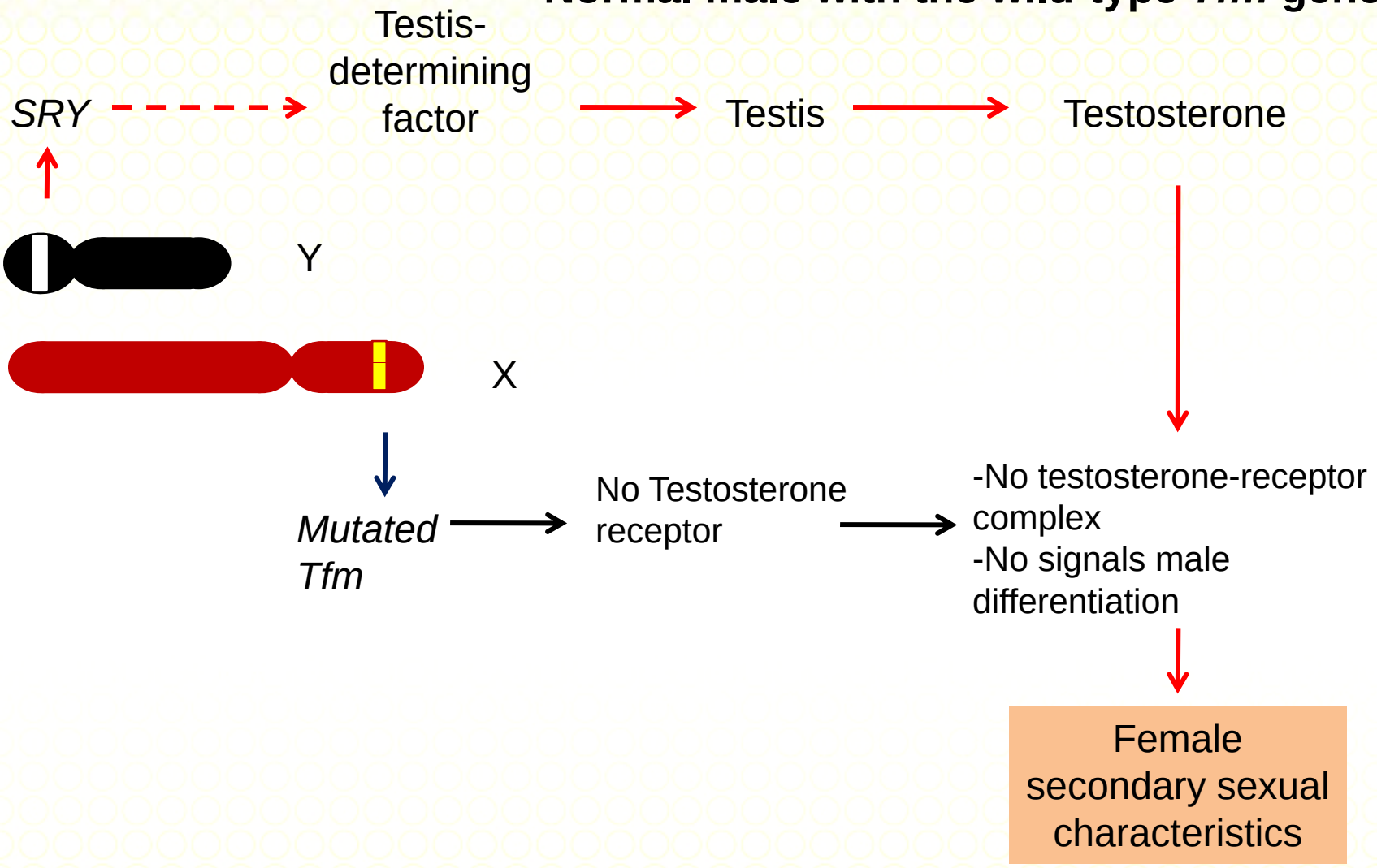
X Chromosomes (X) and sets of Autosomes (A)	X: A Ratio	Phenotype
1X 2A	0.5	Male
2X 2A	1.0	Female
3X 2A	1.5	Metafemale
4X 3A	1.33	Metafemale
4X 4A	1.0	Tetraploid female
3X 3A	1.0	Triploid female
3X 4A	0.75	Intersex
2X 3A	0.67	Intersex
2X 4A	0.5	Tetraploid male
1X 3A	0.33	Metamale

Sex Determination in Human Beings

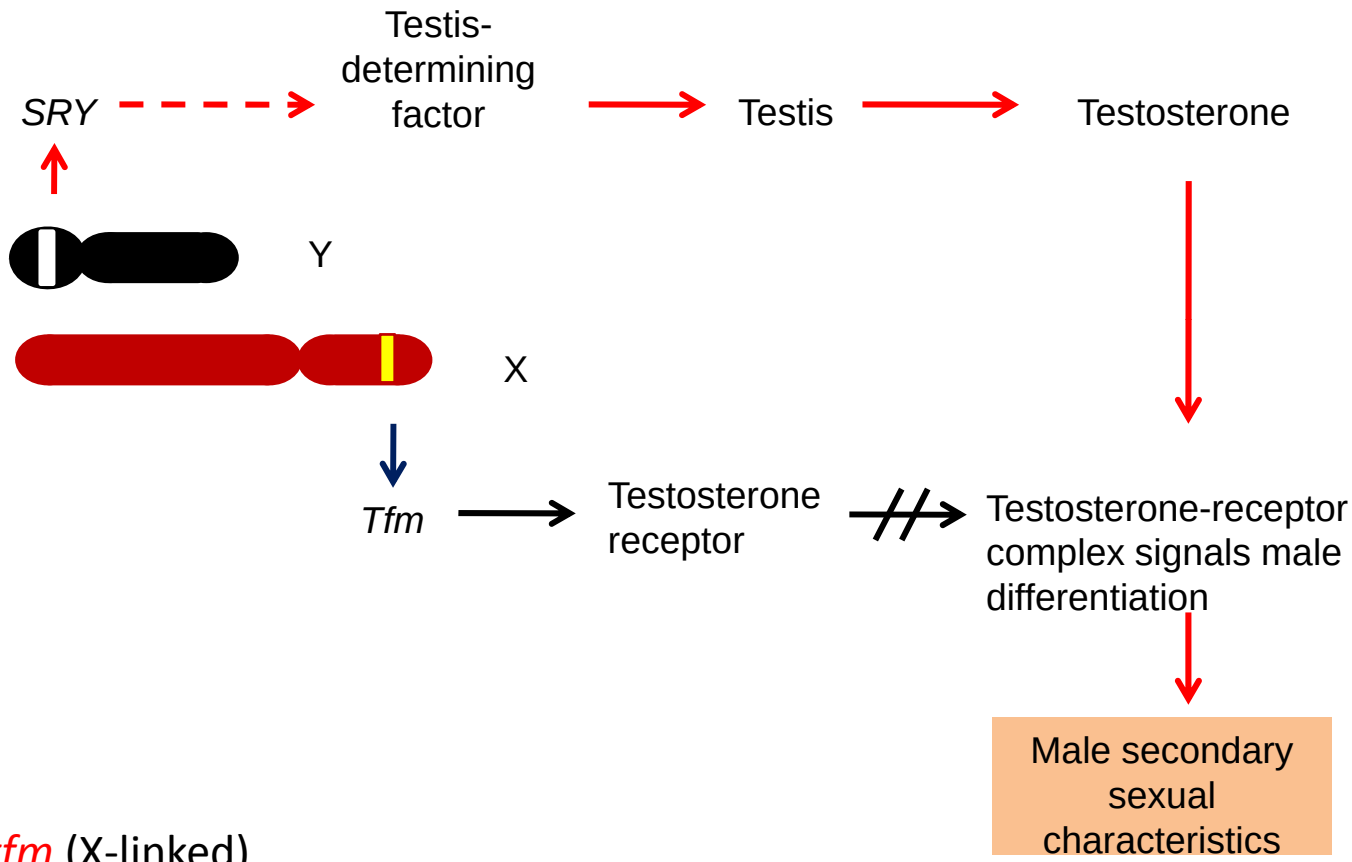
- SRY gene –sex-determining region Y;
  - Gene product- testis determining factor (TDF)



Normal male with the wild-type *Tfm* gene



Male with the *tfm* mutation and testicular feminization



Notes:

- Mutation – *tfm* (X-linked)
- No testosterone receptor
- Female characteristics – ovary → sterile

Key Points

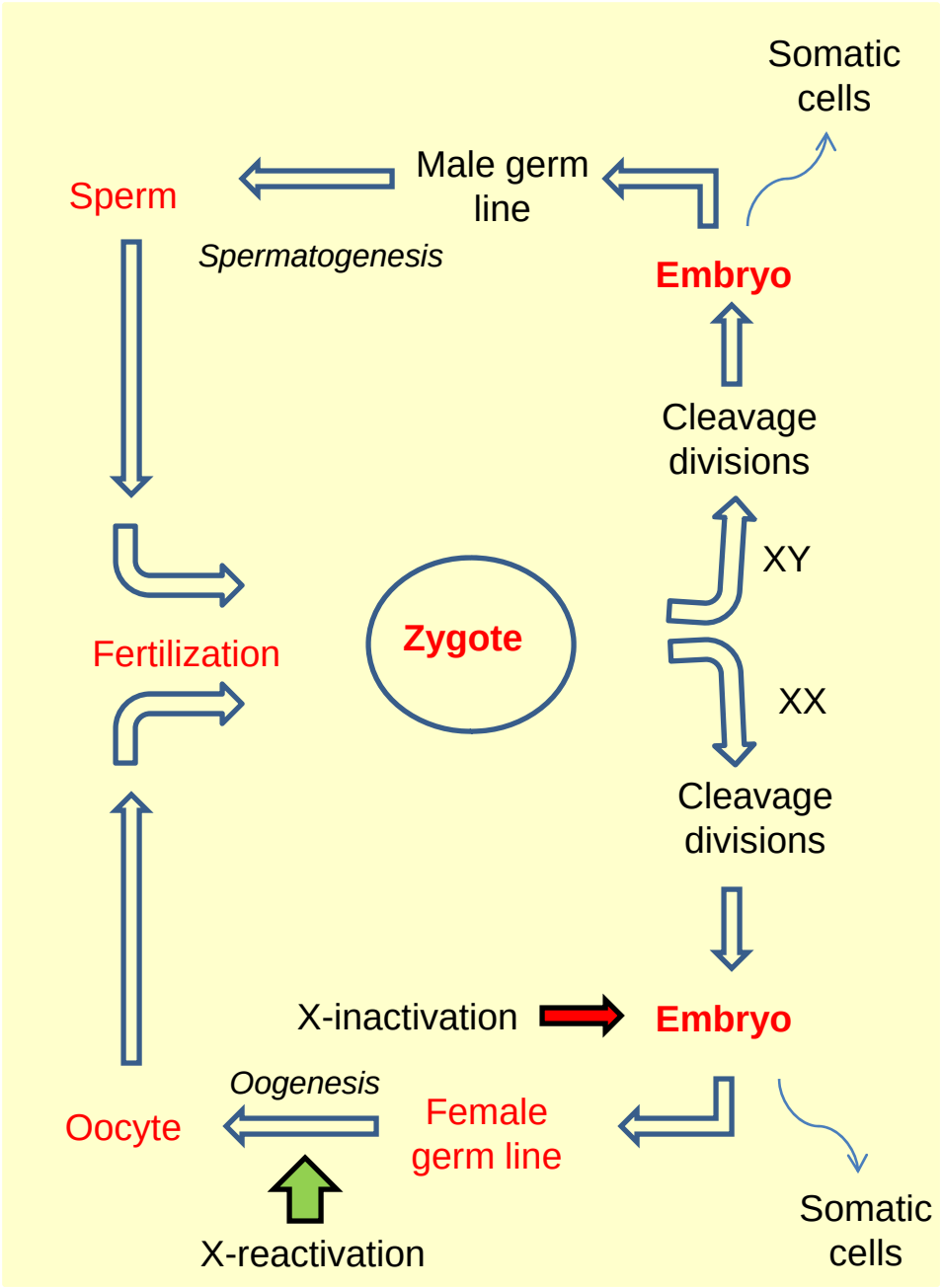
- In humans sex is determined by a dominant effect of the *SRY* gene on the Y chromosome; the product of this gene, the testis-determining factor (TDF), causes a human embryo to develop as a male.
- In *Drosophila*, sex is determined by the ratio of X chromosomes to sets of autosomes (X:A).
- In honeybees, sex is determined by the number of chromosome sets; haploid embryos develop into males and diploid embryos develop into females.

DOSAGE COMPENSATION OF X-LINKED GENES

Hyperactivation of X-linked genes in male *Drosophila*

- Each X-linked gene works twice as hard in males as it does in females.
- X-linked gene in male *Drosophila* is hyperactivated (protein complex binds to the X chromosome and stimulates gene expression)

Phenotype	Genotype	X:A ratio	*Sxl* gene	Cause
Male	XY AA	0.5	off	Increase in X-linked gene expression
Female	XX AA	1.0	on	No increase in X-linked gene expression



X chromosome inactivation in mammals

X is activated during oogenesis in female

One copy of each X-linked gene is inactivated in females

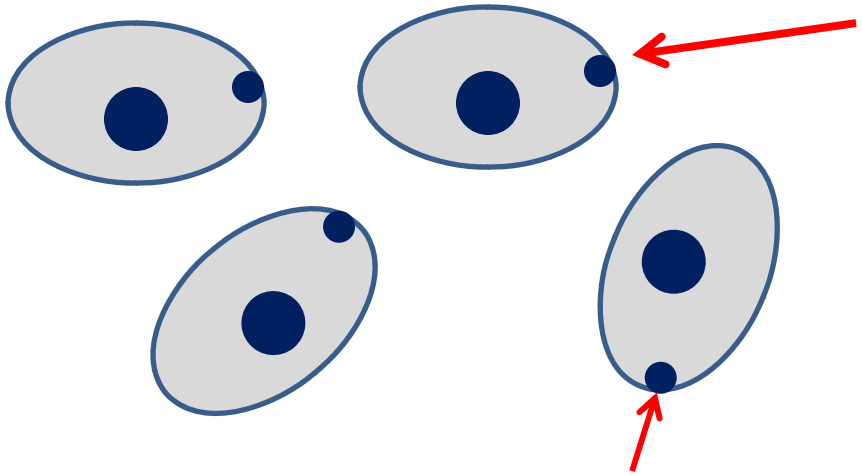
X-inactivation center (XIC) – initiating site – long arm of X chromosome.

inactivated form of X chromosome – darkly staining structure called a **Barr body**.

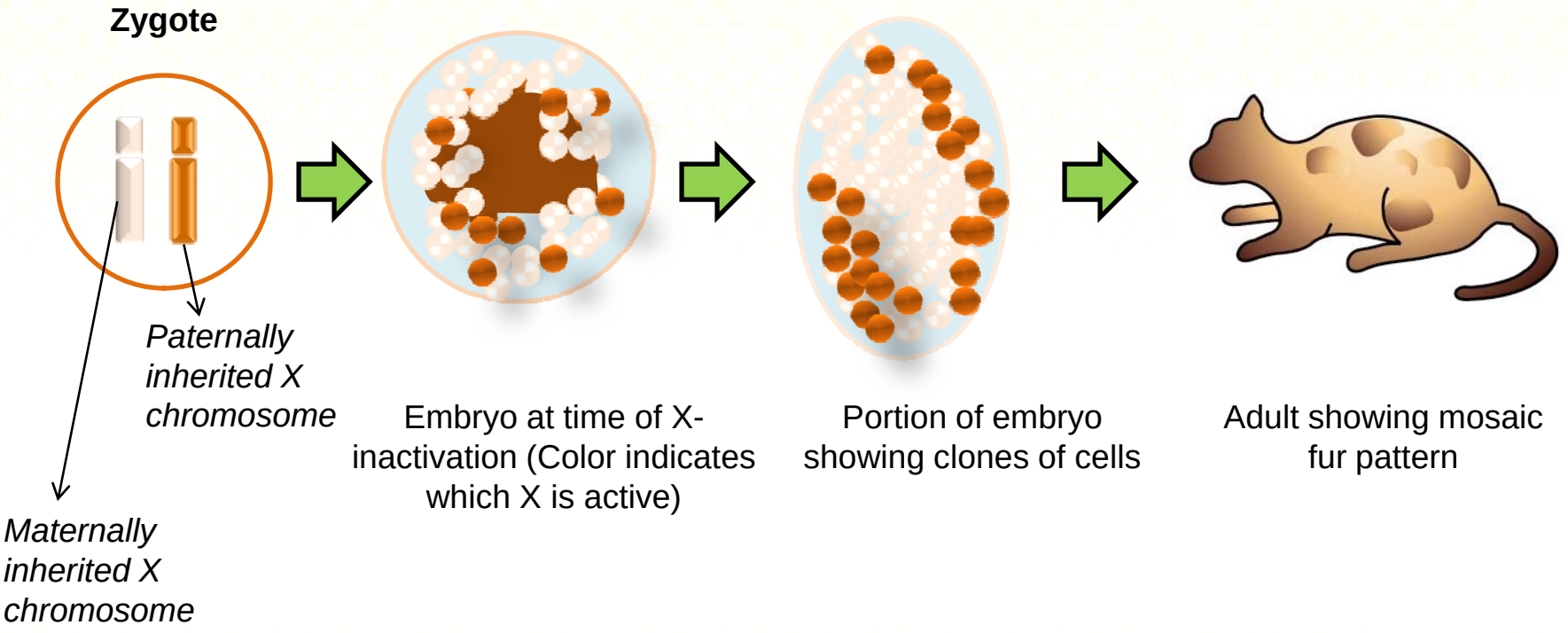
Barr Bodies

- The inactivated X chromosomes are called Barr bodies
- These X chromosomes are replicated mitotically, and reactivated for meiosis
- Once inactivated, the same X chromosome remains inactivated in all descendent cells

Barr Bodies



The Barr bodies (arrows) are visible only in the female nuclei


Zygote
Paternally inherited X chromosome
Maternally inherited X chromosome
Embryo at time of X-inactivation (Color indicates which X is active)
Portion of embryo showing clones of cells
Adult showing mosaic fur pattern

Tortoiseshell or calico cat

- The orange and black patches – inactivation of alleles - pigmentation

Key Points

- In *Drosophila*, dosage compensation for X-linked genes is achieved by hyperactivating the single X chromosome in males.
- In mammals, dosage compensation for X-linked genes is achieved by inactivating one of the two X chromosomes in females.

References

- Snustad DP, Simmons, MJ (2010) Principles of Genetics Fifth Ed. John Wiley & Sons, Inc., USA.
- Klug WS, Cummings MR, Spencer CA, Palladino MA (2012) Concepts of Genetics. 10th Ed. Pearson, California.
- Hartwell LH, Hood L, Goldberg ML,Reynolds AE, Silver LM (2011) Genetics: From Genes to Genomes. 4th Ed. McGraw-Hill Companies, Inc.,NY